Statistical Analysis Plan	
Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.
eTrack study number and Abbreviated Title	212494 (RSV OA=ADJ-006)
Scope:	All data pertaining to the above study (except IDMC analysis and Correlate of Protection analysis).
Date of Statistical Analysis Plan	Amendment 8 Final: 20 Jun 2024

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Illness
BMI	Body Mass Index
CD	Community Dwelling
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ED60	Estimated Dilution 60
ELISA	Enzyme-linked immunosorbent assay
ELU/mL	ELISA Laboratory Units per milliliter
EQ-5D	EuroQol 5 dimension health questionnaire
ES	Exposed Set
FLU-PRO	InFLUenza Patient-Reported Outcome
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HCRU	Healthcare Resource Utilization
HLT	High Level Term
hMPV	Human Metapneumovirus
HR	Hazard Ratio

HR-QoL	Health-Related Quality of Life
IDMC	Independent Data Monitoring Committee
IES	Independent External Statistician
IgG	Immunoglobulin G
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit Of Quantification
LRTD	Lower Respiratory Tract Disease
LSMEANS	Least Squares Mean
LTCF	Long-Term Care Facility
MedDRA	Medical Dictionary for Regulatory Activities
mES	modified Exposed Set
MGI	Mean Geometric Increase
NA	Not Applicable
NH	Northern Hemisphere
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pIMD	Potential Immune-Mediated Disease
PoS	Probability of Success
PPSe	Per-Protocol Set for efficacy
PPSi	Per-Protocol Set for immunogenicity
PT	Preferred Term
RR	Relative Risk
RSV	Respiratory Syncytial Virus

RT-PCR	Reverse Transcription Polymerase Chain Reaction
S1/S2/S3	Season 1/2/3
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SF-12	A Short Form 12-item health survey
SH	Southern Hemisphere
SOC	System Organ Class
SR	Study Report
UL	Upper Limit of the confidence interval
ULOQ	Upper Limit Of Quantification
US	United States
VE	Vaccine Efficacy
YOA	Years Of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
22 October 2020	First version for consultations	Final: 16 October 2020
20 May 2021	Final version	Amendment 1: 25 February 2021
22 October 2021	Amendment 1	Amendment 2: 6 October 2021
08 March 2022	Amendment 2 • Change in definition of subgroup categories for comorbidity using Charlson index (Table 3) • Change in adjudication process (6.2.2.1) • Add sensitivity analysis (6.2.2.3.5 and 6.3.2.1.3) • Threshold for subgroups analysis has been removed (6.2.2.4) • Add analysis of Non-serious AEs and immediate AEs (6.4.2.4) • Remove analysis on subjects with safety follow-up of at least 6 months (6.4.2.4) • Clarify success criterion for interim (8.1) • Clarify time of VE analysis 1 in case of enrolment of second cohort (8.2)	Amendment 2: 6 October 2021
12 May 2022	Amendment 3 • Adapt to protocol amendment 3 • Add sensitivity safety analysis excluding RSV positive ARI cases	Amendment 3: 24 January 2022
20 December 2022	Amendment 4 Additional descriptive analyses and clarification on VE analysis 2 (end of season 1) were added but no change in planned analysis were performed. • Adapt analysis sets definition (5.1) and elimination codes for Dose 2/Dose 3 (5.2) • Add sensitivity analysis for hospitalization/complications (6.3.2.1.1), and any deaths (6.4.2.2) • Add summary of RSV LRTD/ARI by calendar month (6.3.2.1.1) • Adapt rules for counting cases and follow-up time (Table 7)	Amendment 3: 24 January 2022

Date	Description	Protocol Version
04 September 2023	Amendment 5 Changes according to Protocol amendment 4, and clarifications for subsequent VE analysis: • Updates in analysis sets and elimination codes for Dose 2/3 (Section 5) • Updates in rules for VE over seasons and censoring (tables 6 and 7) • Add efficacy analysis post-Dose 2 only (Section 6.4.2.5)	Amendment 4: 23 March 2023
07 December 2023	Amendment 6 Changes according to Protocol amendment 5, and clarifications for subsequent VE analysis: • Updates in analysis sets and elimination codes for Dose 2/3 (Section 5) • Updates in rules for VE over seasons and censoring (tables 6 and 7) • Update in definition of season parameter in the VE model (6.3.2.1.1) • Add estimand description for primary and secondary endpoints (12.4)	Amendment 5: 12 July 2023
22 May 2024	Amendment 7 CBER update and clarifications for subsequent VE analysis: • Changes according to the CBER recommendation to align to the suggested rule of computing duration of a solicited AEs in SDTM. Updates in the definition of duration of events (Section 10.2.2) and also update in the wording for summary of reactogenicity analysis (Section 6.3.1.3) • Add efficacy analysis from start of season 3 up to end of season 3 only (Section 6.4.2.5) • Add an additional sensitivity analysis to be performed excluding RSV cases with respiratory co-infections for VE against RSV-confirmed ARIs over several seasons (Section 6.3.2.1.3)	Amendment 5: 12 July 2023
20 Jun 2024	***Amendment 8*** - Add clarification on population used for Season 3/Year 3 analysis for annual revaccination (Table 7 and Section 6.4.2.5)	Amendment 5: 12 July 2023

Date	Description	Protocol Version
	- Add exploratory analysis on VE at season 3 using a Cox model with time-varying vaccine effect (Section 6.4.2.5)	

2. OBJECTIVES/ENDPOINTS

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

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by season in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by season.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by year in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by year.
To evaluate the evolution of efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over time.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by baseline frailty status in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by baseline frailty status.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe RSV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of any ARI and any LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of ARI or LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalization due to respiratory diseases in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons† and during the entire follow-up. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related

Objectives	Endpoints
	to RSV-confirmed respiratory diseases during the RSV seasons† and during the entire follow-up.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition* and during the entire follow-up.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean EQ-5D utility score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean SF-12 Physical Functioning score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To describe RSV-confirmed ARI cases and RSV-confirmed LRTD cases in the RSVPreF3 and Placebo groups.	Descriptors of RT-PCR-confirmed RSV A and/or B ARI and LRTD cases, including duration of episodes, reported symptoms/signs and respiratory tract infection severity.
Secondary – Immunogenicity	
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Season 3: • RSVPreF3 IgG-binding antibody concentrations. • Neutralizing titers against RSV A. • Neutralizing titers against RSV B.
Secondary – Safety	
To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine.	In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination (i.e., the day of vaccination and 3 subsequent days).

Objectives	Endpoints
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from the day of vaccination up to 6 months after each vaccination. • Occurrence of all pIMDs from the day of vaccination up to 6 months after each vaccination. • Occurrence of SAEs related to study vaccination from Day 1 up to study end. • Occurrence of pIMDs related to study vaccination from Day 1 up to study end. • Occurrence of any fatal SAEs from Day 1 up to study end.
Tertiary	
Tertiary – Efficacy	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV and/or hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV and/or hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination up to the end of Season 2 and Season 3.	First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed hMPV-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by season, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.

Objectives	Endpoints
To evaluate the evolution of efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI over time.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of all-cause mortality during the RSV seasons† in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Occurrence of any death during the RSV seasons†.
To estimate the proportion of participants with > 1 case of ARI or LRTD by season and participants reporting respiratory diseases in consecutive seasons, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Number of participants with > 1 case of ARI, LRTD, RT-PCR-confirmed RSV A and/or B-associated ARI and RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definitions* by season and in consecutive seasons.
To estimate the proportion of co-infections with other viral pathogens for RSV-confirmed or hMPV-confirmed ARI cases, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Number of participants with other viral pathogens (detected by RT-PCR) co-existing with RSV or hMPV among RT-PCR-confirmed RSV or RT-PCR-confirmed hMPV ARI episodes.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on upper respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the Placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Maximum FLU-PRO upper respiratory symptom score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To assess the impact of the RSVPreF3 OA investigational vaccine on healthcare resource utilization (HCRU) for participants with RSV-confirmed ARI and any ARI, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	• Hospitalization rate during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*. • Antibiotic use during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on patient-reported severity of respiratory symptoms in participants with RSV-confirmed LRTD in the RSVPreF3 groups compared to the Placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Maximum patient global impression of severity (PGI-S) score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated LRTD.
Tertiary - Immunogenicity and Safety	
To assess the correlation of the humoral immune response to the RSVPreF3 OA investigational vaccine at 30 days post-Dose 1 with protection against RSV disease.	RSVPreF3 IgG-binding antibody concentrations at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31) and pre-Season 3** in all participants with RSV disease compared to a subset of controls.‡

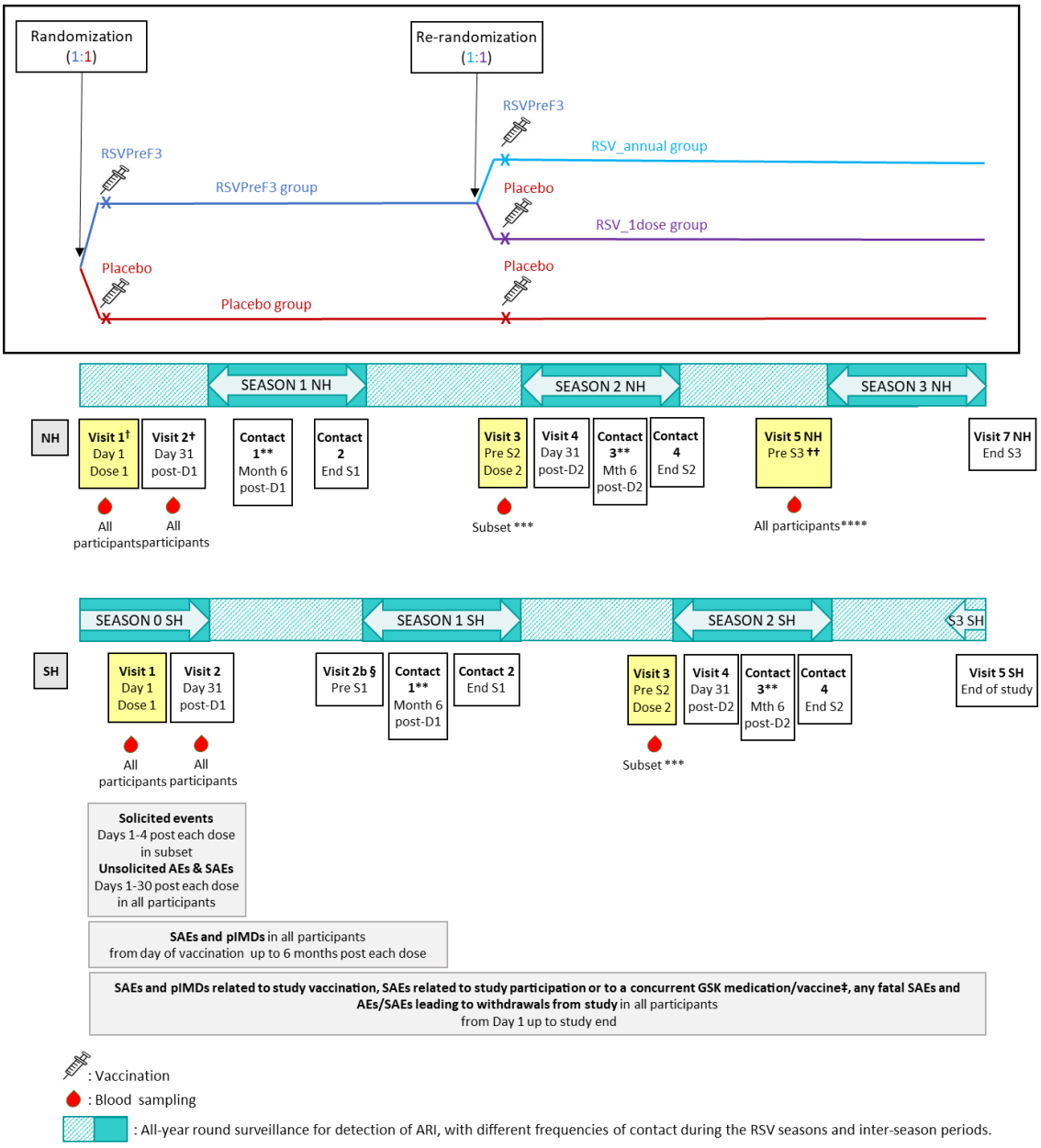
Objectives	Endpoints
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Season 3: • RSVPreF3 IgG-binding antibody concentrations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

* Case definitions are described in Section 4.
† The RSV seasons defined for this study are from 1 October to 30 April in NH and from 1 March to 30 September in SH.
‡ Additional testing such as but not limited to neutralization assay(s) and systems serology testing might be performed on the same subset of participants to investigate a correlate of protection.
** Blood sample at pre-Season 3 is applicable for all participants in the NH who have their Visit 5NH after the approval of the Protocol Amendment 5.

Description of estimand attributes associated to the main secondary endpoints is provided in Section 12.4.

3. STUDY DESIGN

Figure 1 Study design overview



Note: For simplicity, the randomization in this figure is presented as 1:1 between the RSVPreF3 OA vaccine and the placebo group. Participants will be randomized with a ratio of 1:1:1:3 to 1 of 4 study groups (RSVPreF3 Lot 1/2/3 versus Placebo) for Part 1 of the study and a ratio of 1:1 to 1 of 2 study groups (RSVPreF3 Lot 4 versus Placebo) for Part 2 before Season 1 (refer to the experimental design below and Section 6.3.2 in the protocol for details).

Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 8.2), the participants enrolled in this cohort will follow the same study design as indicated in this figure.

RSV_annual: RSVPreF3 OA annual revaccinations group

RSV_1dose: RSVPreF3 OA single vaccination group

AE: adverse event; ARI: acute respiratory illness; NH: Northern hemisphere; SH: Southern hemisphere; pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event

* Dose 3 only applies to participants in NH.

† Depending on the time of enrollment, Visit 1 and Visit 2 in NH can take place during Season 1.

** Contacts 1 and 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.

§ Visit 2b in SH (Pre-Season 1 visit) should be performed at the earliest 3 months before the start of Season 1 in SH. This Visit 2b should not be performed for participants that have their Visit 2 planned within 3 months before the start of Season 1. For all participants in SH that have their Visit 2 more than 3 months before the start of Season 1, Visit 2b should be planned as a stand-alone visit.

*** Blood samples should only be taken from participants in the reactogenicity and immunogenicity subset in Part 1.‡ All SAEs related to study participation, or a GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study. All other SAEs are to be reported after the first study vaccine administration.

†† Some participants in the NH may have Visit 5NH before the approval of the Protocol Amendment 5. These participants should receive Dose 3 pre-Season 3 and all subsequent study procedures should be performed as planned in Protocol Amendment 4. Please refer to the Table 1 in the protocol for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of this amendment.

**** For participants in the NH who have their Visit 5NH before the approval of the Protocol Amendment 5, a blood sample should be taken only if the participant is in the reactogenicity and immunogenicity subset. Please refer to the Table 1 in the protocol for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of Protocol amendment 5.

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

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

At the time of pre-Season 3 (Visit 5NH), participants in the NH who will have their Visit 5NH before approval of the Protocol Amendment 5, will receive the study intervention as planned according to their group allocation. Participants having their Visit 5NH after approval of the Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).

Note: Part 2 with the RSVPreF3 OA interventional vaccine Lot 4 was not initiated and only the vaccine Lots 1/2/3 of Part 1 were used for Dose 1 administration.

- **Randomization for the additional cohort enrolled in NH after sample size re-assessment:** If following sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 8.2), the participants in this additional cohort will be enrolled in 3 study groups (RSV_annual group, RSV_1dose group and Placebo group) according to a 1:1:2 randomization ratio and will follow

the same study design as indicated in Figure 1. They will have a blood sampling at Visit 1 and Visit 2 as for all study participants. There will be no subset for immunogenicity and reactogenicity for this cohort.

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

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

Table 1 Study groups, intervention and blinding foreseen in the study

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

Study groups	Number of participants*			Age	Intervention	Blinding	
	NH	SH	Total			Visit 1 → Visit *3* (Observer-blind)	Visit 3 → Visit 7NH/Visit 5SH (Observer-blind)
RSV_L2_1dose	Up to 5 750	375-500	Up to 6 250	≥ 60 years			X
RSV_L3_1dose							X
RSV_L4_1dose							X
Placebo	Up to 11 500	750-1 000	Up to 12 500	≥ 60 years	Placebo		X
Total	Up to 23 000	1 500-2 000	Up to 25 000				

NH: Northern hemisphere; SH: Southern hemisphere; L1: Lot 1; L2: Lot 2; L3: Lot 3; L4: Lot 4
* Numbers are approximate (see Section 9.2.1 of the protocol for details on the sample size calculation).
** Participants enrolled in the RSVPreF3 groups will receive vaccine Lots 1, 2 or 3. When these lots are no longer available at the site, the site will switch to Lot 4. This is applicable in both SH and NH.
*** Re-supply lot for Part 2.

Note: Part 2 with the RSVPreF3 OA interventional vaccine Lot 4 was not initiated and only the vaccine Lots 1/2/3 of Part 1 were used for Dose 1 administration.

- **Vaccination schedule:** First dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1 followed by annual revaccination doses of study vaccine (RSVPreF3 OA investigational vaccine or placebo) as follows:
  - Participants from the NH who will have their Visit 5NH before the approval of the Protocol Amendment 5, will receive 2 additional doses, 1 before Season 2 and 1 before Season 3.
  - Participants from the NH who will have their Visit 5NH after the approval of the Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH). These participants had received 1 additional dose before Season 2.
  - Participants from the SH will receive 1 additional dose before Season 2.
- **Safety monitoring:** An IDMC, in addition to the existing GSK's Safety Review Team (SRT), will oversee the safety of the study participants and study conduct (refer to Section 8.2.3 of the protocol).
- **ARI surveillance:** Surveillance for ARI detection will be carried out during the entire study via spontaneous reporting by the study participant (starting on the first vaccination day [Visit 1]) and via scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods (refer to Section 8.1.1 of the protocol). Swab samples will be taken in all participants meeting pre-specified criteria for ARI case definition (refer to Section 4). Diagnosis and treatment of each ARI should be performed according to the local standard of care.
- **RSV season**: RSV season considered for analysis is defined as the period from 1 October to 30 April in NH and from 1 March to 30 September in SH. Based on the observed RSV circulation during the season, the ARI surveillance and/or the DLP for analyses could be adapted for the ongoing and/or subsequent seasons.

- **Subset:** Evaluation of solicited events and the humoral immune response will be performed in a subset of participants, referred to as reactogenicity and immunogenicity subset. This subset will include approximately 1800 participants from the 3 RSVPreF3 OA investigational vaccine lot groups and placebo group (1:1:1:3 ratio) in Part 1, including participants from NH and SH.
- **Groups and sub-groups definition for analysis:** Refer to the tables below for a description of the groups and subgroups labels used in the Tables Figures and Listings (TFLs).

For all statistical analyses, the RSVPreF3 vaccine lots will be pooled, and results will be presented by group as follows:

  – In **RSVPreF3** and **Placebo** groups for analysis after the first vaccination (season 1, over seasons).
  – In **RSV_annual**, **RSV_1dose** and **Placebo** groups for analysis after dose 2 (season 2 and season 3 in NH).

The pooled groups labels and definition for footnote are provided in Table 2.

Table 2 Group names and definition for footnote in the TFLs

Analysis	Group label	Group definition	Pooled Groups label in tables	Group order in tables	Pooled definition for footnote
Dose 1 (season 1)	RSVPreF3_L1	Participants receiving RSVPreF3 OA investigational vaccine Lot 1	**RSVPreF3**	1	Participants receiving RSVPreF3 OA investigational vaccine (pooled lots)
	RSVPreF3_L2	Participants receiving RSVPreF3 OA investigational vaccine Lot 2			
	RSVPreF3_L3	Participants receiving RSVPreF3 OA investigational vaccine Lot 3			
	Placebo	Participants receiving Placebo	**Placebo**	2	Participants receiving Placebo

Analysis	Group label	Group definition	Pooled Groups label in tables	Group order in tables	Pooled definition for footnote
Dose 2/ Dose 3 (seasons 2 and 3)	RSV_L1_annual	NA	**RSV_annual**	1	Participants receiving annual revaccination of RSVPreF3 OA investigational vaccine
	RSV_L2_annual	NA			
	RSV_L3_annual	NA			
	RSV_L1_1dose	NA	**RSV_1dose**	2	Participants receiving 1 dose of RSVPreF3 OA investigational vaccine
	RSV_L2_1dose	NA			
	RSV_L3_1dose	NA			
	Placebo		**Placebo**	3	Participants receiving Placebo

Table 3 Subgroup names and definitions for footnote in the TFLs

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
By age[1]	1	≥65YOA	≥65 years old participants
	2	≥70YOA	≥70 years old participants
	3	≥80YOA	≥80 years old participants
	4	60-69YOA	60-69 years old participants
	5	70-79YOA	70-79 years old participants
By hemisphere	1	NH	Participants from Northern Hemisphere
	2	SH	Participants from Southern Hemisphere
By region[2]	1	North Am	Participants from North America (US, Canada, Mexico)
	2	EU	Participants from Europe (Belgium, Estonia, Finland, Germany, Italy, Poland, Russia, Spain, UK)
	3	Asia	Participants from Asia (Japan, South Korea)
	4	SH	Participants from Southern hemisphere (Australia, South Africa, New Zealand)
By Ethnicity	1	Hisp_Lat	Hispanic or Latino
	2	No_Hisp_Lat	Not Hispanic or Latino

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
By Race	1	African	Black or African American
	2	Asian	Asian - Central/South Asian Heritage or Asian - East Asian Heritage or Asian - Japanese Heritage or Asian - South East Asian Heritage
	3	White	White - Caucasian / European Heritage or White - Arabic / North African Heritage
	4	Other	Other races, including American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander
By Sex	1	Male	Male
	2	Female	Female
By baseline frailty status – Gait speed test	1	Frail	Participants with a walking speed <0.4m/s or who were not able to perform the test[3]
	2	Pre-Frail	Participants with a walking speed between 0.4-0.99 m/s
	3	Fit	Participants with a walking speed ≥1 m/s
By comorbidity	1	Low/medium Risk	Participants with co-morbidity score at baseline less than or equal to 3 (Charlson Index)
	2	High Risk	Participants with co-morbidity score at baseline greater than 3 (Charlson Index)
By Subset	1	Subset	Participants included in the reactogenicity and immunogenicity subset
	2	Non-subset	Participants not included in the reactogenicity and immunogenicity subset

YOA = Years of age

[1]Age categories: 60-69YOA, 70-79YOA, ≥70YOA and ≥80YOA will be defined according to the categories used in SBIR for minimization (see Section 10.2).

[2]In case of enrollment of a second cohort, the definition of regions might be adapted to add new countries.

[3] Participants who were not able to perform the test for the following reasons in the eCRF: Tried but unable, Could not walk unassisted, Not attempted – study staff or participant felt unsafe, participants unable to understand the instructions.

4. CASE DEFINITIONS FOR EVALUATION OF VACCINE EFFICACY

All participants reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 4) will be followed-up for ARI assessment. Diagnosis and treatment of each ARI should be performed according to the local standard of care. RT-PCR testing for RSV/hMPV will be performed at GSK clinical laboratory or designated laboratory. Therefore, all participants with ARI will be requested to follow all study procedures and study contacts defined for the ARI surveillance (i.e., reporting of ARI symptoms/signs, ARI visit and follow-up contacts, completion of QoL questionnaires, etc.).

Table 4 Case definitions for evaluation of vaccine efficacy

<table>
<tr><th>Endpoint</th><th>Case definition</th></tr>
<tr><td>ARI
(Trigger for swabbing)</td><td>Presence of:
• at least 2 respiratory symptoms/signs for at least 24 hours
OR
• at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours
Respiratory symptoms and signs
- Nasal congestion/rhinorrhea
- Sore throat
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]
Systemic symptoms and signs
- Fever[1]/feverishness[2]
- Fatigue
- Body aches
- Headache
- Decreased appetite</td></tr>
<tr><td>RT-PCR-confirmed RSV-ARI or hMPV-ARI[5]</td><td>An event meeting the case definition of ARI with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.[6]</td></tr>
<tr><td>LRTD</td><td>Presence of:
• at least 2 lower respiratory symptoms/signs for at least 24 hours including at least 1 lower respiratory SIGN
OR
• at least 3 lower respiratory symptoms for at least 24 hours
Lower respiratory symptoms
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)
Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV-LRTD or hMPV-LRTD[5]</td><td>An event meeting the case definition of LRTD with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.[6]</td></tr>
<tr><td>RT-PCR-confirmed severe RSV LRTD or severe hMPV LRTD – Definition 1 “Clinical symptomology”[5]</td><td>Presence of a LRTD with at least one of the following criteria:
• at least 2 lower respiratory SIGNS
• an LRTD episode assessed as ‘severe’ by the investigator[7]
AND
• with at least one RSV-positive or hMPV-positive swab detected by RT-PCR
Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
</table>

Endpoint	Case definition
RT-PCR-confirmed **severe** RSV LRTD or **severe** hMPV LRTD – Definition 2 "Supportive therapy"[5]	Presence of a LRTD with at least one of the following criteria[8]: • Need for oxygen supplementation[4] • Need for positive airway pressure therapy (e.g. CPAP) • Need for other types of mechanical ventilation AND • with at least one RSV-positive or hMPV-positive swab detected by RT-PCR

ARI: acute respiratory illness; LRTD: lower respiratory tract disease; RSV: respiratory syncytial virus
hMPV: human metapneumovirus; RT-PCR: reverse transcription polymerase chain reaction
[1] Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route.
[2]Feverishness is defined as the feeling of having fever without objective measurement.
[3] Reported by study participant or investigator.
[4] Reported by investigator.
[5] Throat and/or nasal swab samples collected at ARI visits for PCR testing will be collected within 6 days after ARI onset (i.e., up to Day 7). In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit and the site swab collection may be extended up to maximum 14 days after ARI onset (i.e., until Day 15).
[6] Refer to Section 10.3.1.4 for details on the counting of cases that are positive for both RSV and hMPV.
[7] The investigator will grade each ARI as mild, moderate or severe based on the grading scale presented in Table 8
[8] In case the participant was already receiving any of these for treating/controlling any pre-existing condition, any significant change or adaptation in the used therapy should be taken into account.

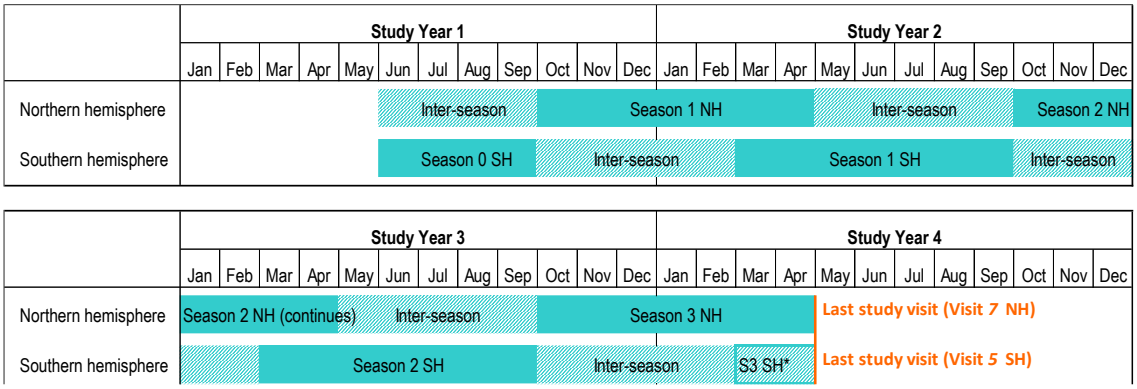
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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

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

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

Figure 2 ARI surveillance in Northern and Southern hemispheres



NH: Northern hemisphere; SH: Southern hemisphere.
In some SH countries, recruitment might start during an RSV Season (Season 0).
Surveillance for ARI will be carried out during the entire study, via spontaneous reporting by the study participant (starting on the day of first vaccination [Visit 1]) and by scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods.

The site staff surveillance contacts will be performed: every 2 weeks during the RSV seasons (Solid blue) and every month during the inter-season periods (Shaded blue). The RSV seasons defined for this study are: from 1 October to 30 April in NH and from 1 March to 30 September in SH. Based on the observed RSV circulation during the season, the ARI surveillance and/or the DLP for analyses could be adapted for the ongoing and/or subsequent seasons.

Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH see Section 8.2), similar ARI surveillance will apply up to the end of the third season for those participants. Study Year 1 corresponds to the year in which the enrollment started for the cohort.

* The last study visit in SH (Visit 5 SH) will occur approximately 2 months after the start of Season 3 in SH; yet the site staff surveillance contacts will be performed monthly during these last months (i.e., continuation of the inter-season frequency of contacts).

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

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

- **ARI end:** will be defined as the first day when all ARI symptoms/signs of the participant have returned to baseline or when they diminished significantly as judged by the investigator.

5. ANALYSIS SETS

5.1. Definitions

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

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

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

In addition, the following populations will be defined for efficacy analyses:

- **Modified Exposed Set (mES):** the mES will be the primary population for efficacy analysis on RSV-confirmed cases. It will include all participants who received at least the first dose of the study intervention (ES) and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination. The allocation in a group is done in function of the administered intervention (see Table 7).

  mES will be defined by dose as follows:

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

  Note that participants who received a third dose (either RSVPreF3 OA vaccine or Placebo) will not be included in the primary evaluation of annual revaccination over 3 seasons, i.e. those participants will be censored at Dose 3 in the RSV_annual and Placebo groups (see details in Table 7).

  For analysis post-Dose 3 in the RSV_annual and Placebo groups:

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

- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): hMPV ARI/LRTD, hospitalization, complications, any ARI/LRTD, all-cause mortality.
- **Per Protocol set for efficacy (PPSe):** the PPSe will include all participants included in the mES who:
  - received at least the first dose of the study vaccine to which they were randomized,
  - did not have any protocol deviations leading to exclusion.

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

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

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis. Detail is provided below for each set.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study intervention not administered at all), 800 (Fraudulent data) and code 900 (invalid informed consent) will be used for identifying participants eliminated from ES (see Table 5).

- Code 1071 will be used to eliminate participants who did not receive Dose 2 or Dose 3 for analysis on ES post-Dose 2 and ES post-Dose 3 (see Table 5).
- Code 2700 will be used to eliminate participants who did not receive Dose 3 according to protocol amendment 5, for analysis on ES post-Dose 3 (see Table 5).

5.2.2. Elimination from modified Exposed Set (mES)

Code 1030 (Study intervention not administered at all), 800 (Fraudulent data), code 900 (invalid informed consent) and code 2500 to 2520 (RSV-confirmed ARI case reported prior to Day 15 post-vaccination) will be used for identifying participants eliminated from mES (see Table 5).

In addition,

- Code 1071 will be used to eliminate participants who did not receive Dose 2 or Dose 3 for analysis on mES post-Dose 2 and post-Dose 3 (see Table 5).
- Code 2700 will be used to eliminate participants who did not receive Dose 3 according to protocol amendment 5, for analysis on mES post-Dose 3 (see Table 5).

5.2.3. Elimination from Per-protocol analysis Set (PPS)

A participant will be excluded from the populations for analysis under the following conditions:

- For codes 800, 1030, 1060 and 2600: participants will be eliminated for all visits.
- For codes 900, 1040, 1050, 1070, 1080, 1090, 2010, 2040, 2050, 2500 and 2700: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 1071, 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.
- In addition: Code 1041 will be used to identify and eliminate participants who received an RSV vaccine not planned in the study.

Table 5 List of elimination codes

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
800	Fraudulent data	All	ES, mES, PPSe, PPSi, SSS
900	Invalid informed consent	Visit 1, Visit 3, Visit 5NH	ES, mES, PPSe, PPSi, SSS
1030	Study intervention not administered at all	Visit 1	ES, mES, PPSe, PPSi, SSS
1040	Administration of concomitant vaccine(s) forbidden in the protocol • Use of any investigational or non-registered vaccine other than the study vaccine during the period beginning 30 days before the study vaccine administration, or	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	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 and ending 30 days after the study vaccine administration, with the exception of inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after the study vaccination. • Previous vaccination with an RSV vaccine.		
1041	Administration of RSV vaccine not planned during the study	All	mES, PPSe, PPSi
1050	Randomization failure: participant not randomized in the correct group (To be attributed by unblinded Statistician only; Check SBIR, replacement, vaccine administration)	Visit 1, Visit 3 (applicable to all groups to avoid unblinding)	PPSe, PPSi
1060	Randomization code was broken	All	PPSe, PPSi
1070	Vaccine administration not according to protocol • Participant was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine	Visit 1, Visit 3, Visit 5NH	PPSe, PPSi
1071	Incomplete vaccination course: participants who did not comply with the vaccination schedule:	Visit 3, Visit 5NH	ES Dose 2/3, m*ES Dose 2/3,* PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	• Participants who did not accept to be revaccinated for any reason • Participants who withdrew before dose 2/dose 3		
1080	Vaccine administration after a Temperature deviation	Visit 1, Visit 3, Visit 5NH	PPSe, PPSi
1090	Vaccine administration after expiration	Visit 1, Visit 3, Visit 5NH	PPSe, PPSi
1160	Participant included in the reactogenicity subset who did not document any post-vaccination solicited safety data	Visit 2, Visit 4, Visit 6NH	Solicited safety set
2010	Protocol deviation linked to inclusion/exclusion criteria	Visit 1	PPSe, PPSi
2040	Administration of any medication forbidden by the protocol • Use of any investigational or non-registered product (drug or medical device) other than the study vaccine during the period beginning 30 days before the study vaccine administration, or planned use during the study period. • 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 study vaccine administration or planned administration during the study period. • Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	prior to the study vaccine administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent.		
2050	Intercurrent medical condition: Participants may be eliminated from the PPS if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.	All	PPSi and PPSe
2080	Participants did not comply with vaccination schedule: • Participants not vaccinated within 01AUG-29OCT in NH or 01JAN-30MAR in SH	Visit 3, Visit 5NH	PPSe, PPSi
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination and visit 2 blood sample is outside [28-42] days. • Date of BS at Pre-season 2 (Visit 3) is outside [01Aug-29Oct] in NH, or outside [01Jan-30Mar] in SH • Date of BS at Pre-season 3 (Visit 5 NH) is outside [01Aug-29Oct]	Visit 2, Visit 3, Visit 5NH	PPSi
2100	Serological results not available post-vaccination: No results available at all at the corresponding visit	Visit 2, Visit 3, Visit 5NH	PPSi
2120	Obvious incoherence/abnormality or error in laboratory data	Visit 2, Visit 3, Visit 5NH	PPSi
2500	Participant who report a RSV-confirmed ARI case prior to Day 15 after first vaccination: • Number of days between first vaccination and day of onset of ARI case < 14 days	ARI visit, post dose 1	mES, PPSe

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
2510	Participant who report a RSV-confirmed ARI case prior to Day 15 after Dose 2: Number of days between Dose 2 and day of onset of ARI case < 14 days	ARI visit, post dose 2	mES Dose 2
2520	Participant who report a RSV-confirmed ARI case prior to Day 15 after Dose 3 in NH: Number of days between Dose 3 and day of onset of ARI case < 14 days	ARI visit, post dose 3 in NH	mES Dose 3
2600	Participants not included in the reactogenicity and immunogenicity subset	Visit 1	Solicited safety set, PPSi
2700	Participants who did not receive Dose 3 (according to protocol amendment 5)	Visit 5NH	ES Dose 3, mES Dose 3

** codes 2500 to ***2700*** are not considered as protocol deviations, but those codes will be used to eliminate participants from ***ES***/mES (elimination codes).

5.2.4. Elimination from Solicited Safety Set (SSS)

Code 800 (fraudulent data), code 900 (invalid informed consent), code 1030 (Study vaccine not administered at all), code 1160 (no post-vaccination solicited safety data) and code 2600 (not included in reactogenicity subset) will be used for identifying participants eliminated from the solicited safety set (see Table 5).

6. STATISTICAL ANALYSES

Standard data derivation rules and stat methods are described in Section 12.1 while the study specific data derivation rules and stat methods are described in Section 10.

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

6.1. Analysis of demography and baseline characteristics

6.1.1. Analysis planned in the protocol

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

- Frequency tables will be generated for categorical variables such as race;

- Mean, median, standard deviation and range will be provided for continuous data as age.

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

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

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

Withdrawal status will be summarized by group using descriptive statistics:

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

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

6.1.2. Additional considerations

A summary of **important protocol deviations** leading to elimination from any analyses will be provided by group, based on the Enrolled Set.

Participants disposition: the number of participants who were eliminated from each analysis set (ES, mES, PPSe, PPSi, SSS) will be tabulated by group with the reason for elimination.

Medical history and baseline comorbidities of interest will be tabulated by System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT).

The study population will also be summarized **for web disclosure** as follows:

- Percentage of enrolled participants by country will be tabulated by group,
- Percentage of enrolled participants by age categories (≤64, 65-84, ≥85 YOA) will be tabulated by group.

6.2. Primary endpoint

6.2.1. Analysis planned in the protocol

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

The primary analysis of VE in terms of occurrence of RSV-confirmed LRTD will be evaluated using the conditional exact binomial method based on the Poisson model [Chan, 1998]. This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccine versus control groups). The analysis will consider the exact inference

on the relative risk, adjusted by age categories and regions, conditionally to the total number of cases observed and time at risk. VE is defined as 1 minus the relative risk.

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

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

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

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

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

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

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

Details on methodology and additional analyses for evaluation of primary endpoint are provided in Section 6.2.2.

6.2.2. Additional considerations

6.2.2.1. Definition of endpoint

The primary endpoint is the first occurrence of qRT-PCR-confirmed RSV A and/or B-associated LRTD, with LRTD cases identified according to case definition:

LRTD:

- ARI cases with presence of the following symptoms/signs as predefined in the case definition (Table 4):
  - at least 2 **lower** respiratory symptoms/signs for at least 24 hours including at least 1 **lower respiratory sign**, OR
  - at least **3 lower** respiratory symptoms for at least 24 hours

All clinically confirmed ARI cases by investigator will be reviewed by blinded, qualified GSK members to determine if the ARI meet the case definition or not (LRTD and severe

LRTD), independently of the RT-PCR results. Confirmation of the LRTD cases and severity will be reported in the eCRF and will be available in the SDTMs (see Section 10.3.1.3).

All RT-PCR confirmed RSV/hMPV cases either fulfilling the LRTD case definition (as confirmed by GSK internal review) or reported as LRTD cases by the investigator will be sent and reviewed by an external adjudication committee. Confirmation of the RSV/hMPV LRTD cases and severity will be reported in the eCRF and will be available in the SDTMs (see Section 10.3.1.3).

Primary analysis: For the primary analysis of VE against RSV-confirmed LRTD, only cases confirmed by the external adjudication will be considered.

RT-PCR confirmed RSV cases:

- ARI episode with at least one RSV-A and/or B -positive swab detected by GSK qRT-PCR or detected by an external PCR test (non-GSK) if GSK RT-PCR result is not available (see details in Section 10.3.1.4).

The final analysis of the primary objective (VE Analysis 1) will be performed when at least 56 cases of RSV RT-PCR confirmed and externally adjudicated LRTDs have been accrued in the primary cohort for efficacy (mES).

- The number of RSV-confirmed LRTD cases will be counted based on the first occurrence of qRT-PCR confirmed RSV-A and/or B associated LRTD, starting on Day 15 post-vaccination and reported up to the database cut-off date for VE Analysis 1 (see Table 7).

6.2.2.2. Main analytical approach

The primary analysis of VE will consider a conditional exact method. The VE will be obtained by estimating the relative risk (RR) as a ratio of incidence rates using the Poisson regression model. This model assumes that the observed number of cases in vaccine and control groups follows a Poisson distribution. Conditional on the total number of cases, the number of cases in the vaccinated group follows a binomial distribution. The model will estimate the mean number of cases (μ) as a function of the different covariates and the follow up time.VE is defined as 1-RR.

The following SAS code will be applied for the primary analysis:

```
PROC GENMOD data=<dataset> EXACTONLY;
 CLASS group age region / PARAM=ref;
 MODEL nb_cases = group age region
       / dist=poisson LINK=log OFFSET=log_fut alpha=0.05;
 EXACT group /ESTIMATE OUTDIST=dist ALPHA=0.05;
 ODS OUTPUT ExactParmEst=estimate ExactTests=ExactTest;
RUN;

/* OFFSET option allows to model the ratio nb_cases/fut */
/* EXACT performs exact tests of the parameters = exact poisson
regression model
/* OUTDIST option outputs the exact conditional distributions*/
```

```
/* ESTIMATE option produces exact parameter estimates for the covariates
*/
```

Where group= treatment group (=0 for placebo, =1 for RSV vaccine), age= age category (60-69y, 70-79y, >=80y), region (North America, Europe, Asia, SH), nb_cases=number of RSV-confirmed LRTD cases, Log_fut= logarithm of follow up time in days.

Note that the above SAS code might be adapted in case of convergence or memory issue.

For the primary analysis on the mES, the follow up time will start on Day 15 post-vaccination and will end

- **for participants who report an RSV-confirmed LRTD:** at the first occurrence of the event. The onset date of the event will be the corresponding ARI onset day defined as the first day when the study participant presents **at least 2 concomitant ARI symptoms/signs** meeting the ARI case definition,

  OR

- **for participants who do not report an RSV-confirmed LRTD:** at the database cut-off date for VE Analysis 1**.** If a participant is dropped-out from the study, his/her date of last contact will be considered as end of the follow-up period.

The follow-up time will be calculated as the time in days between the date of end of follow-up period and the date of start of follow-up period, as follows: End date – start date + 1 (see description of start and end date in Table 7). This will be expressed in person-years at risk (number of days/365.25).

For each group: the number of participants with RSV-confirmed LRTD cases, the incidence rates, the VE with 95% Confidence Interval (CI) and p-value will be tabulated for primary efficacy endpoint.

The p-value reported will be the 2-sided exact p-value comparing incidence rates and testing the null hypothesis of VE≤0%.

The efficacy of RSV vaccine against RSV-confirmed LRTD will be demonstrated if the LL of the two-sided 95% CI of VE is above 20%.

Descriptive statistics (mean, min, q1, median, q3, max) of the follow-up time of each participant will also be tabulated by group, from Day 15 or from vaccination up to the database cut-off date for VE Analysis 1.

6.2.2.3. Sensitivity analyses

6.2.2.3.1. *Vaccine efficacy using Cox regression model*

In order to complement the primary analysis, VE and its 95% CI will be estimated using a Cox proportional hazard regression model, adjusted for covariates: age and region. This model estimates the ratio of hazard rates (HR) of disease in the vaccinated relative to the control group. VE is then defined as 1-HR and the 95% CI for VE can be derived from the Wald CI for Hazard Ratio. This method is implemented in the PHREG procedure:

```
PROC PHREG data=<dataset> SIMPLE OUTEST=test COVOUT;
CLASS group age region;
MODEL futime*status(0)=group age region / RL ALPHA=0.05 TIES=EFRON ;
RUN;
/* COVOUT= adds the estimated covariance matrix of the parameter
estimates to the OUTEST= data set
   SIMPLE= displays simple descriptive statistics for each explanatory
variable in the MODEL statement
   RL= RISKLIMITS produces confidence intervals for hazard ratios of
main effects */
```

Kaplan-Meier survival curves for the vaccine and control groups will be presented together with p-values from the logrank test. This will be produced using the LIFETEST procedure:

```
PROC LIFETEST data=<dataset> ;
 TIME futime*status(0);
 STRATA group;
 ID USUBJID;
RUN
```

The model assumes that the ratio between two hazards (vaccine vs placebo) does not depend on time. This assumption will be checked by a test based on the Schoenfeld residuals:

```
PROC PHREG data=<dataset> OUTEST=test COVOUT NOPRINT;
CLASS group age region;
MODEL futime*status(0)=group age region / TIES=EFRON ;
OUTPUT OUT=sch_res xbeta= ressch= wtressch= ;
RUN;
```

If there is strong evidence that the hazard rate is not constant over the surveillance period, then a non-parametric analysis might be performed.

6.2.2.3.2. *Time-to-first event methodology: follow-up time and status*

The follow-up time and the status will be computed for each participant as follows:

- If the participant reports an RSV-confirmed LRTD during the considered period, the status will be equal to 1 (1=event), and the follow-up time will be the number of days between start date of the considered period (Day 15 post-vaccination) and the onset date of the event.
- If the participant does not report an RSV-confirmed LRTD during the considered period, the status will be equal to 0 (0=no event), and the follow-up time will be the number of days between start date of the considered period (Day 15 post-vaccination) and the end of considered period (i.e., the database cut-off date for VE Analysis 1).

  If a participant is dropped-out from the study, his/her date of last contact will be considered as end of the follow-up period.

6.2.2.3.3. *Re-randomization*

A re-randomization test will be performed in order to validate the results of the primary objective.

The distribution of the relative risk (RR) under the null hypothesis (H_0: VE≤20% or RR≥80%) will be obtained by re-randomizing treatment assignment according to the original minimization algorithm (see Section 6.3.3 of the protocol), while keeping other covariates as observed and modifying the incidence rates according to the null hypothesis. The procedure to follow is based on the method presented in [Wang, 2020] and is described in Section 12.3.

6.2.2.3.4. *Analysis sets*

The primary analysis of the primary efficacy endpoint will be performed on the mES.

Additional analysis will also be performed on the PPSe and on the ES to complement the primary analysis on the mES-RSV.

Time of follow up for analysis on the PPSe will be the same as for mES: count cases starting from Day 15 post-vaccination until the first occurrence of RSV-confirmed LRTD or until the database cut-off date for VE Analysis 1 or until last contact date in case of withdrawal (see Section 6.2.2.2).

For the analysis on the ES, the time of follow up and the counting of cases will start from vaccination (Day 1) until the first occurrence of RSV-confirmed LRTD or until the database cut-off date for VE Analysis 1 or until last contact date in case of withdrawal.

6.2.2.3.5. *RSV-LRTD case counting*

- A sensitivity analysis of the primary efficacy endpoint will be performed to include all RSV RT-PCR confirmed LRTD cases either fulfilling case definition (as confirmed by GSK internal review) and/or confirmed by the study Investigators.
- A second sensitivity analysis of the primary efficacy endpoint will be performed considering the RSV LRTD cases confirmed by the GSK qRT-PCR only, i.e., excluding the ones identified by an external laboratory.
- A third sensitivity analysis of the primary efficacy endpoint will be performed excluding RSV LRTD cases with respiratory co-infections (e.g. hMPV, SARS-COV-2, FLU, etc.). Cases without co-infection results available at the time of VE Analysis 1 will also be excluded from this analysis.

6.2.2.3.6. *Second cohort in NH*

If following sample size re-assessment during season 1 in NH, an additional cohort of participants is enrolled before the next season in NH (see Section 8.2), an additional analysis of the primary efficacy endpoint will be performed per cohort (1st cohort vs 2nd cohort).

6.2.2.4. Subgroup analyses

On top of subgroup analyses planned as secondary objectives (see Section 6.3.1.1), VE analysis of primary efficacy endpoint will also be performed according to the following subgroups (see Table 3 for subgroups definition):

- By hemisphere: in NH and SH participants,
- By region: in North America, Europe, Asia and SH participants.
- By ethnicity
- By race
- By sex

These analyses will be descriptive and should be interpreted with caution considering that the study is not powered to demonstrate significance of VE in those subgroups (except NH), and considering that there is no adjustment for multiplicity for these VE evaluations.

6.3. Secondary endpoints

6.3.1. Analysis planned in the protocol

6.3.1.1. Efficacy

The primary analysis of secondary efficacy endpoints related to RSV-confirmed cases will be performed on the mES or on the mES by Dose as applicable (see Section 5.1 and Table 7). In addition, for secondary confirmatory objectives**,** an analysis will be performed on the PPSe and on the ES to complement the primary analysis (see Section 6.3.2.1.2).

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

The same methodology as described for the primary endpoint (see Section 6.2) will be used to analyze the secondary efficacy endpoints described below. For the analysis over 2 or 3 seasons, the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

Analysis of secondary efficacy endpoints will be performed at each VE analysis when applicable (see Section 8.3).

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

Note that participants who received a third dose will not be included in the primary evaluation of annual revaccination over 3 seasons, i.e. participants who received Dose 3

will be censored at Dose 3 in the RSV_annual and Placebo groups (see details in Table 7).

Exploratory analysis of the annual revaccination on participants who received 3 doses of RSVPreF3 OA investigational vaccine might be performed depending on the number of participants who will receive the Dose 3 (see Section 6.4.2.5).

Confirmatory objective

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

Other secondary descriptive objectives

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

  VE will also be computed for participants in 60-69 YOA and 70-79 YOA.
- VE against RSV-confirmed LRTD by season:
  - VE during Season 1 in NH and SH, including first occurrence of cases reported during Season 1 from Day 15 after the first vaccination (see Table 7);
  - VE during Season 2 in NH and SH, including first occurrence of cases reported during Season 2 and after Day 15 post-Dose 2, and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 2 (see Table 7);
  - VE during Season 3 in NH and SH (partial Season 3 in SH), including first occurrence of cases reported during Season 3 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 3 (see Table 7).

The time at risk for the analysis by season will be the period from the start of the corresponding season and after Day 15 post-vaccination until the event, until the end of the season or until the last contact date for drop-out participants (see description of the season in each hemisphere in Figure 2 and description of follow-up time in Table 7).

- VE against RSV-confirmed LRTD by year:
  - VE during the first year post-vaccination (Year 1) in NH and SH, including first occurrence of cases reported from Day 15 post-Dose 1 up to Dose 2 administration;

  - VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases reported from Day 15 post-dose 2 up to 12 months post-Dose 2 in NH and SH, or up to Dose 3 administration in NH;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases reported from 12 months post-dose 2 up to study end.
- VE against RSV-confirmed LRTD by baseline comorbidities: using the Charlson Comorbidity Index and according to comorbidities of interest:
  - COPD,
  - Asthma,
  - Any chronic respiratory/pulmonary disease,
  - Diabetes mellitus Type 1 or Type 2,
  - Chronic heart failure,
  - Advanced liver or renal disease.
- VE against RSV-confirmed LRTD by baseline frailty status.
- VE against severe RSV-confirmed LRTD according to the case definition 1 and case definition 2;
- VE against RSV-confirmed ARI.
- VE against any ARI and any LRTD.
- Hospitalizations and complications:
- VE in the prevention of hospitalization and complications during the RSV seasons and during the entire follow-up will be evaluated for:
  - Hospitalization due to respiratory diseases and due to complication related to respiratory diseases,
  - Hospitalization due to RSV-confirmed respiratory diseases and due to complication related to RSV-confirmed respiratory diseases,
  - Complications related to RSV-confirmed ARI,
  - Complications related to any ARI.
- VE over time: The evolution of VE of a single dose of the RSVPreF3 OA vaccine against RSV-confirmed LRTDs over time will be explored using the Cox proportional hazard regression model. The model assumes that the ratio between 2 hazards (vaccine versus placebo) does not depend on time. This assumption will be checked by a test based on the Schoenfeld residuals. In addition, the VE analysis will be performed by splitting participants in 2 groups according to the time of vaccination.
- For all RSV-confirmed ARI and LRTD cases, descriptive statistics will also be computed to summarize the number of episodes reported, the duration of the RSV episodes, the occurrence of each reported symptoms and signs, including the need for

oxygen supplementation, and the occurrence of cases according to severity (see Table 8).

6.3.1.2. Immunogenicity

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

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

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

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

- Percentage of participants with antibody titers/concentrations above pre-defined assay cut-offs and their 95% CIs;
- Geometric mean antibody titers/concentrations (GMTs/GMCs) and their 95% CIs;
- Distribution of antibody titers/concentrations using reverse cumulative curves;
- Mean Geometric Increase (MGI) with 95% CI.

6.3.1.3. Safety

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

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

Reactogenicity analyses will include the following summaries by group:

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

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

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

- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments and fever resulting in medically attended visit during the 4-day follow-up period after vaccination will be tabulated after each dose.
- The duration in days of solicited events will be tabulated after each dose for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for the number of days with Grade 3 solicited events.

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

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

  The analyses of unsolicited AEs will include SAEs (unless otherwise specified) and AESIs (including pIMDs and atrial fibrillation (AF)).
- The verbatim reports of unsolicited AEs, including SAE, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PTs and reported from vaccination up to 6 months after vaccination will be tabulated after each dose with exact 95% CI. The same tabulation will be presented for pIMDs, fatal SAEs, causally related SAEs and causally related pIMDs.
- The number and percentage of participants with at least one report of causally related SAE classified by the MedDRA Primary SOC, HLT and PTs will be tabulated after each dose and from Day 1 up to study end with exact 95% CI. The same tabulation will be presented for fatal SAEs and causally related pIMDs.
- SAEs/pIMDs/AF AESIs will also be described in detail in a tabular listing.
- The number and percentage of participants starting a concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after each dose will be tabulated with exact 95% CI.
- AEs/SAEs leading to study/intervention discontinuation from first vaccination up to study end will be tabulated.
- AF AESIs will be tabulated within the summary of AEs or SAEs according to their classification.

6.3.1.4. Quality of life

All analysis of patient-reported outcomes (i.e., EQ-5D, SF-12 and the daily health questionnaires) for RSV-confirmed cases will be carried out on the mES RSV-confirmed

ARI cohort and mES RSV-confirmed LRTD cohort. Data will be analyzed using descriptive statistics for the multi-item SF-12, EQ-5D and FLU-PRO scales for each study group at each time point.

Descriptive statistics of the EQ-5D, SF-12 and FLU-PRO scales completed at planned pre-Season timepoints will be presented for the mES.

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

Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of RSV-ARI episode for participants with RT-PCR-confirmed RSV, will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will be fitted including terms for age category (60-69y, 70-79y, >=80y), region (North America, Europe, Asia, SH) and a study group by time interaction. The least squares mean (LSMEANS) estimates for time by study group and the difference in least squares means and associated P-values will be obtained from the ANOVA model. The PROC MIXED procedure in *SAS* will be used to carry out the ANOVA, with all terms fitted as fixed effects.

The study group difference in LSMEANS of the SF-12 physical functioning scores and EQ-5D utility score at the initial ARI visit will be estimated using repeated measures mixed effects model including the timepoints: pre-season, initial ARI visit, and pre-next-season visit. The model will include age category (60-69y, 70-79y, >=80y) and region (North America, Europe, Asia, SH) as fixed effects.

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

6.3.2. Additional considerations

6.3.2.1. Efficacy

6.3.2.1.1. *Definition of endpoints*

The case definitions for evaluation of efficacy endpoints are provided in Section 4.

The primary analysis of VE endpoints related to RSV/hMPV-confirmed LRTD will consider only the externally adjudicated cases. Description and identification of RSV-confirmed LRTDs is further described in Section 6.2.2.1.

For analysis of VE against **RSV-confirmed cases**, the number of cases will be counted based on the first occurrence of the RSV-confirmed case, starting on Day 15 post-vaccination, tested by GSK qRT-PCR or by an external PCR test (non-GSK) if the GSK PCR results is not available (see detail in Section 10.3.1.4).

For analysis of VE against **hMPV-confirmed cases**, the number of cases will be counted based on the first occurrence of the hMPV-confirmed case, starting from vaccination, tested by GSK multiplex RT-PCR or by an external PCR test (non-GSK) if the GSK PCR results is not available.

- **VE over several seasons**

For VE analysis during season 1, the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, starting on Day 15 post-vaccination and reported up to the end of season 1 (VE Analysis 2).

For analysis over 2 and 3 seasons, the VE analysis will include season 1 data (S1) of all participants who received Dose 1, and season 2 and season 3 data of participants who received the 2 doses.

Comparison will be done as follows:

- RSVPreF3 group versus Placebo group to demonstrate VE of annual revaccination after season 2 (S1+A2NH) and after season 3 (S1+A2+A3NH) in alignment with protocol amendment 5. For this comparison,
  - participants from the RSV_1dose group will contribute to season 1 data only (S1) and will be censored before Dose 2 administration,
  - participants from the RSV_annual and from the Placebo groups who received a third dose (of vaccine or placebo) will contribute to season 1 and season 2 data and will be censored before Dose 3 administration for the primary evaluation of annual revaccination over 3 seasons.
- ***RSVPreF3* group versus Placebo group** to demonstrate VE of one single dose after season 2 (S1+S2NH) and after season 3 (S1+S2+S3NH). For this comparison,
  - participants from the RSV_annual group will contribute to season 1 data only (S1) and will be censored before Dose 2 administration,
  - participants from the RSV_1dose and Placebo groups will contribute to season 1 data, and to seasons 2 and 3, regardless of Dose 3 administration.

The season 1 data will include data collected up to 30SEP2022 (end of season 1 in SH) if no Dose 2 administration or up to Dose 2 administration.

The season 2 data will include data collected up to 30SEP2023 (end of season 2 in SH) if no Dose 3 administration or up to Dose 3 administration.

Table 6 below describes the data that will be included in analysis of secondary confirmatory endpoint.

Table 6 Description of data to be included in VE analysis over several seasons (confirmatory endpoints)

Analysis	Endpoint	Data included in the analysis (mES)
VE analysis 3 (end of S2NH)	Annual revaccination (S1+A2NH)	Data collected during the first season: from Day 15 post-Dose 1 up to Visit 3 (Pre-Dose 2)* for all participants who received 1 dose of RSV vaccine or placebo (S1) + Data collected during the second season: from Dose 2 up to end of season 2 in NH for all participants who received 2 doses in RSV_annual group or in Placebo group (A2NH)
	Single dose (S1+S2NH)	Data collected during the first season: from Day 15 post-Dose 1 up to Visit 3 (Pre-Dose 2)* for all participants who received 1 dose of RSV vaccine or placebo (S1) + Data collected during the second season: from Dose 2 up to end of season 2 in NH for all participants who received 2 doses in RSV_1dose group or in Placebo group (S2NH)
VE analysis 5 (end of S3NH)	Annual revaccination (S1+A2+A3NH)	Data collected during the first season: from Day 15 post- Dose 1 up to Visit 3 (Pre-Dose 2)* for all participants who received 1 dose of RSV vaccine or placebo (S1) + Data collected during the second season: from Dose 2 up to end of season 2** in SH for all participants who received 2 doses in RSV_annual group or in Placebo group (A2) + Data collected during the third season: if no Dose 3 administration, from end of S2SH up to end of S3NH
	Single dose (S1+S2+S3NH)	Data collected during the first season: from Day 15 post- Dose 1 up to Visit 3 (Pre-Dose 2)* for all participants who received 1 dose of RSV vaccine or placebo (S1) + Data collected during the second season: from Dose 2 up to end of season 2** in SH for all participants who received 2 doses in RSV_1dose group or in Placebo group (S2) + Data collected during the third season: from end of S2SH up to end of S3NH

S1/S2/S3 = Seasons 1/2/3; A2/A3=Annual evaluation during season 2/3
NH= Northern Hemisphere; SH= Southern Hemisphere.
* The season 1 data will include data collected up to 30SEP2022 if no Dose 2 administration or up to Dose 2 administration.
** The season 2 data will include data collected from Dose 2 up to 30SEP2023 if no Dose 3 administration or up to Dose 3 administration in NH.

- **VE by season:** For the VE analysis by season, participants reporting RSV ARI cases between 15 days post-vaccination and the start of the season will be censored at the time of the event. Only the first occurrence of the RSV-confirmed LRTD occurring during the RSV seasons will be counted for the analysis.

- **VE by baseline co-morbidities**

VE analysis will be performed on participants who reported, at baseline, at least one co-morbidity of interest and according to the following subgroups: cardiorespiratory and endocrinometabolic conditions (see table below).

Comorbidity of Interest	Grouping
COPD	Cardiorespiratory conditions
Asthma	
Any chronic respiratory/pulmonary disease	
Chronic heart failure	

Comorbidity of Interest	Grouping
Diabetes mellitus Type 1 or Type 2	Endocrinometabolic conditions
Advanced liver or renal disease	

VE analysis will also be performed according to the updated Charlson comorbidity index (uCCI) (see Section 10.3.1.5), on the following sub-groups:

- Low/medium Risk = Participants with co-morbidity score at baseline less or equal to 3
- High Risk = Participants with co-morbidity score at baseline greater than 3.

- **VE against any ARI, any LRTD**

The assessment of this secondary objective will include all investigator-reported ARI cases and LRTD cases either fulfilling case definitions (as confirmed by GSK internal review) and/or confirmed by the study investigators, regardless of RT-PCR result.

- **Hospitalizations and complications**

VE in the prevention of hospitalizations and complications will be analyzed according to the first occurrence of the following endpoints during the RSV seasons and during the entire follow-up:

  – Hospitalizations due to respiratory diseases, i.e., due to any respiratory complications,

  – Hospitalizations due to RSV-confirmed respiratory diseases,

  – Hospitalizations due to respiratory diseases or complication related to respiratory diseases, i.e., any respiratory complications or any non-respiratory complications related to ARI,

  – Hospitalizations due to RSV-confirmed respiratory diseases or complication related to RSV-confirmed respiratory diseases,

  – Complications related to RSV-confirmed ARI reported during the RSV seasons,

  – Complications related to any ARI reported during the RSV seasons.

- **VE over time**

The VE analysis will be performed by splitting participants in 2 groups according to the time of vaccination at Dose 1: participants who were vaccinated before the 1st of September, and participants who were vaccinated from the 1st of September onwards. This cut-off has been chosen to have approximately half of the NH participants in each subgroup and to have participants vaccinated at least 1 month before the start of the season versus the ones who were vaccinated later.

- **Description of RSV-confirmed cases**

The following analysis will be performed in order to characterize the RSV-confirmed cases:

  – The number and percentage of participants who reported 1, 2, 3 or more RSV-confirmed ARI or RSV-confirmed LRTD cases will be tabulated with exact 95% CI, by group, overall and by season.

- The duration in days of the RSV-confirmed ARI episodes will be tabulated by group using descriptive statistics (mean, min, Q1, median, Q3, maximum).
- The number and percentage of participants with RSV-confirmed ARI case who reported each of the symptoms/signs associated to ARI episode will be tabulated by group with exact 95% CI. The same tabulation will be done for RSV-confirmed LRTD cases.
- The number and percentages of participants who reported 2, 3, 4 or more symptoms/signs for RSV-confirmed ARI and RSV-confirmed LRTD cases will be tabulated by group with exact 95% CI,
- The number and percentages of participants who reported an RSV-confirmed LRTD case will be tabulated by group and by intensity (mild, moderate, severe) assessed by investigator. The same tabulation will be done for RSV-confirmed ARI cases.

In addition, the distribution of the RSV confirmed LRTD and ARI cases will be summarized by calendar month.

6.3.2.1.2. *Main analytical approach*

The same methodology as described for the primary endpoint (see Section 6.2.2.2) will be used to analyze the secondary efficacy endpoints.

Cases counting and follow-up time

Table 7 summarizes the rules for counting of the cases and the start and end date of follow up time for each VE analysis.

The end date of the follow-up period will be defined as:

- the time of onset of the first occurrence of the event, for participants who reported the event of interest,

  OR

- the last contact date for drop-out participants,

  OR

- The follow-up end date described in Table 7, depending on the type of analysis, for participants who do not report the event of interest.

Table 7 Rules for counting cases and follow-up time

VE analysis	Time period	Start date 1 for Cases count and FU time[1]	End date 1 for case count and FU time[2]	Participants to be excluded from analysis	*Additional Censoring*[5]	Model Covariates	Analysis Set
Case-driven (VE analysis 1)	Season 1	Day 15 post-Dose 1	database cut-off date for VE Analysis 1 for all participants (NH and SH)	RSV cases before Day 15 post-first vaccination	NA	Age, region	mES, PPSe, ES[3]
End of season 1 (VE analysis 2)	Season 1	Day 15 post-Dose 1	End of season 1 in SH (30SEP) or Dose 2 administration	RSV cases before Day 15 post-first vaccination	NA	Age, region	mES
Over 2 seasons: S1+A2NH/S2NH (VE analysis 3)	Season 1 (S1) and Season 2 (A2NH/S2NH)	Day 15 post- Dose 1	End of season 2 in NH for all participants (NH and SH)	RSV cases before Day 15 post-first vaccination	If no Dose 2 administration: censoring at end of S1SH (30SEP). If elimination code at Visit 3: censoring at Dose 2.	Age, region, season	mES, PPSe, ES[3]
Over 2 seasons - End of season 2 in SH (VE analysis 4)	Season 1+ Season 2	Day 15 post-Dose 1	End of season 2 in SH (30SEP) or Dose 3 administration	RSV cases before Day 15 post-first vaccination	If no Dose 2 administration: censoring at end of S1SH (30SEP). If elimination code at Visit 3: censoring at Dose 2.	Age, region, season	mES
Over 3 seasons S1+A2/S2+A3NH/S3NH (VE analysis 5)	Season 1 + Season 2 + Season 3	Day 15 post Dose 1	End of season 3 NH	RSV cases before Day 15 post-first vaccination	If no Dose 2 administration: censoring at end of S1SH (30SEP). If elimination code at Visit 3: censoring at Dose 2. For Annual revaccination, if Dose 3 is administered: censoring at Dose 3 in RSV_annual and Placebo groups	Age, region, season	mES, PPSe, ES[3]

VE analysis	**Time period**	**Start date 1 for Cases count and FU time[1]**	**End date 1 for case count and FU time[2]**	**Participants to be excluded from analysis**	***Additional Censoring*[5]**	**Model Covariates**	**Analysis Set**
Over 3 seasons (VE analysis 6 - EoS)	Season 1 + Season 2 + Season 3	Day 15 post Dose 1	End of study	RSV cases before Day 15 post-first vaccination	If no Dose 2 administration: censoring at end of S1SH (30SEP). If elimination code at Visit 3: censoring at Dose 2. For Annual revaccination: if Dose 3 is administered: censoring at Dose 3 in RSV_annual and Placebo groups	Age, region, season	mES
By Season	Season 1	Start of season 1, after Day 15 post-Dose 1	End of season 1 in NH and SH	RSV cases before Day 15 post-first vaccination	Participants with RSV ARI cases between 15 days post-Dose 1 and start of S1	Age, region	mES
	Season 2	Start of season 2, after Day 15 post-Dose 2	End of season 2 in NH and SH	RSV cases before Day 15 post-Dose 2	Participants with RSV ARI cases between 15 days post-Dose 2 and start of S2	Age, region	mES Dose 2
	Season 3	Start of season 3	End of season 3 in NH and end of study for SH			Age, region	mES Dose 2, ***For Annual revaccination: on participants who did not receive Dose 3***
By Year	Year 1	Day 15 post-Dose 1	Visit 3 (Pre-Dose 2)	RSV cases before Day 15 post-Dose 1	If no Dose 2 administration: censoring at end of S1SH (30SEP).	Age, region	mES

VE analysis	**Time period**	**Start date 1 for Cases count and FU time[1]**	**End date 1 for case count and FU time[2]**	**Participants to be excluded from analysis**	***Additional Censoring[5]***	**Model Covariates**	**Analysis Set**
	Year 2	Day 15 post-Dose 2	12 months post-Dose 2	RSV cases before Day 15 post-Dose 2	For Annual revaccination: if Dose 3 is administered: censoring at Dose 3 in RSV_annual and Placebo groups	Age, region	mES Dose 2
	Year 3	12 months post-Dose 2	EoS[4] in NH			Age, region	mES Dose 2, ***For Annual revaccination: on participants who did not receive Dose 3***

[1]Start of season is defined as 1st October in NH and 1st March in SH

[2]End of season is defined as 30th April in NH and 30th September in SH

[3] for analysis on the ES, the time of follow up and the counting of cases will start from vaccination (Day 1) until the first occurrence of RSV-confirmed LRTD or until the time of VE Analysis.

[4]EoS= End of study visit, i.e., Visit 7NH or Visit 5SH.

[5]Censoring: if a participant received an RSV vaccine not planned in the study, he will be censored at the date of the RSV vaccine administration. Participants will be identified with code 1041 and this rule will be applicable from VE analysis 5.

Visual representation of the time periods for each analysis is also presented in Figure 5.

When analysis is done over seasons, season will be used as covariate and the follow-up time will be defined as follows, in order to take into account the follow-up time during each season separately:

- Follow-up time during Season 1 for all the participants who received Dose 1,
- Follow-up time during Season 2 for participants not censored before Dose 2 and who received Dose 2
- Follow-up time during Season 3 for participants not censored before season 3.

Censoring: if a participant received an RSV vaccine not planned in the study, he will be censored at the date of the RSV vaccine administration. Participants will be identified with code 1041 and this rule will be applicable from VE analysis 5.

For each secondary efficacy endpoint:

- The follow-up time will be calculated as the time in days between the date of end of follow-up period and the date of start of follow-up period, as follows: End date – start date + 1. This will be and expressed in person-years at risk (number of days/365.25).
- The number of participants who reported confirmed cases, the incidence rates, the VE with 95% CI and p-value will be tabulated by group.

Descriptive statistics (mean, min, q1, median, q3, max) of the follow-up time of each participant will be tabulated by group, from Day 15 of from vaccination up to the time of data lock point for VE Analysis will be tabulated by group.

In addition, a visual representation of the VE results will be presented in a forest plot.

6.3.2.1.3. *Sensitivity analysis*

- **Analysis sets**

Analysis on the secondary objectives will also be performed on the PPSe, and on the ES to complement the primary analysis on the mES for secondary confirmatory objective (VE over several seasons, see Table 7).

Time of follow up for analysis on the PPSe will be the same as for mES (see Table 7).

For the analysis on the ES, the time of follow up and the counting of cases will start from vaccination (Day 1) until the first occurrence of RSV-confirmed LRTD or until the efficacy data lock point (DLP) for VE Analysis or until withdrawal date if before the efficacy DLP.

- **LRTD cases counting rules**
  - A sensitivity analysis of the secondary confirmatory efficacy endpoint will be performed to include all RT-PCR confirmed RSV LRTD cases either fulfilling case definition (as confirmed by GSK internal review) and/or confirmed by the study Investigators.
  - A second sensitivity analysis of the secondary confirmatory efficacy endpoints (VE over several seasons) will be performed considering the RSV-LRTD cases confirmed by the GSK qRT-PCR only, i.e., excluding the ones identified by an external laboratory.

The same analysis on GSK PCR only will be performed for hMPV-LRTD cases.

- A third sensitivity analysis will be performed excluding RSV cases with respiratory co-infections (hMPV, SARS-COV-2, FLU, etc.) for the following endpoints:
  - VE against RSV-confirmed LRTDs over several seasons (confirmatory secondary endpoints)
  - VE against severe RSV-confirmed LRTDs according to case definition 1 and case definition 2.
  - VE against RSV-confirmed ARIs over several seasons

    Cases without co-infection results available at the time of each VE Analysis will also be excluded from this analysis.
  - For confirmatory endpoints of VE over 2 and 3 seasons, a sensitivity analysis will be performed considering the cases during the season 1 in the RSVPreF3 group only for the participants allocated to the RSV_annual group or for those allocated in the RSV_1dose group for the corresponding analysis. Therefore, the season 1 data of the RSVPreF3 group will be split according to the allocation after re-randomization performed before season 2 (see Figure 1) and the comparisons will be done for RSV_annual vs Placebo and RSV_1 dose vs Placebo.

- **Severity**

For all ARI cases, the investigator should provide a clinical diagnosis and assess the intensity of the ARI according to the intensity grading provided in Table 8.

A supplementary analysis will be performed to evaluate the VE against RSV-confirmed LRTDs based on that severity scale, i.e., for mild, moderate and severe cases.

Table 8 Intensity grading for ARI/LRTD episode

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

- **Hospitalizations and complications**

VE analysis of hospitalizations and complications will also be performed excluding the confirmed COVID-19 cases.

6.3.2.1.4. *Subgroup analysis*

On top of subgroup analyses planned as secondary objectives (see Section 6.3.1.1), analysis of VE of a single dose and annual revaccination doses against RSV-confirmed LRTD over several seasons will also be performed by hemisphere, by region, by ethnicity, by race and by sex (see definition of subgroups in Table 3).

These analyses will be descriptive and should be interpreted with caution considering that the study is not powered to demonstrate significance of VE in those subgroups (except NH), and considering that there is no adjustment for multiplicity for these VE evaluations.

6.3.2.2. Safety

6.3.2.2.1. *Solicited events*

- Compliance in completing solicited events information will be tabulated by group.
- The number and percentage of participants with at least one administration site event (solicited only), with at least one systemic event (solicited only) and with any solicited event during the 4-day follow-up period after each dose will be tabulated with exact 95% CI. The same computations will be done for Grade 3 AEs and for AEs resulting in a medically attended visit.
- The percentage of participants reporting each individual solicited event (any grade, Grade 3) during the 4-day follow-up period after each dose will also be represented graphically per group with exact 95% CI.
- The number of days with solicited symptoms (any, Grade 3) will also be tabulated after each dose for ongoing events beyond the follow-up period using descriptive statistics (mean, min, Q1, median, Q3, maximum).
- The list of solicited administration site and systemic events, and definition of intensity are described in Section 10.3.3 and Section 10.3.9 of the protocol.

- Each participant's data will be summarized according to the maximal intensity observed during the follow-up period. The measurement of erythema/swelling (in mm) and fever (in °C) will be categorized as follows:

Table 9 Intensity grading scale for solicited events

Grading	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)

6.3.2.2.2. *Unsolicited AEs and SAEs*

The number and percentage of participants with any unsolicited AEs with exact 95% CI will also be tabulated after each dose by group and by MedDRA Primary SOC, HLT and PT for:

- Unsolicited AEs (Any, Grade 3) reported during the 30-day follow-up period on the Solicited safety set (reactogenicity subset)
- Unsolicited AEs (Any, Grade 3) reported during the 4-day follow-up period on the ES and on the Solicited safety set (reactogenicity subset).

Those analyses of unsolicited AEs will include SAEs.

For analysis of SAEs/pIMDs within 6 months after each dose, the reporting period will start at vaccination and will end at Day 183 after each dose, computed as 6 x 30.5 days=183 days.

AF AESIs

Potential AF AESIs will be identified through the MedDRA preferred term of interest atrial fibrillation (10003658). Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF. Additional analysis might be performed on those additional data collected for AF AESIs.

AF AESIs will be described in a tabular summary including the characteristics of the AE (***e.g.*** seriousness, causality, maximum intensity), time to onset and outcome.

6.3.2.2.3. *Combined solicited events and unsolicited AEs*

For clinicaltrials.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

Solicited events will be coded by MedDRA as per the following codes:

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia

Note that those codes might be adapted depending on the current version of MedDRA at the time of analysis.

6.3.2.2.4. *Concomitant medication*

Medications will be coded using the GSKDRUG and the WHO Drug dictionaries.

6.3.2.2.5. *Additional exploratory safety comparisons*

Exploratory comparisons will be performed after each dose for the following groups:

- Post-Dose 1: RSVPreF3 versus Placebo,
- Post-Dose 2: RSV_annual versus Placebo and RSV_annual vs RSV_1dose,
- Post-Dose 3: RSV_annual versus Placebo and RSV_annual vs RSV_1dose , in NH participants,
- Post-dose 1 up to DLP or up to study end (related SAEs/pIMDs and Fatal SAEs): RSV_annual versus Placebo, RSV_1dose vs Placebo, RSV_annual vs RSV_1dose**.**

The relative risk and exact CI (exact conditional to total number of cases) between the two groups will be computed for the following endpoints on the ES:

- The number and percentage of participants with unsolicited AEs (Any, Grade 3/related/Grade 3 related/with medically attended visit) during the 30-day follow-up period, presented by MedDRA Primary SOC, HLT and PT, with RR and 95% CIs.
- The number and percentage of participants with at least one report of [SAEs/pIMDs/fatal SAEs/causally related SAEs/causally related pIMDs] from vaccination up to 6 months after each dose or after each dose up to DLP/study end, and presented by MedDRA Primary SOC, HLT and PT, with RR and 80% CIs.

The purpose of those analyses is to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e., a report of an event with an unknown causal relationship to study vaccine that is recognized as worthy of further exploration and continues surveillance. It is recognized that the use of any method to identify safety signals has the potential to identify a large number of events which may or may not have a causal relationship to study vaccine due to multiplicity of endpoints.

The following quantitative criteria will be used to identify potential safety signal:

- Adverse events that occurred at a rate statistically higher than placebo (lower limit of the 95%/80% CI around the relative risk >1).

Then a qualitative evaluation taking into account clinical significance and biological plausibility will be performed to determine if there is sufficient evidence of a causal association with the product.

6.3.2.3. Quality of Life

HRQoL data will be collected through the following questionnaires:

- Short-Form 12 Version 2.0 (SF-12®) [Ware, 2002]
- EuroQoL 5-Dimension (EQ-5D) Version 1.0 (non UK) & 2.0 (UK) [Kind, 1996]

The daily health questionnaires consist of:

- The Influenza patient-reported outcome (FLU-PRO) questionnaire version 2.0 [Powers, 2015],
- The Patient Global Impression of Severity (PGI-S),
- The Patient Global Impression of Change (PGI-C).

The daily health questionnaires are scheduled to be completed daily at the beginning of the ARI episode (see Table 4) until resolution of all ARI symptoms or a maximum of 14 days from the initiation of completion of the first questionnaire.

EQ-5D and SF-12 will be completed by all participants pre-seasons 1 and 2 and also pre-season 3 for participants in the northern hemisphere.

During an ARI episode both the EQ-5D and SF-12 are scheduled to be completed by participants once at the beginning of the episode.

Adherence to the scheduled completion of QoL questionnaires will be assessed at each timepoint i.e., the number of questionnaires actually completed at a certain timepoint will be compared to the number of questionnaires that were expected to be completed according to the study schedule.

The pre-season adherence to completion of questionnaires will be presented for each season by vaccination group. The adherence to completion of the daily health questionnaires, SF-12 and EQ-5D during the RT-PCR-confirmed RSV episode will be presented by vaccination group and timepoint.

6.3.2.3.1. Timepoints used in the QoL analysis

The analyses of the daily health questionnaires will be presented by timepoint (day) relative to ARI onset:

Day=date of assessment of FLU-PRO – onset date of second symptom+1.

Questionnaires without a date of assessment will be considered not evaluable.

The SF-12 and EQ-5D related to the ARI episode are to be completed once at the ARI visit. The day of questionnaire completion is calculated as follows:

Day=date of assessment of SF-12/ EQ-5D – ARI onset +1.

To be considered evaluable the SF-12/ EQ-5D questionnaire must have been filled in within 0-7 days of the start of the ARI episode. Questionnaires without a date of assessment will be considered not evaluable.

Note that all questionnaires completed before the start date of the second respiratory sign/symptom or before the start date of the second respiratory/systemic sign/symptom will be excluded from the analysis.

6.3.2.3.2. SF-12

The SF-12® is a multi-purpose health survey with 12 questions. The SF-12 covers 8 HRQoL domains (1) physical functioning (Q2a, Q2b); (2) role-physical, that is, role limitations due to physical problems (Q3a, Q3b); (3) bodily pain (Q5); (4) general health (Q1); (5) vitality (Q6b); (6) social functioning (Q7); (7) role emotional, that is, role limitations due to emotional problems (Q4a, Q4b); and (8) mental health (Q6a, Q6c). Four of the eight scales are based on single-item measures and the remaining four scales are composed of two items. The standard scoring algorithms require that both items in the two-item scales be present in order to calculate that scale. See Section 10.3.3.1 for further details.

The pre-season domain scores will be presented for the mES RSV-confirmed ARI cohort by vaccination group. The domain scores recorded at the beginning of the confirmed RSV-ARI episode will also be presented by vaccination group for participants in the mES RSV-confirmed ARI cohort.

6.3.2.3.3. EQ-5D

The EQ-5D questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value [Kind, 1996]. The EQ-5D defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The numeric scores of the 5 items are combined, in the exact order listed above, to generate health profiles, i.e., a respondent who responds 1 (no problem\no symptom) to all 5 items has a profile “11111” and similarly a participant who responds with the highest level of difficulty or symptom to all items has a profile “33333”. There is a total of 243 different profile combinations. These profiles are subsequently converted to a continuous single index utility score using a one to one matching using value sets (i.e., matching profiles to single index utility scores). See Section 10.3.3.2 for further details.

The UK TTO (Time-Trade-Off) EQ-5D value sets will be used to generate the utility score and an alternative utility score based on the Country Specific TTO will also be calculated. For countries participating in this study with no published value sets an alternative value set based on geographical location will be used as detailed in Section 10.3.3.2.

The optional part of the EQ-5D that uses a visual analogue scale (VAS) to measure the participant's health on the day of assessment using a range of 0 to 100 is also included in the study.

The pre-season utility (both UK and country specific) and VAS scores will be presented for participants in the mES by vaccination group for each season.

The utility and VAS scores recorded at the beginning of the confirmed RSV episode will be presented by vaccination group, for participants in the mES RSV-confirmed ARI cohort.

The difference between vaccination groups in least squares (LS) means of the SF-12 physical functioning scores and EQ-5D utility score, at the initial ARI site visit, will be estimated using repeated measures mixed effects model including the timepoints: pre-season, initial ARI site visit, and pre-next-season visit. The model will include age category and region as fixed effects and will include participants in the mES RSV-confirmed ARI cohort. For the VE Analysis 1 and 2, only the pre-season and initial ARI site visit timepoints will be included in the model. See Section 10.3.3.5 for further details.

6.3.2.3.4. FLU-PRO 2.0

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

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 (symptom free) to 4 (very severe symptoms).

In addition, a score assessing the symptoms associated with upper respiratory systems will be computed as the mean score across the 10 items that make up the Nose, Throat and Eyes domains. The mean scores will range from 0 to 4. If less than 6 non-missing items out of the 10 are available, then the score will be set to missing.

Six individual domain scores will also be computed, representing symptom severity in each of the assessed body areas: Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal and Body/Systemic. Each domain score is calculated as the mean of all items comprising that domain, with scores ranging from 0 to 4. The domain scores are composed of the items detailed in Section 10.3.3.3.

For both the total scores and the domain scores a minimum of 50% of the items must be non-missing for that score to be calculated. If more than 50% of the items are missing the

score will be set to missing. For example, if more than 16 of the 32 items are missing then the total score will be set to missing and if more than 5 of the 11 items from the Body/Systemic domain are missing that score will be set to missing.

The analysis of FLU-PRO domain and total scores will be presented on the mES RSV-confirmed ARI cohort.

The maximum (worst) score for each of the FLU-PRO domain scores during the first 7 days of the RSV-confirmed ARI episode will be calculated and presented by vaccination group. In addition, the differences between vaccination groups will be compared for the Chest and Upper respiratory scores using a non-parametric Wilcoxon rank test.

The frequency of symptoms by timepoint will be presented by vaccination group.

Descriptive statistics of the individual domain scores will be presented by time and vaccination group.

The estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV, will be analyzed using a repeated measures ANOVA model. The model will be fitted including terms for, age category, region and vaccination group by day interaction. The least squares mean (LSMEANS) estimates for time by vaccination group and the difference in least squares means and associated P-values will be obtained from the ANOVA model. The estimate of the mean score over the 7 days will also be presented by vaccination group. The PROC MIXED procedure in SAS® will be used to carry out the ANOVA, with all terms fitted as fixed effects. If the model does not converge for season 1 analysis (in NH), the region term might be dropped. If the model does not converge for the end of study analysis, the region term might be replaced by hemisphere (Northern and Southern). See Section 10.3.3.4 for further details.

6.4. Tertiary/Exploratory endpoints

6.4.1. Analysis planned in the protocol

6.4.1.1. Efficacy

The same methodology as described for the primary and secondary endpoints (see Section 6.2 and Section 6.3, respectively) will be used to analyze the tertiary efficacy endpoints. The following endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following the annual revaccination given before Season 2:

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

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

The first occurrence of the event meeting the case definition according to the endpoint will be considered for the efficacy analysis.

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

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

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

6.4.1.2. Analysis of HCRU

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

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

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

6.4.1.3. Quality of Life

The analysis of the PGI-S and PGI-C will be presented on the mES RSV-confirmed LRTD cohort for combined season data.

The frequency and percentage of participants in each category will be presented by timepoint.

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

6.4.1.4. Immunogenicity

6.4.1.4.1. Correlate of protection

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

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

For this analysis, only the data post-Dose 1 will be taken into account. This means that all data of the RSVPreF3 and Placebo groups will be used for season 1, but only the data of the RSV_1dose group vs Placebo will be used after revaccination (not the RSV_annual group).

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

Statistical analysis will be done in several steps:

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

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

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

6.4.1.4.2. *Sub-groups analysis*

For each immunological assay and at each time point that blood samples are collected: The immunogenicity analysis will also be performed by age category (≥ 65 YOA, ≥ 70 YOA, ≥ 80 YOA, 60-69 YOA, 70-79 YOA), by hemisphere (NH and SH), by region (North America, Europe, Asia, SH) and by baseline frailty status.

6.4.1.5. Safety

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

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

Those analyses will be performed after each dose.

6.4.2. Additional considerations

6.4.2.1. Analysis of recurrent events

At the end-of-study analysis, VE analysis of RT-PCR confirmed RSV ARI and RSV LRTD cases will also be performed by considering all episodes reported (not only the first occurrence). This analysis will be performed by comparing incidence rates using a negative binomial regression model, controlling for interdependence between episodes within the same participant. This model accounts for heterogeneity among individuals and considers non-independent multiple episodes [Lievens, 2011].

6.4.2.2. All-cause mortality

VE in the prevention of any death (all-cause mortality) during the respective RSV seasons will also be performed excluding the confirmed COVID-19 cases.

In addition, a sensitivity analysis will be performed on any death reported from Day 1 post-vaccination up to the database cut-off date for VE Analysis, in the ES.

6.4.2.3. Co-infections

The number and percentage of participants with other viral pathogens (detected by multiplex RT-PCR) co-existing with RSV or hMPV will be tabulated by group for:

- RSV-confirmed ARI and RSV-confirmed LRTD episodes
- hMPV-confirmed ARI and hMPV-confirmed LRTD episodes.

6.4.2.4. Additional safety analyses

The following additional safety analyses will be performed after each dose:

- Reactogenicity and Safety analyses by ethnicity, race and sex:
  - Number and percentage of participants reporting each individual solicited administration site or systemic event within 4 days following vaccination on SSS,
  - Number and percentage of participants reporting [any/Grade 3] unsolicited AEs within 30 days following vaccination on ES,

  - Number and percentage of participants with at least one SAE/pIMD/Fatal SAE with onset within 6 months following vaccination, on ES.

- Number and percentage of participants with at least one Non-Serious unsolicited AE (Any, Grade 3/related/Grade 3 related/with medically attended visit) within 30 days following vaccination, with RR and 95% CIs, on the ES.

- Number and percentage of participants with at least one unsolicited AE (Any, Grade 3) reported within 30 minutes following vaccination, on the ES.

As sensitivity safety analysis, the following tables will also be presented:

- The number and percentage of participants with unsolicited AEs (Any) excluding RT-PCR confirmed RSV ARIs during the 30-day follow-up period, presented by MedDRA Primary SOC, HLT and PT, with RR and 95% CIs.
- The number and percentage of participants with at least one report of SAEs excluding RT-PCR confirmed RSV ARIs, from vaccination up to 6 months post-vaccination, presented by MedDRA Primary SOC, HLT and PT, with RR and 80% CIs.

Safety analyses listed below will be generated after each dose as Annex tables (not included in the CSR) and will be described in additional safety summaries:

- Number and percentage of participants reporting each individual solicited administration site or systemic event within 4 days following vaccination, with RR and 95% CIs, on the SSS,
- Number and percentage of participants with at least one SAE reported within 30 days following vaccination, with RR and 80% CIs, on the ES.

6.4.2.5. Additional efficacy analysis

In addition to VE analysis over ***2*** seasons, efficacy analysis will also be performed post Dose 2, i.e. on cases reported from Day 15 post Dose 2 up to end of season 2 (efficacy DLP). This analysis will include the following comparisons:

- RSV_annual vs Placebo
- RSV_1dose vs Placebo
- RSV_annual vs RSV_1dose,

and will be assessed for the following endpoints:

- RSV LRTD
- RSV LRTD by subtype, by age category, by baseline comorbidity of interest, by frailty status
- RSV severe LRTD
- RSV ARI

VE analysis will also be performed from start of season 3 up to end of season 3 (efficacy DLP). This analysis will be assessed for the endpoint mentioned above and include the following comparisons only:

- RSV_annual vs Placebo (mES Dose 2***, on participants who did not receive Dose 3***)
- RSV_1dose vs Placebo (mES Dose 2)

As described in Protocol Amendment 5, participants in the NH who had their Visit 5NH (i.e. pre-Season 3 visit) before approval of the Protocol Amendment 5, should receive the study intervention (Dose 3) as planned according to their group allocation. Therefore, depending on the protocol Amendment 5 approval timings, a portion of participants should receive the third dose of study intervention.

The following exploratory analyses will be performed for RT-PCR confirmed RSV LRTD, severe LRTD and RSV ARI:

- Analysis of VE of the annual revaccination over 3 seasons for participants who received 3 doses of RSVPreF3 OA vaccine in the RSV_annual and Placebo groups.
- Analysis of the VE post-dose 3 (season 3), i.e. on cases reported from Day 15 post Dose 3 up to end of season 3 (efficacy DLP), in RSV_annual versus Placebo groups and in RSV_1dose versus Placebo groups (mES Dose 3).

VE at Season 3: Model-based approach

To estimate the VE of season 3, with respective 95% CIs, using individual data over the three seasons (from 15 days post-Dose 1 up to end of S3NH), the following Cox model (adjusted for age and region) with a time-varying vaccine effect will be used:

- ***Continuous time-varying efficacy. Various time-varying functions (e.g., polynomials) will be evaluated, and the final model will be chosen based on the AIC criteria.***
- ***A piecewise time-varying efficacy model will be evaluated in order to estimate seasonal VE.***

Those analyses will be performed on RSV LRTD and RSV severe LRTD.

More advanced methods, such as survival machine learning techniques, might be explored.

7. ANALYSIS INTERPRETATION

The overall Type I error is equal to 2.5% (1-sided alpha=0.025).

With respect to confirmatory analyses, the interpretation must be done in a hierarchical manner: Testing of the confirmatory objectives will be done sequentially, meaning that one objective will be demonstrated conditionally to the success of the previous objective (success indicated by the black arrows in Figure 3).

Therefore, for analysis of season 1, no adjustment of alpha for multiplicity will be applied. and each testing will be done with a 1-sided alpha of 2.5%.

The efficacy of RSV vaccine against RSV-confirmed LRTD during the first season will be demonstrated if the LL of the two-sided 95% CI of VE is above 20%.

For VE analysis over 2 and 3 seasons:

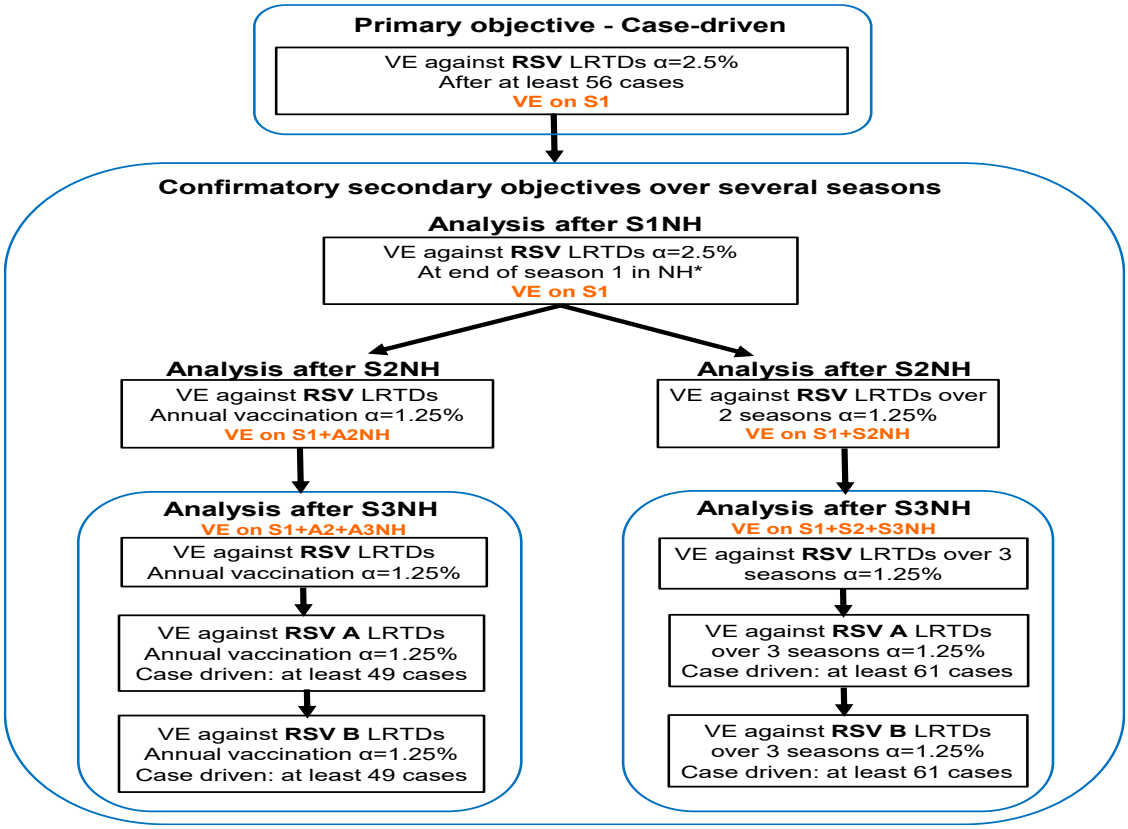
The confirmatory objectives will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 3). A Bonferroni adjustment of alpha for multiplicity will be applied to assess in parallel the VE of the annual revaccination (sequence on the left in Figure 3) and the VE of a single dose (sequence of the right in Figure 3). Therefore, those analyses will be done using a 1-sided test at alpha=1.25% level.

- The confirmatory secondary objective assessing VE of a single dose or annual revaccination given before season 2 of RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD after Season 2 in NH will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 3). The efficacy will be demonstrated if the LL of the two-sided 97.5% CI of VE is above 20%.
- The confirmatory secondary objective assessing VE of a single dose or annual revaccination given before season 2 of RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD after Season 3 in NH will be evaluated conditionally to the success of the single dose or annual revaccination objective after Season 2 (see Figure 3). The efficacy will be demonstrated if the LL of the two-sided 97.5% CI of VE is above 20%.
- For the confirmatory secondary objective of VE of a single dose or annual revaccination given before season 2 of RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately after 3 seasons in NH, the analysis will be case-driven and will be performed if the trigger is reached for both RSV-A and RSV-B separately. The trigger has been computed to have 90% power to demonstrate each objective sequentially:
  - For VE of a single dose: at least 61 cases are needed to have at least 90% power to demonstrate a significant VE (LL of 97.5% CI >0%);
  - For VE of annual revaccination: at least 49 cases are needed to have at least 90% power to demonstrate a significant VE (LL of 97.5% CI >0%).

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

Figure 3 presents the sequence of analysis if at least 56 cases have been accrued before the end of Season 1 in NH.

Figure 3 Sequential evaluation of primary and confirmatory secondary objectives



S1/S2/S3=Season 1/2/3
A2/A3 = Annual evaluation during Season 2/3 (after 1 revaccination given before Season 2)
NH = Northern Hemisphere; Season 3 is only applicable in the NH
VE=Vaccine efficacy
* The end of S1NH analysis will be performed if at least 1 additional RSV-confirmed ARI has been reported since the analysis of the primary objective and if there are at least 2-3 weeks between the database cut-off dates of the 2 analyses.
Note: VE analysis by subtype will be case-driven and will be performed if at least 49/61 cases are accrued for each subtype, i.e., RSV A and RSV B.

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

Except for analysis on objectives with predefined success criterion and an appropriate type I error control, other comparative analyses are descriptive with the aim to characterize the difference between groups. The use of these descriptive analyses should be limited to supportive analysis of confirmatory analyses or hypothesis generation.

Subgroups

Subgroup analysis will be descriptive, and comparisons will be exploratory. They should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

8. INTERIM ANALYSES

8.1. Statistical considerations for interim analyses

The final analysis of the primary objective will be case-driven. It will be performed when at least 56 cases of RSV-confirmed and externally adjudicated LRTDs have been accrued in the primary cohort for efficacy (mES). The efficacy of RSV vaccine against RSV-confirmed LRTD will be demonstrated if the LL of the two-sided CI of VE is above 20%.

If the number of events triggering VE Analysis 1 (at least 56 cases) is not achieved at the end of Season 1 in NH, an optional interim analysis might be performed when at least 35 cases have been accrued (at the end of Season 1 in NH or later). In that case, an adjustment of the Type I error will be done in order to maintain the overall significance level at 2.5%. The Wang-Tsiatis approach which is an alpha spending method giving boundaries between O'Brien-Fleming and Pocock boundaries will be used [Wang, 1987] to determine the adjusted alpha levels for the interim (α1) and the final (α2) analyses. The same success criterion will be applied at both interim and final analyses (LL>20%).

If the interim analysis is performed, then the final analysis will be performed when at least 60 cases are accrued in the primary cohort for efficacy or when all data associated to the primary objective are available. The final analysis will be performed irrespective of the outcome of the interim analysis, but if the primary endpoint is demonstrated at the interim analysis (LL>20%), the results of this analysis will be considered as final for the primary objective, and the subsequent analysis will be performed at the latest at end of S1SH and will be supportive of those results.

Table 10 provides the 1-sided adjusted alpha levels obtained using the Wang-Tsiatis method with $\Delta = 0.3$, depending on the quantity of information accumulated at the time of interim analysis (using gsDesign package in R).

Table 10 One-sided alpha levels for interim and final analyses using Wang-Tsiatis method, according to information accumulated at interim analysis

	Interim			Final	
Information	α1	n1	Power	α2	n2
0.59	0.0108	35	54%	0.0193	59
0.65	0.0120	38	59%	0.0191	59
0.7	0.0130	41	66%	0.0191	59
0.75	0.0141	44	69%	0.0191	59
0.8	0.0153	47	77%	0.0193	58

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

The same alpha will be used for the primary endpoint and for the sensitivity analyses of the primary. Secondary endpoints and subgroups analysis will be tested at the one-sided alpha level of 0.025.

There will be no interim analysis for the secondary confirmatory objectives, as they will be tested at a pre-specified timing after the final analysis of the primary (end of S2NH or S3NH, see Figure 3). Therefore, the secondary confirmatory objectives will be tested at the one-sided alpha level of 0.025. Simulations were performed and confirmed that there is no need to adjust the alpha level in that case.

8.2. Sample size re-assessment

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

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

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

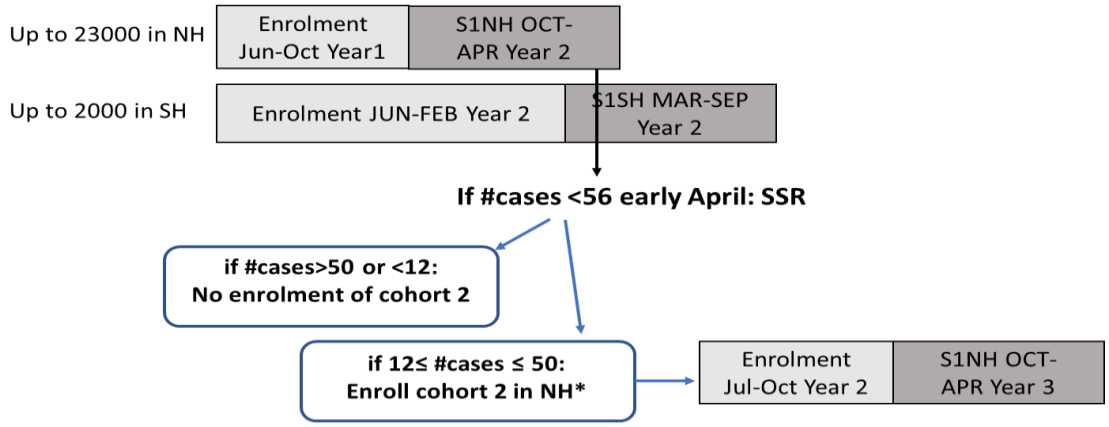
- If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed as described in Section 8.1 .
- If the total number of cases is included in [12, 50 cases]: Enrollment of a second cohort. In that case, new participants in NH will be enrolled and vaccinated before the next season in NH. The monitoring will continue and VE Analysis 1 will be performed as described in Section 8.1.

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

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

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

Figure 4 Decision rules for sample size re-assessment analysis based on cohort 1 with up to 25000 participants



S1NH= Season 1 in North Hemisphere
S1SH= Season 1 in South Hemisphere
SSR=Sample size re-assessment
*Enrollment of Cohort 2 might be cancelled if the 56 cases are accrued or if the interim analysis is successful.

8.3. Sequence of analyses

This section is presenting the timing for each analysis. More information on the statistical link between the confirmatory objectives can be found in Figure 3.

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

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

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

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

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

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

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

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

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

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

3. **Safety analysis:**

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

This analysis will include safety post-Dose 1 data only (no data post-Dose2).

4. **VE Analysis 3**: after at least 2 seasons in NH and 1 season in SH

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

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

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

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

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

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

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

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

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

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

Individual data listings will only be generated at this stage.

9. CHANGES TO THE PROTOCOL DEFINED STATISTICAL ANALYSES

This statistical analysis plan complements the analyses described in the protocol with descriptive summaries, sensitivity and supportive analyses.

The changes compared to the planned statistical analysis specified in the Protocol amendment 5 (Dated: 12 July 2023) are described below:

- Clarification on the adjudication of the LRTD cases: internal review of all ARI cases to identify LRTD cases according to case definition, and external review by adjudication committee of all RT-PCR confirmed RSV/hMPV LRTD cases either identified by internal review or by the investigator (see Section 6.2.2.1 and Section 10.3.1.3)
- Clarification on the allowed interval between nasal swab taken on site and ARI onset date for the counting of the RSV cases (see Section 10.3.1.4).
- Analysis sets section have been adapted to define the ES by dose (Section 5.1).
- Clarification on data included for analysis of VE over several seasons in Section 6.3.2.
- Details added in Section 6.3.1.3 and Section 6.3.2.2 for Atrial fibrillation (AF) AESIs.
- Description of estimands was added in Section 12.4.

10. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in Section 12.1.

10.1. Handling of missing data

10.1.1. Dates

When partially completed dates (i.e., with missing day or month) are used in calculations, the following rules will be applied:

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.
- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first vaccine dose given during that year.
  - Adverse event end dates with missing day: the imputed end date will be the last day of the month (30 or 31) or the study conclusion date whichever comes first.
  - Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the rules described above.

10.2. Data derivation

10.2.1. Age category at vaccination

As only the year of birth will be collected in the eCRF, there might be some discrepancies between the age computed using standard derivation rules and the age category used in SBIR for the minimization.

Therefore, for the analysis by age, the age categories defined in Table 3 will be determined according to the information entered in SBIR (variable AGEGRP in SDTM SUPPDM), except for "≥65 YOA" category which will be obtained using the derived age because this category is not used in SBIR for minimization.

10.2.2. Duration of events

For the duration of solicited AEs following each dose and overall:

The duration of an event with a start and end date will be the difference between the end and the start date plus one day, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of a solicited AE with at least one day Grade > 0 is defined as End date (CEENDY) – Start date (CESTDY) + 1, with Start date defined as the first day with the symptom and End date defined as the last day with the symptom in or beyond the solicited period.

A missing start date will be imputed with the vaccination date.

The number of days with grade 3 solicited event will be defined considering each day with a known grading=3, irrespective of whether the days are consecutive.

For paper diaries only:

If an ongoing symptom has a missing end date, the end date will be considered equal to vaccination date + 29 days. Partial end dates will be imputed according to Section 10.1.1.

If the max intensity during the ongoing period is 3, each day of the ongoing period will be counted as grade 3.

For e-diaries only:

If a solicited event intensity is still Grade > 0 at day 30, the end date will be considered equal to vaccination date + 29 days.

10.3. Statistical method

10.3.1. Efficacy

Vaccine efficacy is calculated using the exact conditional binomial method [Tang, 2004]. The between group relative risk (RR) and its confidence interval are computed. Vaccine efficacy is derived as 100 x (1-RR), and the VE confidence limits are 1 minus each of the RR confidence limits.

Vaccine efficacy with adjustment for time-to-first-event is calculated using a Cox's Proportional Hazards regression model [Cox, 1972]. All covariates to be included in the regression model are described in Table 7. The between-group hazard ratio (HR) and its confidence limits are computed using the model, and vaccine efficacy is derived as 100 x (1-HR). The corresponding VE confidence limits are 1 minus each of the HR confidence limits. When applying a Cox's Proportional Hazards regression model, the proportional hazards assumption should be verified by means of a Schoenfeld residual plot (Schoenfeld residuals versus time) and a log cumulative hazard plot (the log of the cumulative hazard versus the log of the survival time).

10.3.1.1. Missing data

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

10.3.1.2. Binomial distribution

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/_{F1}}{n2/_{F2}} = 1 - \frac{n1}{r * n2}$$

Where:

n1 = number of cases in the vaccinated group

F1 = follow-up time the vaccinated group

n2 = number of cases in the control group

F2 = follow-up time in the control group

and

$$r = \frac{F1}{F2}$$

In large studies where the disease incidence is low, it is assumed that the number of events in the vaccine and control groups may be approximated by independent Poisson distributions. Conditional on the total number of events n=n1+n2 and r=F1/F2, the number of events in the vaccinated group follows a binomial distribution [Kind, 1996; Lachin, 2011]. The hypothesis testing and statistical inference about the vaccine efficacy are based on this binomial distribution.

Let p denote the proportion of cases in the vaccine group, VE can be written as follows:

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

Therefore, there is a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of cases in the vaccine group among the total number of cases in the two groups.

The CI for vaccine efficacy can then be derived from the exact CI from p [Dragalin, 2002].

10.3.1.3. Adjudication of LRTD cases

All investigator-reported ARI cases will be reviewed by blinded, qualified GSK members to determine which investigator-reported events meet the definition of efficacy endpoints (LRTD and severe LRTD), using pre-defined endpoint criteria as specified in the study

protocol. This review will be made on clinical criteria (signs/symptoms) and independently of the results of the RT-PCR testing.

All RSV and/or hMPV RT-PCR confirmed cases either fulfilling the LRTD case definition (as confirmed by GSK internal review) or reported as LRTD by the investigator will be sent to an external LRTD adjudication committee.

Confirmation (internal and external) of the LRTD case (Yes/No/Unable to conclude) and the severity criteria (Presence of 2 signs, as per investigator's judgment or need for supportive therapy) will be reported in the eCRF and will be available in the SDTMs. Detailed information on this adjudication process can be found in the adjudication charter.

10.3.1.4. Assessment of RSV or hMPV cases

For the throat/nasal swab samples collected at ARI visits for PCR testing, only the swab samples that are collected within 14 days after the ARI onset (i.e., up to Day 15) will be considered for the case counting and the analysis.

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

A case will be considered as RSV positive if the quantitative RT-PCR results is

- ≥304 copies/ml for RSV-A,
- ≥475 copies/ml for RSV-B.

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

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

If the result of GSK PCR is not available and if an external local PCR test has been performed, this result will be used in the primary analysis for RSV and hMPV. Only local test performed in a certified laboratory and using a CE-marked or an FDA-approved kit will be considered for analysis. This information will be available in SDTMs.

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

Therefore, for the primary objective, the number of RSV-confirmed LRTD will be computed on the first occurrence of RT-PCR confirmed RSV A and/or RSV B associated

LRTD, starting from Day 15 after the first vaccination for the primary analysis on the mES and for the analysis on the PPSe.

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

10.3.1.5. Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a method for measuring patient comorbidity based on the International Classification of Diseases (ICD) diagnoses codes of individual patients using administrative data, such as Hospital Abstracts data. Each comorbidity category has an associated weight, based on the adjusted risk of one-year mortality, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in higher resource use or mortality [Charlson, 1987].

While validating the derived comorbidity index, the age was the only significant predictor for death from a comorbid disease. This led to creating a combined age-comorbidity variable, which suggested to be useful in longitudinal studies with follow-up periods of 5 year or more. The Age-comorbidity combined variable was derived by adding 1 point to risk for each decade of age as of 40 years; e.g. 60 years old patient with CCI score 1, would be rated as 3 (1+1+1) [Charlson, 1987].

With the advances in the medical management of chronic diseases and new treatments and technologies, patient with different comorbidities live longer than they did at the time when the CCI was developed and validated. Hence, the comorbidities and weights in the classical CCI (cCCI) were revaluated and validated in 6 developed countries (Australia, Canada, France, Japan, New Zealand, Switzerland) [Powers, 2015; Quan, 2011].

Of the 17 comorbidities used in the cCCI, 5 were not associated with mortality within the 1-year follow-up period and were assigned a weight of 0 (see Table 11).

Therefore, the updated CCI (uCCI) results in 12 conditions with weight ≥1.

This uCCI will be computed for each participant according to the table below and will be used for VE analysis by baseline comorbidities.

Table 11 List of comorbidities and corresponding weight as per updated Charlson Comorbidity Index

Comorbidities	Weight (RR)
Myocardial infarction, Peripheral vascular disease, Cerebrovascular disease, Peptic ulcer disease, Diabetes without chronic complications	0 (RR<1.2)
Chronic Pulmonary Disease Rheumatologic Disease Diabetes with chronic complications Renal Disease	1 (1.2<=RR<1.5)
Congestive Heart Failure	2 (1.5<=RR<2.5)

Comorbidities	Weight (RR)
Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	
Moderate or Severe Liver Disease AIDS/HIV	4 (3.5<=RR<4.5)
Metastatic Solid Tumor	6 (RR>=6)
Age:	
60-69YOA	2
70-79YOA	3
80-89YOA	4
90-99YOA	5
100-109YOA	6

Those comorbidities will be identified based on general medical history and a pre-defined list of comorbidities reported in the eCRF at baseline.

The Charlson Comorbidity Index (CCI) is a based on the International Classification of Diseases (ICD) diagnosis codes. In order to compute CCI based on MedDRA codes, the mapping of ICD-10 codes for the comorbidities included in CCI to corresponding MedDRA codes will be performed. This mapping and selection will happen with the MedDRA version at the time of analysis.

10.3.2. Immunogenicity

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

The following rules will be applied in the derivation of immunogenicity results:

- Antibody titers/concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMT/GMC calculation.
- Antibody titers/concentrations above the upper limit of quantification (ULOQ) of the assay will be given an arbitrary value of the ULOQ for the purpose of GMT/GMC calculation.
- Antibody titers/concentrations above the upper limit of detection (ULOD, ISORRES=SUP_LIMIT) of the assay will be given an arbitrary value of the ULOQ for the purpose of GMT/GMC calculation and an arbitrary value of the ULOD for the individual data presentation (RCCs).

The mean geometric increase (MGI) is defined as the geometric mean of the within participant ratios of the post-vaccination titer/concentration over the pre-vaccination titer/concentration.

10.3.3. Quality of Life

10.3.3.1. SF-12

Derivation of the 8 domain scores

If a single item of a domain score is missing that domain score will be classified as missing. For example, the physical functioning score will not be derived if either of its component parts, Q2A or Q2B, are missing. Before applying the scoring algorithm, the score for Q1 is realigned as follows:

SF-12 Question	Original Score	Mapped Score
Q1	1	5
	2	4.4
	3	3.4
	4	2.0
	5	1.0

The derivation of the SF-12 domain scores is detailed in the following table:

Domain	Score
Physical Functioning (PF)	100*(Q2A+Q2B-2)/4
Role Physical (RP)	100*(Q3A+Q3B-2)/8
Bodily Pain (BP)	100*((6-Q5)-1)/4
General Health (GH)	100*(Q1^-1)/4
Vitality (VT)	100*((6-Q6B)-1)/4
Social Functioning (SF)	100*(Q7-1)/4
Role Emotional (RE)	100*(Q4A+Q4B-2)/8
Mental Health (MH)	100*((6-Q6A)+Q6C-2)/8

^Mapped Q1 score

10.3.3.2. EQ-5D

Generating Utility Score

Two utility values will be calculated, one based on the UK TTO (Time-Trade-Off) and the other based on the Country Specific TTO. For countries participating in this study with no published value sets an alternative value set based on geographical location as detailed in the following table:

Country	EQ-5D Time Trade off Value Set
Australia	NZ
Belgium	Belgium
Brazil	US
Canada	US
Estonia	Finland
Finland	Finland
Germany	Germany
Italy	Italy

Country	EQ-5D Time Trade off Value Set
Japan	Japan
Mexico	US
Poland	Europe
Russia	Europe
South Africa	UK
South Korea	Japan
Spain	Spain
UK	UK
USA	USA

The profile scores will be mapped to utility scores by means of a SAS dataset.

Example:

A theoretical participant has no mobility problems (score=1), has no problems with personal care (score=1), does not have any problems with performing usual activities (score=1), has moderate pain and discomfort (score=2) and is extremely anxious and depressed (score=3).

The raw score is created as follows:

Mobility || Personal Care || Usual activities ||Pain Discomfort || Anxiety Depression

1||1||1||2||3=11123.

The following table contains an extract from the UK value set. The utility score corresponding to the raw score of 11123 is 0.291.

	RAW score	Mapped Utility score
1	11111	1.000
2	11112	0.848
3	11113	0.414
4	11121	0.796
5	11122	0.725
6	11123	0.291
238	33321	-0.095
239	33322	-0.166
240	33323	-0.331
241	33331	-0.358
242	33332	-0.429
243	33333	-0.594

10.3.3.3. FLU-PRO 2.0

The following domain scores are derived from the 32 components of the FLU-PRO questionnaire:

Domain	Component Questions
Nose*	Runny or dripping nose
	Congested or stuffy nose
	Sinus pressure
	Sneezing
Throat*	Scratchy or itchy throat
	Sore or painful throat

Domain	Component Questions
	Difficulty swallowing
Eyes*	Teary or watery eyes
	Sore or painful eyes
	Eyes sensitive to light
Chest / Respiratory	Trouble Breathing
	Chest Congestion
	Chest Tightness
	Dry or Hacking Cough
	Wet or Loose Cough
	Coughing
	Coughed up mucus or phlegm
Gastrointestinal	Felt nauseous (feeling like you wanted to throw-up)
	Stomach Ache
	Vomit (frequency)
	Diarrhea (frequency)
Body/Systemic	Felt dizzy
	Head Congestion
	Headache
	Lack of Appetite
	Sleeping More than usual
	Body aches or pains
	Weak or tired
	Chills or Shivering
	Felt Cold
	Felt Hot
	Sweating

* *Upper respiratory systems* comprised the 10 items that make up the Nose, Throat and Eyes domains

10.3.3.4. Longitudinal model to estimate mean FLU-PRO total score

A longitudinal model will be applied to estimate the mean flu-pro total score over the first 7 days of the ARI episode. The least squares mean (LSMEANS) estimates for time by vaccination group and the difference in least squares means and associated P-values will be obtained from the ANOVA model. The PROC MIXED procedure in SAS® will be used to carry out the ANOVA, with all terms fitted as fixed effects. Age category and region will also be included. The model will include only data from day 1 to day 7 inclusive.

The SAS code for the analysis post-season 1 is as follows:

```
ODS OUTPUT LSMEANS=LS;
ODS OUTPUT ESTIMATES=ESTIM;
ODS OUTPUT DIFFS=DIFFS;
PROC MIXED DATA=FLUPRO;
     CLASS pid day group agecat region;
     MODEL flu_pro=region agecat day group day*group/s cl;
     REPEATED day/type=un subject=pid;
     LSMEANS day*group/pdiff cl;
     ESTIMATE "Day 1 - Day 7 Placebo" intercept 1 group 1 0;
     ESTIMATE "Day 1 - Day 7 Vacc group" intercept 1 group 0 1;
     ESTIMATE "Day 1 - Day 7 Diff" group -1 1;
RUN;
```

Where group= vaccination group (=0 for placebo, =1 for RSV vaccine), agecat= age category (60-69y, 70-79y, >=80y), region (North America, Europe, Asia, Southern Hemisphere).

The differences in LSMeans and associated CI's and P-Values are obtained from the following data step:

```
DATA diffs;
   SET diffs;
   WHERE GROUP ne _GROUP AND DAY=_DAY;
RUN;
```

The above code can be adapted for the comparison between vaccination groups for season 2 and season 3.

10.3.3.5. Longitudinal model to estimate mean SF-12/EQ5D scores

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

In the following SAS code, Time can have 3 values: "Pre-season ", "RSV-ARI visit" or "Pre next season":

```
  ODS OUTPUT LSMEANS=LS;
  ODS OUTPUT DIFFS=DIFFS;
  PROC MIXED DATA=PF;
       CLASS pid time group agecat region;
       MODEL PF=region agecat time group time*group/s cl;
       REPEATED time/type=un subject=pid;
       LSMEANS time*group/pdiff cl;
  RUN;
```

Where group= vaccination group (=0 for placebo, =1 for RSV vaccine), agecat= age category (60-69y, 70-79y, >=80y), region (North America, Europe, Asia, SH).

The differences in LSMeans are obtained from the following data step:

```
 DATA diffs;
   SET diffs;
   WHERE GROUP ne _GROUP AND TIME=_TIME;
 RUN;
```

For the End of study analysis, the differences in LSMeans are obtained from the following data step:

```
 DATA diffs;
   SET diffs;
   WHERE GROUP ne _GROUP AND TIME=_TIME AND _GROUP=2;
 RUN;
```

Where group= vaccination group (=0 for RSV annual, =1 for RSV 1 dose, =2 for Placebo).

11. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

A specific COVID-19 eCRF page has been designed and will be used to collect any event related to COVID-19 pandemic.

An evaluation of the impact of COVID-19 will be provided. Depending on how the COVID-19 situation evolves, the SAP might be amended to reflect the analysis corresponding to COVID-19.

11.1. Study population

11.1.1. Participant disposition

A summary of recruitment by country and site, relative to the phases of COVID-19 Pandemic measures will be produced. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of each wave of pandemic measures within each country.

The summary of study completion with the number of withdrawn participants will be produced with reasons for withdrawal/discontinuation due to issues related to the COVID-19 pandemic.

11.1.2. Additional displays for participants with a COVID-19 infection

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF.

Numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized.

Additionally, if greater than 5% participants have a suspected, probable of confirmed COVID-19 infection, the following data displays might be produced:

- Summary of COVID-19 Assessments for participants who reported COVID-19 infection
- Summary of COVID-19 symptoms for participants who reported COVID-19 infection
- Summary of Baseline Characteristics for participants who reported COVID-19 infection.

11.1.3. Concomitant vaccination with COVID vaccine

The number and percentage of participants with concomitant vaccination (COVID-19) before and during the study will be tabulated with exact 95% CI.

11.2. Efficacy

See Section 6.2.2.3 for sensitivity analyses on VE related to primary objective.

Depending on number of COVID-19 cases and real impact, re-assessment of the methods used for VE will be performed and this section will be amended.

11.3. Safety

11.3.1. Assessment of COVID-19 cases

COVID-19 cases that will occur during the safety event reporting timeframe will be reported as non-serious or serious AEs, respectively i.e., during the 30-day period for non-serious AEs and during the 6-months post-vaccination period for SAEs. In addition, all COVID-19 cases leading to withdrawal will be reported as AEs during the entire study period.

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 cases reported as AEs.

The overall incidence of COVID-19 AEs and SAEs (Fatal and Non-Fatal), COVID-19 AEs leading to study withdrawal, and COVID-19 AEs by severity, will be obtained from standard AE and SAE summaries (i.e., by SOC and PT).

If more than 5% of participants report at least one COVID-19 case reported as AE, then the onset and duration of the first occurrence of COVID-19 AEs and COVID-19 AE symptoms might be summarized. The same rule will apply to COVID-19 SAEs.

11.3.2. Impact of COVID-19 pandemic on safety results

The impact of the COVID-19 pandemic on the safety results will be assessed. Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of each wave of pandemic measures within each country.

Summaries of the incidence rates of AEs and SAEs, during the pandemic and outside of the pandemic will be produced overall.

12. ANNEXES

12.1. Business rules for standard data derivations and statistical methods

This section contains standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in Section 10 (additional study-specific rules).

12.1.1. Attributing events to vaccine doses

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (eCRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the event will not be considered as related to the vaccination.

12.1.2. Handling of missing data

12.1.2.1. Dates

When partially completed dates (i.e., dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

See also exceptions in Section 10.1.1.

12.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

12.1.2.3. Daily recording of solicited events

For **studies using paper diaries** which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e., SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e., SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to

allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.

The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

12.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the Adverse Events (AE) domain but they do not contribute to the summaries of unsolicited adverse events.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

12.1.3. Data derivation

12.1.3.1. Age at first dose in years

When age at first dose is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of first dose. For example:

DOB = 10SEP1983, Date of first dose = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of first dose = 10SEP2018 -> Age = 35 years

In this study, only the year of birth will be collected. The rules for handling missing day and/or month in the DOB are given in Section 12.1.2.1.

Specific rules used to determine age category are also described in Section 10.

12.1.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

12.1.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

12.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)2

12.1.3.5. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

12.1.3.6. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and <=ULOQ	value
"value" and value is >ULOQ	ULOQ
All other cases	missing

12.1.3.7. Geometric mean titers (GMTs) and concentrations (GMCs)

Geometric Mean Titer (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titer or concentration transformations. Non quantifiable antibody titers or concentrations will be converted as described in Section 12.1.3.6 the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

12.1.3.8. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

12.1.3.9. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. Unsolicited adverse events with missing administration site flag will also be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

12.1.3.10. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

12.1.4. Display of decimals

12.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

12.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

12.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-dose body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height/weight variables will be displayed without decimals, with the exception of infant studies where one decimal will be displayed for the transformed weight.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

12.1.4.4. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is assay specific based on the magnitude of the assay result post-dose and the clinically relevant assay threshold. The same number of decimals will be used for a given assay regardless of the timepoint presented.

For each assay, GMTs or GMCs and their confidence limits will be presented with **one decimal**, as well as GMT/GMC fold increase from pre-vaccination.

12.1.5. Statistical methodology

12.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

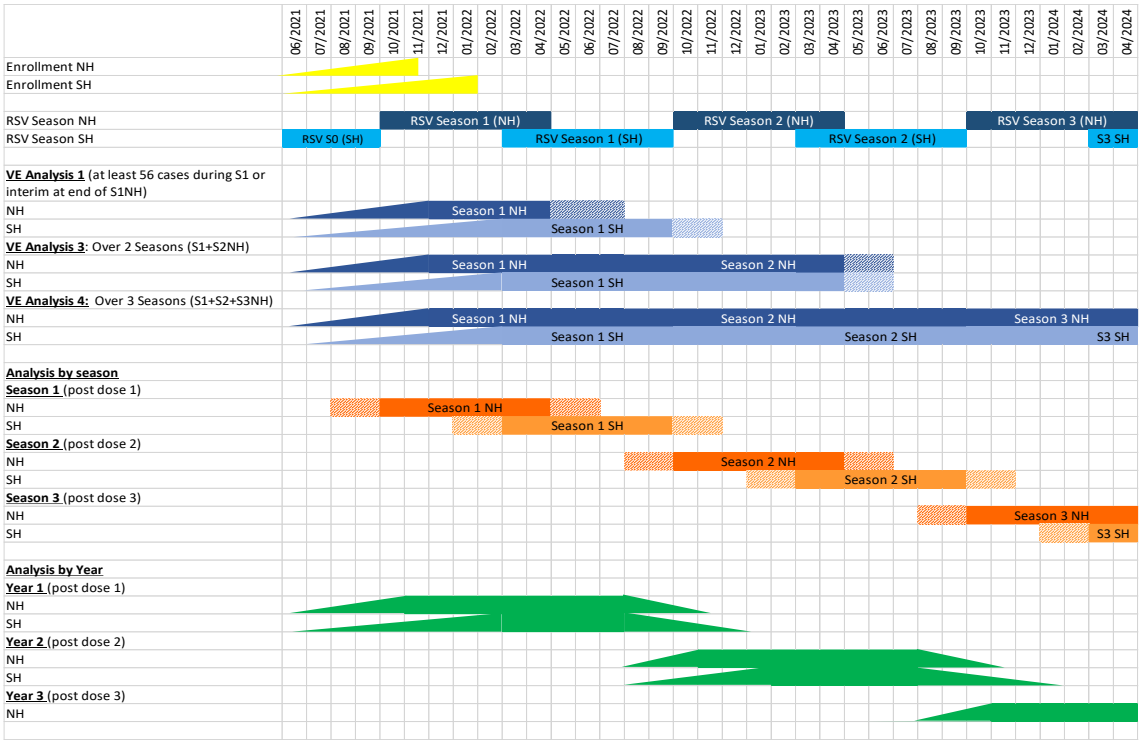
12.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardised asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

12.2. Case counting periods for each analysis

The figure below presents the time periods for case counting and follow-up time of each analysis, as described in Table 7.

Figure 5 Time periods for case counting and follow-up time according to VE analysis



12.3. Re-randomization

The following steps will be performed for the re-randomization test:

1. Compute the test statistic test_stat_obs on the original data set as the estimate for the relative risk adjusted for age and region, based on the model specified in Section 6.2.2.2
2. Generate a new randomization list, using the subject order as observed and the minimization algorithm as defined for the study
3. Keep other covariates (age and region) as observed and modify the incidence rates according to the null hypothesis H0= VE≤20% = RR≥80% as described in [Wang, 2020].
4. Compute the test statistic test_stat* based on the re-randomization list and the modified incidence rates. This is computed as the exact estimate for the relative risk adjusted for age and region, based on the model specified in Section 6.2.2.2 applied to the modified data.
5. Once all iterations are done, compute the p-value as the proportion of re-randomized test statistics test_stat* that are as or more extreme than the observed test_stat_obs and are thus evidence against the null hypothesis.

5000 re-randomizations will be performed to compute the randomization test p-value.

For the participants for which SBIR was not available at randomization and for whom treatment allocation was not done using the minimization algorithm, no re-randomization will be performed and participants will be assigned to their original assignment.

12.4. Estimands

12.4.1. Efficacy

The primary objective of the study is to demonstrate the efficacy of a single dose of RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥60 YOA.

The estimand attributes associated to the primary objective are described below:

- Population: Older adults ≥ 60 YOA at the time of vaccination included in the modified Exposed Set (mES)
- mES: Participants are eliminated from the mES in case of: screening failure, no vaccination at all, invalid inform consent, or if they reported an RSV ARI case within the first 14 days after vaccination.

Objective	Treatment (group)	Population	Endpoint	Population summary	Intercurrent events (ICEs)
					Description and Handling strategy
Primary	RSVPreF3 group who received 1 dose of RSV vaccine at Day 1 and Placebo group	Older adults ≥60 years at the time of vaccination (Dose 1) included in the mES	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition from 15 days post-dose 1 up to data lock point for analysis (end of season 1 in NH)	Percentage of vaccine efficacy calculated via relative risks as VE(%) = 100*(1-RR). RR is calculated as the ratio of the incidence rates (number of cases divided by the total follow-up time) of the vaccine group over the Placebo group. Follow-up time= time from day 15 post dose 1 up to first occurrence of RSV LRTD or up to withdrawal or DLP for analysis, whichever comes first.*	• Vaccination administration errors (Treatment policy). • Use of prohibited medication/vaccination (Treatment policy). • Prohibited medical condition (Treatment policy). • Incorrect treatment randomised (Treatment policy) • RSV ARI cases within the first 14 days after vaccination (participants eliminated from the mES as follow up start 15 days after vaccination) • Death (participants included up to death, equivalent to while on treatment strategy described in the framework)

*see Table 7 for details on case counting and follow-up time

The secondary confirmatory objectives of the study are:

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

Estimand attributes of this secondary objective are described in table below.

Objective	Treatment (group)	Population	Endpoint	Population summary	Intercurrent events (ICEs) Description and Handling strategy
Secondary – Single dose	RSVPreF3 group who received 1 dose of RSV vaccine at Day 1, and placebo at Dose 2 (RSV_1dose group) and Placebo group	Older adults ≥60 years at the time of vaccination (Dose 1) included in the mES	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition from 15 days from vaccination up to data lock point for analysis (end of S2 in NH and end of S3 in NH)	Percentage of vaccine efficacy calculated via relative risks as VE(%) = 100*(1-RR). RR is calculated as the ratio of the incidence rates (number of cases divided by the total follow-up time) of the vaccine group over the Placebo group. Follow-up time= time from day 15 post dose 1 up to first occurrence of RSV LRTD or up to withdrawal or DLP for analysis, whichever comes first.*	• Vaccination administration errors (Treatment policy). • Use of prohibited medication/vaccination (Treatment policy). • Prohibited medical condition (Treatment policy). • Incorrect treatment randomised (Treatment policy) • RSV ARI cases within the first 14 days after vaccination (participants eliminated from the mES as follow up start 15 days after vaccination) • Death (participants included up to death, equivalent to while on treatment strategy described in the framework).
Secondary – Annual revaccination	RSVPreF3 group who received 1 dose of RSV vaccine at Day 1 and a second dose before season 2 (RSV_annual group) and Placebo group	Older adults ≥60 years at the time of vaccination (Dose 1) included in the mES	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition from 15 days from vaccination up to data lock point for analysis (end of S2 in NH and end of S3 in NH)	Percentage of vaccine efficacy calculated via relative risks as VE(%) = 100*(1-RR). RR is calculated as the ratio of the incidence rates (number of cases divided by the total follow-up time) of the vaccine group over the Placebo group. Follow-up time= time from day 15 post dose 1 up to first occurrence of RSV LRTD or up to withdrawal or DLP for analysis, whichever comes first.*	

*see Table 7 for details on case counting, follow-up time and censoring.

Estimand attributes of other secondary efficacy objectives are similar to those described for confirmatory objectives above.

12.4.2. Immunogenicity

The secondary immunogenicity objective is to evaluate the humoral immune response to the RSVPreF3 OA vaccine in a subset of participants, in terms of RSV-A and RSV-B neutralizing titers and RSVPreF3 IgG-binding antibody concentrations (GMT, MGI).

Treatment (group)	Population	Endpoint*	Population summary	Intercurrent events (ICEs)	
				Description	Handling strategy
RSVPreF3 OA vaccine at Dose 1 (RSV_1dose), annual revaccination pre-season 2 (RSV_annual) and Placebo group	Older adults ≥60 years at the time of first vaccination in RSV OA=ADJ-006 study, included in immunogenicity subset	• Titers/concentrations at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Season 3 • Fold increase in titers/concentrations from Day 1 to Day 31, pre-Season 32 and pre-Season 3 • Titers/concentrations ≥cut-off at Day 1, Day 31, pre-Season 2 and pre-Season 3	• GMT • MGI • Percentage of participants	Study vaccination not administered as per protocol. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE

*Titers/concentrations refer to results from a blood draw taken according to protocol defined allowed visit interval (see Table 5).

12.4.3. Safety

The safety secondary endpoints are:

- To evaluate the reactogenicity of the RSVPreF3 OA vaccine in a subset of participants, and
- To evaluate the safety of the RSVPreF3 OA vaccine in all participants.

Treatment	Population	Endpoint	Population summary	Intercurrent events (ICEs)	
				Description	Handling strategy
RSVPreF3 OA vaccine at Dose 1 (RSV_1dose), annual revaccination pre-season 2 (RSV_annual) and Placebo group	Older adults ≥60 years at the time of first vaccination in RSV OA=ADJ-006 study, included in reactogenicity subset	• Occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination (i.e., the day of vaccination and 3 subsequent days).	Percentage of participants Mean/median duration in number of days	Study vaccination not administered as per protocol Prohibited medication or intercurrent medical condition prior to the corresponding end of follow-up (i.e., Day 4, Day 31, Month 6 after vaccination or study end)	Summaries will be presented on all the data collected. (Treatment policy) Rationale: treatment policy strategy is used as all data will contribute to evaluate the safety parameters
RSVPreF3 OA vaccine at Dose 1 (RSV_1dose), annual revaccination pre-season 2 (RSV_annual) and Placebo group	Older adults ≥60 years at the time of first vaccination in RSV OA=ADJ-006 study	• Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days) • Occurrence of all SAEs/pIMDs from the day of vaccination up to 6 months after each vaccination • Occurrence of SAEs/pIMDs related to study vaccination from Day 1 up to study end. • Occurrence of fatal SAEs from Day 1 up to study end.	Percentage of participants		

12.5. Quality of Life

The secondary objectives are:

- To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI,
- To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI,
- To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI,
- To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI,

in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.

Treatment	Population	Endpoint	Population summary	Intercurrent events (ICEs)
				Description and handling strategy
RSVPreF3 OA vaccine at Dose 1 (RSV_1dose), annual revaccination pre-season 2 (RSV_annual) and Placebo group	Older adults ≥60 years at the time of first vaccination in RSV OA=ADJ-006 study, with RT-PCR confirmed RSV ARI in mES	• Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms • FLU-PRO total score during the first 7 days from the onset of ARI symptoms, EQ-5D utility score at the ARI visit , SF-12 Physical Functioning score at the ARI visit.	• Mean/median • Estimated Least Squares mean	• Vaccination administration errors (Treatment policy). • Use of prohibited medication/vaccination (Treatment policy). • Prohibited medical condition (Treatment policy). • Incorrect treatment randomised (Treatment policy) • RSV ARI cases within the first 14 days after vaccination (participants eliminated from the mES as follow up start 15 days after vaccination) • Death (participants included up to death, equivalent to while on treatment strategy described in the framework).

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