Statistical Analysis Plan	
Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose 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 4 Final: 20 Dec 2022

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

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Infection
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 Dec 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

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 annual revaccination doses in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons. Criterion: The LL of the 2-sided CI for VE is above 20%.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To demonstrate the efficacy of a single dose and annual revaccination doses of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons. Criterion: The LL of the 2-sided CI for VE is above 0%.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To demonstrate the efficacy of a single dose and annual revaccination doses of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA over 3 seasons. Criterion: The LL of the 2-sided CI for VE is above 20%.	First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.
Other secondary descriptive	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed hMPV-associated 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 doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by season in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by season.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by year in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by year.
To evaluate the 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 doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by baseline frailty status in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by 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 doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of any ARI and any LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of ARI or LRTD, according to the case definition*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalization due to respiratory diseases during the RSV seasons† in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons†. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI during the RSV seasons† in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	Estimated Least Squares mean EQ-5D utility score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	Estimated Least Squares mean SF-12 Physical Functioning score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
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-Dose 3 (pre-Season 3): • RSVPreF3 IgG-specific antibody concentrations. • Neutralizing antibody titers against RSV A. • Neutralizing antibody titers against RSV B.

Objectives	Endpoints
Secondary – Safety	
To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine.	In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from the day of vaccination up to 6 months after each-vaccination. • Occurrence of all pIMDs from the day of vaccination up to 6 months after each vaccination. • Occurrence of SAEs related to study vaccination from Day 1 up to study end. • Occurrence of pIMDs related to study vaccination from Day 1 up to study end. • Occurrence of any fatal SAEs from Day 1 up to study end.
Tertiary	
Tertiary – Efficacy	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV and/or hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV and/or hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed hMPV-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.

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

Objectives	Endpoints
investigational vaccine and following annual revaccination doses.	
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-specific antibody concentrations at pre-Dose 1 (Day 1) and 30 days post-Dose 1 (Day 31) in all participants with RSV disease compared to a subset of controls.‡
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Dose 3 (pre-Season 3): • RSVPreF3 IgG-specific antibody concentrations classified by baseline frailty score. • Neutralizing antibody titers against RSV A classified by baseline frailty score. • Neutralizing antibody 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.

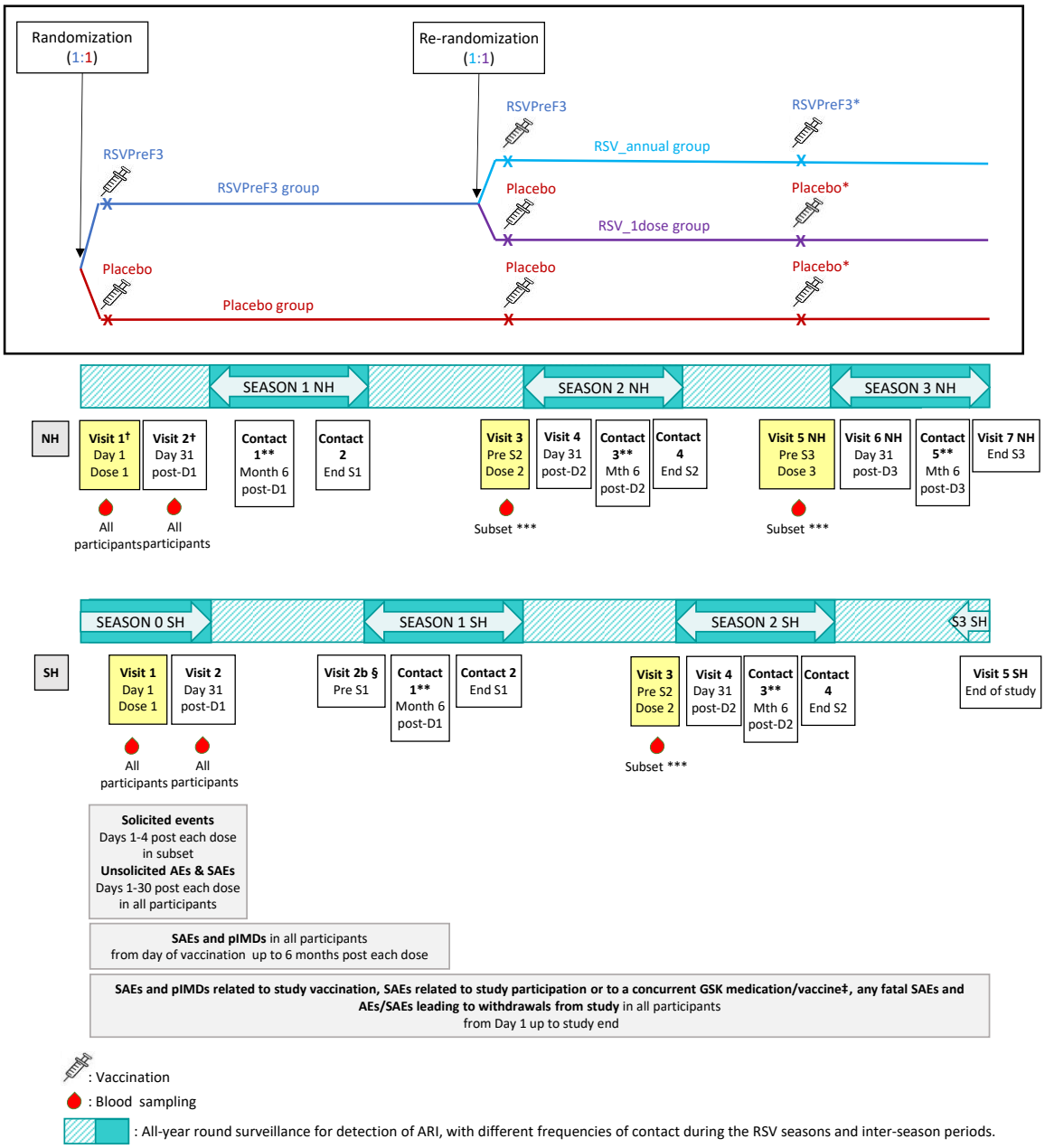
* Case definitions are described in Section 4

† 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.

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 6.3.1 of 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 infection; 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, 3 and 5 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
§ 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.

- **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 RSVPreF3 lots 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.

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.
- **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 doses							
RSV_L1_annual	Up to 5 750	375-500	Up to 6 250	≥ 60 years	RSVPreF3 OA investigational vaccine		X
RSV_L2_annual							X
RSV_L3_annual							X
RSV_L4_annual							X
RSV_L1_1dose	Up to 5 750	375-500	Up to 6 250	≥ 60 years	Placebo		X
RSV_L2_1dose							X
RSV_L3_1dose							X
RSV_L4_1dose							X
Placebo	Up to 11 500	750-1 000	Up to 12 500	≥ 60 years	Placebo		X
Total	**Up to 23 000**	**1 500-2 000**	**Up to 25 000**				

NH: Northern hemisphere; SH: Southern hemisphere; L1: Lot 1; L2: Lot 2; L3: Lot 3; L4: Lot 4
* Numbers are approximate (see Section 9.2.1 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 will receive 2 additional doses, 1 before Season 2 and 1 before Season 3.
  - 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. This period might be extended, i.e., starting few months earlier and/or ending few months later, in case a shift in the peak incidence of seasonal viruses due to special circumstances (e.g., COVID-19 pandemic) is observed in the national surveillance systems and/or in epidemiological studies.
- **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).
  - In **RSV_annual**, **RSV_1dose** and **Placebo** groups for analysis after dose 2 and dose 3 (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	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
Dose 2/ Dose 3	RSV_L1_annual	NA	**RSV_annual**	1	Participants receiving annual revaccinations 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)

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
	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
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. 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

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

Endpoint	Case definition
severe hMPV LRTD – Definition 1 "Clinical symptomology"[5]	• 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]
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 infection; 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.

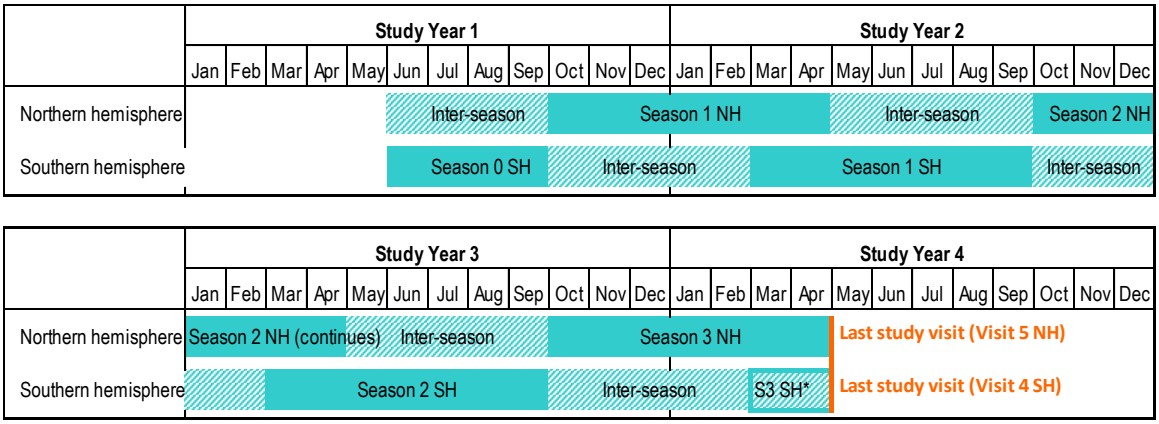
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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 data obtained at VE Analysis 1, the ARI surveillance could be adapted for the 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 4 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.

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

- **Modified Exposed Set (mES) - RSV:** the mES-RSV 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,***
  - ***mES Dose 3: participants who received Dose 3 and who did not report RSV ARI within 15 days post-Dose 3.***

- **mES – hMPV:** the mES-hMPV will be the primary population for efficacy analysis on hMPV-confirmed cases. It will include all participants from the ES who did not report a hMPV-confirmed ARI prior to Day 15 after each vaccination.
- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): 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,
  - have data available for efficacy endpoint measures,
  - did not have any protocol deviations leading to exclusion.

As for the mES, two PPSe will be defined: one for RSV endpoints and one for hMPV endpoints.

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

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

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 ES and mES post-Dose 2 and post-Dose 3 (see Table 5).
- Code 2700 will be used to eliminate participants who report a hMPV-confirmed ARI case prior to Day 15 after vaccination from mES-hMPV cohort.

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, 900, 1030, 1050,1060 and 2600: participants will be eliminated for all visits.
- For codes 1040, 1070, 1071, 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 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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	All	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 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.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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	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: • Participants who did not accept to be revaccinated for any reason • Participants who withdrew before dose 2/dose 3	Visit 3, Visit 5NH	***mES Dose 2/3***, PPSe, PPSi
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

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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 prior to the study vaccine administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent.	All	PPSe, PPSi
2050	Intercurrent medical condition:	All	PPSi and PPSe

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	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.		
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. For participants in the immunogenicity subset: • 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	For participants in the immunogenicity subset: 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

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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
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**	Participant who reports a hMPV-confirmed ARI case prior to Day 15 after vaccination: • Number of days between ***first*** vaccination and day of onset of ARI case < 14 days	ARI visit	mES-hMPV, PPSe-hMPV

** codes 2500 to 2700 are not considered as protocol deviations, but those codes will be used to eliminate participants from 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-RSV, mES-hMPV, PPSe-RSV, PPSe-hMPV, 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-***RSV***. In addition, a second analysis will be performed on the PPSe and on the ES to complement the primary analysis.

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

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

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

During the surveillance period, all events related to the efficacy endpoints will be collected (see Section 8.1.1 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-RSV.

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 (mES-RSV or mES-hMPV depending on the endpoints) 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 6.3.2.1.3).

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

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 (VE Analysis 3 and 4), the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

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 annual revaccination doses:

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

  VE in the prevention of hospitalization and complications during the RSV seasons 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 number of days with solicited events with an onset during the 4-day follow-up period will be tabulated after each dose for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for 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).

- 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 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.

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 pre-Seasons 1 and 2 will be presented for the mES-RSV.

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 annual revaccination doses.

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 on Day 15 post-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 after season 1 in NH, 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 participants who received the 2 or the 3 doses respectively, and the following groups will be compared:

- **RSV_annual group versus Placebo group** to demonstrate VE of annual revaccination after season 2 (S1+A2NH) and after season 3 (S1+A2+A3NH).
- **RSV_1dose versus Placebo group** to demonstrate VE of one single dose after season 2 (S1+S2NH) and after season 3 (S1+S2+S3NH).

Table 6 below describes the data that will be included in each analysis.

Table 6 Description of data to be included in VE analysis over several seasons

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: ***form 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 4 (EoS)	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 Visit 5NH (Pre-Dose 3) in NH or up to start of season 3 in SH for all participants who received 2 doses in RSV_annual group or in Placebo group (A2) + Data collected during the third season: ***from Dose 3*** up to study end for participants in NH who received 3 doses in RSV_annual group or in Placebo group (A3NH)
	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 Visit 5NH (Pre-Dose 3) in NH or up to study end 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 Dose 3*** up to study end for participants in NH who received 3 doses in RSV_1dose group or in Placebo group (S3NH)

S1/S2/S3 = Seasons 1/2/3; A2/A3=Annual evaluation during season 2/3
NH= Northern Hemisphere; SH= Southern Hemisphere.

- **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	
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:

- 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.

In addition, a sensitivity analysis will be performed on first occurrence of hospitalizations and complications reported from Day 15 (from Day 1) post-vaccination up to the database cut-off date for VE Analysis, in the mES (in the ES).

- **VE over time**

The VE analysis will be performed by splitting participants in 2 groups according to the time of vaccination: 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	End date 1 for case count and FU time	Participants to be excluded from analysis	*Additional Censoring*	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 in NH (VE analysis 2)	Season 1	Day 15 post-Dose 1	End of season 1 in ***SH or Dose 2 administration***	RSV cases before Day 15 post-first vaccination	***NA***	Age, region	mES, PPSe, ES[3]
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	***Participants who did not received Dose 2 will be censored at Visit 3***	Age, region, season	mES, PPSe, ES
Over 3 seasons S1+A2/S2+A3NH/S3NH (VE analysis 4)	***Season 1 +*** Season 2 (A2)	Day 15 post Dose 1	Visit 5NH (Pre-Dose 3) in NH or start of season 3 in SH	RSV cases before Day 15 post-***first*** vaccination	***Participants who did not received Dose 2 will be censored at Visit 3***	Age, region, season	mES, PPSe, ES
	Season 1 + Season 2 (S2)	Day 15 post dose ***1***	Visit 5NH (Pre-Dose 3) in NH or end of study in SH				
	Season 3 (A3NH/S3NH)	***Dose 3 in NH***	End of study in NH		***Participants who did not received Dose 3 will be censored at Visit 5NH***		
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-***	Age, region	mES

VE analysis	Time period	Start date 1 for Cases count and FU time	End date 1 for case count and FU time	Participants to be excluded from analysis	*Additional Censoring*	Model Covariates	Analysis Set
					Dose 1 and start of S1		
	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	Start of season 3, after Day 15 post-Dose 3	End of season 3 in NH and end of study for SH	***RSV cases before Day 15 post-Dose 3***	***Participants with RSV ARI cases between 15 days post-Dose 3 and start of S3***	Age, region	mES ***Dose 3***
By Year	Year 1	Day 15 post-Dose 1	Visit 3 (Pre-Dose 2)	RSV cases before Day 15 post-Dose 1	***NA***	Age, region, season	mES
	Year 2	Day 15 post-Dose 2	12 months post-Dose 2 in SH, Visit 5NH (Pre-Dose 3)	RSV cases before Day 15 post-Dose 2	***NA***	Age, region, season	mES ***Dose 2***
	Year 3	Day 15 post-Dose 3	EoS in NH	RSV cases before Day 15 post-Dose 3	***NA***	Age, region, season	mES ***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 2 or 3.
[4]EoS= End of study visit, i.e., Visit 5NH or Visit 4SH.

Visual representation of the time periods for each analysis is also presented in Figure 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 2, 3 and 4 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 time of VE Analysis 2, 3 or 4 or until withdrawal date if before the efficacy data lock point.

- **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.

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 S2 and S3, a sensitivity analysis will be performed considering the cases during the S1 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).

- **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 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

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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.

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 groups
- Post-Dose 2: RSV_annual versus Placebo groups
- Post-Dose 3: RSV_annual versus Placebo groups, in NH

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 post-vaccination, presented by MedDRA Primary System Organ Class (SOC), 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 2001]
- 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 [Leidos Biomedical research 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: CCI [redacted] 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 CCI [redacted] to 4 CCI [redacted].

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 CCI [redacted] to 4 CCI [redacted].

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 Sections 6.2 and 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 annual revaccination doses:

- VE against RSV and/or hMPV-confirmed LRTDs,
- 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) and 1 month post-Dose 1 (Day 31) 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.

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 any ARI and any 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.

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:

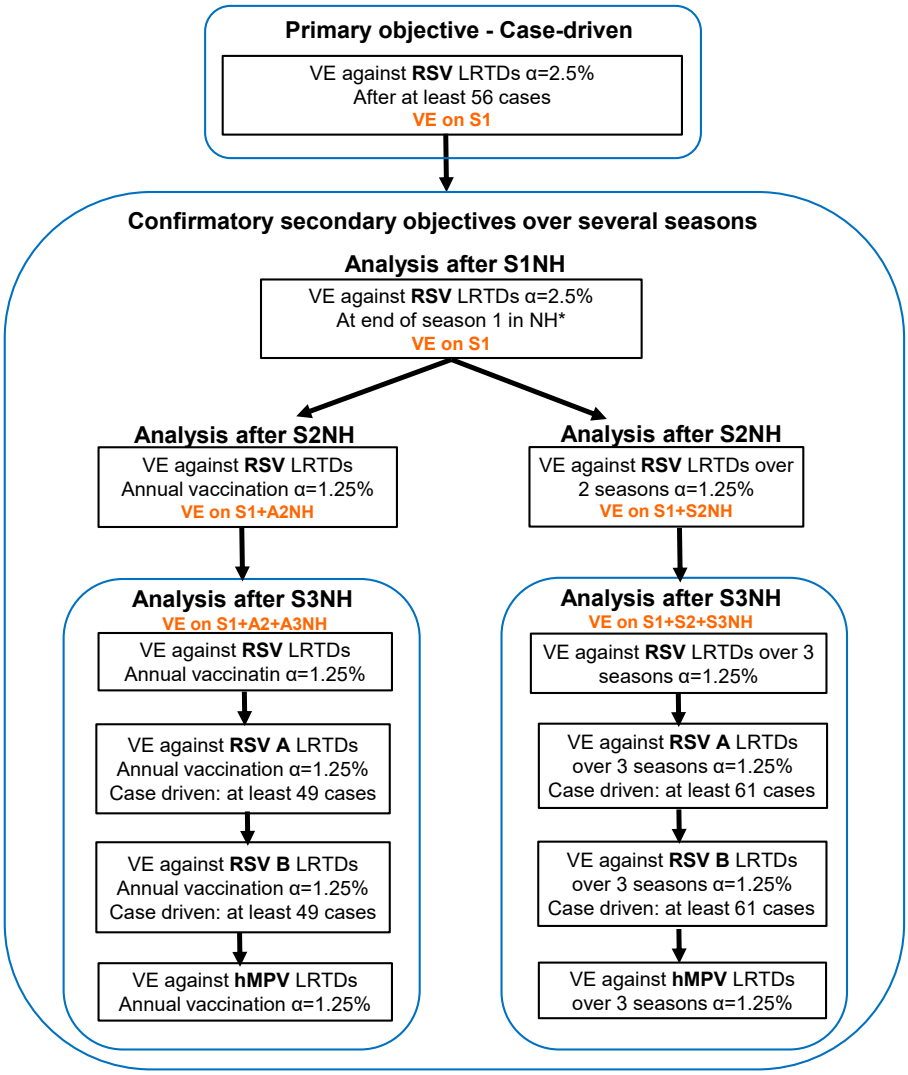
The confirmatory objectives will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 3). A Bonferroni adjustment of alpha for multiplicity will be applied to assess in parallel the VE of the annual revaccination (sequence on the left in Figure 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 revaccinations with 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 revaccinations with 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 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 revaccinations with 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%).
- The confirmatory secondary objective assessing VE of a single dose or annual revaccinations with RSVPreF3 OA vaccine in the prevention of hMPV-confirmed

LRTD after Season 3 in NH will be evaluated conditionally to the success of the RSV objective for each RSV subtype (A and B) after Season 3 (see Figure 3). The efficacy will be demonstrated if the LL of the two-sided 97.5% CI of VE is above 20%.

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 revaccination)
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 ($\alpha 1$) and the final ($\alpha 2$) 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:

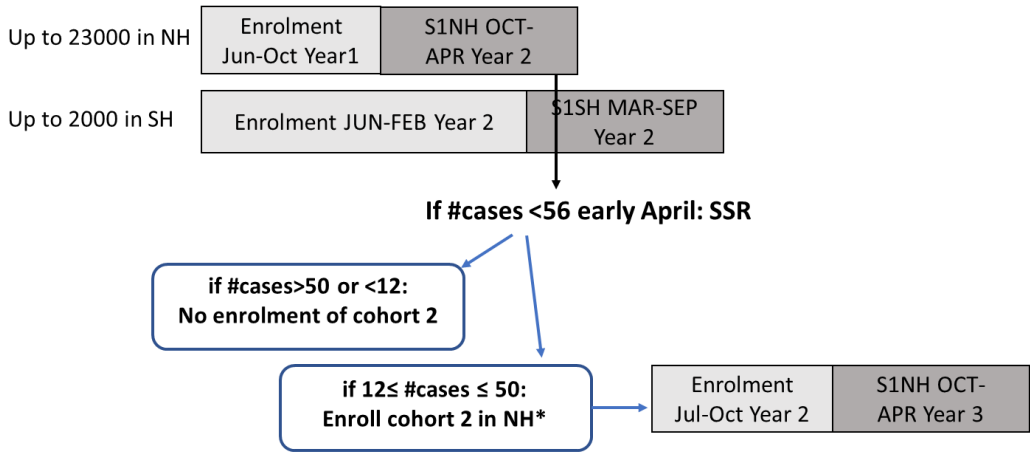
- If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed as described in section 8.1 .
- If the total number of cases is included in [12, 50 cases]: Enrollment of a second cohort. In 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 (α1) and the final (α2) 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 study team. Further details of this approach can be found in the firewall charter.

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

5. **VE Analysis 4:** after at least 3 seasons in NH and 2 seasons in SH (End of Study)

   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 3 (Dated: 24 January 2022) 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 sections 6.2.2.1 and 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).
- In the immunogenicity analysis: the mean geometric increase will be generated instead of the distribution of fold increase (see section 6.3.1.2).
- Summary tables of unsolicited adverse events and SAEs/pIMDs will be generated by SOC, HLT and PTs.
- Related SAEs/pIMDs ad Fatal SAEs will be tabulated after each dose.
- ***Analysis sets section have been adapted to define the mES by dose and to remove the specific mES defined by season/by year (section 5.1).***
- ***Analysis by year in section 6.3.1 have been updated to remove: "excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1 (Year 2)".***

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 within the 4-day period:

- The duration of the event will be calculated as the sum of the individual days with the event reported as grade 1 or higher, or reported as missing during the solicited event period (see section 12.1.2.3 for missing data). For grade 3, the duration will be calculated as the sum of individual days with the event reported as grade 3 or reported as missing during the solicited event period.

For the duration of solicited AEs ongoing beyond the 4-day period:

- The duration of the event will be calculated as the difference between the start (during the solicited period) and end date (if known) plus one day regardless of the intensity. For grade 3, the entire duration of symptoms with a maximum intensity equal to grade 3 will be considered.

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 [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***-RSV*** 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) [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 Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	2 (1.5<=RR<2.5)
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
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 CCI [redacted] (score=1), has CCI [redacted] (score=1), CCI [redacted] (score=1), CCI [redacted] (score=2) and CCI [redacted] (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
	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)

Domain	Component Questions
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 SAS code for the end of study analysis is:

```
  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 RSV Annual" intercept 1 group 1 0 0;
      ESTIMATE "Day 1 - Day 7 RSV 1 dose" intercept 1 group 0 1 0;
      ESTIMATE "Day 1 - Day 7 Placebo" intercept 1 group 0 0 1;
      ESTIMATE "Day 1 - Day 7 RSV annual-Placebo Diff" group 1 0 -1;
      ESTIMATE "Day1 - Day7 RSV 1 dose - Placebo Diff" group 0 1 -1;
RUN;
```

Where group= vaccination group (=0 for RSV annual, =1 for RSV 1 dose, =2 for Placebo), 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 day=_day and group ne _group and _group=2;
RUN;
```

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. Duration of events

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

Refer also to section 10.2.2 for specific rules used to compute the duration of solicited events.

12.1.3.10. 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.

12.1.3.11. 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].

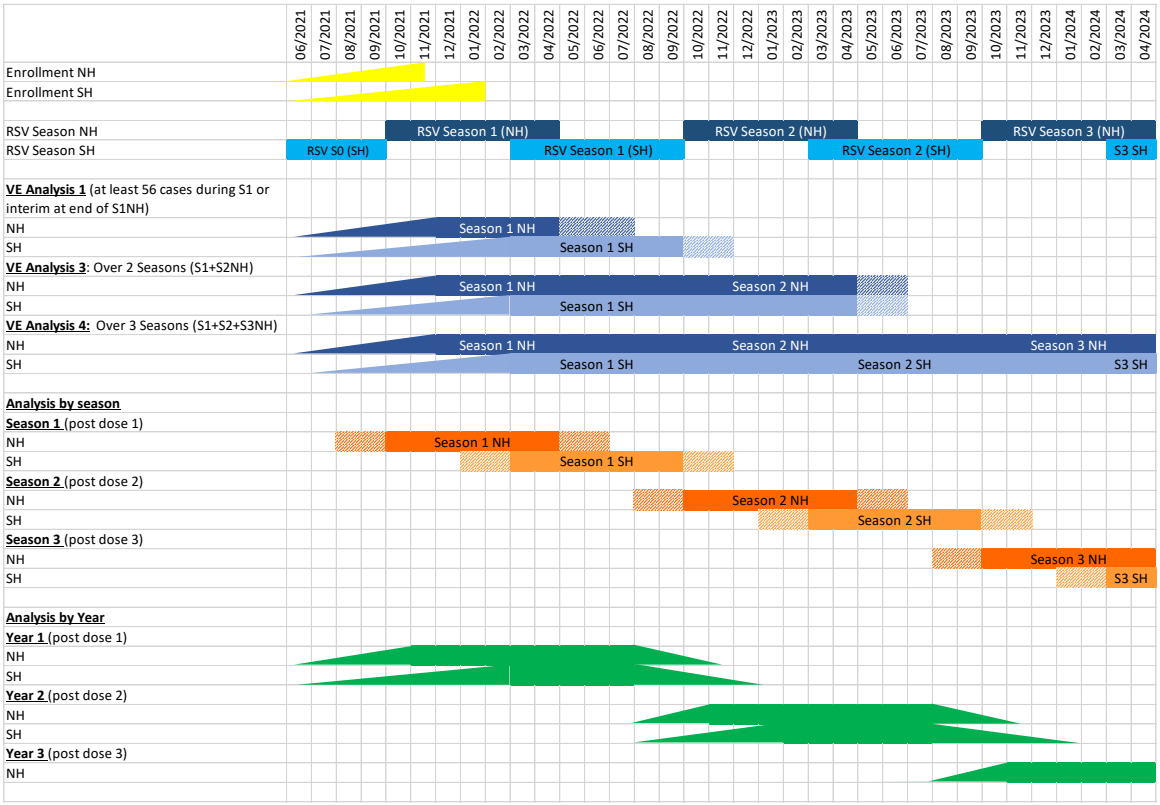
12.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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.

13. REFERENCES

Borgan Ø., Langholz B., Samuelsen S.O., et al. Exposure stratified case-cohort designs. *Lifetime Data Analysis.* 2000; 6, 39–58.

Chan ISF., Bohidar N.R., Exact power and sample size for vaccine efficacy studies. *Communications in Statistics - Theory and Methods* 1998; 27: 1305-22.

Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chrin Dis* 1987; 40(5), 373-383.

Clopper C.J., Pearson E., The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Cox, D. R. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. Series B (Methodological), 1972; 34: 187–220.

Dragalin V., Fedorov V. and Cheuvart B., Statistical approaches to establishing vaccine efficacy, *Statistics in Medicine* 2002; 21: 877-893.

Lachin, J. M., Biostatistical methods: the assessment of relative risks, *John Wiley & Sons* 2011; 807

Lievens et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children'. *Malaria* journal 2011.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

Quan H., Li B., Couris C.M., Fushimi K., Graham P., Hider P., Januel J-M., Sundararajan V., Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries, *American Journal of Epidemiology* 2011; 173 (6).

Tang M.I. and Hon Keung Tony, Letter to the Editor, Comment on: Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method, *Statistics in Medicine*; 2004; 23: 685-693

Wang S.K and Tsiatis A.A. Approximately Optimal One Parameter Boundaries for Group Sequential Trials. Biometrics. 1987; 43: 193–199.

Wang Y., Rosenberger W.F. Randomization-based interval estimation in randomized clinical trials. *Statistics in medicine* 2020; 39(21): 2843-2854. DOI: 10.1002/sim.8577.

Statistical Analysis Plan

Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose 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 3 Final: 12 May 2022

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

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Infection
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

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 annual revaccination doses in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons. ***Criterion: The LL of the 2-sided CI for VE is above 20%.***	***First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.***
To demonstrate the efficacy of a single dose and annual revaccination doses of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons. ***Criterion: The LL of the 2-sided CI for VE is above 0%.***	***First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.***
To demonstrate the efficacy of a single dose and annual revaccination doses of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA over 3 seasons. ***Criterion: The LL of the 2-sided CI for VE is above 20%.***	***First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.***

Objectives	Endpoints
Other secondary descriptive	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.	***First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.***
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by season in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by season.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by year in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by year.
To evaluate the 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 doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by baseline frailty status in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by 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 doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of any ARI and any LRTD in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of ARI or LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalization due to respiratory diseases during the RSV seasons† in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons†. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI during the RSV seasons† in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Estimated Least Squares mean EQ-5D utility score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.

Objectives	Endpoints
To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Estimated Least Squares mean SF-12 Physical Functioning score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
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-Dose 3 (***pre-Season 3***)***: • RSVPreF3 IgG-specific antibody concentrations. • Neutralizing antibody titers against RSV A. • Neutralizing antibody titers against RSV B.
Secondary – Safety	
To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine.	In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after ***each*** vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after ***each*** vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from ***the day of vaccination*** up to 6 months ***after each***-vaccination. • Occurrence of all pIMDs from ***the day of vaccination*** up to 6 months ***after each*** vaccination. • Occurrence of SAEs related to study vaccination from Day 1 up to study end. • Occurrence of pIMDs related to study vaccination from Day 1 up to study end. • Occurrence of any fatal SAEs from Day 1 up to study end.
Tertiary	
Tertiary – Efficacy	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV and/or hMPV-confirmed LRTD in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV and/or hMPV-associated LRTD, according to the case definition*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe hMPV-confirmed LRTD in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed hMPV-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI for each RSV subtype (A and B) separately in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by season***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.
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 doses***.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of all-cause mortality during the RSV seasons† in adults ≥ 60 YOA***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Occurrence of any death during the RSV seasons†.
To estimate the proportion of participants with > 1 case of ARI or LRTD by season and participants reporting respiratory diseases in consecutive seasons***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Number of participants with > 1 case of ARI, LRTD, RT-PCR-confirmed RSV A and/or B-associated ARI and RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definitions* by season and in consecutive seasons.
To estimate the proportion of co-infections with other viral pathogens for RSV-confirmed or hMPV-confirmed ARI cases***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Number of participants with other viral pathogens (detected by RT-PCR) co-existing with RSV or hMPV among RT-PCR-confirmed RSV or RT-PCR-confirmed hMPV ARI episodes.

Objectives	Endpoints
To evaluate the impact of the RSVPreF3 OA investigational vaccine on upper respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the Placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Maximum FLU-PRO upper respiratory symptom score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To assess the impact of the RSVPreF3 OA investigational vaccine on healthcare resource utilization (HCRU) for participants with RSV-confirmed ARI and any ARI***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	• Hospitalization rate during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*. • Antibiotic use during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on patient-reported severity of respiratory symptoms in participants with RSV-confirmed LRTD in the RSVPreF3 groups compared to the Placebo group***, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses***.	Maximum patient global impression of severity (PGI-S) score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated LRTD.
Tertiary - Immunogenicity and Safety	
To assess the correlation of the humoral immune response to the RSVPreF3 OA investigational vaccine at 30 days post-***Dose 1*** with protection against RSV disease.	RSVPreF3 IgG-specific antibody concentrations at pre-***Dose 1*** (Day 1) and 30 days post-***Dose 1*** (Day 31) in all participants with RSV disease compared to a subset of controls.‡
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-***Dose 1*** (Day 1), 30 days post-***Dose 1*** (Day 31), ***pre-Dose 2 (***pre-Season 2***)*** and ***pre-Dose 3 (***pre-Season 3***)***: • RSVPreF3 IgG-specific antibody concentrations classified by baseline frailty score. • Neutralizing antibody titers against RSV A classified by baseline frailty score. • Neutralizing antibody 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.

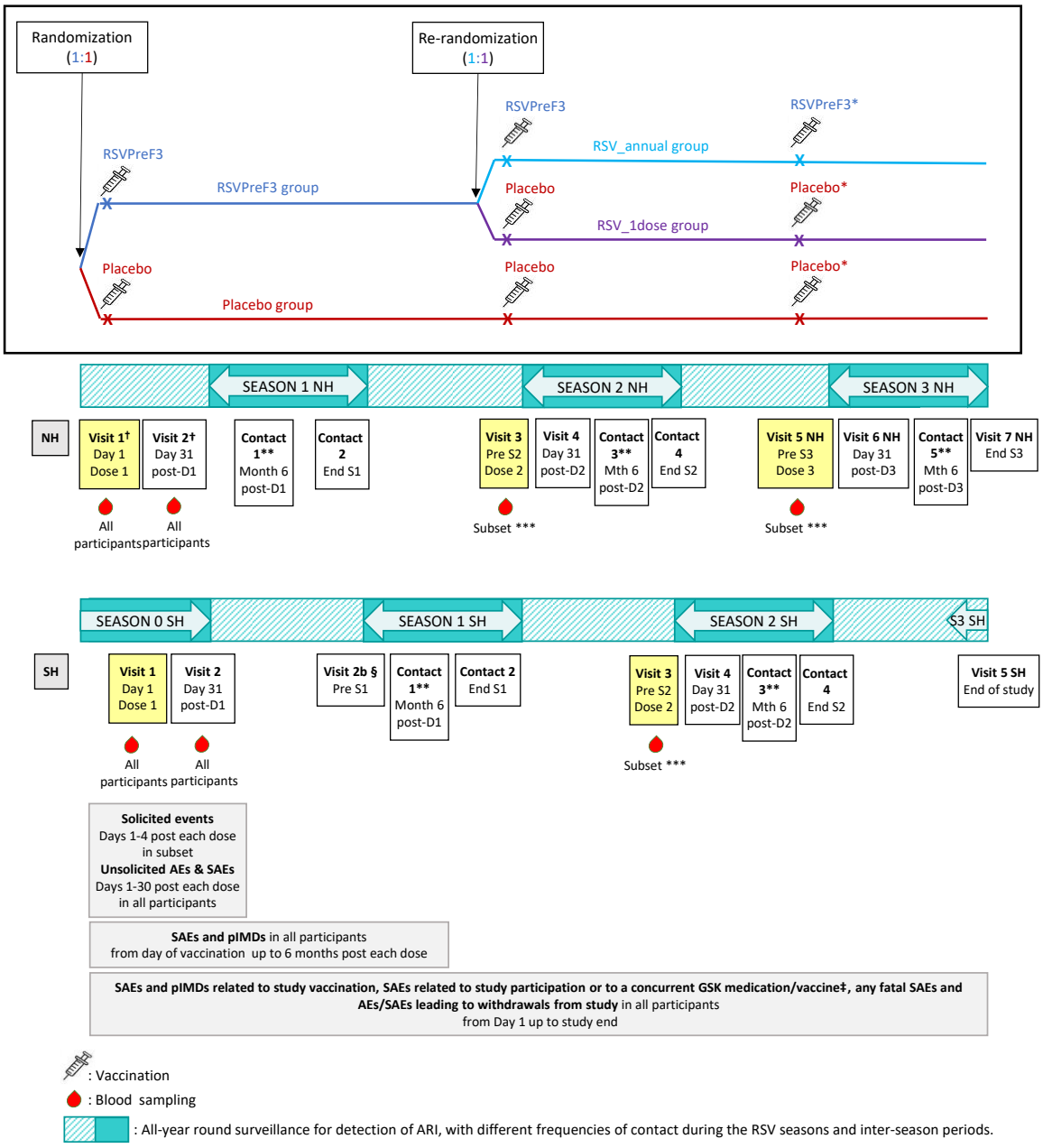
* Case definitions are described in Section 4

† 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.

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 6.3.1 of 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 infection; 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.
** Contact***s*** 1***, 3 and 5*** must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months ***after each*** vaccination for each participant. ***These*** contact***s*** 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.

- **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 RSVPreF3 lots 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.

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.
- **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 doses							
RSV_L1_annual	***Up to 5 750***	***375-500***	***Up to 6 250***	***≥ 60 years***	***RSVPreF3 OA investigational vaccine***		***X***
RSV_L2_annual							***X***
RSV_L3_annual							***X***
RSV_L4_annual							***X***
RSV_L1_1dose	***Up to 5 750***	***375-500***	***Up to 6 250***	***≥ 60 years***	***Placebo***		***X***
RSV_L2_1dose							***X***
RSV_L3_1dose							***X***
RSV_L4_1dose							***X***
Placebo	***Up to 11 500***	***750-1 000***	***Up to 12 500***	***≥ 60 years***	***Placebo***		***X***
Total	***Up to 23 000***	***1 500-2 000***	***Up to 25 000***				

NH: Northern hemisphere; SH: Southern hemisphere; L1: Lot 1; L2: Lot 2; L3: Lot 3; L4: Lot 4
* Numbers are approximate (see Section 9.2.1 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 will receive 2 additional doses, 1 before Season 2 and 1 before Season 3.***
  - ***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. This period might be extended, i.e., starting few months earlier and/or ending few months later, in case a shift in the peak incidence of seasonal viruses due to special circumstances (e.g., COVID-19 pandemic) is observed in the national surveillance systems and/or in epidemiological studies.
- **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).
  - In **RSV_annual**, **RSV_1dose** and **Placebo** groups for analysis after dose 2 and dose 3 (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	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
Dose 2/ Dose 3	RSV_L1_annual	NA	**RSV_annual**	1	Participants receiving annual revaccinations 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)

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
	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
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. 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

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

Endpoint	Case definition
severe hMPV LRTD – Definition 1 "Clinical symptomology"[5]	• 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]
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 infection; 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.

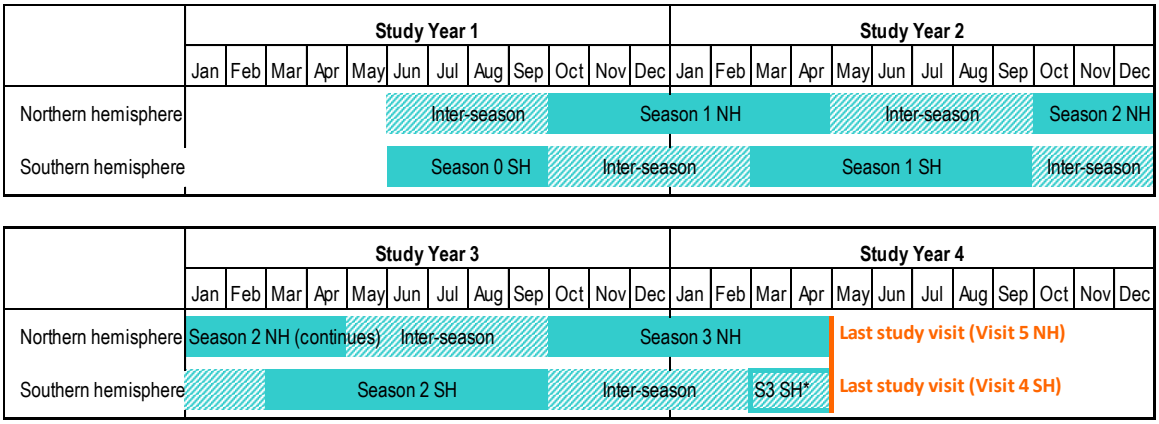
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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 data obtained at VE Analysis 1, the ARI surveillance could be adapted for the 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 4 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.

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

- **Modified Exposed Set (mES) - *RSV*:** the mES-***RSV*** 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 – hMPV: the mES-hMPV will be the primary population for efficacy analysis on hMPV-confirmed cases. It will include all participants from the ES who did not report a hMPV-confirmed ARI prior to Day 15 after each vaccination.***
- Additional specific mES will be defined including all participants who received the study intervention and who did not report an RSV-confirmed ARI prior to the start of the case count depending on the analysis to be performed, i.e analysis by season/by year (see Table 7).
- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): 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,
  - have data available for efficacy endpoint measures,
  - did not have any protocol deviations leading to exclusion.

As for the mES, two PPSe will be defined: one for RSV endpoints and one for hMPV endpoints.

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

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

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 (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,

- codes 2510 to 2550 will be used to eliminate participants from specific mES for analyses by season and by year (see Table 5).
- Code 1071 will be used to eliminate participants who did not receive Dose 2 or Dose 3 for analysis on ES and mES post-Dose 2 and post-Dose 3 (see Table 5).
- Code 2700 will be used to eliminate participants who report a hMPV-confirmed ARI case prior to Day 15 after vaccination from mES-hMPV cohort.

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, 900, 1030, 1050,1060 and 2600: participants will be eliminated for all visits.
- For codes 1040, 1070, 1071, 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 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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	All	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 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.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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	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: • Participants who did not accept to be revaccinated for any reason • Participants who withdrew before dose 2/dose 3	Visit 3, Visit 5NH	ES, mES, PPSe, PPSi
1080	Vaccine administration after a Temperature deviation	Visit 1, Visit 3, Visit 5NH	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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 prior to the study vaccine administration or planned administration	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	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
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination and visit 2 blood sample is outside [28-42] days. For participants in the immunogenicity subset: • Date of BS at Pre-season 2 (Visit 3) is outside [15Aug-30Sep] in NH, or outside [15Jan-28Feb] in SH • Date of BS at Pre-season 3 (Visit 5 NH) is outside [15Aug-30Sep]	Visit 2, Visit 3, Visit 5NH	PPSi
2100	For participants in the immunogenicity subset: 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 vaccination:	ARI visit	mES-RSV*, PPSe-RSV

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	• Number of days between vaccination and day of onset of ARI case < 14 days		
2510**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 1	ARI visit	mES-season 1
2520**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 2	ARI visit	mES-season 2
2530**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 3	ARI visit	mES-season 3
2540**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of year 2	ARI visit	mES-year 2
2550**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of year 3	ARI visit	mES-year 3
2600	Participants not included in the reactogenicity and immunogenicity subset	Visit 1	Solicited safety set, PPSi
2700**	Participant who reports a hMPV-confirmed ARI case prior to Day 15 after vaccination: • Number of days between vaccination and day of onset of ARI case < 14 days	ARI visit	mES-hMPV, PPSe-hMPV

*Applicable for the mES-RSV and all the specific mES-RSV for by season and by year analyses (mES-season 1, mES-season 2, mES-season 3, mES-year 2, mES-year 3)
** codes 2500 to 2550 and 2700 are not considered as protocol deviations, but those codes will be used to eliminate participants from specific 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-RSV, mES-hMPV, PPSe-RSV, PPSe-hMPV, 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-***RSV***. In addition, a second analysis will be performed on the PPSe and on the ES to complement the primary analysis.

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

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

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

During the surveillance period, all events related to the efficacy endpoints will be collected (see Section 8.1.1 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 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-RSV.**

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 ***(mES-RSV or mES-hMPV depending on the endpoints)*** or on the specific mES as applicable (see 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 6.3.2.1.3).

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

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 (VE Analysis 3 and 4), the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

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 annual revaccination doses:

<u>Confirmatory objective</u>

- VE against RSV-confirmed LRTD over several 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 hMPV-confirmed LRTD over 3 seasons. This will be evaluated after 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.***

<u>Other secondary descriptive objectives</u>

- VE against RSV-confirmed LRTD by RSV subtype: on RSV-A and RSV-B qRT-PCR-confirmed cases separately.
- VE against hMPV-confirmed LRTD.
- 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 and after Day 15 post-Dose 1;
  - 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;
  - VE during Season 3 in NH and SH (partial Season 3 in SH), including first occurrence of cases reported during Season 3 and after Day 15 post-Dose 3 in NH, and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 3.

  The time at risk for the analysis by season will be the period from the start of the corresponding season 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 Dose 3 administration in NH, and up to 12 months post-Dose 2 in SH, and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases reported from Day 15 post-Dose 3 in NH up to study end, and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1 and/or Year 2.
- 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 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 number of days with solicited events with an onset during the 4-day follow-up period will be tabulated ***after each dose*** for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for 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).

- 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 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.

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 pre-Seasons 1 and 2 will be presented for the mES***-RSV.***

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 annual revaccination doses.

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 on Day 15 post-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 after season 1 in NH, 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 in NH (VE Analysis 2).

For analysis over 2 and 3 seasons, the VE analysis will include participants who received the 2 or the 3 doses respectively, and the following groups will be compared:

- **RSV_annual group versus Placebo group** to demonstrate VE of annual revaccination after season 2 (S1+A2NH) and after season 3 (S1+A2+A3NH).
- **RSV_1dose versus Placebo group** to demonstrate VE of one single dose after season 2 (S1+S2NH) and after season 3 (S1+S2+S3NH).

Table 6 below describes the data that will be included in each analysis.

Table 6 Description of data to be included in VE analysis over several seasons

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: form Day 15 post-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 Day 15 post-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 4 (EoS)	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 Day 15 post-Dose 2 up to Visit 5NH (Pre-Dose 3) in NH or up to start of season 3 in SH for all participants who received 2 doses in RSV_annual group or in Placebo group (A2) + Data collected during the third season: from Day 15 post-Dose 3 up to study end for participants in NH who received 3 doses in RSV_annual group or in Placebo group (A3NH)
	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 Day 15 post-Dose 2 up to Visit 5NH (Pre-Dose 3) in NH or up to study end 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 Day 15 post-Dose 3 up to study end for participants in NH who received 3 doses in RSV_1dose group or in Placebo group (S3NH)

S1/S2/S3 = Seasons 1/2/3; A2/A3=Annual evaluation during season 2/3
NH= Northern Hemisphere; SH= Southern Hemisphere.

- VE by season: For the VE analysis by season, 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	
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:

- 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: 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.

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	End date 1 for case count and FU time	Participants to be excluded from analysis	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-vaccination	Age, region	mES, PPSe, ES[3]
End of season 1 in NH (VE analysis 2)	Season 1	Day 15 post-Dose 1	End of season 1 in NH for all participants (NH and SH)	RSV cases before Day 15 post-vaccination	Age, region	mES, PPSe, ES[3]
Over 2 seasons: S1+A2NH/S2NH (VE analysis 3)	Season 1 (S1)	Day 15 post- Dose 1	Visit 3 (Pre-Dose 2)	RSV cases before Day 15 post-vaccination	Age, region, season	mES PPSe, ES
	Season 2 (A2NH/S2NH)	Day 15 post- Dose 2	End of season 2 in NH for all participants (NH and SH)			
Over 3 seasons S1+A2/S2+A3NH/S3NH (VE analysis 4)	Season 1 (S1)	Day 15 post Dose 1	Visit 3 (Pre-Dose 2)	RSV cases before Day 15 post-vaccination	Age, region, season	mES PPSe, ES
	Season 2 (A2)	Day 15 post-Dose 2	Visit 5NH (Pre-Dose 3) in NH or start of season 3 in SH			
	Season 2 (S2)	Day 15 post dose 2	Visit 5NH (Pre-Dose 3) in NH or end of study in SH			
	Season 3 (A3NH/S3NH)	Day 15 post dose 3	End of study in NH			
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 the start of season 1	Age, region	mES – season 1
	Season 2	Start of season 2, after Day 15 post-Dose 2	End of season 2 in NH and SH	RSV cases before the start of season 2	Age, region	mES – season 2
	Season 3	Start of season 3, after Day 15 post-Dose 3	End of season 3 in NH and end of study for SH	RSV cases before the start of season 3	Age, region	mES – season 3

VE analysis	Time period	Start date 1 for Cases count and FU time	End date 1 for case count and FU time	Participants to be excluded from analysis	Model Covariates	Analysis Set
By Year	Year 1	Day 15 post-Dose 1	Visit 3 (Pre-Dose 2)	RSV cases before Day 15 post-Dose 1	Age, region, season	mES
	Year 2	Day 15 post-Dose 2	12 months post-Dose 2 in SH, Visit 5NH (Pre-Dose 3)	RSV cases before Day 15 post-Dose 2	Age, region, season	mES – Year 2
	Year 3	Day 15 post-Dose 3	EoS in NH	RSV cases before Day 15 post-Dose 3	Age, region, season	mES – Year 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 2 or 3.
[4]EoS= End of study visit, i.e., Visit 5NH or Visit 4SH.

Visual representation of the time periods for each analysis is also presented in Figure 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 2, 3 and 4 will be tabulated by group.

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 time of VE Analysis 2, 3 or 4 or until withdrawal date if before the efficacy data lock point.

- **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.

    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 S2 and S3, a sensitivity analysis will be performed considering the cases during the S1 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).***

- **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 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

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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.

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 groups
- Post-Dose 2: RSV_annual versus Placebo groups
- Post-Dose 3: RSV_annual versus Placebo groups, in NH

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 post-vaccination, presented by MedDRA Primary System Organ Class (SOC), 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 2001]
- 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 [Leidos Biomedical research 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: CCI [redacted] CCI [redacted] 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 CCI to 4 CCI.

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 CCI to 4 CCI CCI

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 Sections 6.2 and 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 annual revaccination doses***:

- VE against RSV and/or hMPV-confirmed LRTDs,
- 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) and 1 month post-***Dose 1*** (Day 31) 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.

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 any ARI and any 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.

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.

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 revaccinations with 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 revaccinations with 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 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 revaccinations with 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:***

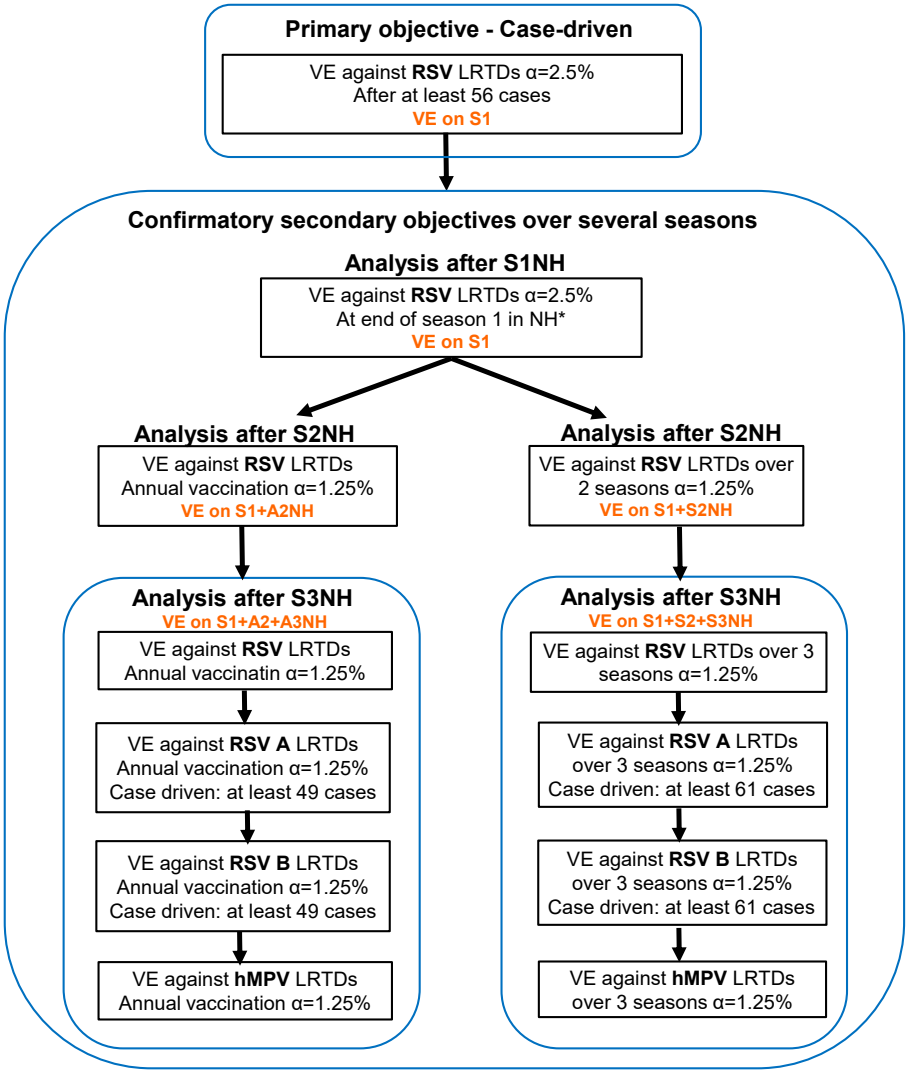
  - ***For VE of a single dose: at least 61 cases are needed to have at least 90% power to demonstrate a significant VE (LL of 97.5% CI >0%);***

  - ***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%).***

- ***The confirmatory secondary objective assessing VE of a single dose or annual revaccinations with RSVPreF3 OA vaccine in the prevention of hMPV-confirmed LRTD after Season 3 in NH will be evaluated conditionally to the success of the RSV objective for each RSV subtype (A and B) after Season 3 (see Figure 3). The efficacy will be demonstrated if the LL of the two-sided 97.5% CI of VE is above 20%.***

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 revaccination)
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 ($\alpha 1$) and the final ($\alpha 2$) 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:

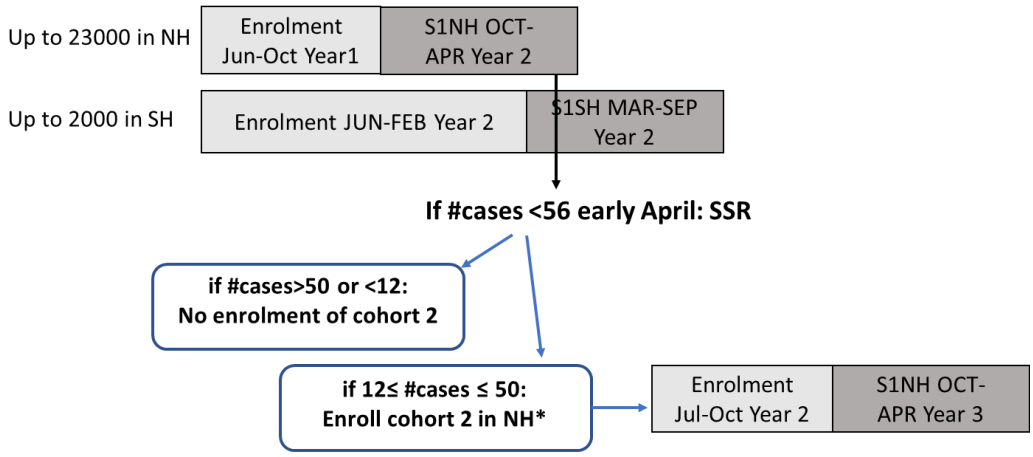
- If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed ***as described in section 8.1 .***
- If the total number of cases is included in [12, 50 cases]: Enrollment of a second cohort. 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 (α1) and the final (α2) 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 study team. Further details of this approach can be found in the firewall charter.

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

5. **VE Analysis 4:** after at least 3 seasons in NH and 2 seasons in SH (End of Study)

   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 3 (Dated: 24 January 2022) 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 sections 6.2.2.1 and 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).
- In the immunogenicity analysis: the mean geometric increase will be generated instead of the distribution of fold increase (see section 6.3.1.2).
- Summary tables of unsolicited adverse events and SAEs/pIMDs will be generated by SOC, HLT and PTs.
- Related SAEs/pIMDs ad Fatal SAEs will be tabulated after each dose.

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 within the 4-day period:

- The duration of the event will be calculated as the sum of the individual days with the event reported as grade 1 or higher, or reported as missing during the solicited event period (see section 12.1.2.3 for missing data). For grade 3, the duration will be calculated as the sum of individual days with the event reported as grade 3 or reported as missing during the solicited event period.

For the duration of solicited AEs ongoing beyond the 4-day period:

- The duration of the event will be calculated as the difference between the start (during the solicited period) and end date (if known) plus one day regardless of the intensity. For grade 3, the entire duration of symptoms with a maximum intensity equal to grade 3 will be considered.

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 [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***-RSV*** 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) [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 Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	2 (1.5<=RR<2.5)
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
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 CCI (score=1), CCI CCI (score=1), CCI (score=1), CCI (score=2) and CCI CCI (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
	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 SAS code for the end of study analysis is:

```
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 RSV Annual" intercept 1 group 1 0 0;
    ESTIMATE "Day 1 - Day 7 RSV 1 dose" intercept 1 group 0 1 0;
    ESTIMATE "Day 1 - Day 7 Placebo" intercept 1 group 0 0 1;
    ESTIMATE "Day 1 - Day 7 RSV annual-Placebo Diff" group 1 0 -1;
    ESTIMATE "Day1 - Day7 RSV 1 dose - Placebo Diff" group 0 1 -1;
RUN;
```

Where group= vaccination group (=0 for RSV annual, =1 for RSV 1 dose, =2 for Placebo), 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 day=_day and group ne _group and _group=2;
RUN;
```

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. Duration of events

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

Refer also to section 10.2.2 for specific rules used to compute the duration of solicited events.

12.1.3.10. 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.

12.1.3.11. 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].

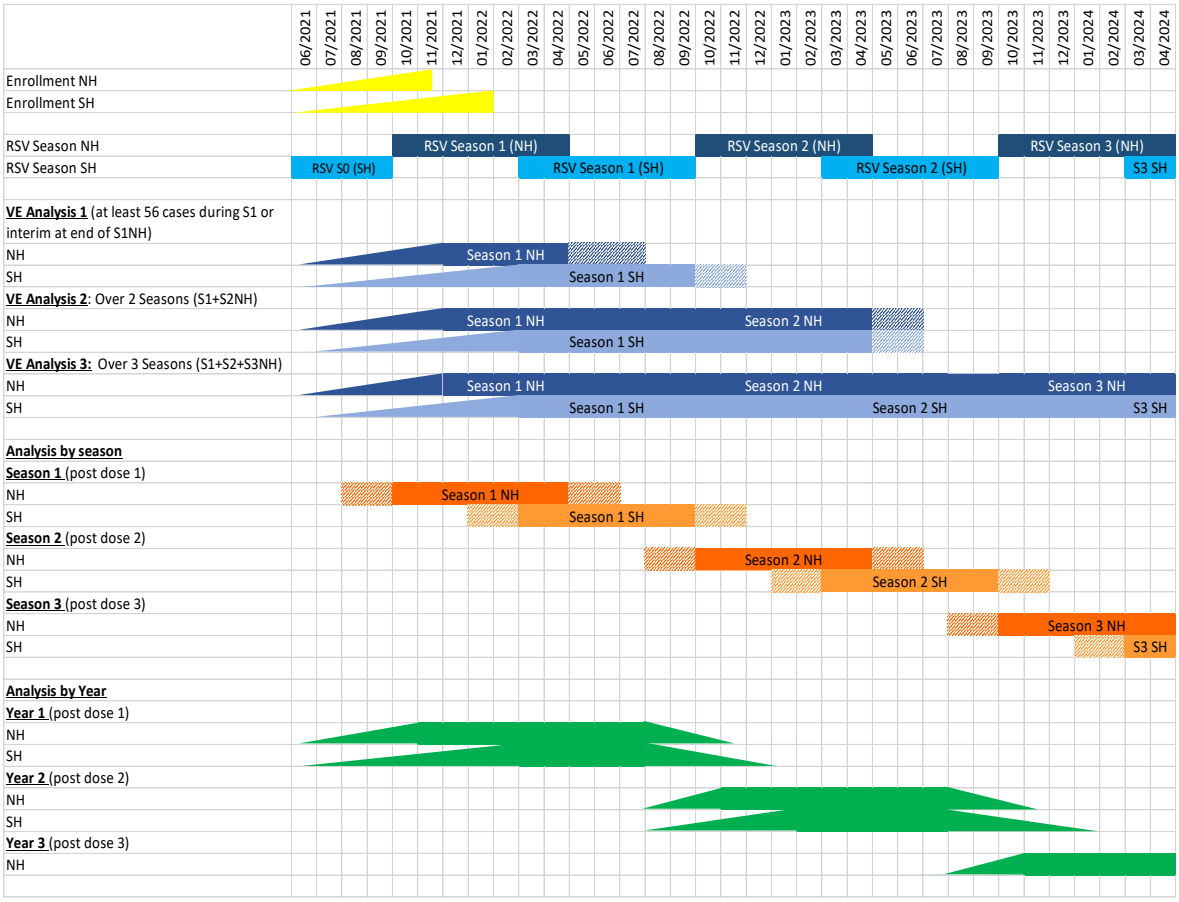
12.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

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.

13. REFERENCES

Borgan Ø., Langholz B., Samuelsen S.O., et al. Exposure stratified case-cohort designs. *Lifetime Data Analysis.* 2000; 6, 39–58.

Chan ISF., Bohidar N.R., Exact power and sample size for vaccine efficacy studies. *Communications in Statistics - Theory and Methods* 1998; 27: 1305-22.

Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chrin Dis* 1987; 40(5), 373-383.

Clopper C.J., Pearson E., The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Cox, D. R. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. Series B (Methodological), 1972; 34: 187–220.

Dragalin V., Fedorov V. and Cheuvart B., Statistical approaches to establishing vaccine efficacy, *Statistics in Medicine* 2002; 21: 877-893.

Lachin, J. M., Biostatistical methods: the assessment of relative risks, *John Wiley & Sons* 2011; 807

Lievens et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children'. *Malaria* journal 2011.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

Quan H., Li B., Couris C.M., Fushimi K., Graham P., Hider P., Januel J-M., Sundararajan V., Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries, *American Journal of Epidemiology* 2011; 173 (6).

Tang M.I. and Hon Keung Tony, Letter to the Editor, Comment on: Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method, *Statistics in Medicine*; 2004; 23: 685-693

Wang S.K and Tsiatis A.A. Approximately Optimal One Parameter Boundaries for Group Sequential Trials. Biometrics. 1987; 43: 193–199.

Wang Y., Rosenberger W.F. Randomization-based interval estimation in randomized clinical trials. *Statistics in medicine* 2020; 39(21): 2843-2854. DOI: 10.1002/sim.8577.

Statistical Analysis Plan

Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose 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 2 Final: 08 Mar 2022

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

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Infection
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 Mar 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

2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the efficacy 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 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*.
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.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category.	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.	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.	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 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.	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.	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.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA.	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 hMPV-confirmed LRTD in adults ≥ 60 YOA.	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 any ARI and any LRTD in adults ≥ 60 YOA.	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 during the RSV seasons† in adults ≥ 60 YOA.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons†. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI during the RSV seasons† in adults ≥ 60 YOA.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition*.
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.	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.	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.	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.	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-vaccination (Day 1), 30 days post- vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations. • Neutralizing antibody titers against RSV A. • Neutralizing antibody titers against RSV B.

Objectives	Endpoints
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 vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from Day 1 up to 6 months post-vaccination. • Occurrence of all pIMDs from Day 1 up to 6 months post-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**.**	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 severe hMPV-confirmed LRTD in adults ≥ 60 YOA.	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 hMPV-confirmed ARI in adults ≥ 60 YOA.	First occurrence of RT-PCR-confirmed hMPV-associated ARI, 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.	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.	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.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.
To evaluate the evolution of efficacy of 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*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA by baseline comorbidities.	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.	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.	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.	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.	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.	• 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.	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-vaccination with protection against RSV disease.	RSVPreF3 IgG-specific antibody concentrations at pre-vaccination (Day 1) and 30 days post-vaccination (Day 31) in all participants with RSV disease compared to a subset of controls.‡
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-vaccination (Day 1), 30 days post-vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations classified by baseline frailty score. • Neutralizing antibody titers against RSV A classified by baseline frailty score. • Neutralizing antibody titers against RSV B by baseline frailty score.

Objectives	Endpoints
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 vaccination (i.e., the day of vaccination and 3 subsequent days) classified by baseline frailty score.

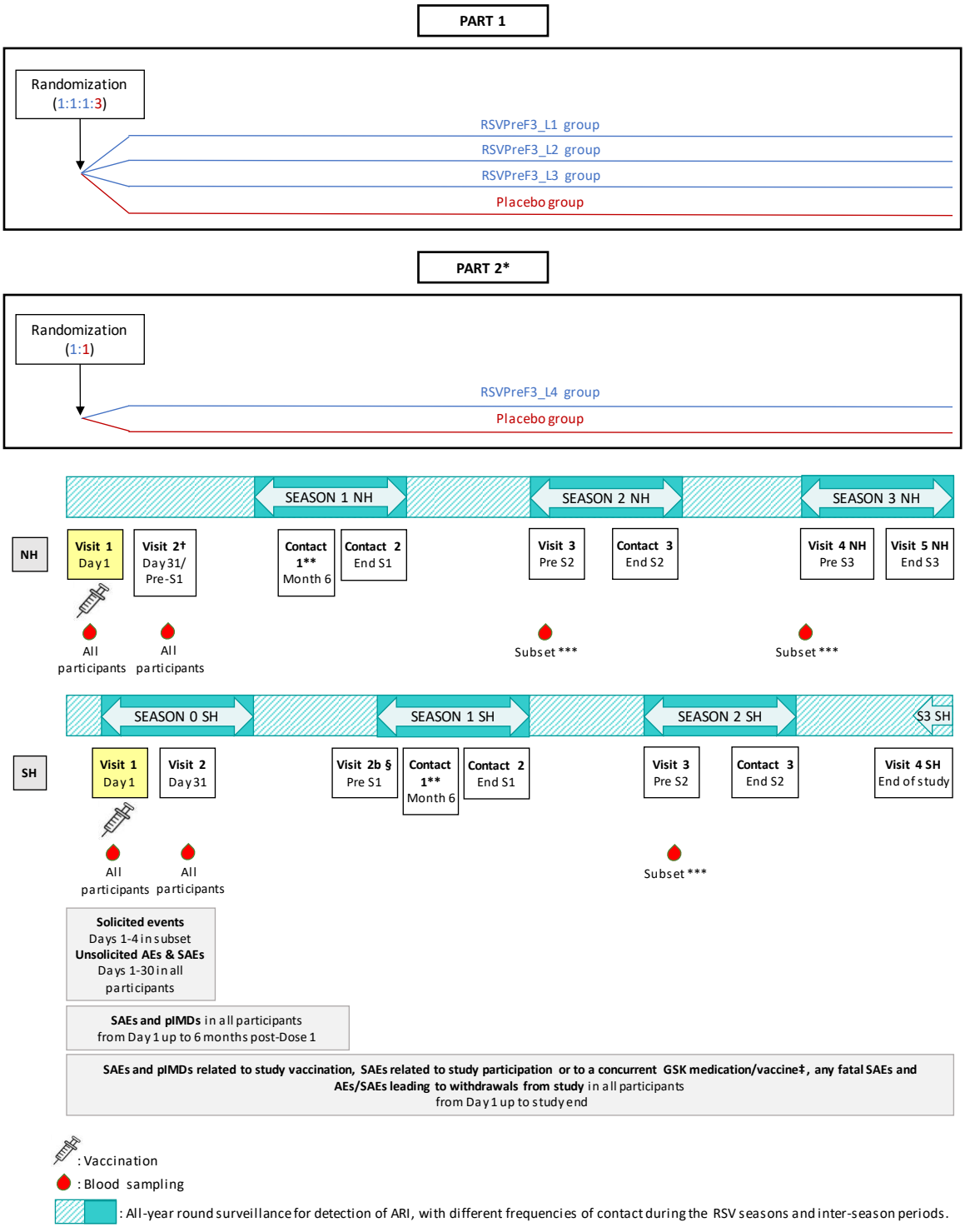
* Case definitions are described in Section 4.

† 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.

3. STUDY DESIGN

Figure 1 Study design overview



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.
AE: adverse event; ARI: acute respiratory infection; NH: Northern hemisphere; SH: Southern hemisphere;

pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
* Part 2 will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.
† Depending on the time of enrollment, Visit 1 and Visit 2 in NH can take place during Season 1.
** Contact 1 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months post-vaccination for each participant. This contact 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 study vaccine administration.

- **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.
- **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 enrolled in this cohort will follow the same study design as indicated in Figure 1. The participants in this additional cohort will be enrolled in 2 study groups (RSVPreF3 and Placebo) according to a 1:1 randomization ratio. 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.
- **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 5NH/Visit 4SH (Observer-blind)
RSVPreF3_L1	Up to 11 500**	750-1 000**	Up to 12 500**	≥ 60 years	RSVPreF3 OA investigational vaccine L1	X
RSVPreF3_L2				≥ 60 years	RSVPreF3 OA investigational vaccine L2	X
RSVPreF3_L3				≥ 60 years	RSVPreF3 OA investigational vaccine L3	X
RSVPreF3_L4				≥ 60 years	RSVPreF3 OA investigational vaccine L4***	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.

- **Vaccination schedule:** A single dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1.
- **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 day of vaccination [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. This period might be extended, i.e. starting few months earlier and/or ending few months later, in case a shift in the peak incidence of seasonal viruses due to special circumstances (e.g., COVID-19 pandemic) is observed in the national surveillance systems and/or in epidemiological studies.
- **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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for **RSVPreF3** group versus **Placebo** group using the pooled groups labels and definition in Table 2.

Table 2 Group names and definition for footnote in the TFLs

Group label	Group definition	Pooled Groups label in tables	Group order in tables	Pooled definition for footnote
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			
RSVPreF3_L4	Participants receiving RSVPreF3 OA investigational vaccine Lot 4			
Placebo	Participants receiving Placebo	**Placebo**	2	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	Female	Female
	2	Male	Male
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 ***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. 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 colspan="2">Case definition</th></tr>
<tr><td>ARI
(Trigger for swabbing)</td><td colspan="2">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</td></tr>
<tr><td></td><td>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]</td><td>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 colspan="2">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 colspan="2">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</td></tr>
<tr><td></td><td>Lower respiratory symptoms
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)</td><td>Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV-LRTD or hMPV-LRTD[5]</td><td colspan="2">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>
</table>

Endpoint	Case definition
RT-PCR-confirmed **severe** RSV LRTD or **severe** hMPV LRTD – Definition 1 "Clinical symptomology"[5]	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]
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 infection; 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 7
[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.

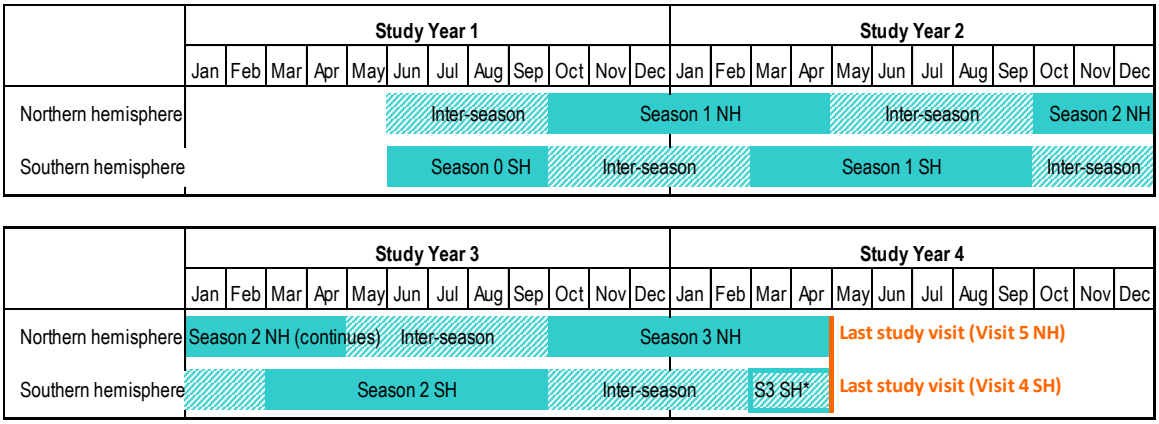
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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 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 data obtained at VE Analysis 1, the ARI surveillance could be adapted for the 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 4 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 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 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 the study intervention (Exposed Set) who have solicited safety data.

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

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 the study intervention and who did not report an RSV-confirmed ARI prior to Day 15 after vaccination. The allocation in a group is done in function of the administered intervention.
- Additional specific mES will be defined including all participants who received the study intervention and who did not report an RSV-confirmed ARI prior to the start of the case count depending on the analysis to be performed, i.e analysis by season/by year (see Table 6).
- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): hMPV-confirmed LRTD/ARI, 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 the study vaccine to which they were randomized,
  - have data available for efficacy endpoint measures,
  - 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 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).

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 (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, codes 2510 to 2550 will be used to eliminate participants from specific mES for analyses by season and by year (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, 900, 1030, 1050,1060, 2500 and 2600: participants will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2010, 2040, 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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	All	ES, mES*, PPSe, PPSi, SSS
1030	Study intervention not administered at all	All	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 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.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
1050	Randomization failure: participant not randomized in the correct group (To be attributed by unblinded Statistician only; Check SBIR, replacement, vaccine administration)	Visit 1	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	PPSe, PPSi
1080	Vaccine administration after a Temperature deviation	Visit 1	PPSe, PPSi
1090	Vaccine administration after expiration	Visit 1	PPSe, PPSi
1160	Participant included in the reactogenicity subset who did not document any post-vaccination solicited safety data	Visit 2	Solicited safety set
2010	Protocol deviation linked to inclusion/exclusion criteria	Visit 1	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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 prior to the study vaccine administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination and visit 2 blood sample is outside [28-42] days. For participants in the immunogenicity subset: • Date of BS at Pre-season 2 (Visit 3) is outside [15Aug-30Sep] in NH, or outside [15Jan-28Feb] in SH • Date of BS at Pre-season 3 (Visit 4 NH) is outside [15Aug-30Sep]	Visit 2, Visit 3, Visit 4NH	PPSi
2100	For participants in the immunogenicity subset: Serological results not available post-vaccination: No results available at all at the corresponding visit	Visit 2, Visit 3, Visit 4NH	PPSi
2120	Obvious incoherence/abnormality or error in laboratory data	Visit 2, Visit 3, Visit 4NH	PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
2500	Participant who report a RSV-confirmed ARI case prior to Day 15 after vaccination: • Number of days between vaccination and day of onset of ARI case < 14 days	ARI visit	mES*, PPSe
2510**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 1	ARI visit	mES-season 1
2520**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 2	ARI visit	mES-season 2
2530**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of season 3	ARI visit	mES-season 3
2540**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of year 2	ARI visit	mES-year 2
2550**	Participant who report a RSV-confirmed ARI case from Day 15 post vaccination up to the start of year 3	ARI visit	mES-year 3
2600	Participants not included in the reactogenicity and immunogenicity subset	Visit 1	Solicited safety set, PPSi

*Applicable for the mES and all the specific mES for by season and by year analyses (mES-season 1, mES-season 2, mES-season 3, mES-year 2, mES-year 3)
** codes 2510 to 2550 are not considered as protocol deviations, but those codes will be used to eliminate participants from specific 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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for RSVPreF3 group versus Placebo group.

6.1. Analysis of demography and baseline characteristics

6.1.1. Analysis planned in the protocol

Demographic characteristics (age at 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 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 and the analysis on the PPSe, the time at risk will correspond to the period starting on Day 15 post-vaccination up to the first occurrence of event or up to censoring.

For the analysis on the ES, the full period post-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 RSV/hMPV RT-PCR confirmed 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.

RSV RT-PCR confirmed 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 reporting up to the database cut-off date for VE Analysis 1 (see Table 6).

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 6). 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 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**.

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 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 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 specific mES as applicable (see Table 6). In addition, an analysis will be performed on the PPSe and on the ES to complement the primary analysis (see section 6.3.2.1.3).

- The **Exposed set** will be the primary population for efficacy analysis for the endpoints not related to RSV: hMPV-confirmed LRTD/ARI, hospitalization, complications, any ARI/LRTD, all-cause mortality.

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

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 (VE Analysis 3 and 4), the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

Confirmatory objective

- VE against RSV-confirmed LRTD over several 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.

Other secondary objectives

- VE against RSV-confirmed LRTD by RSV subtype: on RSV-A and RSV-B qRT-PCR-confirmed cases separately.
- VE against RSV-confirmed LRTD by age category: on participants ≥65 YOA, ≥70 YOA and ≥80 YOA at the time of 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 post-vaccination;
  - VE during Season 2 in NH and SH, including first occurrence of cases reported during Season 2 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 2;
  - VE during Season 3 in NH and SH (partial Season 3 in SH), including first occurrence of cases reported during Season 3 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 3.

  The time at risk for the analysis by season will be the period from the start of the corresponding season until the event or the end of the season or the last contact date for drop-out participants (see description of the season in each hemisphere in Figure 2 and Table 6).
- 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-vaccination, and up to 12 months post-vaccination;
  - VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases during Year 2 (12 to 24 months post-vaccination) and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases during Year 3 (24 months post-vaccination up to study end)

and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1 and/or Year 2.

- 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 hMPV-confirmed LRTD.
- VE against any ARI and any LRTD.
- Hospitalizations and complications:

  VE in the prevention of hospitalization and complications during the RSV seasons 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 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 7).

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. 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.
- 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.

- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for 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 during the 30-day follow-up period with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The analyses of unsolicited AEs will include SAEs (unless otherwise specified).
- The verbatim reports of unsolicited AEs, including SAE, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PTs and reported from vaccination up to 6 months post-vaccination will be tabulated 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 and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be presented for fatal SAEs and causally related pIMDs.
- SAEs/pIMDs will also be described in detail in a tabular listing.
- The number and percentage of participants using concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after vaccination will be tabulated with exact 95% CI.
- AEs/SAEs leading to study/intervention discontinuation from vaccination up to study end will be tabulated.

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 pre-Seasons 1 and 2 will be presented for the **mES.**

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

Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of RSV-ARI episode for participants with RT-PCR-confirmed RSV, will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will be fitted including terms for age category (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.

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**, 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**, the number of cases will be counted based on the first occurrence of the hMPV-confirmed case, starting on Day 15 post-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 and VE by season**

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

For analysis over the first 2 seasons (S1+S2) and over 3 seasons (S1+S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, starting ***on Day 15*** post-vaccination and reporting up to the end of season 2 in NH (VE Analysis ***3***) or up to end of season 3 in NH or up to study end for SH participants (VE Analysis ***4***).

For analysis over the last 2 seasons (S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, reporting from the start of season 2 in each hemisphere up to the end of season 3 in NH or up to study end for SH participants (VE Analysis ***4***).

For the VE analysis **by season**, 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	
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:

- 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: 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.

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 6 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 6 depending of the type of analysis, for participants who do not report the event of interest.

Table 6 Rules for counting cases and follow-up time

VE time period	Start date1 for Cases count and FU time	Participants to be excluded from analysis	End date2 for case count and FU time	Model Covariates	Analysis Set
Case-driven (VE analysis 1)	Day 15 post-vaccination	Participants who reported RSV cases before Day 15 post-vaccination	database cut-off date for VE Analysis 1 for all participants (NH and SH)	Age, region	mES, PPSe, ES[3]
After 1 season in NH (VE analysis 2)	Day 15 post-vaccination	Participants who reported RSV cases before Day 15 post-vaccination	End of season 1 in NH for all participants (NH and SH)	Age, region	mES, PPSe, ES[3]
Over 2 seasons (S1+S2)	Day 15 post-vaccination	Participants who reported RSV cases before Day 15 post-vaccination	End of season 2 in NH for all participants (NH and SH)	Age, region, season	mES, PPSe, ES[3]
Over 3 seasons (S1+S2+S3)	Day 15 post-vaccination	Participants who reported RSV cases before Day 15 post-vaccination	End of season 3 in NH and end of study for SH	Age, region, season	mES, PPSe, ES[3]
Over 2 seasons (S2+S3)	Start of season 2	Participants who reported RSV cases before start of season 2	End of season 3 in NH and end of study for SH	Age, region, season	mES – season 2, PPSe - season 2, ES
Season 1	Start of season 1, after Day 15 post-vaccination	Participants who reported RSV cases before the start of season 1	End of season 1 in NH and SH	Age, region	mES – season 1
Season 2	Start of season 2	Participants who reported RSV cases before the start of season 2	End of season 2 in NH and SH	Age, region	mES – season 2
Season 3	Start of season 3	Participants who reported RSV cases before the start of season 3	End of season 3 in NH and end of study for SH	Age, region	mES – season 3

VE time period	Start date1 for Cases count and FU time	Participants to be excluded from analysis	End date2 for case count and FU time	Model Covariates	Analysis Set
Year 1	Day 15 post-vaccination	Participants who reported RSV cases before Day 15 post-vaccination	12 months post-vaccination	Age, region, season	mES
Year 2	>12 months post-vaccination	Participants who reported a RSV case up to 12 months post-vaccination	24 months post-vaccination (Year 1 + 12 months)	Age, region, season	mES – Year 2
Year 3	>24 months post-vaccination	Participants who reported a RSV case up to 24 months post-vaccination	EoS4	Age, region, season	mES – Year 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 2 or 3.
[4]EoS= End of study visit, i.e. Visit 5NH or Visit 4SH.

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

Confirmatory secondary objective: The efficacy of RSV vaccine against RSV-confirmed LRTD after 1 season in NH, over 2 seasons and over 3 seasons 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 be tabulated by group, from Day 15 of from vaccination up to the time of data lock point for VE Analysis 2, 3 and 4 will be tabulated by group.

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 6).

Time of follow up for analysis on the PPSe will be the same as for mES (see Table 6).

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 time of VE Analysis 2, 3 or 4 or until withdrawal date if before the efficacy data lock point.

- **LRTD cases counting rules**
  - ***A sensitivity analysis of the secondary confirmatory efficacy endpoint will be performed to include all 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.

    Cases without co-infection results available at the time of each VE Analysis will also be excluded from this analysis.

- **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 7.

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 7 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 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).

Analysis by subgroup will be performed if at least n=15 RSV-LRTD cases are reported in at least one of the subgroup categories.

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 vaccination 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 vaccination will also be represented **graphically** per group with exact 95% CI.
- The number of days with solicited symptoms reported during the whole post-vaccination period will also be tabulated ***for ongoing events beyond the follow-up period.***
- The list of solicited administration site and systemic events, and definition of intensity are described in Section 10.3.3 and 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 8 Intensity grading scale for solicited events

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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 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 post-vaccination, the reporting period will start at vaccination (Day 1) and will end at Day 183, computed as 6 x 30.5 days=183 days.

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

The relative risk and exact CI (exact conditional to total number of cases) between the two groups will be computed for the following endpoint 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 post-vaccination, presented by MedDRA Primary System Organ Class (SOC), 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% confidence interval 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 2001]
- 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 [Leidos Biomedical research 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: CCI [redacted] CCI [redacted] 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 CCI [redacted] to 4 CCI [redacted]

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 CCI [redacted] to 4 CCI [redacted] CCI [redacted].

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 Sections 6.2 and 6.3, respectively) will be used to analyze the following tertiary endpoints:

- VE against RSV and/or hMPV-confirmed LRTDs,
- 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 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 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-vaccination (Day 1) and 1 month post-vaccination (Day 31) and may be tested for correlate of protection analysis in all participants with RSV-confirmed disease and in a subset of control participants.

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

Statistical analysis will be done in several steps:

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

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

6.4.1.4.2. Sub-groups analysis

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

6.4.2. Additional considerations

6.4.2.1. Analysis of recurrent events

At the end-of-study analysis, VE analysis of any ARI and any 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.

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:

- Reactogenicity and Safety analyses by ethnicity, race and sex:
  - Number and 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.***

Safety analyses listed below will be generated 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.

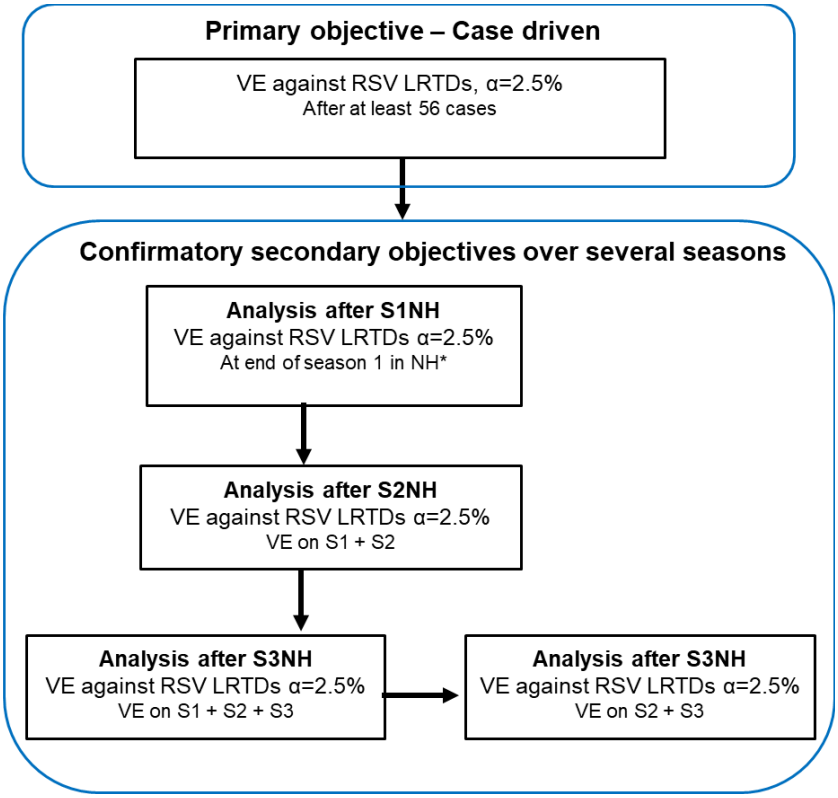
7. ANALYSIS INTERPRETATION

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

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%.

Figure 3 ***Sequential evaluation of primary and confirmatory secondary objectives***



S1/S2/S3=Season 1/2/3
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.

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

Subgroups 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 whatever the outcome of the interim analysis.***

Table 9 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 9 One-sided alpha levels for interim and final analyses using Wang-Tsiatis method, according to information accumulated at interim analysis

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

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

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:

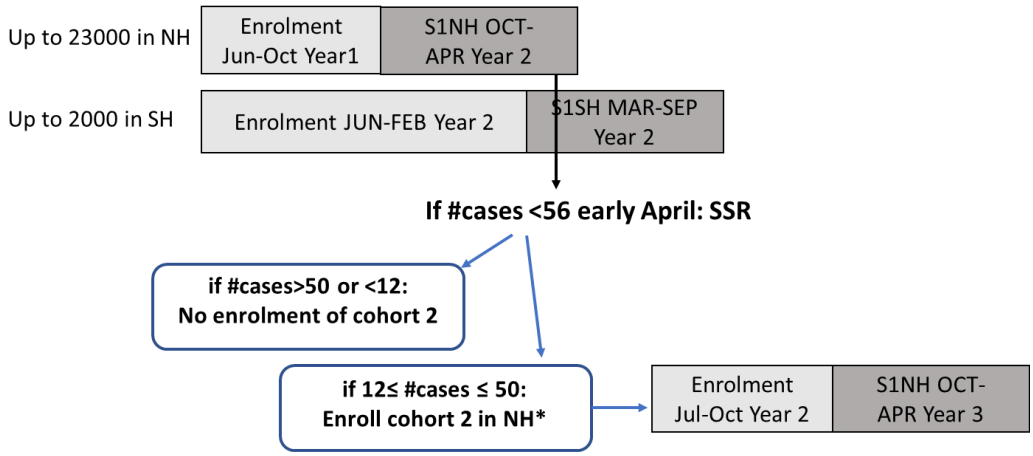
- If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed ***as described in section 8.1*** **.**
- If the total number of cases is included in [12, 50 cases]: Enrollment of a second 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).

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

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-vaccination will be available for all participants in NH and SH.

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 study team. Further details of this approach can be found in the firewall charter.

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

5. **VE Analysis 4:** after at least 3 seasons in NH and 2 seasons in SH (End of Study)

   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 5NH) and end of study in SH (Visit 4SH).

   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 2 (Dated: 6 October 2021) 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 RSV/hMPV RT-PCR confirmed LRTD cases either identified by internal review or by the investigator (see sections 6.2.2.1 and 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).
- In the immunogenicity analysis: the mean geometric increase will be generated instead of the distribution of fold increase (see section 6.3.1.2).

- Summary tables of unsolicited adverse events and SAEs/pIMDs will be generated by SOC, HLT and PTs.

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. 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.

10.3. 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 6. 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 [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 cases by the investigator will be sent to an external 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 post-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) [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 10).

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 10 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 Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	2 (1.5<=RR<2.5)
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

Comorbidities	Weight (RR)
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.

Antibody titers/concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMT/GMC calculation. Antibody titers/concentrations above the upper limit of quantification (ULOQ) of the assay will be given an arbitrary value of the ULOQ for the purpose of GMT/GMC calculation.

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

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
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 CCI (score=1), CCI CCI (score=1), CCI

(score=1), CCI (score=2) and CCI CCI (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
	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)

Domain	Component Questions
	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 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;
```

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;
```

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. Duration of events

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

For solicited AEs:

- The duration of the event will be calculated as the sum of the individual days with the event reported as grade 1 or higher, or reported as missing during the solicited event period (see section 12.1.2.3 for missing data).

12.1.3.10. 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.

12.1.3.11. 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

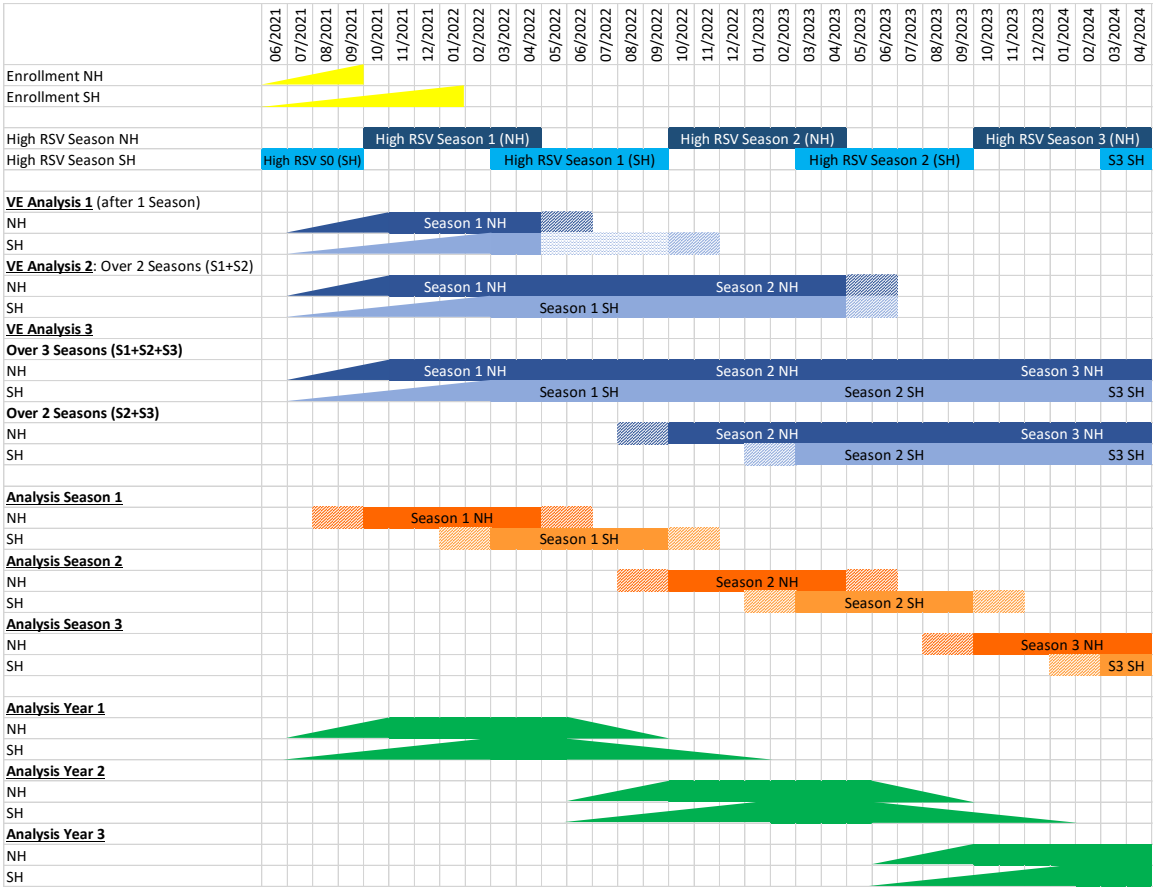
The standardised asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

12.2. Case counting periods for each analysis

The figure below presents the time period for case counting and follow-up time of each analysis, as described in Table 6.

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

Figure below presents a visual representation of the periods for case counting. More details can be found in Table 6.



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.

13. REFERENCES

Borgan Ø., Langholz B., Samuelsen S.O., et al. Exposure stratified case-cohort designs. *Lifetime Data Analysis.* 2000; 6, 39–58.

Chan ISF., Bohidar N.R., Exact power and sample size for vaccine efficacy studies. *Communications in Statistics - Theory and Methods* 1998; 27: 1305-22.

Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chrin Dis* 1987; 40(5), 373-383.

Clopper C.J., Pearson E., The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Cox, D. R. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. Series B (Methodological), 1972; 34: 187–220.

Dragalin V., Fedorov V. and Cheuvart B., Statistical approaches to establishing vaccine efficacy, *Statistics in Medicine* 2002; 21: 877-893.

Lachin, J. M., Biostatistical methods: the assessment of relative risks, *John Wiley & Sons* 2011; 807

Lievens et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children'. *Malaria* journal 2011.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

Quan H., Li B., Couris C.M., Fushimi K., Graham P., Hider P., Januel J-M., Sundararajan V., Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries, *American Journal of Epidemiology* 2011; 173 (6).

Tang M.I. and Hon Keung Tony,_Letter to the Editor, Comment on: Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method, *Statistics in Medicine*; 2004; 23: 685-693

Wang S.K and Tsiatis A.A. Approximately Optimal One Parameter Boundaries for Group Sequential Trials. Biometrics. 1987; 43: 193–199.

Wang Y., Rosenberger W.F. Randomization-based interval estimation in randomized clinical trials. *Statistics in medicine* 2020; 39(21): 2843-2854. DOI: 10.1002/sim.8577.

Statistical Analysis Plan

Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose 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 1 Final: 22 October 2021

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

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Infection
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

2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the efficacy 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 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*.
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.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category.	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.	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.	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 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*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA by baseline comorbidities.	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.	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.	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.	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 hMPV-confirmed LRTD in adults ≥ 60 YOA.	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 any ARI and any LRTD in adults ≥ 60 YOA.	***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 during the RSV seasons† in adults ≥ 60 YOA.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons†. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI during the RSV seasons† in adults ≥ 60 YOA.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition*.
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.	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.	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.	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.	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.

Objectives	Endpoints
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-vaccination (Day 1), 30 days post- vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations. • Neutralizing antibody titers against RSV A. • ***Neutralizing antibody 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 vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from Day 1 up to 6 months post-vaccination. • Occurrence of all pIMDs from Day 1 up to 6 months post-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***.***	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 severe hMPV-confirmed LRTD in adults ≥ 60 YOA.	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 hMPV-confirmed ARI in adults ≥ 60 YOA.	***First occurrence of RT-PCR-confirmed hMPV-associated ARI, 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.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category.	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.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.
To evaluate the evolution of efficacy of 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.	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.	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.	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.	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.	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.	• 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.	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-vaccination with protection against RSV disease.	RSVPreF3 IgG-specific antibody concentrations at pre-vaccination (Day 1) and 30 days post-vaccination (Day 31) 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-vaccination (Day 1), 30 days post-vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations classified by baseline frailty score. • Neutralizing antibody titers against RSV A classified by baseline frailty score. • ***Neutralizing antibody titers against RSV B 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 vaccination (i.e., the day of vaccination and 3 subsequent days) classified by baseline frailty score.

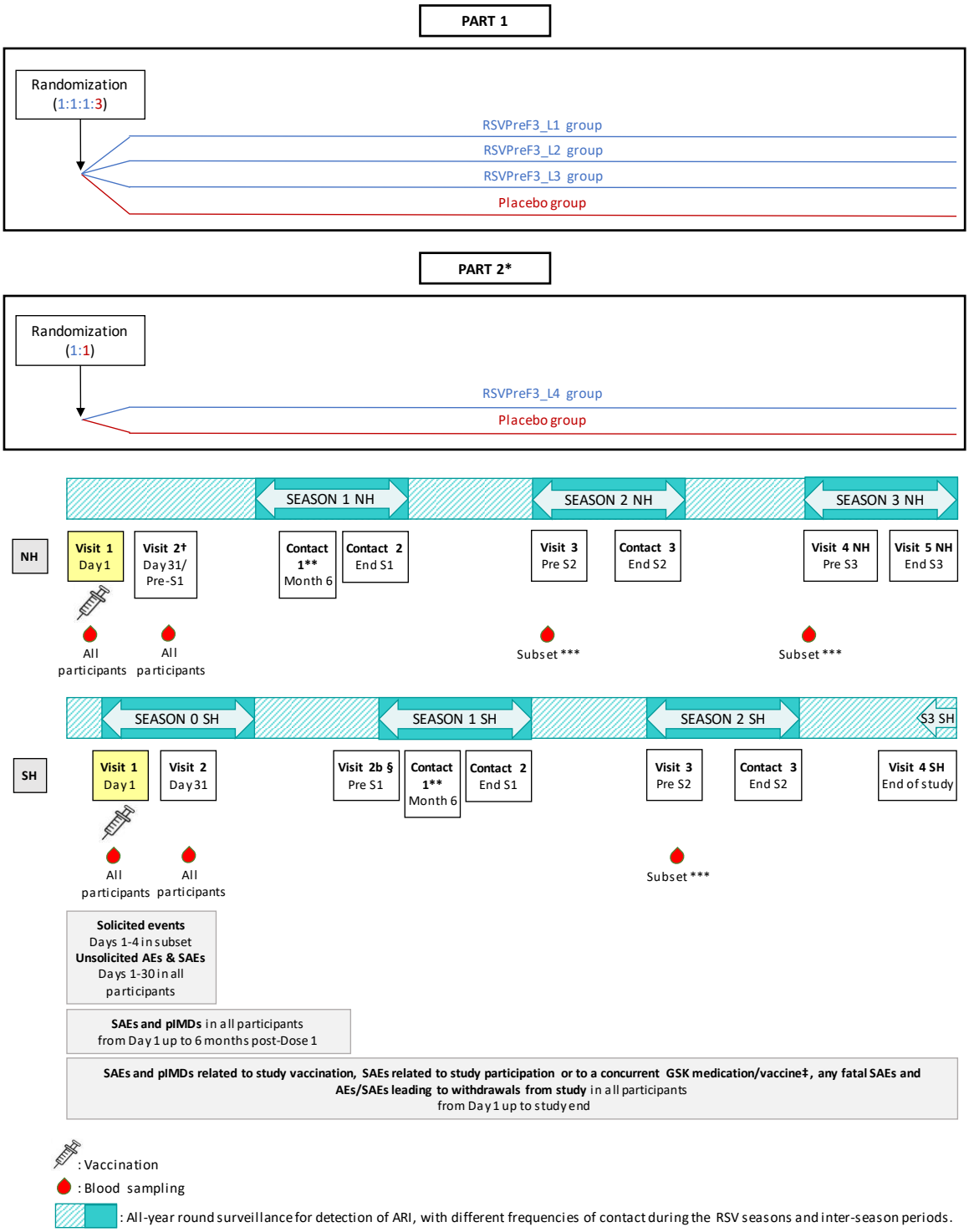
***** Case definitions are described in Section 4.

† 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.

3. STUDY DESIGN

Figure 1 Study design overview



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.
AE: adverse event; ARI: acute respiratory infection; NH: Northern hemisphere; SH: Southern hemisphere;

pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
* Part 2 will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.
† Depending on the time of enrollment, Visit 1 and Visit 2 in NH can take place during Season 1.
** Contact 1 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months post-vaccination for each participant. This contact 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 study vaccine administration.

- **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.
- ***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 enrolled in this cohort will follow the same study design as indicated in Figure 1. The participants in this additional cohort will be enrolled in 2 study groups (RSVPreF3 and Placebo) according to a 1:1 randomization ratio. 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.
- **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 5NH/Visit 4SH (Observer-blind)
RSVPreF3_L1	Up to 11 500**	750-1 000**	Up to 12 500**	≥ 60 years	RSVPreF3 OA investigational vaccine L1	X
RSVPreF3_L2				≥ 60 years	RSVPreF3 OA investigational vaccine L2	X
RSVPreF3_L3				≥ 60 years	RSVPreF3 OA investigational vaccine L3	X
RSVPreF3_L4				≥ 60 years	RSVPreF3 OA investigational vaccine L4***	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.

- **Vaccination schedule:** A single dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1.
- **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 day of vaccination [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. This period might be extended, i.e. starting few months earlier and/or ending few months later, in case a shift in the peak incidence of seasonal viruses due to special circumstances (e.g., COVID-19 pandemic) is observed in the national surveillance systems and/or in epidemiological studies.
- **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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for **RSVPreF3** group versus **Placebo** group using the pooled groups labels and definition in Table 2.

Table 2 Group names and definition for footnote in the TFLs

Group label	Group definition	Pooled Groups label in tables	Group order in tables	Pooled definition for footnote
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			
RSVPreF3_L4	Participants receiving RSVPreF3 OA investigational vaccine Lot 4			
Placebo	Participants receiving Placebo	**Placebo**	2	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)

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
	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
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	Female	Female
	2	Male	Male
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 7 (Charlson Index)
	2	High Risk	Participants with co-morbidity score at baseline greater than or equal to 7 (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. 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 colspan="2">Case definition</th></tr>
<tr><td>ARI
(Trigger for swabbing)</td><td colspan="2">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</td></tr>
<tr><td></td><td>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]</td><td>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 colspan="2">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 colspan="2">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</td></tr>
<tr><td></td><td>Lower respiratory symptoms
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)</td><td>Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV-LRTD or hMPV-LRTD[5]</td><td colspan="2">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>
</table>

Endpoint	Case definition
RT-PCR-confirmed **severe** RSV LRTD or **severe** hMPV LRTD – Definition 1 "Clinical symptomology"[5]	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]
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 infection; 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 7
[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.

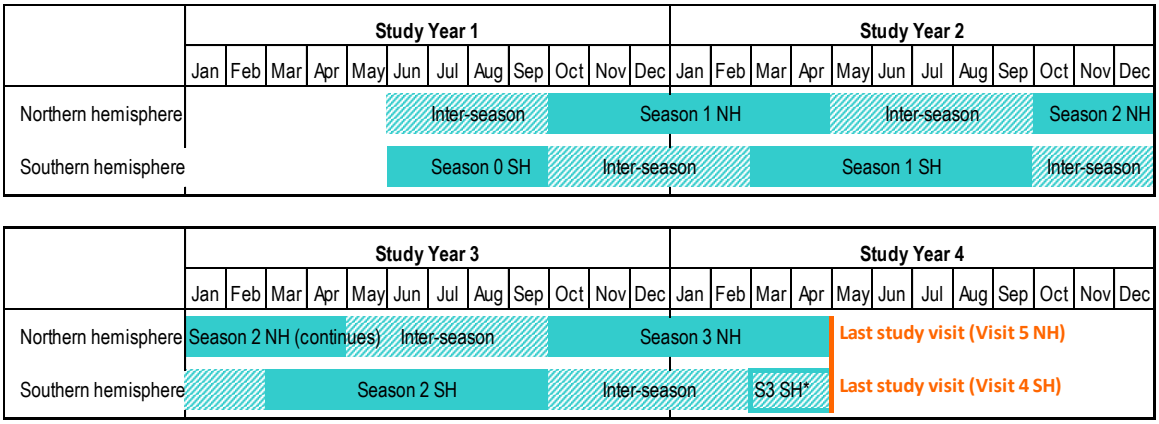
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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 vaccination [Visit 1])*** and by ***scheduled*** site staff contact***s (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 data obtained at VE Analysis 1, the ARI surveillance could be adapted for the 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 4 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 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 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 the study intervention (Exposed Set) who have solicited safety data.

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

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 the study intervention and who did not report an RSV-confirmed ARI prior to ***Day 15*** after vaccination. The allocation in a group is done in function of the administered intervention.
- Additional specific mES will be defined including all participants who received the study intervention and who did not report an RSV-confirmed ARI prior to the start of the case count depending on the analysis to be performed, i.e analysis by season/by year (see Table 6).
- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): hMPV-confirmed LRTD/ARI, 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 the study vaccine to which they were randomized,
  - have data available for efficacy endpoint measures,
  - 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 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).

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 (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, codes 2510 to 2550 will be used to eliminate participants from specific mES for analyses by season and by year (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, 900, 1030, 1050,1060, 2500 and 2600: participants will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2010, 2040, 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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	All	ES, mES*, PPSe, PPSi, SSS
1030	Study intervention not administered at all	All	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 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.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
1050	Randomization failure: participant not randomized in the correct group (To be attributed by unblinded Statistician only; Check SBIR, replacement, vaccine administration)	Visit 1	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	PPSe, PPSi
1080	Vaccine administration after a Temperature deviation	Visit 1	PPSe, PPSi
1090	Vaccine administration after expiration	Visit 1	PPSe, PPSi
1160	Participant included in the reactogenicity subset who did not document any post-vaccination solicited safety data	Visit 2	Solicited safety set
2010	Protocol deviation linked to inclusion/exclusion criteria	Visit 1	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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 prior to the study vaccine administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent.	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
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
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination and visit 2 blood sample is outside [28-42] days. For participants in the immunogenicity subset: • Date of BS at Pre-season 2 (Visit 3) is outside [15Aug-30Sep] in NH, or outside [15Jan-28Feb] in SH • Date of BS at Pre-season 3 (Visit 4 NH) is outside [15Aug-30Sep]	Visit 2, Visit 3, Visit 4NH	PPSi
2100	For participants in the immunogenicity subset: Serological results not available post-vaccination: No results available at all at the corresponding visit	Visit 2, Visit 3, Visit 4NH	PPSi
2120	Obvious incoherence/abnormality or error in laboratory data	Visit 2, Visit 3, Visit 4NH	PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
2500	Participant who report a RSV-confirmed ARI case prior to ***Day 15*** after vaccination: • Number of days between vaccination and day of onset of ARI case < 14 days	ARI visit	mES*, PPSe
2510**	Participant who report a RSV-confirmed ARI case ***from Day 15*** post vaccination ***up to the*** start of season 1	ARI visit	mES-season 1
2520**	Participant who report a RSV-confirmed ARI case ***from Day 15*** post vaccination ***up to the*** start of season 2	ARI visit	mES-season 2
2530**	Participant who report a RSV-confirmed ARI case ***from Day 15*** post vaccination ***up to the*** start of season 3	ARI visit	mES-season 3
2540**	Participant who report a RSV-confirmed ARI case ***from Day 15*** post vaccination ***up to the*** start of year 2	ARI visit	mES-year 2
2550**	Participant who report a RSV-confirmed ARI case ***from Day 15*** post vaccination ***up to the*** start of year 3	ARI visit	mES-year 3
2600	Participants not included in the reactogenicity and immunogenicity subset	Visit 1	Solicited safety set, PPSi

*Applicable for the mES and all the specific mES for by season and by year analyses (mES-season 1, mES-season 2, mES-season 3, mES-year 2, mES-year 3)
** codes 2510 to 2550 are not considered as protocol deviations, but those codes will be used to eliminate participants from specific 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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for RSVPreF3 group versus Placebo group.

6.1. Analysis of demography and baseline characteristics

6.1.1. Analysis planned in the protocol

Demographic characteristics (age at 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 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 and the analysis on the PPSe, the time at risk will correspond to the period starting ***on Day 15*** post-vaccination up to the first occurrence of event or up to censoring.

For the analysis on the ES, the full period post-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 ***q***RT-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 cases identified as follows:

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 external case reviewers*** (adjudication committee) in order to confirm if they meet the LRTD case definition or not. Confirmation of the LRTD case will be reported in the eCRF and will be available in the SDTMs (see Section 10.3.1.3).
- ARI cases for which the information of signs and symptoms is not available (for example if the study participant is hospitalized or seen by another health care provider) ***and for which the adjudication committee is not able to conclude, will be considered as LRTD if an LRTD diagnosis was confirmed by the study investigator.***

RSV-confirmed LRTD:

- ***An event confirmed as LRTD*** 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-confirmed 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 reporting ***up to the database cut-off date for VE Analysis 1*** (see Table 6).

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
/* OUTIST 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.

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 6). 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 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 do 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**.

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 considering the RSV LRTD 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 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 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 additional analyses by subgroup will be performed if at least 15 RSV-LRTD cases are reported in at least one of the subgroup categories.

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 specific mES as applicable (see Table 6). In addition, an analysis will be performed on the PPSe and on the ES to complement the primary analysis (see section 6.3.2.1.3).

- The **Exposed set** will be the primary population for efficacy analysis for the endpoints ***not related to RSV***: hMPV-confirmed LRTD/ARI, hospitalization, complications, any ARI/LRTD, all-cause mortality.

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

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 (VE Analysis 3 and 4), the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.***

Confirmatory objective

- VE against RSV-confirmed LRTD over several 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.

Other secondary objectives

- ***VE against RSV-confirmed LRTD by RSV subtype: on RSV-A and RSV-B qRT-PCR-confirmed cases separately.***
- VE ***against RSV-confirmed LRTD*** by age category: on participants ≥65 YOA, ≥70 YOA and ≥80 YOA at the time of 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*** post-vaccination;
  - VE during Season 2 in NH and SH, including first occurrence of cases reported during Season 2 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 2;
  - VE during Season 3 in NH and SH ***(partial Season 3 in SH)***, including first occurrence of cases reported during Season 3 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 3.

  The time at risk for the analysis by season will be the period from the start of the corresponding season until the event or the end of the season or the last contact

date for drop-out participants (see description of the season in each hemisphere in Figure 2 and Table 6)**.**

- 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-vaccination, and up to 12 months post-vaccination;
  - VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases during Year 2 (12 to 24 months post-vaccination) and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases during Year 3 (24 months post-vaccination up to study end) and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1 and/or Year 2.
- 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 hMPV-confirmed LRTD.***
- ***VE against any ARI and any LRTD.***
- ***Hospitalizations and complications:***

  VE in the prevention of hospitalization ***and complications*** during the RSV seasons 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 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 7).

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. 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.
- 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.
- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for 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 during the 30-day follow-up period with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class (SOC), ***High Level Term (HLT) and*** Preferred Term (PT). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The analyses of unsolicited AEs will include SAEs (unless otherwise specified).
- The verbatim reports of unsolicited AEs, including SAE, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA ***Primary SOC, HLT and PTs*** and reported from vaccination up to 6 months post-vaccination will be tabulated 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*** and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be presented for fatal SAEs and causally related pIMDs.
- SAEs/pIMDs will also be described in detail in a tabular listing.
- The number and percentage of participants using concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after vaccination will be tabulated with exact 95% CI.
- AEs/SAEs leading to study/intervention discontinuation from vaccination up to study end will be tabulated.

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 pre-Seasons 1 and 2 will be presented for the **mES.**

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

Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of RSV-ARI episode for participants with RT-PCR-confirmed RSV, will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will be fitted including terms for age category (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.

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. Description and identification of RSV-confirmed LRTDs is further described in Section 6.2.2.1.

For analysis of VE against **RSV**, 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**, the number of cases will be counted based on the first occurrence of the hMPV-confirmed case, starting ***on Day 15*** post-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 and VE by season

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

For analysis over the first 2 seasons (S1+S2) and over 3 seasons (S1+S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, starting ***on Day 15*** post-vaccination and reporting up to the end of season 2 in NH (VE Analysis ***3***) or up to end of season 3 in NH ***or up to study end for SH participants*** (VE Analysis ***4***).

For analysis over the last 2 seasons (S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, reporting from the start of season 2 in each hemisphere up to the end of season 3 in NH ***or up to study end for SH participants*** (VE Analysis ***4***).

- For the VE analysis **by season**, 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	
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 than 7
- High Risk = Participants with co-morbidity score at baseline greater than or equal to 7.

VE analyses by co-morbidities will be performed at ***VE Analysis 1, 2 and 3*** if at least 15 RSV-LRTD cases are reported in at least one of the categories. At VE analysis ***4*** (EoS), analysis will be performed whatever the number of cases in each category.

- **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:

  - 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: 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.

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 6 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 6 depending of the type of analysis, for participants who do not report the event of interest.

Table 6 Rules for counting cases and follow-up time

VE time period	Start date1 for Cases count and FU time	Participants to be excluded from analysis	End date2 for case count and FU time	Model Covariates	Analysis Set
Case-driven (VE analysis 1)	***Day 15*** post-vaccination	Participants who reported RSV cases before ***Day 15*** post-vaccination	***database cut-off date*** for VE Analysis 1 ***for all participants (NH and SH)***	Age, region	mES, PPSe, ES[3]
After 1 season ***in NH (VE analysis 2***)	***Day 15*** post-vaccination	Participants who reported RSV cases before ***Day 15*** post-vaccination	End of season 1 in NH ***for all participants (NH and SH)***	Age, region	mES, PPSe, ES[3]
Over 2 seasons (S1+S2)	***Day 15*** post-vaccination	Participants who reported RSV cases before ***Day 15*** post-vaccination	End of season 2 in NH for all participants (NH and SH)	Age, region, season	mES, PPSe, ES[3]
Over 3 seasons (S1+S2+S3)	***Day 15*** post-vaccination	Participants who reported RSV cases before ***Day 15*** post-vaccination	End of season 3 in NH and end of study for SH	Age, region, season	mES, PPSe, ES[3]
Over 2 seasons (S2+S3)	Start of season 2	Participants who reported RSV cases before start of season 2	End of season 3 in NH and end of study for SH	Age, region, season	mES – season 2, PPSe - season 2, ES
Season 1	Start of season 1, after ***Day 15*** post-vaccination	Participants who reported RSV	End of season 1 in NH and SH	Age, region	mES – season 1

VE time period	Start date1 for Cases count and FU time	Participants to be excluded from analysis	End date2 for case count and FU time	Model Covariates	Analysis Set
		cases before the start of season 1			
Season 2	Start of season 2	Participants who reported RSV cases before the start of season 2	End of season 2 in NH and SH	Age, region	mES – season 2
Season 3	Start of season 3	Participants who reported RSV cases before the start of season 3	End of season 3 in NH and end of study for SH	Age, region	mES – season 3
Year 1	***Day 15*** post-vaccination	Participants who reported RSV cases before ***Day 15*** post-vaccination	12 months post-vaccination	Age, region, season	mES
Year 2	>12 months post-vaccination	Participants who reported a RSV case up to 12 months post-vaccination	24 months post-vaccination (Year 1 + 12 months)	Age, region, season	mES – Year 2
Year 3	>24 months post-vaccination	Participants who reported a RSV case up to 24 months post-vaccination	EoS4	Age, region, season	mES – Year 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 2 or 3.
[4]EoS= End of study visit, i.e. Visit 5NH or Visit 4SH.

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

Confirmatory secondary objective: The efficacy of RSV vaccine against RSV-confirmed LRTD ***after 1 season in NH***, over 2 seasons and over 3 seasons 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 be tabulated by group, from Day 15 of from vaccination up to the time of data lock point for ***VE Analysis 2, 3 and 4*** will be tabulated by group.

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 6).

Time of follow up for analysis on the PPSe will be the same as for mES (see Table 6).

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 time of VE Analysis 2, 3 or 4 or until withdrawal date if before the efficacy data lock point.

- **LRTD cases counting rules**
  - A first 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 second 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.

    Cases without co-infection results available at the time of each VE Analysis will also be excluded from this analysis.

- **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 7.

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 7 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 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).

Analysis by subgroup will be performed if at least n=15 RSV-LRTD cases are reported in at least one of the subgroup categories.

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 vaccination 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 vaccination will also be represented **graphically** per group with exact 95% CI.
- ***The number of days with solicited symptoms reported during the whole post-vaccination period will also be tabulated, to report the total number of days for solicited events ongoing beyond the follow-up period).***

- The list of solicited administration site and systemic events, and definition of intensity are described in Section 10.3.3 and 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 8 Intensity grading scale for solicited events

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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 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 post-vaccination, the reporting period will start at vaccination (Day 1) and will end at Day 183, computed as 6 x 30.5 days=183 days.

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

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

- ***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 post-vaccination, presented by MedDRA Primary System Organ Class (SOC), 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% confidence interval 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 2001]
- 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 [Leidos Biomedical research 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:CCI [redacted] CCI [redacted] 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 CCI [redacted] to 4 CCI [redacted]

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 CCI [redacted] to 4 CCI [redacted] CCI [redacted].

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 Sections 6.2 and 6.3, respectively) will be used to analyze the following tertiary endpoints:

- VE against RSV and/or hMPV-confirmed LRTDs,
- 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 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 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-vaccination (Day 1) and 1 month post-vaccination (Day 31) and may be tested for correlate of protection analysis in all participants with RSV-confirmed disease and in a subset of control participants.

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

Statistical analysis will be done in several steps:

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

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

6.4.1.4.2. Sub-groups analysis

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

6.4.2. Additional considerations

6.4.2.1. Analysis of recurrent events

At the end-of-study analysis, VE analysis of any ARI and any 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.

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. Analysis for additional safety summary

Safety analyses described in this section will be generated as Annex tables (not included in the CSR) in order to be described in additional safety summaries. The following analyses will be performed:

- ***Reactogenicity and Safety analyses by ethnicity, race and sex:***
  - ***Number and percentage of participants with at least one administration site or systemic event (solicited and unsolicited) and with any AE (solicited and unsolicited) within 4 days and 30 days following vaccination on ES,***
  - ***Number and 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/pIMDs/Fatal SAEs with onset within 6 months following vaccination, on ES.***
- ***Analysis on the subset of participants with a safety follow-up of at least 6 months at the time of analysis, i.e. who completed the contact 1 at least 180 days after vaccination ("6 months subset"), overall and by age categories:***
  - ***Number and percentage of participants with at least one [SAE/pIMDs/fatal SAEs/causally related SAEs/causally related pIMDs] reported from vaccination up to 6 months post-vaccination, on the "6 months subset", with RR and 80% CIs,***
  - ***Number and percentage of participants reporting [any/Grade 3/related/Grade 3 related/with medically attended visit] unsolicited AEs within 30 days following vaccination, on the "6 months subset", with RR and 95% CIs,***
- ***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.***

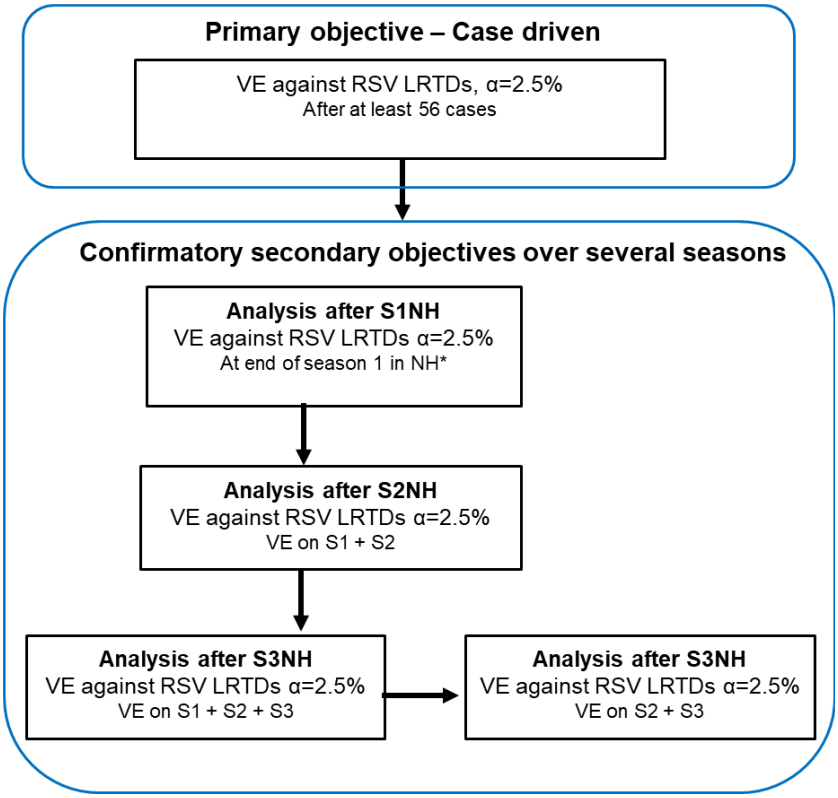
7. ANALYSIS INTERPRETATION

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

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%.

Figure 3 ***Sequential evaluation of primary and confirmatory secondary objectives***



S1/S2/S3=Season 1/2/3
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.***

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

Subgroups 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 LRTDs have been accrued in the primary cohort for efficacy (mES).

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 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. If the interim analysis is performed, then the final analysis will be performed when at least 60 cases are accrued in the primary cohort for efficacy or when all data associated to the primary objective are available.

Table 9 provides the 1-sided adjusted alpha levels obtained using the Wang-Tsiatis method with Δ = 0.3, depending on the quantity of information accumulated at the time of interim analysis (using gsDesign package in R).

Table 9 One-sided alpha levels for interim and final analyses using Wang-Tsiatis method, according to information accumulated at interim analysis

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

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

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:

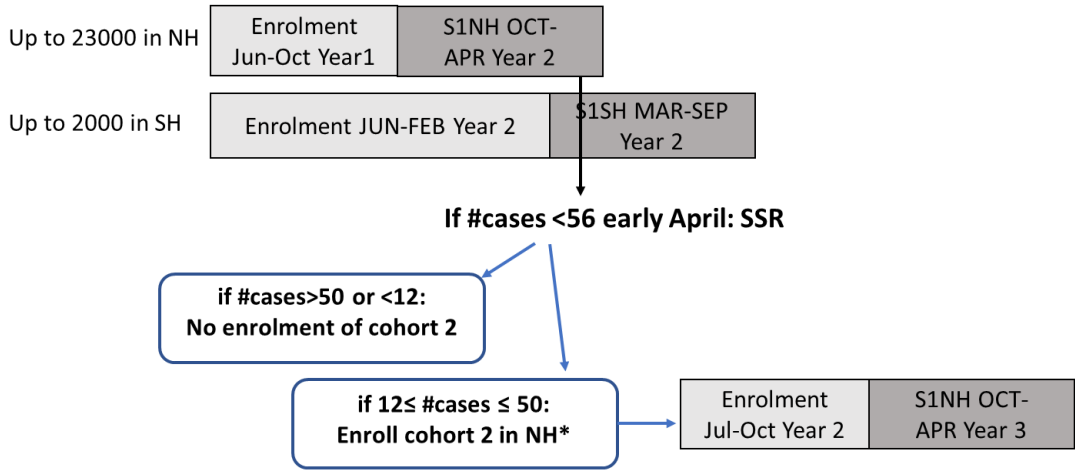
- ***If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed when at least 56 cases will be accrued or at the latest at the end of Season 1 in SH.***
- ***If the total number of cases 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 when at least 56 cases will be accrued or at the latest at the end of the Season 1 for this second cohort.***

  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). 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 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).

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

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-vaccination will be available for all participants in NH and SH.

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 study team. Further details of this approach can be found in the firewall charter.

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

5. VE Analysis *4*: after at least 3 seasons in NH and 2 seasons in SH (End of Study)

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 5NH) and end of study in SH (Visit 4SH).

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 2 (Dated: 6 October 2021) are described below:

- ***Clarification on the confirmation of the LRTD cases: external reviewers from adjudication committee will review all the ARI cases and will confirm if the case is an LRTD or not (see 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).***
- ***In the immunogenicity analysis: the mean geometric increase will be generated instead of the distribution of fold increase (see section 6.3.1.2).***
- ***Summary tables of unsolicited adverse events and SAEs/pIMDs will be generated by SOC, HLT and PTs.***

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. 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.

10.3. 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 6. 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 [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 clinically confirmed ARI cases by the investigator (i.e. an ARI meeting the case definition according to investigator's assessment) will be reviewed ***by external case reviewers (adjudication committee)*** in order to confirm if they meet the LRTD case definition or not. This review will be performed independently of the results of the RSV RT-PCR. ***Confirmation 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*** post-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) [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 10).

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 10 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 Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	2 (1.5<=RR<2.5)
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.

Antibody titers/concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMT/GMC calculation. Antibody titers/concentrations above the upper limit of quantification (ULOQ) of the assay will be given an arbitrary value of the ULOQ for the purpose of GMT/GMC calculation.

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

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
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 CCI (score=1), CCI CCI (score=1), CCI (score=1), CCI (score=2) and CCI CCI (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
	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

Domain	Component Questions
	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 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;
```

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;
```

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. Duration of events

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

For solicited AEs:

- ***The duration of the event will be calculated as the sum of the individual days with the event reported as grade 1 or higher, or reported as missing during the solicited event period (see section 12.1.2.3 for missing data).***

12.1.3.10. 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.

12.1.3.11. 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

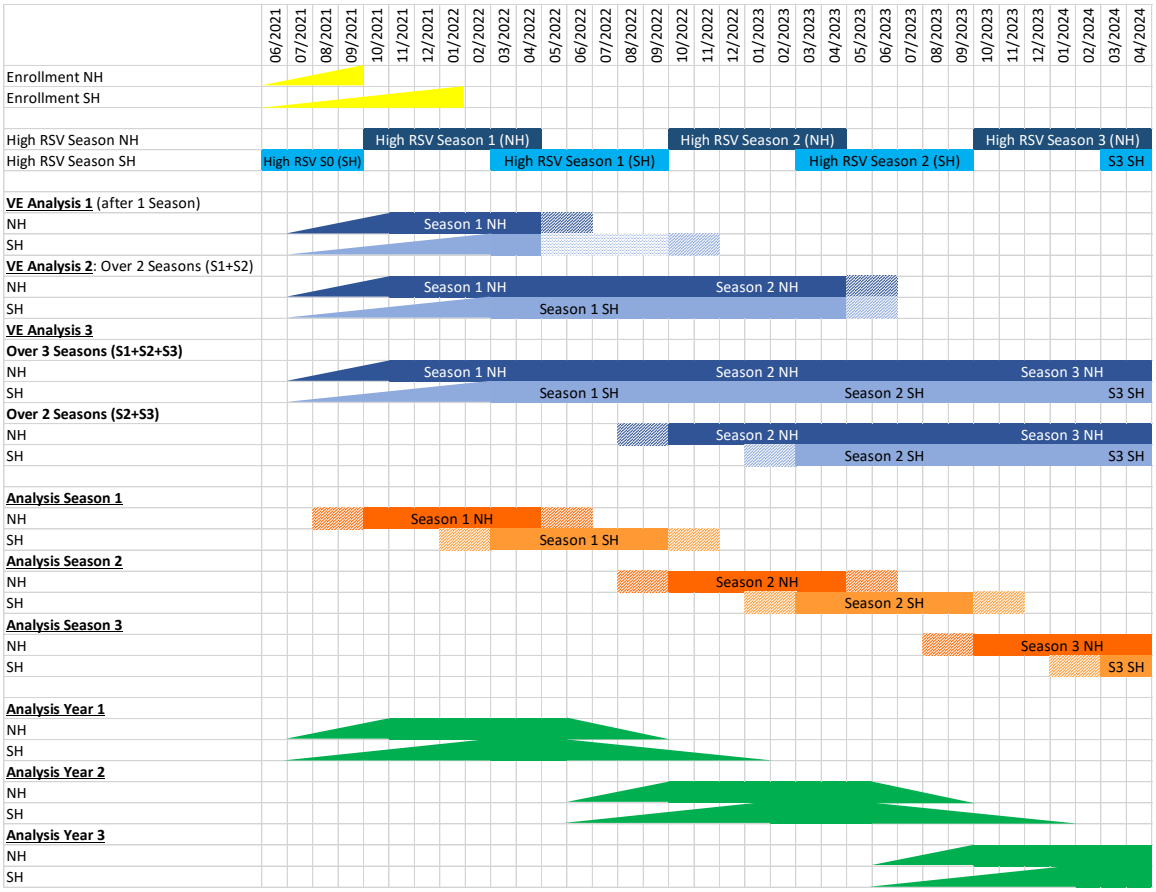
The standardised asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

12.2. Case counting periods for each analysis

The figure below presents the time period for case counting and follow-up time of each analysis, as described in Table 6.

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

Figure below presents a visual representation of the periods for case counting. More details can be found in Table 6.



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.

13. REFERENCES

Borgan Ø., Langholz B., Samuelsen S.O., et al. Exposure stratified case-cohort designs. *Lifetime Data Analysis.* 2000; 6, 39–58.

Chan ISF., Bohidar N.R., Exact power and sample size for vaccine efficacy studies. *Communications in Statistics - Theory and Methods* 1998; 27: 1305-22.

Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chrin Dis* 1987; 40(5), 373-383.

Clopper C.J., Pearson E., The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Cox, D. R. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. Series B (Methodological), 1972; 34: 187–220.

Dragalin V., Fedorov V. and Cheuvart B., Statistical approaches to establishing vaccine efficacy, *Statistics in Medicine* 2002; 21: 877-893.

Lachin, J. M., Biostatistical methods: the assessment of relative risks, *John Wiley & Sons* 2011; 807

Lievens et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children'. *Malaria* journal 2011.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

Quan H., Li B., Couris C.M., Fushimi K., Graham P., Hider P., Januel J-M., Sundararajan V., Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries, *American Journal of Epidemiology* 2011; 173 (6).

Tang M.I. and Hon Keung Tony,_Letter to the Editor, Comment on: Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method, *Statistics in Medicine*; 2004; 23: 685-693

Wang S.K and Tsiatis A.A. Approximately Optimal One Parameter Boundaries for Group Sequential Trials. Biometrics. 1987; 43: 193–199.

Wang Y., Rosenberger W.F. Randomization-based interval estimation in randomized clinical trials. *Statistics in medicine* 2020; 39(21): 2843-2854. DOI: 10.1002/sim.8577.

Statistical Analysis Plan

Title:	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose 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	Final: 20 May 2021

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

CONFIDENTIAL

212494 (RSV OA=ADJ-006)
Statistical Analysis Plan

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Attack Rate
ARI	Acute Respiratory Infection
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
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
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
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

2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD after at least 1 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	
To demonstrate the efficacy 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 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.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category.	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.	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.	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 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.	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.	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.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA.	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 hMPV-confirmed LRTD in adults ≥ 60 YOA.	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 hospitalization due to respiratory diseases during the RSV seasons† in adults ≥ 60 YOA.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons†. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI during the RSV seasons† in adults ≥ 60 YOA.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition*.
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.	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.	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.	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.	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-vaccination (Day 1), 30 days post- vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations. • Neutralizing antibody titers against RSV A.
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 vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days).

Objectives	Endpoints
	• Occurrence of all serious adverse events (SAEs) from Day 1 up to 6 months post-vaccination. • Occurrence of all pIMDs from Day 1 up to 6 months post-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	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 severe hMPV-confirmed LRTD in adults ≥ 60 YOA.	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.	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.	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.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.
To evaluate the evolution of efficacy of 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 any ARI and any LRTD in adults ≥ 60 YOA.	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 RSV-confirmed ARI in adults ≥ 60 YOA by baseline comorbidities.	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.	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.	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 and hMPV-confirmed ARI cases.	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.

Objectives	Endpoints
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.	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.	• 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.	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-vaccination with protection against RSV disease.	RSVPreF3 IgG-specific antibody concentrations at pre-vaccination (Day 1) and 30 days post-vaccination (Day 31) in all participants with RSV disease compared to a subset of controls.‡
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-vaccination (Day 1), 30 days post-vaccination (Day 31), pre-Season 2 and pre-Season 3: • RSVPreF3 IgG-specific antibody concentrations classified by baseline frailty score. • Neutralizing antibody titers against RSV A 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 vaccination (i.e., the day of vaccination and 3 subsequent days) classified by baseline frailty score.

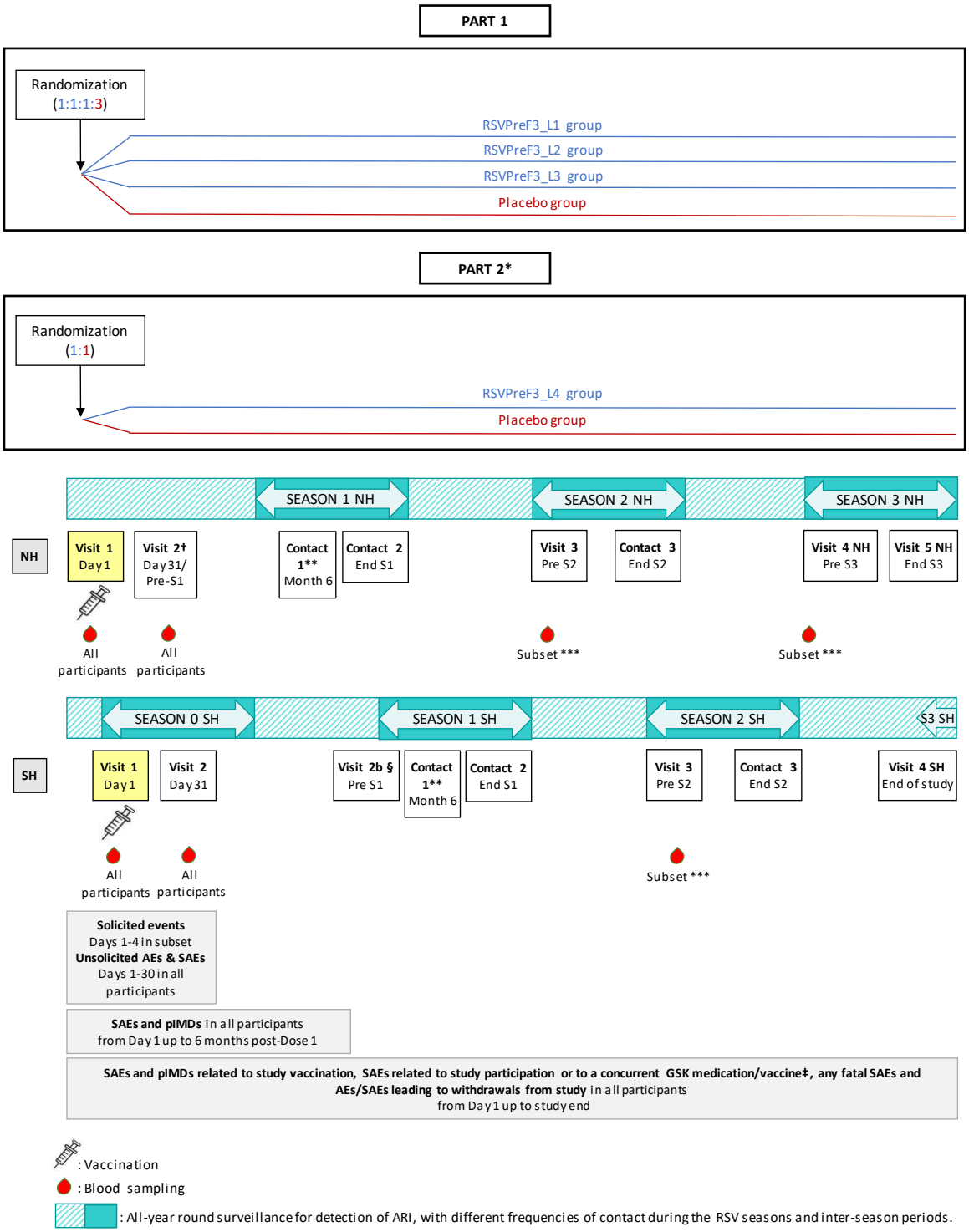
* Case definitions are described in Section 4.

† 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 and systems serology testing might be performed on the same subset of participants to investigate a correlate of protection.

3. STUDY DESIGN

Figure 1 Study design overview



Note: In case of a sample size re-assessment and an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3 of the protocol), the participants enrolled in this cohort will follow the same study design as indicated in this figure.
AE: adverse event; ARI: acute respiratory infection; NH: Northern hemisphere; SH: Southern hemisphere.
pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
* Part 2 will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.
† Depending on the time of enrollment, Visit 1 and Visit 2 in NH can take place during Season 1.
** Contact 1 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months post-vaccination for each participant. This contact 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 study vaccine administration.

- **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.
  - Part 2 with 2 parallel groups, which will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.
- **Design for 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 enrolled in this cohort will follow the same study design as indicated in Figure 1. The participants in this additional cohort will be enrolled in 2 study groups (RSVPreF3 and Placebo) according to a 1:1 randomization ratio. 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.
- **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:** Time- and event-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 5NH/Visit 4SH (Observer-blind)
RSVPreF3_L1	Up to 11 500**	750-1 000**	Up to 12 500**	≥ 60 years	RSVPreF3 OA investigational vaccine L1	X
RSVPreF3_L2				≥ 60 years	RSVPreF3 OA investigational vaccine L2	X
RSVPreF3_L3				≥ 60 years	RSVPreF3 OA investigational vaccine L3	X
RSVPreF3_L4				≥ 60 years	RSVPreF3 OA investigational vaccine L4***	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.

- **Vaccination schedule:** A single dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1.
- **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, starting on the day of vaccination (Visit 1) via spontaneous reporting by the study participant and via scheduled site staff contacts 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. This period might be extended, i.e. starting few months earlier and/or ending few months later, in case a shift in the peak incidence of seasonal viruses due to special circumstances (e.g., COVID-19 pandemic) is observed in the national surveillance systems and/or in epidemiological studies.
- **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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for **RSVPreF3** group versus **Placebo** group using the pooled groups labels and definition in Table 2.

Table 2 Group names and definition for footnote in the TFLs

Group label	Group definition	Pooled Groups label in tables	Group order in tables	Pooled definition for footnote
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			
RSVPreF3_L4	Participants receiving RSVPreF3 OA investigational vaccine Lot 4			
Placebo	Participants receiving Placebo	**Placebo**	2	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)

Sub-analysis	Subgroup order in tables	Subgroup label in tables	Subgroup definition for footnote
	4	SH	Participants from Southern hemisphere (Australia, Brazil, South Africa)
By Ethnicity	1	Hisp_Lat	Hispanic or Latino
	2	No_Hisp_Lat	Not Hispanic or Latino
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 Alsaka Native, Native Hawaiian or Other Pacific Islander
By Sex	1	Female	Female
	2	Male	Male
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 7(Charlson Index)
	2	High Risk	Participants with co-morbidity score at baseline greater than or equal to 7 (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 enrolment 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. 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 colspan="2">Case definition</th></tr>
<tr><td>ARI
(Trigger for swabbing)</td><td colspan="2">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</td></tr>
<tr><td></td><td>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]</td><td>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</td><td colspan="2">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.[5]</td></tr>
<tr><td>LRTD</td><td colspan="2">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</td></tr>
<tr><td></td><td>Lower respiratory symptoms
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)</td><td>Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV-LRTD or hMPV-LRTD</td><td colspan="2">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.[5]</td></tr>
</table>

Endpoint	Case definition
RT-PCR-confirmed **severe** RSV LRTD or **severe** hMPV LRTD – **Definition 1** "Clinical symptomology"	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[6] **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]
RT-PCR-confirmed **severe** RSV LRTD or **severe** hMPV LRTD – **Definition 2** "Supportive therapy"	Presence of a LRTD with at least one of the following criteria[7]: • 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 infection; 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] Refer to Section 10.3.1.4 for details on the counting of cases that are positive for both RSV and hMPV.
[6] The investigator will grade each ARI as mild, moderate or severe based on the grading scale presented in Table 7.
[7] 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.

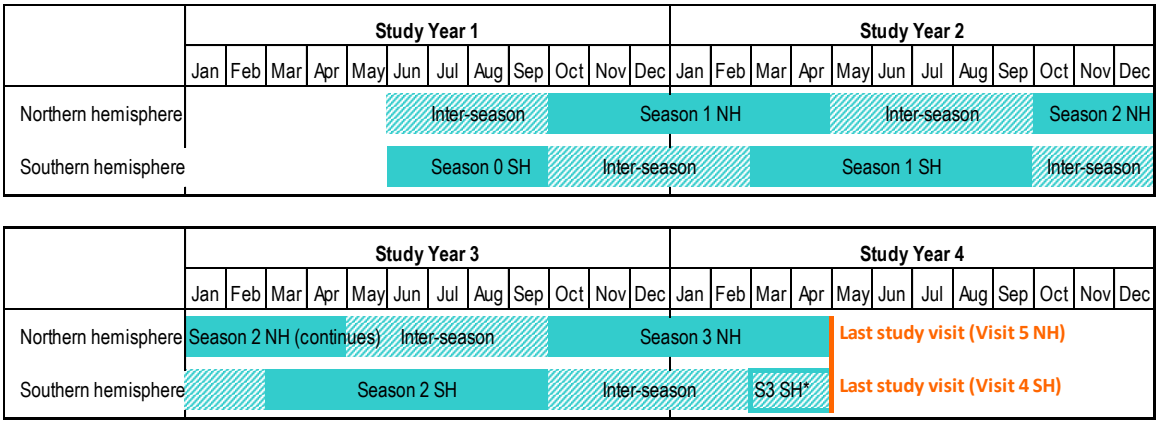
ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant and 2) scheduled site staff contacts.

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, starting on the day of vaccination (Visit 1), via spontaneous reporting by the study participant and by regular site staff contact 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 data obtained at VE Analysis 1, the ARI surveillance could be adapted for the subsequent seasons.
Note: In case of a sample size re-assessment and 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 4 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 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 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 the study intervention (Exposed Set) who have solicited safety data.

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

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 the study intervention and who did not report a RSV-confirmed ARI prior to 1 month after vaccination. The allocation in a group is done in function of the administered intervention.
- Additional specific mES will be defined including all participants who received the study intervention and who did not report a RSV-confirmed ARI prior to the start of the case count depending on the analysis to be performed, i.e analysis by season/by year (see Table 6).
- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints (not related to RSV): hMPV-confirmed LRTD/ARI, 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 the study vaccine to which they were randomized,
  - have data available for efficacy endpoint measures,
  - 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 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).

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 (RSV-confirmed ARI case reported prior to 1 month post-vaccination) will be used for identifying participants eliminated from mES (see Table 5).

- In addition, codes 2510 to 2550 will be used to eliminate participants from specific mES for analyses by season and by year (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, 900, 1030, 1050,1060, 2500 and 2600: participants will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2010, 2040, 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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	All	ES, mES*, PPSe, PPSi, SSS
1030	Study intervention not administered at all	All	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 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.	All	PPSe, PPSi
1050	Randomization failure: participant not randomized in the correct group (To be attributed by unblinded	Visit 1	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	Statistician only; Check SBIR, replacement, vaccine administration)		
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	PPSe, PPSi
1080	Vaccine administration after a Temperature deviation	Visit 1	PPSe, PPSi
1090	Vaccine administration after expiration	Visit 1	PPSe, PPSi
1160	Participant included in the reactogenicity subset who did not document any post-vaccination solicited safety data	Visit 2	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	All	PPSe, PPSi

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	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 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	All	PPSi and PPSe

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	alteration of their initial immune status.		
2090	Participants did not comply with blood sample schedule: • Number of days between vaccination and visit 2 blood sample is outside [28-42] days. For participants in the immunogenicity subset: • Date of BS at Pre-season 2 (Visit 3) is outside [15Aug-30Sep] in NH, or outside [15Jan-28Feb] in SH • Date of BS at Pre-season 3 (Visit 4 NH) is outside [15Aug-30Sep]	Visit 2, Visit 3, Visit 4NH	PPSi
2100	For participants in the immunogenicity subset: Serological results not available post-vaccination: No results available at all at the corresponding visit	Visit 2, Visit 3, Visit 4NH	PPSi
2120	Obvious incoherence/abnormality or error in laboratory data	Visit 2, Visit 3, Visit 4NH	PPSi
2500	Participant who report a RSV-confirmed ARI case prior to 1 month after vaccination: • Number of days between vaccination and day of onset of ARI case <30days	ARI visit	mES*, PPSe
2510**	Participant who report a RSV-confirmed ARI case after 1 month post vaccination and before start of season 1	ARI visit	mES-season 1
2520**	Participant who report a RSV-confirmed ARI case after 1 month post vaccination and before start of season 2	ARI visit	mES-season 2

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
2530**	Participant who report a RSV-confirmed ARI case after 1 month post vaccination and before start of season 3	ARI visit	mES-season 3
2540**	Participant who report a RSV-confirmed ARI case after 1 month post vaccination and before start of year 2	ARI visit	mES-year 2
2550**	Participant who report a RSV-confirmed ARI case after 1 month post vaccination and before start of year 3	ARI visit	mES-year 3
2600	Participants not included in the reactogenicity and immunogenicity subset	Visit 1	Solicited safety set, PPSi

*Applicable for the mES and all the specific mES for by season and by year analyses (mES-season 1, mES-season 2, mES-season 3, mES-year 2, mES-year 3)
** codes 2510 to 2550 are not considered as protocol deviations, but those codes will be used to eliminate participants from specific 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 4 RSVPreF3 vaccine lots will be pooled, and results will be presented for RSVPreF3 group versus Placebo group.

6.1. Analysis of demography and baseline characteristics

6.1.1. Analysis planned in the protocol

Demographic characteristics (age at 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 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.

Participant flow through the study will be presented in a summary table of participant disposition in analysis sets, visit attendance and withdrawals (consort table).

Medical history and baseline comorbidities will be tabulated by System Organ Class (SOC) 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 and the analysis on the PPSe, the time at risk will correspond to the period starting 1 month post-vaccination up to the first occurrence of event or up to censoring.

For the analysis on the ES, the full period from 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 RT-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 cases identified as follows:

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

- ARI cases for which signs and symptoms were not available (for example if the study participant is hospitalized or seen by another health care provider) but that had a confirmed LRTD diagnosis by the study investigator.
- **RSV-confirmed LRTD**: An event meeting the case definition of LRTD 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).

All clinically confirmed ARI cases by the investigator will be reviewed by GSK qualified staff in order to confirm if they meet the LRTD case definition of the study. Confirmation of the LRTD case will be reported in the eCRF and will be available in the SDTMs (see details in Section 10.3.1.3).

- For the primary analysis of the primary objective, 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 after at least 1 month post-vaccination (≥Day 31) and reporting up to the end of season 1 in NH for NH participants, and up to VE analysis 1 for SH participants (see Table 6).

The primary efficacy analysis (VE Analysis 1) will be performed:

- when participants enrolled in NH have been followed **at least** until the end of the first season (S1) in NH,
- **AND when at least 56 cases** of RSV-confirmed LRTDs have been accrued in the mES (in NH and SH).

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
/* OUTIST 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.

For the primary analysis on the mES, the follow up time will start at 1 month post-vaccination (Day 31) and will end

- **for participants who report a 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 a RSV confirmed LRTD:** at the end of season 1 in NH for NH participants, and at the cut-off date for VE Analysis 1 for SH participants. 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 6). 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% CI and p-value will be tabulated for primary efficacy endpoint.

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 computed from vaccination up to the time of data lock point for VE Analysis 1 will also be tabulated by group.

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>;
CLASS group age region;
MODEL futime*status(0)=group age region / TIES=EXACT RISKLIMITS;
RUN;
```

Kaplan-Meier survival curves for the vaccine and control groups will be presented together with p-values from the logrank test.

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.

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 a 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 (1 month post-vaccination (Day 31)) and the onset date of the event.
- If the participant do not report a 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 (1 month post-vaccination (Day 31)) and the end of considered period (end of season 1 in NH and cut-off for VE Analysis 1 in SH, i.e. the data lock point for efficacy).

  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 12.4.

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**.

Time of follow up for analysis on the PPSe will be the same as for mES: count cases starting from 1 month post-vaccination (Day 31) until the first occurrence of RSV-confirmed LRTD or until the time of VE Analysis 1 (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 efficacy data lock point or until withdrawal date if before the efficacy data lock point.

6.2.2.3.5. RSV-LRTD cases counting

- 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.).

6.2.2.3.6. Enrolment of a second cohort in NH

If following sample size re-assessment 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 (first 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 additional analyses by subgroup will be performed if at least 15 RSV-LRTD cases are reported in at least one of the subgroup categories.

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 endpoint(s)

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 specific mES as applicable (see Table 6). In addition, an analysis will be performed on the PPSe and on the ES to complement the primary analysis (see section 6.3.2.1.3).

- The **Exposed set** will be the primary population for efficacy analysis on the following endpoints: hMPV-confirmed LRTD/ARI, hospitalization, complications, any ARI, all-cause mortality.

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

The same methodology as described for the primary endpoint (see section 6.2) will be used to analyze the secondary efficacy endpoints listed below:

- VE against RSV confirmed LRTD over several seasons: VE will be evaluated over 2 seasons at the end of season 2 in NH, and over 3 seasons at the end of season 3 in NH (confirmatory objective),
- VE against severe RSV-confirmed LRTD according to case definition 1 and case definition 2,
- VE against RSV-confirmed ARI,
- VE against hMPV LRTD.

For analysis over 2 or 3 seasons (VE Analysis 2 and 3), the model will include season as covariates, 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.

In addition, **VE against RSV-confirmed LRTD** will be evaluated on the following sub-categories:

- **VE by age category:** on participants ≥65 YOA, ≥70 YOA and ≥80 YOA at the time of vaccination. VE will also be computed for participants in 60-69 YOA and 70-79 YOA.
- **VE by RSV subtype**: on RSV A and RSV B RT-PCR confirmed cases separately.
- **VE by season:**
  - VE during Season 1 in NH and SH including first occurrence of cases reported during season 1 after at least 1 month post-vaccination;

- VE during Season 2 in NH and SH, including first occurrence of cases reported during Season 2 and excluding from the analysis participants who already reported a RSV-confirmed LRTD before the start of Season 2;
- VE during Season 3 in NH and SH (partial S3 in SH), including first occurrence of cases reported during Season 3 and excluding from the analysis participants who already reported a RSV-confirmed LRTD before the start of season 3.

The time at risk for the analysis by season will be the period from the start of the corresponding season until the event or until withdrawal date or until the end of the season (see description of the season in each hemisphere in Figure 2).

- **VE by year:**
  - VE during the first year post-vaccination (Year 1) in NH and SH including first occurrence of cases reported after at least 1 month post-vaccination, and up to 12 months post-vaccination;
  - VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases during Year 2 (12 to 24 months post-vaccination) and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases during Year 3 (24 months post vaccination up to study end) and excluding from the analysis participants who already reported a RSV-confirmed LRTD during Year 1 and/or Year 2.
- **VE by baseline comorbidities**: using the Charlson index and according to comorbidities of interest (see details in section 6.3.2.1.1):
  - COPD,
  - Asthma,
  - Any chronic respiratory/pulmonary disease,
  - Diabetes mellitus Type 1 or Type 2,
  - Chronic heart failure,
  - Advanced liver or renal disease.
- **VE by baseline frailty status.**

VE in the prevention of hospitalization during the RSV seasons 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.

VE in the prevention of complications related to RSV-confirmed ARI and related to any ARI during the RSV seasons will also be evaluated.

VE against RSV-confirmed LRTDs over time will be explored using the Cox proportional hazard regression model. 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. In addition, 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 7).

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;
- GMT/GMCs and their 95% CIs;
- Distribution of antibody titers/concentrations using reverse cumulative curves;
- MGI (mean geometric increase) with 95% CI.
- Distribution of the fold increase of the antibody titers/concentrations post-vaccination over pre-vaccination.

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 on the Solicited Safety set:

- 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. 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).
- 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.
- 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.
- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for 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 during the 30-day follow-up period with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class and Preferred Term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The analyses of unsolicited AEs will include SAEs (unless otherwise specified).
- The verbatim reports of unsolicited AEs, including SAE, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Preferred Terms and reported from vaccination up to 6 months post-vaccination will be tabulated 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 Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be presented for fatal SAEs and causally related pIMDs.
- SAEs/pIMDs will also be described in detail in a tabular listing.
- The number and percentage of participants using concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after vaccination will be tabulated with exact 95% CI.
- AEs/SAEs leading to study/intervention discontinuation from vaccination up to study end will be tabulated.

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 pre-Seasons 1 and 2 will be presented for the **mES.**

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

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

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

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 is provided in Section 4. Description and identification of RSV-confirmed LRTDs is further described in Section 6.2.2.1.

For analysis of VE against **RSV**, the number of cases will be counted based on the first occurrence of the RSV-confirmed case, starting after at least 1 month post-vaccination (≥Day 31), 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**, the number of cases will be counted based on the first occurrence of the hMPV-confirmed case, starting after at least 1 month post-vaccination (≥Day 31), 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 and VE by season

For analysis over the first 2 seasons (S1+S2) and over 3 seasons (S1+S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, starting after at least 1 month post-vaccination (≥Day 31) and reporting up to the end of season 2 in NH (VE Analysis 2) or up to end of season 3 in NH (VE Analysis 3).

For analysis over the last 2 seasons (S2+S3), the number of cases will be counted based on the first occurrence of the RSV-confirmed LRTD, reporting from the start of season 2 in each hemisphere up to the end of season 3 in NH (VE Analysis 3).

- For VE reported **by season**, only cases 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	
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 than 7
- High Risk = Participants with co-morbidity score at baseline greater than or equal to 7.

Those VE analyses will be performed at VE analysis 1 and VE analysis 2 **only if at least 15 RSV-LRTD cases** are reported in at least one of the categories. At VE analysis 3 (EoS), analysis will be performed whatever the number of cases in each category.

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:

- Hospitalizations due to respiratory diseases, i.e. due to any respiratory complications,
- The same analysis will be performed on 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,

- The same analysis will be performed on 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.

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 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 LRTD cases.
- The number and percentages of participants who reported 2, 3, 4 or more symptoms/signs for RSV-ARI and RSV-LRTD cases will be tabulated by group with exact 95% CI,
- The number and percentages of participants who reported a 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 ARI cases.

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 6 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 6 depending of the type of analysis, for participants who do not report the event of interest.

Table 6 Rules for counting cases and follow-up time

VE time period	Start date1 for Cases count and FU time	Participants to be excluded from analysis	End date2 for case count and FU time	Model Covariates	Analysis Set
After 1 season (VE analysis 1)	1 month post-vaccination (>=D31)	Participants who reported RSV cases before 1 month post-vaccination	End of season 1 in NH for NH participants, and cut-off date for VE Analysis 1 for SH participants	Age, region	mES, PPSe, ES[3]
Over 2 seasons (S1+S2)	1 month post-vaccination (>=D31)	Participants who reported RSV cases before 1 month post-vaccination	End of season 2 in NH for all participants (NH and SH)	Age, region, season	mES, PPSe, ES[3]
Over 3 seasons (S1+S2+S3)	1 month post-vaccination (>=D31)	Participants who reported RSV cases before 1 month post-vaccination	End of season 3 in NH and end of study for SH	Age, region, season	mES, PPSe, ES[3]
Over 2 seasons (S2+S3)	Start of season 2	Participants who reported RSV cases before start of season 2	End of season 3 in NH and end of study for SH	Age, region, season	mES – season 2, PPSe - season 2, ES
Season 1	Start of season 1, after at least 1 month post-vaccination (>=D31)	Participants who reported RSV cases before the start of season 1	End of season 1 in NH and SH	Age, region	mES – season 1
Season 2	Start of season 2	Participants who reported RSV cases before the start of season 2	End of season 2 in NH and SH	Age, region	mES – season 2
Season 3	Start of season 3	Participants who reported RSV cases before the start of season 3	End of season 3 in NH and end of study for SH	Age, region	mES – season 3
Year 1	1 month post-vaccination (>=D31)	Participants who reported RSV cases before 1 month post-vaccination	12 months post-vaccination	Age, region, season	mES
Year 2	>12 months post-vaccination	Participants who reported a RSV case up to 12 months post-vaccination	24 months post-vaccination (Year 1 + 12 months)	Age, region, season	mES – Year 2
Year 3	>24 months post-vaccination	Participants who reported a RSV case up to 24 months post-vaccination	EoS4	Age, region, season	mES – Year 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 2 or 3.

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

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

Confirmatory secondary objective: The efficacy of RSV vaccine against RSV-confirmed LRTD over 2 seasons and over 3 seasons 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 computed from vaccination up to the time of data lock point for VE Analysis 2 and 3 will be tabulated by group.

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 6).

Time of follow up for analysis on the PPSe will be the same as for mES (see Table 6).

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 time of VE Analysis 2 or 3 or until withdrawal date if before the efficacy data lock point.

LRTD cases counting rules

- A 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 second 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.

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 7.

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 7 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 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).

Analysis by subgroup will be performed if at least n=15 RSV-LRTD cases are reported in at least one of the subgroup category.

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 vaccination 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 vaccination will also be represented **graphically** per group with exact 95% CI.
- The list solicited administration site and systemic events, and definition of intensity are described in Section 10.3.3 and 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 8 Intensity grading scale for solicited events

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

6.3.2.2.2. Unsolicited AEs

- The number and percentage of participants with any unsolicited AEs with exact 95% CI will also be tabulated by group and by MedDRA Primary System Organ Class and Preferred Term for:
- Any unsolicited AEs reported during the 30-day follow-up period, on the Solicited safety set (reactogenicity subset)
- Any unsolicited AEs 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.

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	10015150	Erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Pyrexia
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

The exact 95% CI for the relative risk (exact conditional to total number of cases) between the two groups and the associated 2-sided p-value will be computed for the following endpoint:

- The percentage of participants with at least one report of SAE from vaccination up to 6 months post-vaccination, presented by MedDRA Primary System Organ Class (SOC), and presented by MedDRA Primary SOC and Preferred Term (PT).

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. In order to put any safety signal in perspective, a permutation test will be conducted to quantify the probability to observe at least one false safety signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility will need to be accounted before establishing causality.

The following section describes the proposed approach to help detection of safety signal.

AE signal method

The following summary tables and figures will be generated:

Analysis by SOC:

- The relative risk between groups of participants reporting the occurrence of SAEs from vaccination up to 6 months post-vaccination, classified by MedDRA Primary SOC.
- The same table presenting a subset of SOC of interest selected by adjusted p-value lower than 15%. This table will be sorted by p-values (lowest to highest).
- The plot of probability of false signal (=adjusted p-values) for analysis on SOC.

Analysis by SOC/PT:

- The relative risk between groups of participants reporting the occurrence of SAEs from vaccination up to 6 months post-vaccination, classified by MedDRA Primary SOC and PT.

- The same table presenting a subset of SOC & PT of interest selected by adjusted p-value lower than 15%. This table will be sorted by p-values (lowest to highest).
- The plot of probability of false signal (=adjusted p-values) for analysis on SOC and PT.

The plot of **probability of false signal** will be built on the whole data set used to produce the summary table by SOC or by SOC/PT. The plot will be zoomed to have in Y-axis adjusted p-values between 0 and 0.15. SOC or SOC/PT with adjusted p-value below 15% will be considered to identify SAE of interest for further review.

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 2001]
- 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 [Leidos Biomedical research 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.

All QoL assessments during the RT-PCR-confirmed RSV episode will be analyzed by timepoint relative to ARI onset (see section 4).

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 (see section 4):

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 by vaccination group for each season and also combined season. The domain scores recorded at the beginning of the confirmed RSV-ARI episode will be presented by vaccination group, season and combined seasons 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 and also combined seasons.

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

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

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 strata and sex as fixed effects and will include participants in the mES RSV-confirmed ARI cohort. 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: CCI [redacted] CCI [redacted] 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 CCI [redacted] to 4 CCI [redacted]

The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 CCI [redacted] to 4 CCI [redacted] CCI [redacted]

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 and will presented by season and combined seasons.

The maximum (worst) score for each FLU-PRO domain during the first 7 days of the episode will also be calculated. The differences between vaccination groups will be compared using a non-parametric Wilcoxon rank test.

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

The individual domain scores will also be presented by 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, region (Southern, Northern Hemisphere), study group and study group by time interaction. The least squares mean (LSMEANS) estimates for time by study group and the difference in least squares means and associated P-values will be obtained from the ANOVA model. The PROC MIXED procedure in SAS® will be used to carry out the ANOVA, with all terms fitted as fixed effects. See section 10.3.3.4 for further details.

6.4. Tertiary/Exploratory endpoint(s)

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 Sections 6.2 and 6.3, respectively) will be used to analyze the following tertiary endpoints:

- VE against RSV and/or hMPV-confirmed LRTDs,
- VE against severe hMPV-confirmed LRTDs according to the case definition 1 and case definition 2,

- VE against RSV-confirmed ARI by RSV subtype, by age category, by season and VE over time,
- VE against any ARI and any LRTD,
- 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.

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. Quality of Life

For each confirmed case of RSV LRTD, 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.

6.4.1.3. Analysis of HCRU

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

- The number/percentage of participants who were hospitalized during the ARI episode or complication related to ARI,
- The number/percentage of participants who received antibiotics for the treatment of ARI or complication related to ARI.
- For any other count variables that will be reported (e.g. any medication or any medical visit), the number and percentage of events/participants will be presented by group.

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-vaccination (Day 1) and 1 month post-vaccination (Day 31) and may be tested for correlate of protection analysis in all participants with RSV-confirmed disease and in a subset of control participants.

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

Statistical analysis will be done in several steps:

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

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

6.4.1.4.2. Sub-groups analysis

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

6.4.2. Additional considerations

6.4.2.1. Analysis of recurrent events

VE analysis of any ARI and any 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.

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. PGI-S, PGI-C

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.

In addition, 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 vaccination groups using a Wilcoxon non-parametric test.

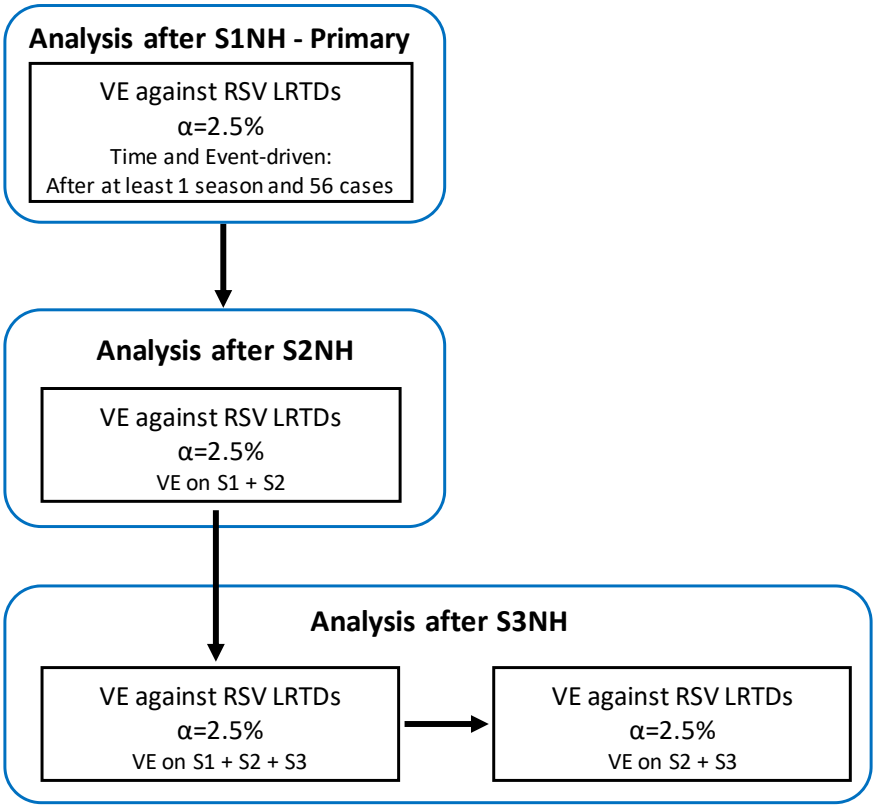
7. ANALYSIS INTERPRETATION

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

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%.

Figure 3 Sequential evaluation of primary and confirmatory secondary objectives



S1/S2/S3=Season 1/2/3
NH= North Hemisphere
VE=Vaccine efficacy

All the objectives will be evaluated, but if one of them fails to be demonstrated, the remaining 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

Subgroups 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

No interim confirmatory analysis will be performed. The first analysis will be performed for the safety and immunogenicity objectives when all safety data up to 6 months post-vaccination will be available for all participants in NH. The second analysis (VE Analysis 1) will be the final analysis of the primary objective.

8.2. Sample size re-assessment

Due to uncertainty about the attack rate and expected VE used for sample size calculation and the potential impact of measures taken for the COVID-19 pandemic on RSV circulation, an analysis will be performed during the first RSV season in NH to evaluate the potential need of sample size increase by enrollment of a second cohort. The analysis will be performed by an independent external statistician (IES) in order to ensure blinding of the GSK study team. It will be conducted before any other analyses.

The analysis for sample size re-assessment will be based on cases reported up to the end of February (Study Year 2 in Figure 2), considered as the end of the peak of the first RSV season in the NH. The outcome will be reviewed by the IDMC who will make recommendations according to pre-specified criteria based on the probability of success (PoS) of the final analysis. This PoS will be computed using observed values of attack rate and vaccine efficacy at the time of interim analysis.

The GSK study team will not have access to the data/analysis and will only receive the recommendation from IDMC to:

- **Continue the study as planned:** In that case, the VE Analysis 1 will be performed as planned or at the end of Season 1 in SH at the latest, OR
- **Enroll a second cohort:** In that case, new participants in NH will be enrolled and vaccinated before the next season in NH (i.e., before 1 October of Study Year 2, see Figure 2). Therefore, Season 1 for the second cohort will start on 1 October of Study Year 2 and will end on 30 April of Study Year 3, and the VE Analysis 1 will be delayed to the end of Season 1 for that second cohort (30 April of Study Year 3, see Figure 2), in order to increase the number of cases needed to demonstrate the primary objective.
- The VE analysis 1 will then be time driven including cases accrued from all participants (first cohort in NH, first cohort in SH and second cohort in NH) during their respective first RSV season. This analysis will be performed irrespective of the total number of cases. 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 preliminary simulated results and feasibility for enrollment before the next season, it is estimated that a maximum number of 10 000 participants might be enrolled in that second cohort.

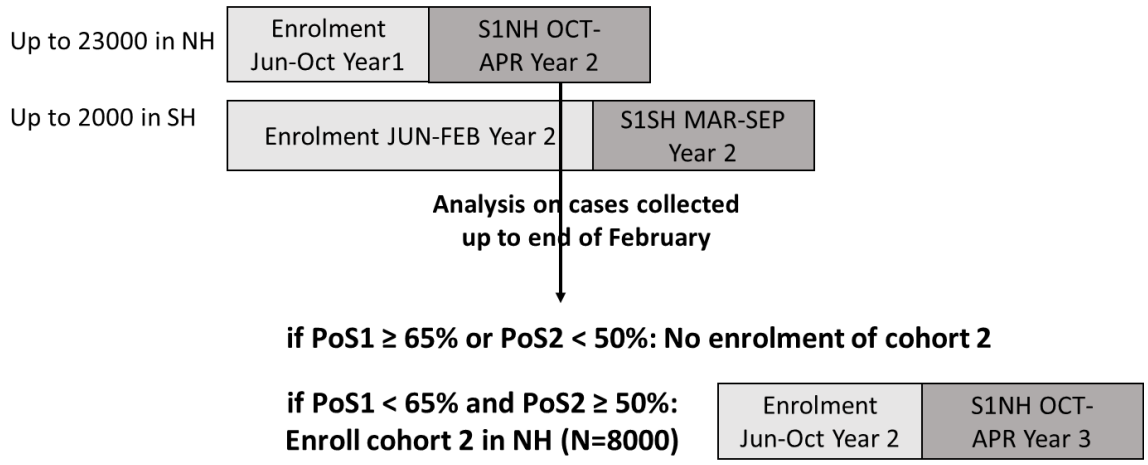
Simulations were performed to evaluate: the control of Type 1 error, the power of the study according to several scenarios of VE and number of cases accrued at the time of interim analysis, the PoS with the first cohort only (PoS1) and with the addition of the second cohort (PoS2), and the power of the adaptive design. The methodology and the results of those simulations are presented in section 12.3.

Results of simulations showed that the proposed design with re-enrolment based on PoS control the Type 1 error of the study (see section 12.3.2).

According to those results, the following criteria have been defined (see Figure 4):

- If the PoS1 is ≥ 65%: the study will continue as planned, and no second cohort will be enrolled.
- If the PoS1 is <65%, then the decision rule will be based on PoS2:
  - If PoS2 is ≥ 50%: the second cohort will be enrolled
  - If PoS2<50%: the study will continue as planned, and no second cohort will be enrolled.

Figure 4 Decision rules for sample size re-assessment analysis based on cohort 1 with up to 25000 participants and cohort 2 with 8000 participants



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 find in Figure 3.

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

1. **Safety/immunogenicity analysis:**

   An analysis of the safety and immunogenicity objectives will be performed when all safety data up to 6 months post-vaccination will be available for all participants in NH. The immunogenicity and reactogenicity analysis will be performed on all participants (NH+SH) included in the subset. The safety analysis up to 30 days post-

vaccination will be performed on all participants (NH+SH) while the safety analysis up to 6 months post-vaccination will be performed on participants in NH.

Additional safety follow-up data (fatalities, other SAEs, pIMDs, other unsolicited AEs of interest) collected from the study participants after the data lock point for the primary safety analysis will be verified to ensure they do not prompt any changes to the safety conclusions.

2. VE Analysis 1: after at least 1 season in NH

An analysis will be performed to evaluate the efficacy and safety objectives after at least 1 season. This analysis will be time and event driven. It will be performed:

- When participants enrolled in NH have been followed **at least** until the end of the first season (S1) in NH,
- **AND when at least 56 cases** of RSV-confirmed LRTDs have been accrued in the primary cohort for efficacy.

This analysis will be considered as the final analysis of the primary objective.

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

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

The 3 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 study team. Further details of this approach can be found in the firewall charter.

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

4. VE Analysis 3: after 3 seasons in NH (End of Study)

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 5NH) and end of study in SH (Visit 4SH).

VE Analysis 3 will be performed when all data related to the primary and secondary objectives have been collected, according to RSV season.

Individual data listings will only be generated at this stage.

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal
Safety/immunogenicity analysis	SR, CTRS
VE Analysis 1	SR, CTRS
VE Analysis 2	SR
VE Analysis 3	SR, CTRS

9. CHANGES TO THE PROTOCOL DEFINED STATISTICAL ANALYSES

There were no changes or deviations to the planned statistical analysis specified in the protocol amendment 1 (Dated: 25 February 2021). This statistical analysis plan complements the analyses described in the protocol with descriptive summaries, sensitivity and supportive analyses.

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. 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.

10.3. 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 6. 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 [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 clinically confirmed ARI cases by the investigator (i.e. an ARI meeting the case definition according to investigator's assessment) will be reviewed by blinded GSK qualified staff in order to confirm if they meet the LRTD case definition of the study. This review will be performed independently of the results of the RSV RT-PCR. Detailed information on this adjudication process can be found in the adjudication charter.

10.3.1.4. Assessment of RSV or hMPV cases

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 that is positive by the **quantitative RT-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 other respiratory virus (co-infection).

If the result of GSK PCR is not available and if a external local PCR test has been performed, this result will be use in the primary analysis for RSV and hMPV. Only local test performed in a certified laboratory and using a CE-marked or a FDA-approved kit will be considered for analysis. Those 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 after at least 1 month post-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) [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 9).

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 9 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 Dementia Mild Liver Disease Hemiplegia or Paraplegia Any malignancy including Leukemia and Lymphoma	2 (1.5<=RR<2.5)
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. They will be reviewed by a qualified person and will be coded according to the MedDRA Dictionary.

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

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
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 CCI (score=1), CCI CCI (score=1), CCI (score=1), CCI (score=2) and CCI CCI (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
	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

Domain	Component Questions
	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. Region (Northern Hemisphere, Southern Hemisphere) will also be included. The model will include only data from day 1 to day 7 inclusive.

The SAS code is as follows:

```
ODS OUTPUT LSMeans=LSMeans;
ODS OUTPUT estimates=estim;

PROC MIXED DATA=FLUPRO;
      CLASS pid day vacc_grp region;
      MODEL flu_pro=region day vacc_grp day*vacc_grp/s cl;
      REPEATED day/type=un subject=pid;
      LSMEANS day/pdiff cl;
      LSMEANS day*vacc_grp/pdiff cl;
      ESTIMATE "Day 1 - Day 7 Vaccinated group" intercept 7 region 3.5 3.5
      vacc_grp 7 0 day 1 1 1 1 1 1 1 day*vacc_grp 1 0 1 0 1 0 1 0 1 0 1 0 1 0/divisor=7;
      ESTIMATE "Day 1 - Day 7 Placebo" intercept 7 region 3.5 3.5 vacc_grp 0 7 day
      1 1 1 1 1 1 1 day*vac_grp 0 1 0 1 0 1 0 1 0 1 0 1 0 1/divisor=7;
RUN;
```

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 strata and sex as fixed effects.

In the following code Visit can have 3 values, “Pre-Season ”, “ARI Visit” or “Pre next season”

```
ODS OUTPUT LSMeans=LSMeans;
ODS OUTPUT estimates=estim;

PROC MIXED DATA=SF12_PF;
      CLASS pid visit vacc_grp age_grp sex;
```

```
MODEL PF=visit age_grp sex vacc_grp visit*vacc_grp/s cl;
REPEATED visit/type=un subject=pid;
 LSMEANS visit/pdiff cl;
 LSMEANS visit*vacc_grp/pdiff cl;
 ESTIMATE "ARI Visit Vaccinated group" intercept 3 age_grp 1.5 1.5 sex 1.5
1.5 vacc_grp 3 0 visit 0 1 0 visit*vacc_grp 1 0 1 0 1 0/divisor=3;
 ESTIMATE "ARI Visit Placebo" intercept 3 age_grp 1.5 1.5 sex 1.5 1.5
vacc_grp 0 3 visit 0 1 0 visit*vacc_grp 0 1 0 1 0 1/divisor=3;
RUN;
```

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. For the definition of the phases of the COVID-19 pandemic measures see Section 11.4.

A country level listing of the dates of the COVID-19 pandemic measures, and a figure showing enrolment over time by country, relative to the COVID-19 pandemic measures will be produced.

The ‘Summary of participant status and participant disposition for the Study Conclusion Record’ will include the reason withdrawal/discontinuation due to issues related to the COVID-19 pandemic.

11.1.2. Protocol deviations

In addition to the overall summary of important protocol deviations, separate summaries will be produced of important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19. A listing of non-important protocol deviations related to COVID-19 will also be produced.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be tabulated.

11.1.3. 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.

Summaries and listings of the numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be based on GSK Core Data Standards.

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.

11.1.4. 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 incidence of COVID-19 AEs and SAEs (Fatal and Non-Fatal), and COVID-19 AEs leading to study withdrawal, and COVID-19 AEs by severity (Grade 3), 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 reported as AE, then the following data displays will be produced:

- Summary of Onset and Duration of the first Occurrence of COVID-19 AEs (produced overall, and for each preferred term mapping to the coronavirus infections high-level term)
- Summary of Characteristics of COVID-19 AEs (produced overall, and for each preferred term mapping to the coronavirus infections high-level term)

For SAEs, the following data displays will be produced:

- Summary of Onset and Duration of the First Occurrence of a COVID-19 reported as SAE (produced overall, and for each preferred term mapping to the coronavirus infections high-level term)
- Summary of Characteristics of COVID-19 reported as SAEs (produced overall, and for each preferred term mapping to the coronavirus infections high-level term)

11.3.2. Impact of COVID-19 pandemic on safety results

The following tables will be produced, showing the incidence rates for events occurring before or after the start of the COVID-19 pandemic measures. The phases (before and after the start of the COVID-19 pandemic) are defined in Section 11.4:

- The overall number of AEs, Grade 3 AEs and SAEs
- The overall number of AEs, Grade 3 AEs and SAEs by region
- The overall number of AEs, Grade 3 AEs and SAEs by age group
- The overall number of AEs, Grade 3 AEs and SAEs by sex
- Most frequent adverse events (those occurring in ≥5% of participants) by preferred term.

11.4. Phases of COVID-19 pandemic measures

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 pandemic measures within each country, if applicable at the time of study conduct. A copy of this dataset will be taken at the time of database freeze (DBF).

If applicable at the time of study conduct, adverse events will be summarized according to whether the onset date was before or after the start of the pandemic measures.

Pandemic Measures Phase	Definition
Before	AE onset date < pandemic measures start date
During	AE onset date within pandemic measures phase
After	AE onset date > Pandemic measures end date

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.

- When the occurrence of a specific solicited event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question) but the group of solicited events (administration site or systemic) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all 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. Duration of events

The duration of an event with a start and end date will be the difference between the start and end 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 solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited event period.

12.1.3.10. 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.

12.1.3.11. 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, geometric mean titers (GMT) or concentrations (GMC) 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].

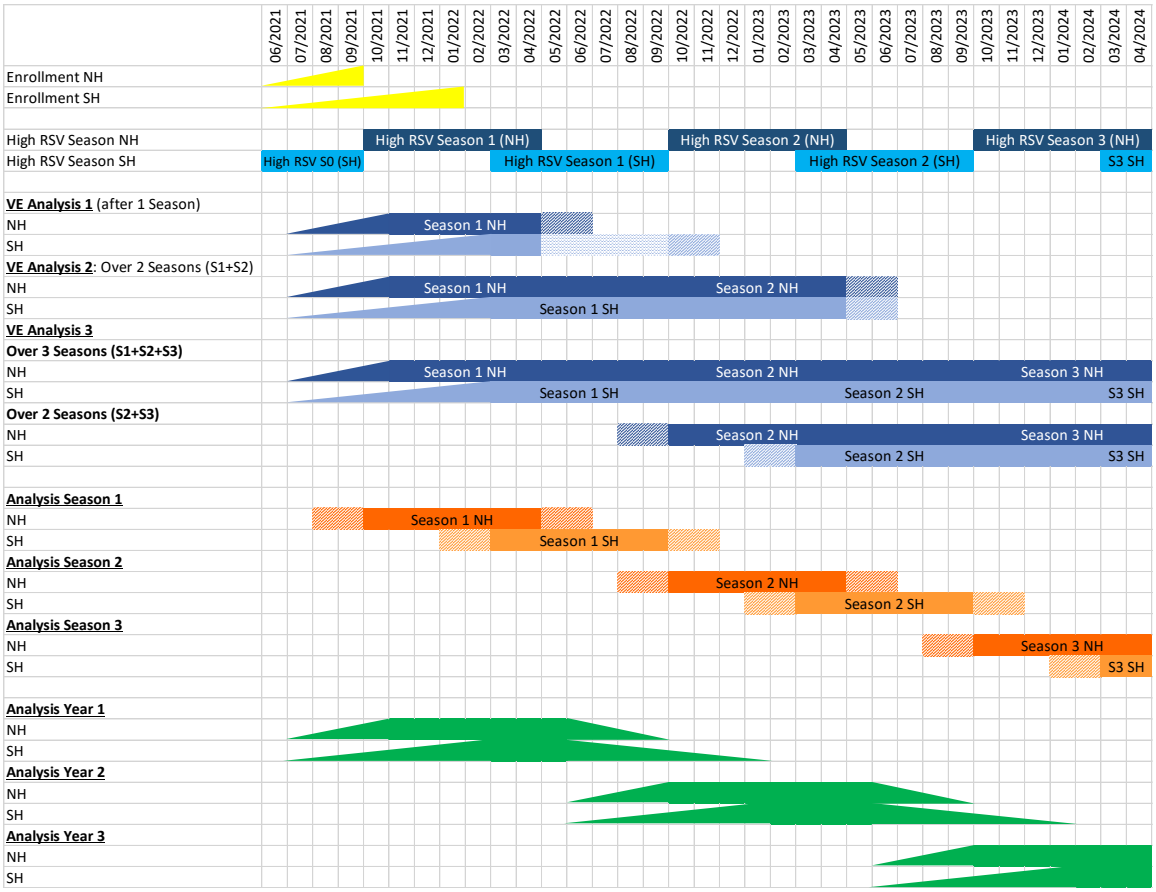
12.1.5.2. Standardised asymptotic confidence intervals around differences in proportions

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 period for case counting and follow-up time of each analysis, as described in Table 6.

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



12.3. Sample size re-assessment

12.3.1. Statistical Methodology

We proposed an adaptive sample size re-estimation based on unblinded interim estimates of the primary effect size similar in spirit to Casula et al [Casula, 2020]. The main difference is that i) they defined the re-enrollment on the VE estimated at interim, while we propose to use the Probability of Success (PoS) [Spiegelhalter, 1986]. The reason why we considered the PoS (instead of VE) is because this measure takes into account the VE and of the attack rate as well (both unknown at the beginning of the trial).

In this section, we will focus on the statistical methodological aspects.

1) Preserving overall type- I error: promising zone approach

Chen, DeMets and Lan (2004) showed that conventional hypothesis test can be performed without inflating the type-1 error if the sample size is increased only when interim results are *promising* [Chen, 2004]. Mehta and Pocock (2011) defined the promising regions for a two-stage design under different adaptive rules based on conditional power [Mehta, 2011]. Other papers discussing the possibility to increase the sample size if the results at the interim analysis are promising [Muller, 2004; Gao, 2008; , Bretz, 2009; Mehta, 2011; Jennison, 2015; Casula, 2020].

The proposed design for this study is based on the promising zone concept (promising interim results) and is similar in spirit to the design proposed by Casula et al. [Casula, 2020].

2) Statistical Methods in more details

Notations

We use a 1:1 randomization ratio, and we denote by n_{int} the number of RSV LRTD cases at the interim analysis and VE_{int} the vaccine efficacy estimated at the interim analysis.

Sample size enrichment based on PoS at interim

Sample size re-assessment is done at interim on the bases of the Probability of Success (PoS) computed at the end of season 1 in cohort 1(PoS1 – no sample size enrichment) and at the end of season 1 in cohort 1 + cohort 2 (PoS2 – sample size enrichment). The following criteria have been defined based on simulation results:

- if PoS1 is ≥ 65%: the study will continue as planned, and no second cohort will be enrolled.
- if PoS1 is <65%, then the decision rule will be based on PoS2:
  - If PoS2 is ≥ 50%: the second cohort will be enrolled
  - If PoS2 <50%: the study will continue as planned, and no second cohort will be enrolled.

Poisson approximation (conditioning to the total number of cases)

We used the Poisson approximation approach. Given the total number of events $n=n_V+n_C$, the number of cases in the vaccine group is $n_V \sim Bin(n|\lambda)$ where $\lambda = (1-VE)/(2-VE)$ (in case of 1:1 randomization). Therefore, the null hypothesis is equivalent to H0: $\lambda > \lambda 0$ vs H1: $\lambda \leq \lambda 0$; where $\lambda 0 = (1-VE0)/(2-VE0)$.

PoS computation

Spiegelhalter and Freedman (1986) proposed to compute the probability of success of a trial using Bayesian methods, so-called the "hybrid classical–Bayesian" approach. This

probability has also been referred to as the "expected power" or "average power" [Gillett, 1994], or Assurance [O'Hagan, 2005].

We denote R the event of rejecting the null hypothesis. The conventional definition of power is Pr(R| λ), where λ is the vaccine effect (as described above). The assurance is the expected power as follows

$$PoS = \int Pr(R|\lambda)Pr(\lambda)d\lambda$$

Following the notation in [O'Hagan, 2005], the asymptotic formula of PoS_j, j=1,2 is given by

$$PoS_j = 1 - \Phi\left(\frac{-\tau_j Z_\alpha + \lambda_{int} - \lambda_0}{\sqrt{\tau_j^2 + \nu}}\right)$$

where λ_{int}= (1−VEint)/(2-VEint) is the effect estimated at interim; λ_0 is the effect under the null hypothesis; $\nu = \lambda_0 (1- \lambda_0)/n$ int is the variance of the vaccine effect at end of j-th stage (under the null hypothesis - score test); $\tau_j^2 = \lambda_0 (1- \lambda_0) /n_j$ is the variance of the effect at the end of the jth stage (under the null hypothesis); z_α is the α quantile of the normal distribution; α is the significance level.

12.3.2. Simulation Scenarios and Operating Characteristics

We evaluated the proposed design through simulation of thousands of trials. We considered several possible scenarios for the attack rate of RSV LRTD and the vaccine efficacy. We generated data according to each of those scenarios and run through interim analyses as specified in the design described above. We repeated this process to create multiple "virtual trials" and track the behavior of each trial.

The following assumptions were taken to perform the simulations:

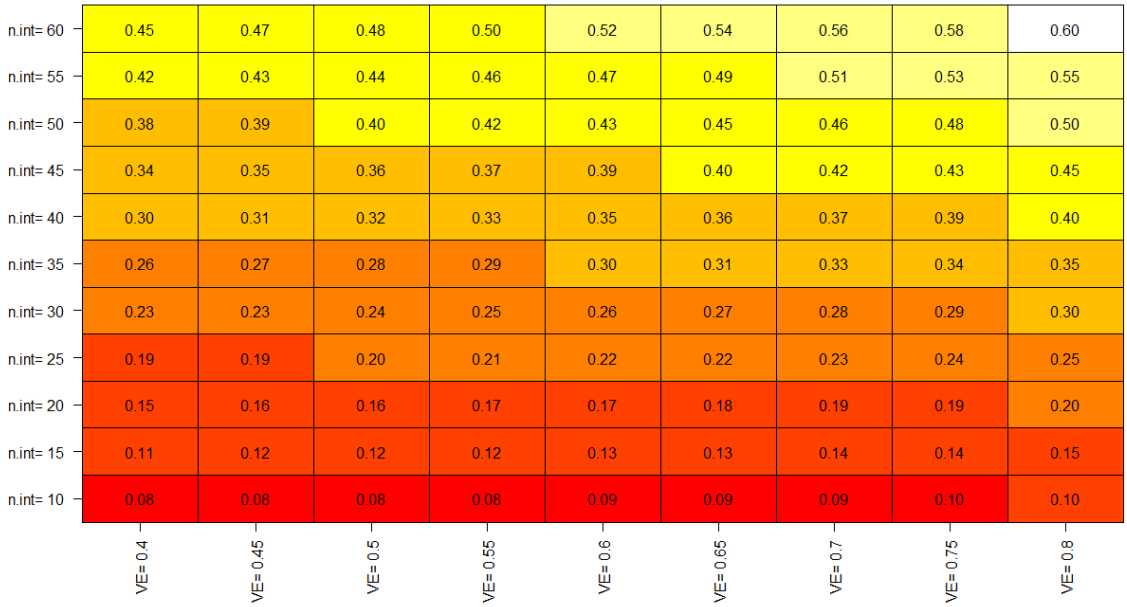
- Cohort 1: 23000 participants in NH and 2000 participants in SH
- constant (and unknown) AR in season 1 for cohort 1 (before and after interim),
- Cohort 2: 8000 participants
- Fixed AR of 0.6% in season 1 for cohort 2 (enrichment),
- Information available at the time of interim (end of the peak): 80% of the cases accrued during season 1 in NH.
- 10% drop-out rate during season 1
- **Vaccine Efficacy**

We consider 9 scenarios for the underlying true vaccine efficacy of the RSV vaccine on RSV LRTD. Ranging from VE=0.4 up to VE=0.8.

- **Attack Rates in cohort 1 (number of cases at interim)**

Since we used the Poisson approximation approach, which is conditioned to the total number of cases, we generated simulation results as a function of the observed number of cases at interim (nint), ranging from 10 to 60. Figure 6 shows the AR as a function of nint and VE.

Figure 6 Attack Rate in Cohort 1 as a function of the number of cases at interim (nint) and VE



We can see from Figure 6 that the AR considered in the different scenarios ranges from 0.08% (n.int=10 and VE=0.4) up to 0.6% (n.int=60 and VE=0.8).

Operating Characteristics

For each of the scenarios described above, we simulate 10,000 trials and track the behavior of each trial, including but not limited to the final outcome of each trial. The results in this section are summarized across all simulated trials for each scenario. Table 10 and Table 11 report the following information per scenario:

- Mean N: The mean total sample size of subjects randomized, computed as Ncohort 1 + Ncohort2 * Pr(Cohort2).
- Pr(Success): probability that the trial declares success (*i.e.*, power or type I error)
- Pr(Cohort2): probability that cohort 2 is enrolled
- Pr(Early Success): probability that the trial achieves success at the end of season 1 in cohort 1.
- Pr(Early fail): probability that the trial continue with cohort 1 only (no enrichment)and fails to meet the final success criterion, while trial would have been successful with enrolment of cohort 2.
- Pr(Delay): probability that cohort 2 is enrolled while trial would have been successful at the end of season 1 with cohort 1 only.

- Median(PoS1): median PoS1
- Median(PoS2): median PoS2

Operational characteristics under the null hypothesis

The type I error is the probability of success of trials under the null hypothesis.Table 10 shows the operating characteristics of the design with PoS1.threshold=0.65 and PoS2.threshold=0.5, under the null hypothesis.

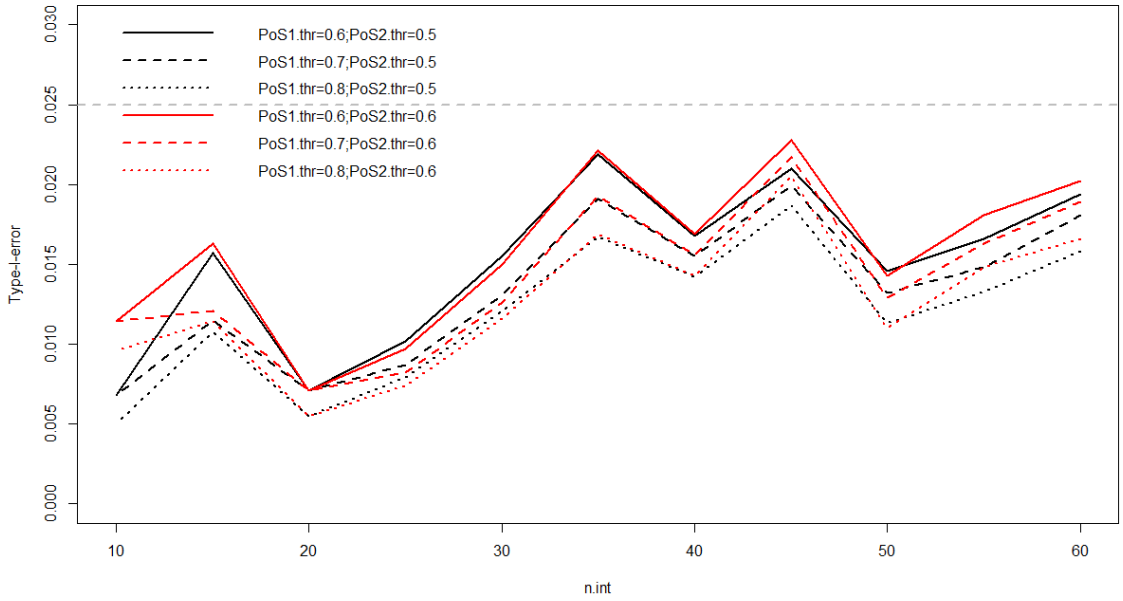
Table 10 Operating Characteristics of the adaptive design under the null hypothesis (VE= 0.2) of the adaptive design with PoS1.threshold=0.65 and PoS.threshold=0.5.

VE	n.int	Mean N	Pr(Success) [type I error]	Pr(Cohort 2)	Pr(Early Succ)	Pr (Early fail)	Pr(Delay)	Median PoS1	Median PoS2
0.2	60	25329	0.018	0.041	0.012	0.006	0.009	0.075	0.096
	55	25364	0.015	0.046	0.009	0.006	0.011	0.099	0.128
	50	25291	0.015	0.036	0.01	0.007	0.006	0.091	0.121
	45	25307	0.021	0.038	0.014	0.012	0.012	0.082	0.112
	40	25579	0.017	0.072	0.007	0.008	0.011	0.073	0.103
	35	25598	0.019	0.075	0.008	0.009	0.015	0.065	0.094
	30	25586	0.013	0.073	0.004	0.009	0.012	0.093	0.14
	25	25482	0.01	0.06	0.005	0.009	0.004	0.082	0.13
	20	25452	0.007	0.056	0.004	0.007	0.009	0.069	0.118
	15	26018	0.012	0.127	0.001	0.01	0.021	0.054	0.104
	10	25834	0.007	0.104	0.002	0.007	0.017	0.098	0.203

Table 10 shows a good control of Type I error (maximum Type I error =2.1%). Under the null hypothesis, only 6% of trials (on average) enroll cohort 2. The average number of enrolled subjects is about 25500.

Figure 7 shows the Type I error for the adaptive design as a function of number of cases at interim and the thresholds used for PoS1 and for PoS2.

Figure 7 Type I error as a function of PoS thresholds (and number of cases at interim (n_{int})).



Irrespectively of some random fluctuation, Figure 7 shows that the Type-I-error is well controlled for the different values of the thresholds considered. In particular, black solid line is always below 0.025.

More details about the relationship between Type-I-error and the two thresholds is provided in the appendix Figure 11.

Operational characteristics under the alternative hypothesis

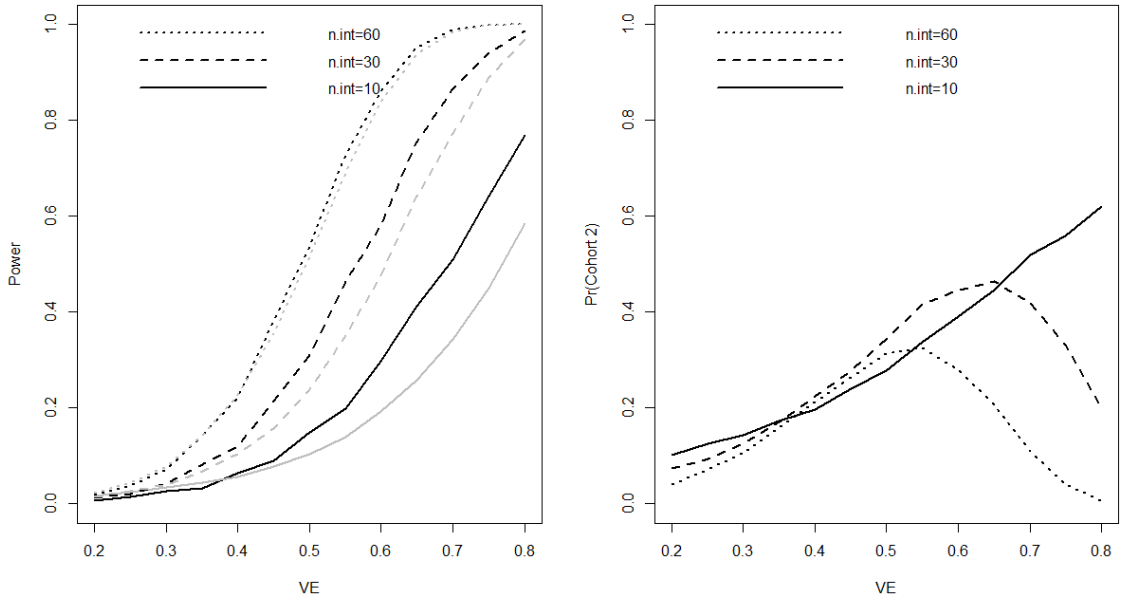
Table 11 shows the operating characteristics of the design with PoS1.threshold=0.65 and PoS2.threshold=0.5, under the alternative hypothesis.

Table 11 Operating characteristics of the design with PoS1.threshold=0.65 and PoS.threshold=0.5, under the alternative hypothesis (VE=0.7).

VE	n.int	Mean N	Pr(succ.) cohort1 only	Pr (succ) [Power]	Pr (Cohort2)	Pr (Early Succ)	Pr (Early fail)	Pr (Delay)	Median PoS1	Median PoS2
0.7	60	25855	0.99	0.99	0.11	0.88	0.01	0.1	0.87	0.92
	55	26144	0.97	0.98	0.14	0.84	0.02	0.13	0.84	0.89
	50	25872	0.94	0.96	0.11	0.85	0.03	0.09	0.85	0.91
	45	26138	0.95	0.96	0.14	0.82	0.02	0.13	0.81	0.88
	40	26977	0.9	0.94	0.25	0.7	0.04	0.2	0.76	0.85
	35	27624	0.88	0.92	0.33	0.61	0.05	0.27	0.71	0.81
	30	28393	0.77	0.87	0.42	0.45	0.1	0.32	0.64	0.76
	25	27665	0.62	0.76	0.33	0.44	0.18	0.17	0.55	0.7
	20	28253	0.56	0.68	0.41	0.3	0.21	0.26	0.45	0.62
	15	30102	0.5	0.7	0.64	0.11	0.18	0.39	0.48	0.68
	10	29147	0.34	0.51	0.52	0.07	0.24	0.27	0.37	0.6

Table 10 shows that only 11% of trials enroll season 2 if n.int=60, while this probability increases at 64% if n.int=15. The average number of enrolled subjects is about 27500. The maximum probability of early fail is about 25% (if n.int=10). The maximum probability of delay is about 40% when n.int=15. The last two columns show the median PoS estimated at interim (and used for sample size enrichment). We can see that Median PoS1 is smaller than 65% only when n.int is lower than 35, and that Median PoS2 is always above 50%. The column "*Pr(succ.) Cohort 1 only*" shows the power of the fixed design where the analysis is done at the end of season 1 in cohort 1 (NH1+SH1=25000, no enrichment). When n.int decreases, then the probability to enroll cohort 2 "Pr(Cohort 2)" increases, and the power of the adaptive design increases with respect to the power of the fixed design. For example, if n.int=15, then the power of the fixed design is 50% while the power of the adaptive design is 70%.

Figure 8 Power and Pr(Cohort 2) as a function of VE and n.int (with PoS1.threshold=0.65 and PoS.threshold=0.5).



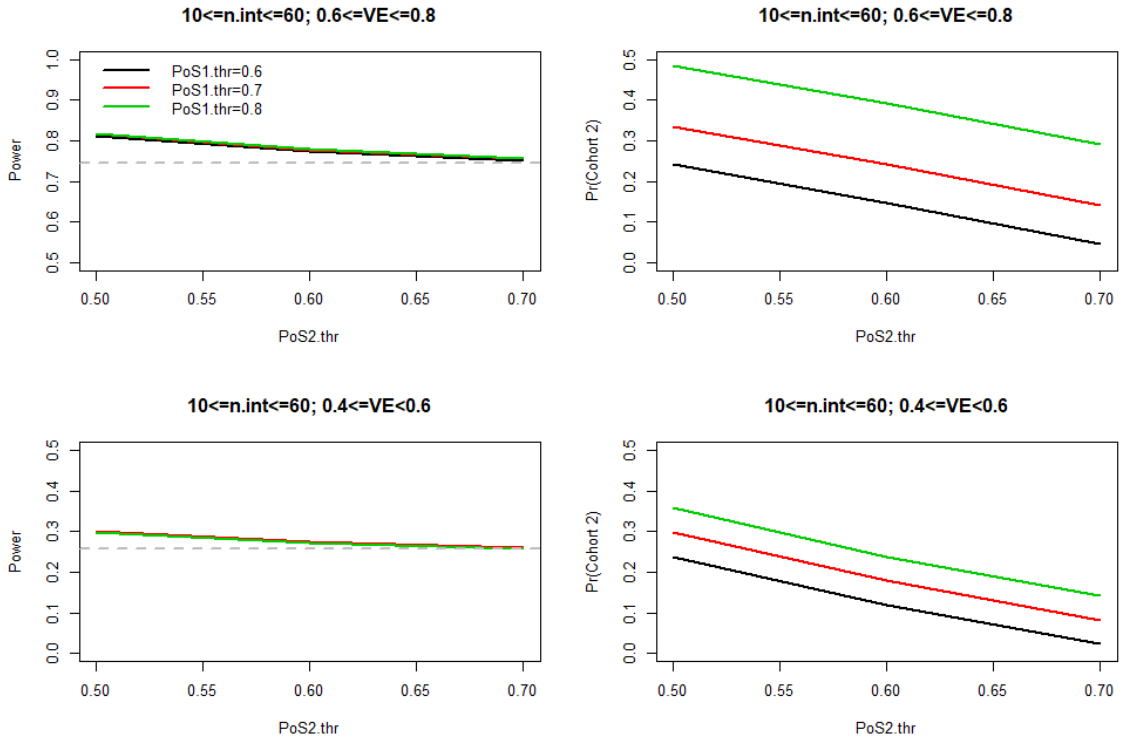
Left panel: power [Pr(succ)] of the adaptive design (in black) and the power of the fixed design [Pr(succ.) Cohort 1 only] (in gray). Right panel: probability of Cohort 2 as a function of VE and n.int.

Figure 8 shows on the left panel that the adaptive design (black lines) is more powerful than the fixed design (gray lines) when n.int is small. Right panel shows the Probability of re-enrollment of cohort 2 as a function of VE and n.int. We can see that the probability of re-enrollment increases up to a certain value of VE (which depends on n.int) and then decreases. For example, if n.int=30, then the probability of re-enrollment is about 20%, 50% and 20% when VE is about 40%, 65% and 80%, respectively.

In the following figure, we explore the impact of the tuning parameters (PoS1.threshold and PoS2.threshold) on the operating characteristics of the design.

Figure 9 shows the power of the adaptive design as a function of the PoS thresholds. To reduce the number figures (and summarize the information), we show the average of the power computed at different scenarios (making the assumption that each scenario has the same prior probability – uniform prior). We computed the average power over all values of n.int (10<=n.int<=60) and we considered two different regions of VE: a range of low VE values (0.4<=VE<=0.6) and a range of high VE values (0.6<VE<=0.8).

Figure 9 Average Power and Pr(Cohort 2) as a function of the PoS thresholds

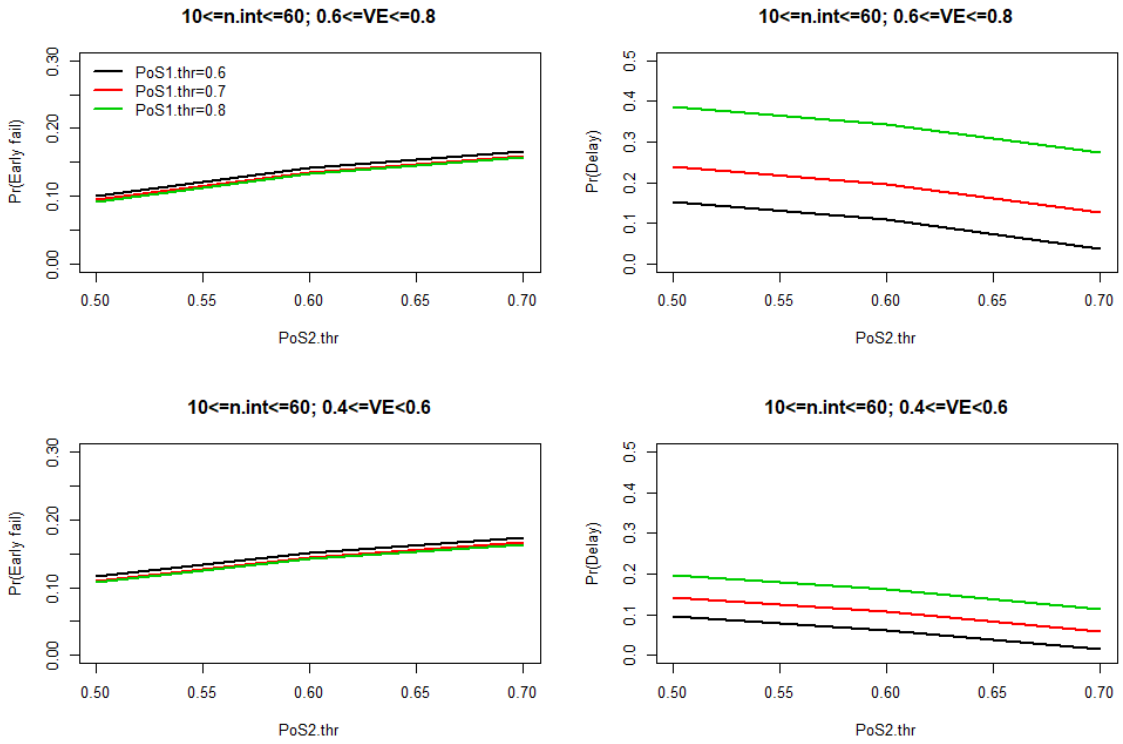


Top figures show results for high VE (0.6<=VE<=0.8) while bottom figures show results for low VE (0.4<=VE<0.6). Dashed gray line represents the power of the fixed design (cohort 1 only).

Figure 9 shows that larger values of PoS1.threshold have a small impact on the power, while they significantly increase the probability of enrolment of Cohort 2.

Smaller values of PoS2.threshold increase the probability of enrolment of Cohort 2, but they increase the power of the adaptive design. For example, if VE is large (top-left panel) then the power of the adaptive design is about 82% if PoS2.thr=0.5, while it is about 75% (similar to the power of the fixed design) if PoS2.thr=0.7.

Figure 10 Average Pr (Early fail) and Pr(Delay) as a function of the PoS thresholds



Top figures show results for high values of VE (0.6<=VE<=0.8) while bottom figures show results for low values of VE (0.4<=VE<0.6).

Figure 10 shows that larger values of PoS1.threshold has a small effect on the probability of early fail, while they increase the probability of delay.

Smaller values of PoS2.threshold decrease the probability of early fail but increase the probability of delay. For example, if VE is large (top-panels) and PoS1.thr=0.6 (black lines), then the probability of Early fail (top-left-panel) is about 10% if PoS2.thr=0.5, while it is about 15% if PoS2.thr=0.7; the probability of delay (top-right-panel) is about 15% if PoS2.thr=0.5, while it is about 3% if PoS2.thr=0.7

Summary

The proposed trial design will provide high-quality evidence for the study of the RSV vaccine efficacy against RSV LRTD in older adults. Simulation results shows that the design controls Type I error below 2.5%. This is due to the fact that the design is following the "promising regions" principle [Chen, 2004; Muller, 2004; Gao, 2008;Bretz, 2009; Mehta,2011; Jennison, 2015; Casula, 2020].

The re-enrollment depends on the PoS [Spiegelhalter, 1986] which is a function of VE and AR estimated at interim. Under the null hypothesis, the probability of re-enrollment is very low (only 6%), while it increases under the alternative hypothesis when the additional samples can (at least partially) recover the loss of power due to low AR.

In summary, the proposed adaptive design mitigates the problem of loss of power due to a lower AR, and at the same time it avoids delay (unnecessary re-enrollment) when the VE is high.

Appendix: relationship between type I error and PoS thresholds

Figure 11 Type I error (average over n.int) as a function of PoS thresholds.

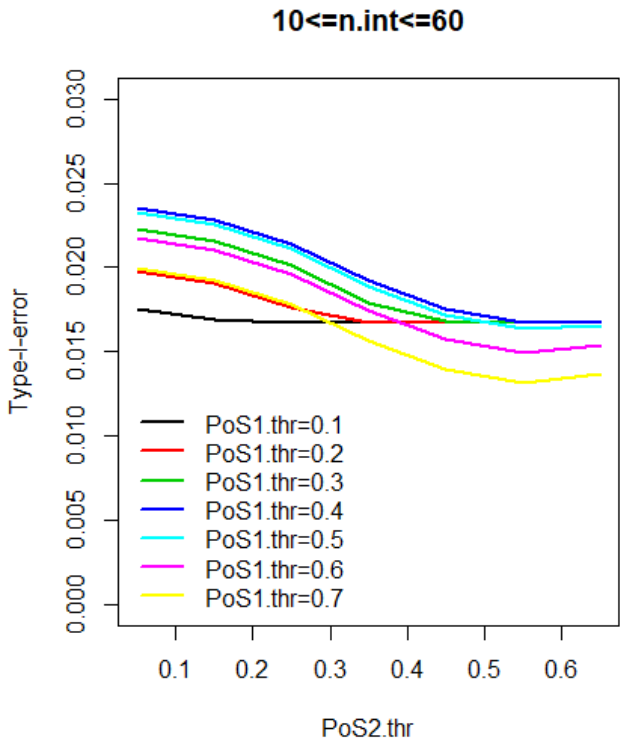


Figure 11 shows that the Type-I-error (averaged over n.int to summarize the results) seems to be well controlled (overall) and depends on both parameters.

It shows a clear trend between Type-I-error and PoS2.threshold: Type-I-error increases when PoS2.threshold decreases. For the relationship between Type-I-error and PoS1.threshold, it seems that Type-I-error increases when PoS1.threshold is close to 0.5.

12.4. 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.

13. REFERENCES

Borgan Ø, Langholz B, Samuelsen SO, et al. Exposure stratified case-cohort designs. *Lifetime Data Analysis.* 2000; 6, 39–58.

Bretz, F., Koenig, F., Brannath, W., Glimm, E., and Posch, M., "Tutorial in Biostatistics: Adaptive Designs for Confirmatory Clinical Trials," *Statistics in Medicine* 2009; 28: 1181–1217.

Casula, D., Callegaro, A., Nakanwagi, P., Weynants, V., & Arora, A. K. Evaluation of an adaptive seamless design for a phase II/III clinical trial in recurrent events data to demonstrate reduction in number of acute exacerbations in patients with chronic obstructive pulmonary disease (COPD). *Statistics in Biopharmaceutical Research* 2020; 12(3): 273-278.

Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. *Communications in Statistics - Theory and Methods* 1998; 27: 1305-22.

Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, *J Chrin Dis* 1987; 40(5), 373-383.

Chen, Y. J., DeMets, D. L., & Gordon Lan, K. K. Increasing the sample size when the unblinded interim result is promising. *Statistics in medicine* 2004; 23(7): 1023-1038.

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Cox, D. R. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. Series B (Methodological), 1972; 34: 187–220.

Dragalin V., Fedorov V. and Cheuvart B., Statistical approaches to establishing vaccine efficacy, *Statistics in Medicine* 2002; 21: 877-893.

Gao, P., Ware, J. H., and Mehta, C, "Sample Size Re-Estimation for Adaptive Sequential Design in Clinical Trials," *Journal of Biopharmaceutical Statistics* 2008; 18: 1184–1196.

Gillett R. An average power criterion for sample size estimation. *The Statistician* 1994; 43: 389-394.

Jennison, C., and Turnbull B.W, "Adaptive Sample Size Modification in Clinical Trials: Start Small Then Ask for More?," *Statistics in Medicine* 2015; 34: 3793–3810

Lachin, J. M, Biostatistical methods: the assessment of relative risks, *John Wiley & Sons* 2011; 807

Lievens et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children'. *Malaria* journal 2011.

Mehta, C. R., and Pocock, S. J, "Adaptive Increase in Sample Size When Interim Results are promising: A Practical Guide With Examples," *Statistics in Medicine* 2011; 30: 3267–3284.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

Muller, H. H., and Schafer H, "A General Statistical Principle for Changing a Design Any Time During the Course of a Trial," *Statistics in Medicine* 2004; 23: 2497–2508.

O'Hagan A, Stevens JW, Campbell MJ. Assurance in clinical trial design. *Pharmaceutical Statistics* 2005; 4(3): 187-201.

Quan H., Li B., Couris C.M., Fushimi K., Graham P., Hider P., Januel J-M., Sundararajan V., Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries, *American Journal of Epidemiology* 2011; 173 (6).

Spiegelhalter DJ, Freedman LS. A predictive approach to selecting the size of a clinical trial based on subjective clinical opinion. *Statistics in Medicine* 1986; 5: 1-13.

Tang M.I. and Hon Keung Tony,_Letter to the Editor, Comment on: Confidence limits for the ratio of two rates based on likelihood scores: non-iterative method, *Statistics in Medicine*; 2004; 23: 685-693

Wang Y., Rosenberger W.F. Randomization-based interval estimation in randomized clinical trials. *Statistics in medicine* 2020; 39(21): 2843-2854. DOI: 10.1002/sim.8577.