Protocol

A Phase III, observer-blind, randomized, multi-country study to evaluate the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK's quadrivalent influenza D-QIV vaccine in healthy non-pregnant women 18-49 years of age.

26-MAY-2022

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention(s) and number(s)	GlaxoSmithKline (GSK) Respiratory Syncytial Virus (RSV) Maternal (RSVPreF3) Vaccine [GSK3888550A]
Other study intervention(s)	• Placebo (Saline solution [NaCl]) • Flu D-QIV vaccine
eTrack study number and abbreviated title	214709 (RSV MAT-010)
EudraCT number	2021-000357-26
Date of protocol	Final: 21 April 2021
Date of protocol amendment	Amendment 1 Final: 24 May 2021 Amendment 2 Final: 17 November 2021 Amendment 3 Final: 26 May 2022
Title	A Phase III, randomized, multi-country study to evaluate the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK's quadrivalent influenza D-QIV vaccine in healthy non-pregnant women 18-49 years of age.
Brief title	A Phase III study to assess the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and the immune response and safety of RSV maternal vaccine when given alone or co-administered with GSK's influenza D-QIV vaccine in healthy non-pregnant women.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and abbreviated title	214709 (RSV MAT-010)
EudraCT number	2021-000357-26
Date of protocol amendment	Amendment 1 Final: 24 May 2021 Amendment 2 Final: 17 November 2021 Amendment 3 Final: 26 May 2022
Title	A Phase III, randomized, multi-country study to evaluate the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK's quadrivalent influenza D-QIV vaccine in healthy non-pregnant women 18-49 years of age
Sponsor signatory	Joon Hyung Kim, Clinical Epidemiology Project Lead, RSV Maternal, Clinical R&D
Signature	_____
Date	_____

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

Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational intervention(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	214709 (RSV MAT-010)
EudraCT number	2021-000357-26
Date of protocol amendment	Amendment 1 Final: 24 May 2021 Amendment 2 Final: 17 November 2021 Amendment 3 Final: 26 May 2022
Title	A Phase III, randomized, multi-country study to evaluate the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK Biologicals' quadrivalent influenza D-QIV vaccine in healthy non-pregnant women 18-49 years of age
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of a Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: refer to the protocol Section 8.3.3.1.

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

5. GSK Helpdesk for emergency unblinding

Refer to the protocol section 6.3.5.1

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 3 (26 May 2022)

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it impacts the scientific value of the study.

Overall rationale for the current Amendment:

This protocol has been amended to reflect the following:

- Following review of data collected so far from the RSV MAT-009 study in pregnant women, safety signals have been identified. An imbalance in the proportion of preterm births and neonatal deaths have been observed in infants born to mothers who received RSV maternal vaccine versus those who received a placebo. The safety signals are being investigated, and although at this time a cause has not been determined, based on the above observations, GSK has nevertheless decided to stop enrolment and vaccination for active enrolment in all RSV MAT studies. When this decision was taken, the enrollment had been completed in RSV MAT-010 study.
- Due to issues in validation of A/Victoria/2570/2019 (H1N1) influenza strain, the primary and secondary objectives were modified to evaluate only 3 influenza strains (A/Tasmania/503/2020 (H3N2), B/Washington/02/2019, B/Phuket/3073/2013). The A/Victoria/2570/2019 (H1N1) will be evaluated as part of the tertiary objectives.
- The secondary safety objective and its corresponding endpoint related to assessment of safety of RSV maternal vaccine when given alone and co-administered with Flu D-QIV from vaccination up to study end was recategorized as a primary objective.
- The interim analysis was removed following GSK's decision to stop enrollment and vaccination for active enrollment in all RSV MAT studies.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 2.3 Benefit/Risk assessment	Updated to provide details on the current status on expected benefits and risks from receiving the RSV MAT (RSVPreF3) vaccine	Updated to reflect potential changes in the benefit-risk profile.
Section 3 Objective(s), Endpoints, and Estimands	• Categorized primary and secondary objectives related the assessment of the A/Victoria/2570/2019 (H1N1) influenza strain as tertiary objectives. • Categorised secondary safety objective related to the assessment of safety of RSVPreF3 when given alone	Updated due to issues in validating the A/Victoria/2570/2019 (H1N1) influenza strain. Updated to reflect the change to study's safety assessment plan.

Section # and title	Description of change	Brief rationale
	and co-administered with Flu D-QIV as a primary objective.	
9.4.1 Primary endpoints/estimands analysis 9.4.2 Secondary endpoints/estimands analysis	• Categorized primary and secondary endpoints related the assessment of the A/Victoria/2570/2019 (H1N1) influenza strain as tertiary endpoints. • Categorised secondary safety endpoint related to the assessment of safety of RSVPreF3 when given alone and co-administered with Flu D-QIV as a primary endpoint.	Updated due to issues in validating the A/Victoria/2570/2019 (H1N1) influenza strain. Updated to reflect the change to study's safety assessment plan.
9.5.1 Sequence of analysis 9.5.2 Statistical considerations for analysis	Updated to remove the interim analysis to evaluate all participant safety, reactogenicity, and immunogenicity data collected up to Day 31 (Visit 2).	Updated to reflect the change to study's statistical analysis plan from the decision to stop further enrollment and vaccination.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis *(Amended 26 May 2022)*

Rationale

GSK is developing an investigational respiratory syncytial virus (RSV) maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization. This study will be a Phase III study to evaluate clinical lot-to-lot consistency in healthy non-pregnant women 18-49 years of age (YOA) by comparing safety and immunogenicity results. In addition, this study will evaluate safety and immunogenicity of the RSVPreF3 vaccine when co-administered with GSK's quadrivalent seasonal influenza (Flu D-QIV) vaccine.

A Phase I/II, observer-blind study (RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 YOA, to determine the safety and immunogenicity of 3 dose levels of the RSVPreF3 vaccine (30, 60, and 120 µg) compared to placebo, has been completed. No safety concerns have been identified.

Based on preliminary results of RSV MAT-001 study, the 60 and 120 µg dose levels were selected for further evaluation in the following 2 additional studies, which are ***completed***:

- RSV MAT-004 (NCT 04126213): A Phase II, observer-blind study to assess safety, reactogenicity, and immunogenicity of 2 dose levels of the RSVPreF3 vaccine in healthy pregnant women and infants born to vaccinated mothers.
- RSV MAT-011 (NCT 04138056): A Phase II, observer-blind study of 2 dose levels of the RSVPreF3 vaccine, given alone or with *Boostrix*, to healthy non-pregnant women to assess safety, reactogenicity and immunogenicity.

Based on the final results of RSV MAT-001, on the Day 31 results of RSV MAT-004 and RSV MAT-011 studies, the 120µg dose level ***was*** selected for evaluation in RSV MAT-010 study. In addition, the 120µg dose level ***was also*** administered ***in*** pregnant women participating in the Phase III study RSV MAT-009.

Objectives and endpoints/estimands of the RSV MAT-010 study are presented in Table 3**.**

1.2. Schema

This Phase III, randomized, multi-country study is observer-blinded to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine, and single-blinded to evaluate the immune response, safety and reactogenicity when co-administered with Flu D-QIV vaccine. A total of 1541 healthy non-pregnant women 18 to 49 YOA will be enrolled in the study.

Approximately 660 non-pregnant women 18 to 49 YOA (inclusive, at the time of the study intervention administration) will be evenly enrolled. The RSV1, RSV2, and RSV3 groups will receive RSVPreF3 (120 µg of RSVPreF3 vaccine), each group receiving a different lot of RSVPreF3 vaccine. Study participants from RSV1, RSV2, and RSV3 groups will be provided with an option of receiving Flu D-QIV vaccine at Day 31 to allow the participants to receive the standard of care.

In addition, approximately 881 non-pregnant women will be enrolled for the co-administration of RSVPreF3 with Flu D-QIV or Flu D-QIV with placebo at their first vaccination in additional 2 groups. The participants in the co-administration (RSVPreF3 with Flu D-QIV) group will receive the RSVPreF3 vaccine from lots 1, 2, or 3 evenly.

Approximately 1541 participants will be randomized with randomization ratio of 3:3:3:2:2:2:6.

- Approximately 220 participants in the RSV1 group (Lot 1)
- Approximately 220 participants in the RSV2 group (Lot 2)
- Approximately 220 participants in the RSV3 group (Lot 3)
- Approximately 441 participants in the RSV + Flu pooled group (split into 3 groups)
  - Approximately 147 participants in the RSV1 (Lot 1) + Flu group
  - Approximately 147 participants in the RSV2 (Lot 2) + Flu group
  - Approximately 147 participants in the RSV3 (Lot 3) + Flu group
- Approximately 440 participants in the Flu + placebo group

Section 4.1 provides an overview of the study design.

Blood samples for humoral immunogenicity will be collected from all participants at Visit 1 and Visit 2 (pre-vaccination at Day 1 and Day 31 post study vaccination).

All participants who receive the study intervention will be followed for safety and reactogenicity and evaluated for solicited administration site and systemic adverse events (AEs) within 7 days of vaccination, unsolicited AEs within 30 days of vaccination, and SAEs throughout the study period and pregnancy outcomes.

All safety data will be reviewed by a Safety Review Team (SRT) on an ongoing basis.

1.3. Schedule of Activities (SoA)

Table 1 presents the Schedule of Activities (SoA).

Table 1 Schedule of Activities

Type of contact	Visit 1	TC 1	Visit 2	TC 2	Comments
Time points	Day 1	Day 8	Day 31	Day 181	
Sampling time points	Pre-Vaccination	Post-Vaccination	Post-Vaccination	Post-Vaccination	
Informed consent	●				[See Section 10.1.3 for details]
Assign participant number	●				
Check inclusion/exclusion criteria	●				See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria]
Check contraindications to subsequent vaccine(s) administration			O		See Sections 7.1.1 and 8.2 for more information
Collect demographic data[1]	●				See Section 8.2 for more information
Medical and vaccination history	●		O		[See Section 8.2 for more information]
Physical examination[2,4]	●				See Section 8.2 for more information
Vital signs[2,4]	●		O		
Urine pregnancy test[3]	●				See Section 8.2 for more information
Pre-vaccination body temperature	●		●		
Randomization	●				
Blood sampling for humoral immune response (~10 mL)[5]	●		●		See Section 8.1.1 for more information
Study group and treatment number allocation (SBIR)	O				
Vaccine administration	●		●[8]		
Recording of administered treatment number	●		●[8]		
30 minutes post-vaccination observation period	O		O		
Distribution of participant card	O				
Training on use of e-diary	O				

Type of contact	Visit 1	TC 1	Visit 2	TC 2	Comments
Time points	Day 1	Day 8	Day 31	Day 181	
Sampling time points	Pre-Vaccination	Post-Vaccination	Post-Vaccination	Post-Vaccination	
Distribution of e-diary device[6]	O				
Review of e-diary	O	O	O		
Return of e-diary device			O		
Collection of solicited adverse events (Days 1 to 7 post-vaccination) [6]	O	O			[See Section 10.3.8 for more information]
Recording of unsolicited adverse events for 30 days (days 1 to 30 post vaccination)	●	●	●		[See Section 10.3.8 for more information]
Recording of AEs/SAEs leading to withdrawal	●	●	●	●	[See Section 10.3.8 for more information]
Recording of SAEs[7]	●	●	●	●	[See Section 10.3.8 for more information]
Recording of pregnancies		●	●	●	[See Section 10.3.8 for more information]
Recording of concomitant medications/vaccinations	●	●	●		[See Section 6.8 for more information]
Record any intercurrent medical conditions	●	●	●		[See Section 9.3.1 for more information]
Phone contact		●		●	
Investigator sign-off on eCRF before analysis			●	●	
COVID-19 eCRFs log page	●	●	●	●	
Screening Conclusion	●				
Study conclusion				●	[See Section 4.4 for more information]

TC= Telephone contact

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

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

[1] Date of birth (month and year or year only, as per local regulations), race, ethnicity and childbearing potential (if participant not of childbearing potential, the specific reason should be documented in the eCRF).

[2] Physical examination including (height and weight) BMI as well as resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest. At Day 1 (Visit 1) both physical exam and vital signs will be measured. At Day 31 (Visit 2) medical and vaccination history and vital signs may be measured.

[3] Only for women of childbearing potential. Urine pregnancy test is sufficient to determine the eligibility to enter the study. Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

[4] Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature in this study is the oral cavity.
[5] Subgroups, method, cut-off, and laboratory locations will be defined in Section 8.
[6] The e-diary device will be distributed at the day of vaccination and will be used for recording solicited AEs for 6 subsequent days (7 days total including day of vaccination).
[7]SAEs related to study participation or concurrent GSK intervention product will be monitored from the time of screening to the time of the immunization. Both will be conducted on the same visit.
[8] Vaccination at Day 31 (Visit 2) is only for RSV 1, 2, 3 groups and optional.

Table 2 Intervals between study visits

Interval	Optimal timing	Allowed interval (Study day)
Visit 1*→ Phone Contact 1	Day 8	Day 7 - 10
Visit 1→ Visit 2	Day 31	Day 31 -38
Visit 1 → Phone Contact 2	Day 181	Day 165 - 195

*The interval between study visits begins at the time of vaccination during Visit 1 timepoint.

2. INTRODUCTION

2.1. Study rationale *(Amended 26 May 2022)*

GSK is developing an investigational RSV maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization. This will be a Phase III study to evaluate clinical lot consistency in 660 healthy non-pregnant women 18-49 YOA. Three different lots of RSVPreF3 (120µg) vaccine will be administered and examined for both immunogenicity and safety outcomes. In addition, this study will evaluate immunogenicity, safety and reactogenicity from co-administration of RSVPreF3 and Flu D-QIV in healthy non-pregnant women 18-49 YOA.

A Phase I/II study (study RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 YOA to determine the safety and immunogenicity of 3 dose levels of RSVPreF3 (30, 60 and 120µg) vaccine compared to placebo is now complete. The results from ***this study*** demonstrated that the RSV maternal (RSVPreF3) vaccine is highly immunogenic and no safety concerns have been identified. Study results for safety and immunogenicity are now available in the Investigator Brochure.

In another ***completed*** Phase II randomized, observer-blinded study (RSV MAT-011) in non-pregnant women 18 to 45 YOA, two dose levels of the RSV maternal vaccine, 60 µg, and 120 µg, are being evaluated. The primary objectives are to evaluate the effects of *Boostrix* co-administration in terms of reactogenicity, safety and immune response to the RSV maternal vaccine at 1-month post study intervention (considering the US and outside the US data pooled). The effects of RSV maternal vaccine co-administration on the safety and immune response to *Boostrix* were evaluated as secondary objectives. Additional secondary objectives included safety assessment up to 6 months post-intervention, and evaluations of the safety and immune response considering the US and outside the US data both separately and pooled. Enrollment is complete and participant's follow-up is ongoing to examine the persistence of antibody 12-18 months post-1st dose and safety of a 2nd dose of RSV PreF3 vaccine given from 12 up to 18 months post 1st dose. Preliminary results are now available in the IB. Briefly, both formulations ***and both dose levels*** of the investigational RSV maternal vaccine elicited an immune response, ***no safety concern was observed in the study population of non-pregnant women***. The safety and immunogenicity profile were also similar in another study (RSV MAT 004) examining RSV maternal vaccine in pregnant women.

Pregnant women are at increased risk for serious consequences of influenza infection. Influenza illness may also pose risks to fetal development, which can lead to adverse pregnancy outcomes such as stillbirth, preterm delivery, and decreased neonatal birth weight [WHO, 2012]. Consequently, many recommending bodies, including the World Health Organisation (WHO), US Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunisation Practices, the European Medicines Agency, the UK National Health Service, and the Australian Technical Advisory group on Immunisation recommend the use of Seasonal Inactivated Influenza Vaccine (sIIVs) during pregnancy.

GSK manufactures a quadrivalent, inactivated, split virion, seasonal influenza vaccine (FLU-D-QIV) / (*Fluarix Quadrivalent, Fluarix Tetra, FluarixTetra, α-RIX-Tetra and Influsplit Tetra*), hereafter referred to as FLU-D-QIV. Flu D-QIV is a quadrivalent vaccine indicated for active immunization of adults and children from 6 months of age for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine.

This study (RSV MAT-010) will be the first to evaluate co-administration of 120 µg of the RSVPreF3 (RSV MAT) vaccine with Flu D-QIV in healthy non-pregnant women (see Figure 1). Selection of the RSVPreF3 antigen dose was based on preliminary results of the ***completed studies*** (RSV MAT-001, RSV MAT-011 and RSV MAT-004).

2.2. Background

Please refer to the current Investigator's Brochure (IB) for background information on RSV infection, the rationale for the maternal immunization approach described in this protocol, and information regarding pre-clinical and clinical studies of the RSVPreF3 vaccine.

2.3. Benefit/Risk assessment *(Amended 26 May 2022)*

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of the RSVPreF3 (RSV MAT) vaccine can be found in the IB.

GSK has included provisions in this trial to ensure participant's safety. Participants will remain under observation for 30 minutes after administration of the study intervention to ensure that immediate treatment may be provided in the event of a hypersensitivity reaction, or syncope. Safety monitoring will be conducted throughout this study by a Safety Review Team.

Measures to suspend the study should a potential safety issue be identified, are described in Section 8.2.

Following a recommendation from the Independent Data Monitoring Committee (IDMC), the Sponsor made the decision to pause the enrollment, randomization and vaccination of pregnant study participants in our active studies based on an observation of imbalance of the proportion of preterm births between the vaccine group and the placebo group in the RSV MAT-009 study in pregnant women. This pause was

to allow for an evaluation of the available data in RSV MAT-009 to better understand the safety signal observed. Following a review of additional unblinded data from RSV MAT-009 trial in which a higher proportion of neonatal deaths reported in the treatment group compared to the placebo group was also observed, the Sponsor decided to STOP enrollment and vaccination in these studies.

The safety signals are being investigated and, although at this time a cause has not been determined, as a precautionary measure GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling both pregnant women on February 25, 2022. We also considered it not appropriate to enroll any additional participants in studies for the RSV maternal program and therefore also stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling non-pregnant women on March 1, 2022. The studies remain ongoing for safety follow-up. Participants already vaccinated will continue to be monitored until the end of the study. At this time, the safety observation has been observed only among pregnant trial participants.

3. OBJECTIVE(S), ENDPOINTS, AND ESTIMANDS (Amended 26 May 2022)

Table 3 Study objectives, endpoints and estimands

Objectives	Endpoints/Estimands
Primary	
Safety • To evaluate the safety and reactogenicity of RSVPreF3 when given alone (pooled lots) or co-administered with Flu D-QIV up to ***study end***.	The number and percentage of participants in each group reporting • Each solicited administration site AE collected during the 7 days follow-up period (Day 1 to Day 7) • Each solicited systemic events in the 7 days follow-up period • Unsolicited AEs collected during the 30 days follow-up period (Day 1 to Day 30) • SAEs in the 30 days follow-up period (Day 1 to Day 30) • ***SAEs in the 180 days follow-up period (Day 1 to Day 181)***
Immunogenicity • To demonstrate the lot-to-lot consistency of 3 lots of the investigational RSVPreF3 vaccine based on GMC of RSVPreF3 IgG ELISA at Day 31	RSVPreF3 IgG ELISA concentration at Day 31 (30 days post administration) Measured by ratio of Geometric mean concentration (GMC) between lots in terms of RSVPreF3 IgG ELISA titers at Day 31 (30 days post administration)
• To demonstrate non-inferiority of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine compared to Flu D-QIV given alone based on Geometric mean titer (GMT) of Flu D-QIV antibody titers against ***3*** influenza strains at Day 31 post administration	Flu D-QIV antibody titers against ***3*** influenza strains at Day 31 (30 days post administration) Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against ***3*** strains at Day 31 (30 days post administration)
Secondary	
*Confirmatory Immunogenicity****	
• To demonstrate the non-inferiority of RSVPreF3 vaccine co-administered with Flu D-QIV compared to given alone based on GMT of RSV A neutralizing antibody at Day 31 post administration	RSV A neutralizing antibody titers at Day 31 (30 days post administration) Measured by ratio of GMT between group of RSVPreF3 vaccine co-administered with Flu D-QIV and RSVPreF3 vaccine alone (pooled lot 1,2,3) group in term of RSV A neutralizing antibody titers at Day 31 (30 days administration)
• To demonstrate the non-inferiority of Flu D-QIV vaccine co-administered with RSVPreF3 compared to given alone based on Seroconversion rate (SCR) of Flu D-QIV HI antibody titers against ***3*** influenza strains at Day 31 post study intervention	• Seroconversion rate to Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 31 Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone

Objectives	Endpoints/Estimands
Descriptive Immunogenicity	
• To evaluate the humoral immune response of RSVPreF3 vaccine when given alone and co-administered with Flu D-QIV in terms of RSV A, RSV B neutralizing antibody and RSVPreF3 IgG concentration at Day 1 (prior to the vaccination) and Day 31 (post study intervention).	• RSV A, RSV B neutralizing antibody titers and RSV PreF3 IgG concentration at Day 1 and Day 31 GMT of RSV A and RSV B neutralizing antibody, GMC of RSVPreF3 IgG at Day 1 and Day 31, in the group of RSVPreF3 vaccine co-administered with Flu D-QIV and the group of RSVPreF3 vaccine alone
• To evaluate the humoral immune response to the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine in terms of antibody titers against ***3*** influenza strains at Day 1 and Day 31	Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 1 and Day 31 HI GMT in the ***3*** influenza strains at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
• To evaluate seroprotection rate (SPR)and Seroconversion rate (SCR)* of the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine	Seroprotection rate to Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 1 and Day 31 Measured by the proportion of participants achieving an HI antibody titer ≥1:40 at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone • Seroconversion rate to Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 31 Measured by the proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
• To evaluate the humoral immune response in 3 individual lots of RSVPreF3	• RSV A, RSV B neutralizing antibody titers and RSVPreF3 IgG antibody concentrations at pre-vaccination and Day 31 Geometric mean titer/concentration (GMT/GMC) in term of RSV A, RSV B neutralizing antibody and RSVPreF3 IgG antibody at Day 1 (pre-vaccination) and Day 31 in each of 3 lots of the investigational PreF3 vaccine.
Tertiary	
To demonstrate non-inferiority of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine compared to Flu D-QIV given alone based on Geometric mean titer (GMT) of Flu D-QIV antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 post administration	***Flu D-QIV* antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 (30 days post administration)*** ***Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against the A/Victoria/2570/2019 (H1N1) strain at Day 31 (30 days post administration)***
To demonstrate the non-inferiority of Flu D-QIV vaccine co-administered with RSVPreF3 compared to given alone based on Seroconversion rate (SCR) of Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 post study intervention	• ***Seroconversion rate to Flu D-QIV* HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31*** ***Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-***

Objectives	Endpoints/Estimands
	administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
To evaluate the humoral immune response to the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine in terms of antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31	***Flu D-QIVHI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31*** ***HI GMT in the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone***
To evaluate seroprotection rate (SPR) and Seroconversion rate (SCR)* of the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine	***Seroprotection rate to Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31*** ***Measured by the proportion of participants achieving an HI antibody titer ≥1:40 at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone*** • ***Seroconversion rate to Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31*** ***Measured by the proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone***
CCI	

*The SCR is defined as the proportion of participants with:
A Day 1 (pre-vaccination) serum anti-HI titer <1:10 and a Day 31 (post-vaccination) serum anti-HI titer ≥1:40, or
A Day 1 (pre-vaccination) serum anti-HI titer ≥ 1:10 and a fold increase (post/pre) ≥ 4 at Day 31
*** Two confirmatory objectives will be tested sequentially.

CCI

4. STUDY DESIGN

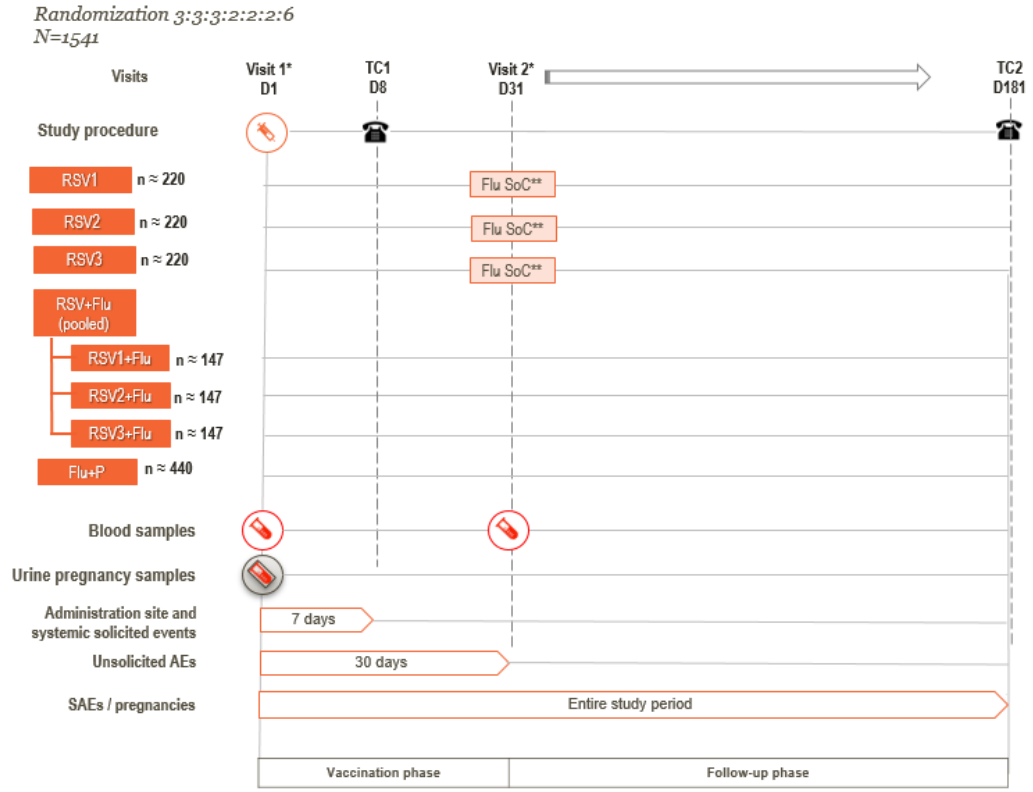
4.1. Overall design

This Phase III, randomized, multi-country study in healthy non-pregnant women 18-49 YOA, is observer-blind to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine and single-blinded to evaluate the immune response, safety and reactogenicity of GSK RSVPreF3 vaccine when co-administered with Flu D-QIV vaccine.

Approximately 660 non-pregnant women age 18 to 49 YOA (inclusive, at the time of the study intervention administration) will be evenly enrolled. The RSV1, RSV2, and RSV3 groups will receive RSVPreF3 vaccine (120 µg of RSVPreF3), each group receiving a different lot of RSVPreF3 vaccine. Study participants from RSV1, RSV2, and RSV3 groups will be provided with an option of receiving Flu D-QIV vaccine at Day 31 to allow the participants receive the standard of care.

In addition, approximately 881 non-pregnant women will be enrolled to the co-administration of RSVPreF3 with Flu D-QIV (RSV+Flu groups) or the co-administration of Flu D-QIV with placebo (Flu+P group) at their first vaccination. The co-administration of RSVPreF3 with Flu D-QIV group will all receive the RSVPreF3 vaccine from lots 1, 2, or 3 evenly. See section 6.3.2 for more detail on the randomization strategy.

Figure 1 Study design overview



SOC=Standard of Care
* Screening and vaccination will happen on Visit 1(Day 1). The blood sample collection must be collected before administering the vaccine(s).

** Visit 2 Flu D-QIV vaccinations are not part of experimental design. It serves as an optional vaccination for the participant to decide if they would like to get the vaccination as part of their standard of care. The blood sample collection must be collected before administering the Flu D-QIV vaccine.

- Study Type: self-contained.
- Study duration: The study vaccine will be administered at Visit 1 and the participant will be followed for 6 months until the study conclusion.
- Blinding: This study will utilize an observer blind design to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine; and single-blinding design to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK quadrivalent influenza that is described in Section 6.3.5.
- Placebo used: Saline (NaCl) solution.
- Vaccination schedules are described in Table 6
- Randomized intervention allocation is described in Table 4 and Section 6.3.
- Study (intervention) groups are described in Table 4**.**
- Data collection: standardized Electronic Case Report Form (eCRF) and e-Diaries will be used to collect solicited and unsolicited event data up to Day 30 (Day 30 inclusive). Serious Adverse event data from Day 31 until the end of the study will be collected through questioning at concluding phone contacts and reported into the eCRF, as appropriate.
- Safety monitoring will be conducted by a Safety Review Team.

Table 4 Study groups and intervention

Study groups**	Approximate number of participants	Age (Min-Max)	Study intervention	Standard of Care Vaccination*
RSV1	220	18 – 49 years	RSV MAT 120 (Lot1)	Flu D-QIV
RSV2	220	18 – 49 years	RSV MAT 120 (Lot2)	Flu D-QIV
RSV3	220	18 – 49 years	RSV MAT 120 (Lot3)	Flu D-QIV
RSV1+Flu	147	18 – 49 years	RSV MAT 120 (Lot 1) Flu D-QIV	
RSV2+Flu	147	18 – 49 years	RSV MAT 120 (Lot 2) Flu D-QIV	
RSV3+Flu	147	18 – 49 years	RSV MAT 120 (Lot 3) Flu D-QIV	
Flu+P	440	18 – 49 years	Flu D-QIV placebo	

RSV MAT 120 =RSVPreF3 vaccine
*Standard of care vaccine administered only to ensure the participants receive the standard of care.
For more information about blinding, refer to Section 6.3.5.

Approximately 1541 participants will be randomized into 7 study groups (5 main study groups including 1 pooled group [RSV1+Flu, RSV2+Flu, RSV3+Flu]) with randomization ratio of RSV1:RSV2:RSV3: RSV1+Flu: RSV2+Flu: RSV3+Flu: Flu+P as 3:3:3:2:2:2:6. An automated internet based system (SBIR) will be used to randomly allocate a study group and treatment number to each participant. Age (18-32 vs. 33-49) and center will be minimization factors. Minimization factors will have equal weight in the algorithm.

4.2. Scientific rationale for study design

This study is part of a clinical development plan of the RSVPreF3 vaccine for the protection of infants from RSV lower respiratory tract infections through maternal immunization. This study will evaluate the safety and immunogenicity of the RSVPreF3 vaccine from 3 lots as well as when co-administered with GSK quadrivalent influenza (Flu D-QIV) vaccine in healthy non-pregnant women 18-49 YOA.

To evaluate lot-to-lot consistency, 3 groups will be vaccinated with 3 different lots. RSV1 vs. RSV2, RSV 2 vs. RSV 3, and RSV3 vs. RSV1 will be compared. An optional Flu D-QIV will be provided to these three groups during Visit 2 as part of the standard of care. To evaluate the impact of co-administration on the flu immunogenicity, the safety and immunogenicity of the Flu + P and Flu + RSV groups will be compared. The study will also evaluate the impact of co-administration on RSVPreF3 immunogenicity; by comparing the immunogenicity of pooled RSV1,2,3 group versus RSV+Flu group. Blood samples for humoral immune response will be collected on Day 1(Vaccination day) and Day 31 (Visit 2).

4.3. Justification for dose

A single formulation of the investigational RSV maternal vaccine (containing 120 µg of the RSVPreF3 antigen) is planned. Currently available data suggest that the 120 µg formulation has an acceptable safety profile and tends to elicit stronger immune responses in non-pregnant (RSV MAT-001 and RSV MAT-011) and pregnant (RSV MAT-004) women, which is likely to result in higher placental transfer of antibodies to the fetus than formulations containing 30 or 60 µg of the RSVPreF3 antigen. Available results from these studies are included in the Investigator Brochure.

Results of study RSV MAT-001 in non-pregnant women indicate that a single dose of the study vaccine is sufficient to boost the neutralizing antibodies induced by previous natural infections.

4.4. End of Study definition

A participant is considered to have completed the study if she is available for the concluding phone contact 2 (Day 181) as described in the protocol.

End of Study (EoS): Last subject last visit (LSLV) (Day 181/phone contact 2) or Date of the last testing/reading released of the Human Biological Samples or imaging data,

related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV**.**

Refer to Section 10.8.2 for the definition of EoS.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the e-Diary, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study specific procedure.
- Healthy female participants; as established by medical history and clinical examination, aged 18 to 49 years at the time of the first study intervention administration.
  - Female participants of childbearing potential may be enrolled in the study, if the participant:
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration.
  - Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception
- No local condition precluding injection in both left and right deltoid muscles.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Current autoimmune disorder (based on medical history and physical examination;), for which the participant has received immune-modifying therapy within 6 months, before study vaccination
- Hypersensitivity to latex
- Acute or chronic clinically significant abnormality or poorly controlled pre-existent co-morbidities or any other clinical conditions, as determined by physical examination or medical history that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study
- Significant or uncontrolled psychiatric illness
- Recurrent history or uncontrolled neurological disorders or seizures
- Documented HIV-positive participant
- Body mass index> 40 kg/m^2
- Any clinically significant* hematological parameter and/or biochemical laboratory abnormality.

  *The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period starting 30 days before study intervention (Day -29 to Day 1), or planned use during the study period;
  - See Section 10.7.1 for additional country-specific considerations
- Administration of long-acting immune-modifying drugs 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 3 months before the study intervention or planned administration during the study period;
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s). For corticosteroids, this will mean prednisone 5 mg/day, or equivalent. Inhaled and topical steroids are allowed;

- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after the vaccination dose*;

  * In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if, necessary for that vaccine, provided it is licensed and used according to its Product Information.

  See Section 5.5 for more details on Criteria for Temporary Delaying Enrolment).

- Administration of a seasonal influenza vaccine during the 6 months preceding entry into the study;
- Previous experimental vaccination against RSV.

5.2.3. Prior/Concurrent clinical study experience

Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device);

5.2.4. Other exclusions

- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions;
- Alcoholism or substance use disorder within the past 24 months based on the presence of two or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglected major roles to use, withdrawal tolerance, use of larger amounts or longer, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving (based on the DSM-5 criteria, [Hasin, 2013]);
- Any study personnel or their immediate dependents, family, or household members.

5.3. Lifestyle considerations

Lifestyle characteristics may include highest level of education, smoking status/exposures, household environment, and other factors that could place study participants at risk of adverse study outcomes.

5.3.1. Demographic data

Demographic data for participants includes geographic ancestry (race)*, ethnicity*, month of birth (if allowed per local regulation) and year of birth.

*Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013] have been observed in

racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all study participants.

5.4. Screen failures

Screen failures are participants who consent to take part in this study but are determined ineligible and subsequently not assigned to a study intervention.

Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

Note: Demography and required forms at Visit 1 should be completed for screening failures.

5.5. Criteria for temporarily delaying enrollment

Enrollment may be postponed until transient conditions cited below are resolved. Participants must be rescreened:

- Participants with abnormal hematological/biochemical values at screening, *if* expected to be temporary at the discretion of the investigator.
- Acute disease and/or fever at the time of enrollment. Refer to the Schedule of Activities (SoA) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or vaccinated at the discretion of the investigator.
- Use of systemic antibiotic or antiviral treatment within 48 hours prior to study vaccination.

The standard time window for planned administration/administration of a vaccine not foreseen by the study protocol is 30 days before and after the day of vaccination with RSV vaccine. There may be an exception that can shorten the time window based on the local guidance, but it will not be less than 15 days before or after Visit 1.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention. Refer to the Study Procedures Manual (SPM) for additional details.

6.1. Study intervention(s) administered

Table 5 Study intervention(s) administered

Study intervention name:	RSV MAT 120	Flu D-QIV*	Placebo
Interventional Products	RSVPreF3 high dose NaCl Solution	Flu Quadrivalent influenza vaccine,15 µg hemagglutinin (HA) per strain/dose*	NaCl Solution
Study intervention formulation:	RSVPreF3(120 µg) Sodium Chloride (NaCl) (0.9%); Water for injections	A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Tasmania/503/2020 (H3N2)*****, IVR-221 (15 µg HA); B/Washington/02/2019 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections q.s. 0.5 mL	Sodium Chloride (NaCl) (0.9%); Water for injections
Presentation:	Powder for solution for injection Solution for solution for injection	Suspension for injection (syringe)	Solution for injection (syringe)
Type	Study	Co-administration	Control
Product Category	Combination Product	Combination Product	Combination Product
Route of administration:	Intramuscular use	Intramuscular use	Intramuscular use
Administration site:			
• **Location**	Deltoid	Deltoid	Deltoid
• **Laterality***	See Table 6	See Table 6	See Table 6
Number of doses to be administered:	1	1	1
Volume to be administered:**	whole content	0.5mL***	whole content****
Packaging, labeling and TM:	Refer to the Study Procedure Manual	Refer to the Study Procedure Manual	Refer to the Study Procedure Manual
Manufacturer:	RSVPreF3: GSK NaCl: GSK	GSK	GSK

RSV MAT 120=RSVPreF3 vaccine
*Flu D-QIV strains will depend on the World Health Organisation recommendation for the 2021/2022 season.
**Refer to the SPM for the volume after reconstitution.
**Full volume (0.5mL) to be administered.
**** The volume of the saline syringe may be between 0.6ml and 0.8 ml. The full volume is to be injected.
*****A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus).

Table 6 Study intervention administered (Part 2)

Day 1 Vaccination					
Interventional Groups	**N**	**Intervention**	**Laterality**	**Intervention**	**Laterality**
RSV1	220	RSVMAT 120 (Lot 1)	Left Arm		
RSV2	220	RSVMAT 120 (Lot 2)	Left Arm		
RSV3	220	RSVMAT 120 (Lot 3)	Left Arm		
RSV1+Flu	147	RSVMAT 120 (Lot 1)	Left Arm	Flu D-QIV	Right Arm
RSV2+Flu	147	RSVMAT 120 (Lot 2)	Left Arm	Flu D-QIV	Right Arm
RSV3+Flu	147	RSVMAT 120 (Lot 3)	Left Arm	Flu D-QIV	Right Arm
Flu+ P	440	Flu D-QIV	Left Arm	Placebo	Right Arm

Day 31 Standard of Care Vaccination*			
Interventional Groups	**N**	**Intervention**	**Laterality**
RSV1	220	Flu D-QIV	Non-dominant arm
RSV2	220	Flu D-QIV	Non-dominant arm
RSV3	220	Flu D-QIV	Non-dominant arm

RSVMAT120=RSV PreF3 vaccine
*Visit 2 Flu D-QIV vaccinations are not part of experimental design and serve as an optional vaccination for participants to provide standard of care.

Study participants must be observed closely for at least 30 minutes after the administration of the study intervention(s). Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope**.**

6.2. Preparation/Handling/Storage/Accountability

The study intervention(s) must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the SPM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

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

6.3.2. Randomization to study intervention

6.3.3. Intervention allocation to the participant

The randomization algorithm will use a minimization procedure accounting age at the time of vaccination (18-32 vs. 33-49) and center. Minimization factors will have equal weight in the algorithm.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the first dose.

When an automated, Internet based system (SBIR) is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about the study intervention number allocation.

6.3.4. Allocation of participants to assay subsets

N/A

6.3.5. Blinding and unblinding

Data will be collected in an observer-blind manner to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine and single-blind manner to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK quadrivalent influenza. To do so, study interventions will be prepared and administered by qualified study personnel who will NOT participate in data collection, evaluation, review or the entry of any study endpoint (i.e. reactogenicity, safety, immunogenicity).

- This study will utilize an observer-blind design as described below:
  - For the Lot-to-Lot consistency groups (RSV1, RSV2, and RSV3), both the participant and investigator will be blinded to the lot received. However, they will both know that the participant is not part of the co-administration study groups.
- This study will utilize a single blind design as described below:
  - For the co-administration groups (Flu+RSV or Flu+P), the investigator and participant will both know that the participant is part of the co-administration study groups. However, the participant will be blinded to the vaccine administration activities. Participant will be administered with either RSVPreF3 or Flu D-QIV on the left arm. On the right arm, participant will be administered with either Flu D-QIV or the placebo.
- This blinding strategy will apply from Visit 1 to ***study end (Day 181) (Amended 26 May 2022)***.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention and the identity of the participant.

6.3.5.1. Emergency unblinding

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

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

The investigator may contact a GSK Helpdesk (refer to the Table 7) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the SBIR).

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

Table 7 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days	
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com	
Toll free numbers are available for the following countries.	
Country	**Toll free number**
Canada	877.870.0019 or 1 833 541 0263
United States	877.870.0019 or 1 844 446 3133
South Korea	001 800 4344 1111
Spain	00 800 4344 1111
Finland	999 800 4344 1111

6.3.5.2. Unblinding prior to regulatory reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study

intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

When the study intervention is administered at the site, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

Before dosing, a qualified member of the site staff other than the person administering the dose will confirm that the intervention number is correct. The intervention number administered, and the administration date and time will be recorded in the source documents.

6.5. Dose modification

Not applicable.

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

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

6.7. Treatment of overdose

Not applicable

6.8. Concomitant therapy

At each study visit/contact, the investigator or his/her delegate should question the participant about all medications/products taken, and vaccinations received by the participant.

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

- All concomitant medication associated with an adverse event, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1 to Day 30).
- All antibiotics, analgesics, and anti-pyretics taken within 7 days before dose administration.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines.
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.3.1 and 10.3.8.2. These must also be recorded in the Expedited Adverse Event report.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination) up to the first 30 days after vaccination.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Criteria for discontinuation of study vaccines / products do not apply since this is a single dose study. However, administration of the study's single dose may be *delayed* if the criteria presented in Section 5.5 are met.

7.1.1. Contraindications to subsequent study intervention(s) administration

Contraindications of study interventions do not apply since this is a single dose study. However, a history of severe allergic reactions (e.g., anaphylaxis) to any component of the Flu D-QIV vaccine, including egg protein, or following a previous dose of any influenza vaccine should be noted when given as standard of care during Visit 2.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who was not available for the concluding contact planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

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

- Adverse events requiring expedited reporting to GSK
- Unsolicited non-serious adverse events
- Solicited adverse event
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

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

7.3. Lost to follow-up

A participant will be considered ‘lost to follow-up’ if she fails to return for scheduled visits and cannot be contacted by the study site.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

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

Study procedures and their timing are summarized in the SoA (Section 1.3).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

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

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

Study Procedures During Special Circumstances

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

- Enrollment of additional participants may be placed on hold. Decisions on re-starting enrollment to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.
- For guidance regarding the temporary delay of participants enrollment because of exposure to COVID-19, please refer to the SPM for details.
- The following measures may be implemented for enrolled participants:
  - If it is not possible to conduct a protocol-specified, scheduled or event-driven visit as described in Section 1.3, the visit may be replaced with a contact conducted by SMS, email, telephone, videotelephony or telemedicine. In such cases:
    - Protocol-specified clinical data that
      - cannot be collected by study staff during the contact (e.g., physical examination results) BUT
      - are available within the allowed interval (Table 2) in the participant's medical records and can be obtained by site staff (as allowed by local law), may be recorded in the participant's source document and entered into the eCRF.
  - Whenever possible, as appropriate per the judgment of the investigator and as allowed by local law, arrangements should be made for qualified personnel to collect any protocol-specified safety data, safety assessment(s), and/or biological samples at an alternate location* within the visit interval (Table 2).

- Samples should not be collected if they cannot be processed in a timely manner and / or appropriately stored until the intended use.
- Blood samples for central assessment must be collected using GSK-provided supplies.

Additional details of how these visits can be conducted are outlined in the SPM.

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

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site.

8.1. Immunogenicity assessments

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

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

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

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

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

Table 8 Biological samples

Sample type Collected to Evaluate	Minimum Quantity per participant	Unit	Time point	Additional Information
Whole blood for immune response	10	ml	Visit 1 (Day 1)	Immune response: 10 mL (~ 4 mL serum).
Whole blood for immune response	10	ml	Visit 2 (Day 31) *	Immune response: 10 mL (~ 4 mL serum).
	20	ml	Minimum Total, not including repeat or unscheduled samples	
Urine for Pregnancy	-	-	Visit 1 (Day 1)	

*The blood sample at Visit 2 for immune must be taken before administering the Flu D-QIV vaccine as a standard of care.

8.1.2. Laboratory assays

All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK.

Table 9 Laboratory assays

Sampling time points	System	Component	Method	Unit	Groups	Laboratory
Visit 1	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	IU* and/or ED60	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus B Ab neutralizing	NEU	IU and/or ED60	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	ELU/ml	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	Nexelis
	Serum	Flu D-QIV ** • A/Victoria/2570/2019 (H1N1) Ab • A/Tasmania/503/2020 (H3N2) Ab • B/Washington/02/2019 Ab • B/Phuket/3073/2013 Ab	HI assay	1/Dil	RSV1+Flu RSV2+Flu RSV3+Flu Flu+P	GSK designated lab

Sampling time points	System	Component	Method	Unit	Groups	Laboratory
Day 31	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	IU and/or ED60*	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus B Ab neutralizing	NEU	IU and/or ED60	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	ELU/mL	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	Nexelis
	Serum	Flu D-QIV** • A/Victoria/2570/2019 (H1N1) Ab • A/Tasmania/503/2020 (H3N2) Ab • B/Washington/02/2019 Ab • B/Phuket/3073/2013 Ab	HI assay	1/Dil	RSV1+Flu RSV2+Flu RSV3+Flu Flu+P	GSK designated lab

*IU=international units ED60= serum dilution inducing 60% inhibition in plaque forming units (ED60)
** Flu D-QIV strains will depend on the World Health Organisation recommendation for the 2021/2022 season

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

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

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

8.1.3. Immunological read-outs

All participants will have Visit 1 (Day 1) and Visit 2 (Day 31) blood samples tested.

Table 10 Immunological read-outs

Blood sampling timepoint		Approximate No. participants	Component*
Type of contact and timepoint	Sampling timepoint		
V1 (Day 1)	pre-vaccination	1101	Respiratory Syncytial Virus A Ab neutralizing
		1101	Respiratory Syncytial Virus B Ab neutralizing
		1101	Respiratory Syncytial Virus PreF3 Ab.IgG concentration
		881	Flu D-QIV *
V2 (Day 31)	post vaccination	1101	Respiratory Syncytial Virus A Ab neutralizing
		1101	Respiratory Syncytial Virus B Ab neutralizing
		1101	Respiratory Syncytial Virus PreF3 Ab.IgG concentration
		881	Flu D-QIV *

V = Visit; IgG: immunoglobulin G; Ab =Antibody
*Testing for COVID-19 in any suspected infected participant should be performed as the standard of care.

8.1.4. Immunological correlates of protection

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

Although there is no accepted correlate of immunity against influenza, the protective role of antibodies against HA and, to a lesser extent, neuraminidase, is well established and has been demonstrated both in experimentally infected animals and humans [Brydak, 2000].

For this reason, the induction of HA-specific antibodies was used as marker of potential vaccine efficacy and the serum HI assay was used to demonstrate this humoral response. HI antibody titers of 1:40 or greater have been associated with protection from influenza illness in at least 50% of participants in challenge studies [Hannoun, 2004] as well as to correlate with vaccine effectiveness [Beyer, 1989].

8.2. Safety Assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study.

The safety analyses will be performed on the Exposed set or Solicited Safety set. Safety endpoints including solicited AEs, unsolicited AEs, SAEs, AEs leading to study termination will be descriptively summarized by group and overall. Numbers and percentage with 95% CI of participants reporting above AEs will be reported.

8.2.1. Pre-vaccination procedures

Obtain the participant's medical/vaccination history by interviewing her and/or reviewing her medical records. Record any pre-existing participant conditions, signs and/or symptoms present prior to the study vaccination in the eCRF.

8.2.1.1. Informed consent agreement

Before performing any study procedure, the signed informed consent of the participant needs to be obtained. Refer to Section 10.1.3 for the requirements on how to obtain informed consent.

8.2.1.2. Collection of demographic data

Demographic data such as age, year of birth, gender, height, weight, race, and ethnicity will be recorded in the participant's eCRF.

8.2.1.3. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to study intervention in the eCRF. All prior therapy including hematological products (e.g. plasma transfusion, blood transfusion etc.), medications, and vaccines received by the participant in the last 30 days prior to study start should be collected and recorded with exception of seasonal flu vaccine. Seasonal flu vaccine history must be collected and recorded for the last 6 months.

8.2.1.4. Physical examination

- Perform a full physical examination of the participant at the Visit 1 [Day 1], including assessment of oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.
- A history directed physical exam and vital signs at Visit 2 [Day 31] may be performed.

8.2.1.5. Pregnancy test

Participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

A serum pregnancy test instead of a urine pregnancy test should be performed if required by country, local or ethics committee regulations.

Refer to the Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.6. Warnings and precautions to vaccination

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention.

8.2.2. Study holding rules and safety monitoring

Not applicable

8.3. AEs, SAEs and other safety reporting

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

An overview of the protocol required reporting periods for AEs, SAEs, and pregnancies is given in Table 11.

Table 11 Reporting periods for collecting safety information

Event	V1		TC1		V2	TC2
	D1	D7	D8	D30	D31	D181
Administration site and systemic solicited events						
Unsolicited AEs						
AEs/SAEs leading to withdrawal from the study						
SAEs*						
Pregnancies						

V: visit; TC: telephone contact; D: Day

*SAEs related to study participation or concurrent GSK medication/vaccine will be monitored from the time of screening to the time of the immunization. Both will be conducted on the same visit

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

A post study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 13.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

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

8.3.2.1. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values reported during the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or LML. Refer to the Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified, and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 12. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

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

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

Please refer to the Section 10.3.10 for further details regarding the reporting of SAEs/pregnancies.

Table 12 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours *	electronic pregnancy report	24 hours *	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE

8.3.3.1. Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Table 13 Contact information for reporting SAEs and pregnancies

Study contact for questions regarding SAEs, pregnancies Refer to the local study contact information document
Back up study contact for reporting SAEs, pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.10.1).

8.3.5. COVID-19 Infection

COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE or SAE criteria, as outlined in Section 10.3.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition, [WHO, 2020] using one of the following terms:

- Suspected COVID-19 infection
- Probable COVID-19 infection
- Confirmed COVID-19 infection

8.3.6. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/care giver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back up.

8.3.7. Medical device deficiencies

The study intervention is a combination product constituted of a device and biologic product (e.g. pre-filled syringes). Refer to the Section 10.6.1 for the definition of combination product and medical device deficiency.

8.3.7.1. Detection, follow-up and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6.1 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

8.3.7.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to section 10.6 for details of reporting.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Pharmacokinetics

Not applicable.

8.5. Genetics

Not applicable.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity

Immunogenicity analysis will be performed on the Per Protocol set. If, in any study group and at any timepoint, the percentage of vaccinated participants with immunogenicity results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set will be performed to complement the Per Protocol analysis.

Refer to Section 8.1. for more details

8.8. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The statistical hypothesis for each confirmatory objective is detailed below.

9.2. Sample size determination

Approximately 1541 participants will be randomized to achieve appropriately 1400 evaluable participants.

Assessments of both immunogenicity and safety data were considered when determining sample size for this study.

Participants who withdraw from the study will not be replaced.

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

9.2.1. Primary objective for Lot-to-Lot consistency

The primary objective of lot-to-lot consistency will be evaluated on the RSVPreF3 immunogenicity as measured by RSVPreF3 IgG ELISA concentration at Day 31.

The lot-to-lot consistency will be demonstrated only if two-sided 95% confidence intervals for the 3 pair-wise geometric mean ratios of RSVPreF3 IgG ELISA concentration at Day 31 (30 days post vaccination) falls within 0.67 and 1.5.

With the assumptions of a SD of log10 transformed RSVPreF3 IgG ELISA concentration of 0.35, true GMC ratio of 1 between 2 lots, type I error of 0.025, and 10% of non-evaluable rate, 220 enrolled participants per lot provides at least 99% global power to conclude lot-to-lot consistency (see details in Table 14 below).

Table 14 Power to demonstrate Lot-to-Lot consistency on immune responses of RSVPreF3 IgG ELISA concentration at Day 31 post vaccination

Endpoint	Clinically acceptable bounds for consistency	Group description	Number of evaluable participants in each lot	Reference SD **	Power
*RSVPreF3 IgG GMC ratio	(0.67, 1.5]	Lot 1/2	200	0.35	99.8%
*RSVPreF3 IgG GMC ratio	(0.67, 1.5]	Lot 1/3	200	0.35	99.8%
*RSVPreF3 IgG GMC ratio	(0.67, 1.5]	Lot 2/3	200	0.35	99.8%
Global power					99.3%

* Pass 2019, Two-Sample T-test for equivalence allowing unequal variance, alpha=2.5%;
**References used for the sample size calculation: Study *RSV MAT 011* (209141)

9.2.2. Primary objective: To demonstrate Non-inferiority of immune response of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine or administered alone at Day 31 post dose vaccination *(Amended 26 May 2022)*

Possible interference of RSVPreF3 on influenza immune responses will be evaluated by using Flu D-QIV HI antibody titers against the ***3*** influenza strains from RSVPreF3 + Flu (pooled of RSV1+Flu, RSV2+Flu, RSV3+Flu) and Flu+P group at Day 31. In the description of the subsequent analysis, the RSVPreF3+ Flu D-QIV vaccine group are RSV1+Flu, RSV2+Flu, RSV3+Flu groups pooled.

The hypothesis is that co-administration of RSVPreF3+ Flu D-QIV vaccine is non-inferior to Flu D-QIV vaccine with respect to GMT ratio for immune response of influenza antigen in non-pregnant women at Day 31 post vaccination.

The criteria to evaluate non-inferiority for A/Tasmania/503/2020 (H3N2) IVR-221, B/Washington/02/2019, and B/Phuket/3073/2013 is that the lower limits of the 95% CI on the GMT ratio (RSV PreF3 + Flu D-QIV divided by Flu D-QIV) is greater than 0.67 at Day 31 post vaccination.

Table 15 presents the power on the ratio of the GMT of Flu D-QIV ***3*** strains. The power is at least ***95***% when the sample size is 400 participants per group with standard deviation (SD) of 0.6 on its log10 transformation and non-inferiority margin of 0.67 between RSVPreF3 co-administrated with Flu D-QIV group and Flu D-QIV vaccine administered alone group.

Table 15 Power to demonstrate non-inferiority of immune response between Flu D-QIV vaccine co-administered with RSVPreF3 or administered alone in term of GMT for Flu D-QIV strains at Day 31 post 1st vaccination with assumed GMT ratio 1 *(Amended 26 May 2022)*

Endpoint	NI criteria	Number of evaluable participants in each group	Reference*	Power
B/Washington/02/2019 GMT ratio	LL of 95% CI for GMC ratio >0.67	400	0.60	98.56%
A/Tasmania/503/2020 (H3N2)** IVR-221 GMT ratio	LL of 95% CI for GMT ratio >0.67	400	0.60	98.56%
B/Phuket/3073/2013 GMT ratio	LL of 95% CI for GMT ratio >0.67	400	0.60	98.56%
Global power				***95.68***%

By Pass 2019, Non-Inferiority Tests for Two Means using Differences, one-sided alpha=2.5%;
*References used for the sample size calculation: Study Flu D-QIV -008 E1_01 Table 34.
**A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus).

9.2.3. Secondary objectives

To control the global type I error, a hierarchical procedure will be used for confirmatory objectives assessment.

For instance, the secondary objective to demonstrate the non-inferiority of RSV A neutralizing antibodies using GMT ratios can only be assessed if the primary objective assessing the non-inferiority of GMT ratio for Flu D-QIV strains is met. As per the hierarchical procedure, secondary objective assessing the non-inferiority based on SCR difference of Flu D-QIV will only be assessed if the non-inferiority of RSV A neutralizing antibodies using GMT ratios is met.

9.2.3.1. To demonstrate the non-inferiority of immune response between RSVPreF3 co-administered with Flu D-QIV and RSVPreF3 alone in term of RSV A Neutralizing antibody titers at Day 31 post administration

Hypothesis under consideration is that immune response when the co-administration of RSVPreF3 vaccine + Flu D-QIV vaccine is non-inferior to that when RSV PreF3 vaccine (pooled RSV1, RSV2 and RSV3 group) is administered alone with respect to GMT ratio for RSV A neutralizing antibody titer in non-pregnant women at Day 31 post vaccination.

This hypothesis test is conducted only if the primary objective of non-inferiority of immune response between Flu D-QIV vaccine when co-administered with RSVPreF3 and Flu D-QIV vaccine administered alone is met.

The criteria to evaluate non-inferiority for RSV A Nab is that the lower limits of the 95% CI on the GMT ratio (RSVPreF3+Flu D-QIV vaccine divided by RSV PreF3 vaccine (pooled RSV1, RSV2 and RSV3 group) is greater than the pre-defined clinical limit of 0.67 at Day 31 post vaccination.

If a SD of log10 transformed RSV A Nab of 0.4 is assumed, with an assumption of GMT ratio of 1.0, there will be at least 99% chance that the lower bound of 95% CI for the ratio of GMT of RSV A Nab titer between RSVPreF3 co-administration with Flu D-QIV and administered alone is above 0.67 (Table 16).

Table 16 Power to demonstrate non-inferiority of immune response of RSVPreF3 vaccine when co-administered with Flu D-QIV vaccine or administered alone at Day 31 post vaccination

Endpoint	NI criteria	N1:N2 (evaluable)	Reference*	Power
RSV A GMT ratio	LL of 95% CI for GMT ratio >0.67	400:600	0.40	99.99%

By Pass 2019 Non-Inferiority Tests for Two Means using Differences, one-sided alpha=2.5%;
*References used for the sample size calculation: Study RSV MAT 011 (209141)
N1: Number of evaluable participants in the co-administration of RSVPreF3 vaccine + Flu D-QIV vaccine.
N2: Number of evaluable participants in the RSVPreF3 vaccine alone group with 3 lots pooled.

9.2.3.2. To demonstrate the non-inferiority of immune response between RSVPreF3 co-administered with Flu D-QIV and Flu D-QIV alone in term of SCR at Day 31 post 1st dose administration *(Amended 26 May 2022)*

Potential interference of RSVPreF3 on influenza immune responses will be evaluated by comparing the Day 31 seroconversion rate of Flu D-QIV HI antibody titers against the ***3*** influenza strains between RSVPreF3+ Flu D-QIV vaccine group and Flu D-QIV+P group.

The criteria to evaluate non-inferiority with respect to the SCR difference for Flu D-QIV antibody titers against ***3*** influenza strains is that the upper limits of the 95% CI on the SCR difference (Flu D-QIV vaccine minus RSVPreF3+Flu D-QIV vaccine) is less than the pre-defined clinical limit of 10% at Day 31 post vaccination.

With the assumptions of SCR for the reference group as indicated in Table 17, significance level 0.025, non-inferiority margin 10%, 400 evaluable participants (10% non-evaluable rate) provides at least 80% power to conclude non-inferiority for each strain (Table 17).

Table 17 Powers to demonstrate non-inferiority in terms of HI antibody SCR for Flu D-QIV strains between Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and administered alone at Day 31 post vaccination *(Amended 26 May 2022)*

Endpoint	NI criteria	Anticipated SCR*	Number of participants per group (evaluable)	Power
B/Washington/02/2019 SCR	10%	65%	400	84.39%
A/Tasmania/503/2020 (H3N2)** IVR-221 SCR	10%	65%	400	84.39%
B/Phuket/3073/2013 SCR	10%	65%	400	84.39%

By Pass 2019, Non-Inferiority Tests for the difference between two proportions, alpha=2.5%
*SCR used in the reference group for power calculation is from Study Tdap-0.3-008, Suppl. Table 36.
**A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus).

9.2.4. Safety consideration

The sample size of 660 participants when pooled 3 lots and 440 participants per group in the co-administration group at the first vaccination were planned to provide reasonable confidence to evaluate the AE rate. The table below illustrates the precision that can be obtained on the percentage of participants with AEs following vaccination. If an AE is not observed in a given treatment group, a sample size of 660 participants for pooled RSV lots can provide at least 95% confidence to rule out an AE incidence greater than 0.56%. Considering the sample size of 440 vaccinated in co-administration groups, it can provide at least 95% confidence to rule out an AE incidence rate greater than 0.83%.

In addition, a sample size of 440 in co-administration group would provide a probability of 98.8% to observe at least one AE if true AE rate is 1%.

Table 18 Exact 95% confidence interval (CI) on the percentage of participants with AEs following vaccination from 660 participants with 3 lots pooled, and 440 participants from RSVPreF3 co-administration group

Number of participants per group	Number (%) of participants with an AE	Exact 95% CI	
		Lower Limit (%)	Upper Limit (%)
660	0 (0%)	0	0.56
660	33 (5%)	3.47	6.95
660	66 (10%)	7.82	12.55
660	99 (15%)	12.36	17.96
440	0 (0%)	0	0.83
440	22 (5%)	3.16	7.47
440	44 (10%)	7.36	13.19
440	66 (15%)	11.79	18.68

9.3. Analysis sets

Table 19 Analysis sets

Analysis Set	Description
Enrolled	Participants who agreed to participate in a clinical study after completion of the informed consent process
Exposed	All Participants who received at least 1 dose of the study treatment. The allocation in a group is done as a function of the administered treatment
Full Analysis	All Participants who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data
Per Protocol	All Participants who received at least 1 dose of the study treatment to which they are randomized and have post-vaccination data minus participants with protocol deviations that lead to exclusion
Solicited Safety	All Participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data

9.3.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned below or ones listed in the Section 7.1.1 she may be eliminated from per protocol analysis**.**

If the participant has a protocol deviation deemed as major, he/she may be eliminated from the per protocol analysis sets.

Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and will be finalized prior to the first analysis defined in Section 9.4.3.

Key major deviations include, but are not limited to, the following:

- Participants enrolled who did not meet entry criteria including age at enrollment
- Participants incorrectly vaccinated
- Participants who did not receive study vaccinations as planned in protocol
- Participants who did not have blood draws as planned in protocol
- Participants with a blood draw outside of allowed time window

These key major deviations will be assessed based on the data collected in the eCRFs

A complete list of criteria for elimination from per protocol analysis will be detailed in the Statistical Analysis Plan (SAP).

9.4. Statistical analyses*(Amended 26 May 2022)*

9.4.1. Primary endpoints/estimands analysis

Primary Safety Endpoints	**Statistical Analysis Methods**
The number and percentage of participants in each group reporting • Each solicited administration site AE collected during the 7 days follow-up period (Day 1 to Day 7). • Each solicited systemic events in the 7 days follow-up period.	The number and percentage with exact 95% CI of participants reporting each **solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day follow-up period after dosing will be tabulated by maximum intensity per participant for each study group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of participants reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported.
The number and percentage of participants in each group reporting • Unsolicited AEs collected during the 30 days follow-up period (Day 1 to Day 30) • SAEs in the 30 days follow-up period (Day 1 to Day 30). • ***SAEs in the 180 days follow-up period (Day 1 to Day 181)***	The number and percentage of participants reporting **unsolicited AEs** within 30 days after dosing with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, and for Grade 3 related unsolicited AEs. The number and percentage of participants reporting at least one SAE within 30 days after dosing with exact 95% CIs will be tabulated by group and by MedDRA terms. ***The number and percentage of participants reporting at least one SAE up to study end with exact 95% CIs will be tabulated by group and by MedDRA terms.*** By-subject listings of SAEs and AEs leading to study withdrawal will be prepared.
Primary Immunological Endpoints	**Statistical Analysis Methods**
RSVPreF3 IgG ELISA concentration at Day 31 (30 days post administration) Measured by ratio of GMC between lots in terms of RSVPreF3 IgG ELISA titers at Day 31 (30 days post administration) Flu D-QIV antibody titers against ***3*** influenza strains at Day 31 (30 days post administration) Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine	**Primary confirmatory analyses:** Lot-to-lot consistency among 3 lots of RSV vaccine for RSVPreF3 IgG ELISA concentration at Day 31: The 2-sided 95% CI for GMC ratio (each pair of comparison is between 2 out of 3 lots) for RSVPreF3 IgG ELISA concentration at Day 31 will be computed based on the fact that the difference in the mean of log10 transformed RSVPreF3 IgG ELISA concentration on Day 31 between 2 lots follows t-distribution. Lot-to-lot consistency will be demonstrated if all 3 two-sided 95% CIs for GMC ratio fall within 0.67 and 1.5. Non-inferiority of Flu D-QIV co-administered with RSVPreF3 vaccine compared to Flu D-QIV group with respect to ***3*** Flu D-QIV strains at Day 31: The 2-sided 95% CIs for A/Tasmania/503/2020 (H3N2) IVR-221 GMT ratio, B/Washington/02/2019 GMT ratio and B/Phuket/3073/2013 GMT ratio

Primary Safety Endpoints	Statistical Analysis Methods
alone group against ***3*** strains at Day 31 (30 days post administration)	(RSVPreF3 co-administered with Flu D-QIV group versus Flu D-QIV group) will be computed based on the fact that the difference in the mean of log10 transformed titers on Day 31 between 2 groups follows a t-distribution. No interference on quadrivalent seasonal influenza vaccine (Flu D-QIV) from RSVPreF3 vaccine is demonstrated if lower bounds of all ***three*** 2-sided 95% CIs are above 0.67.

9.4.2. Secondary endpoints/estimands analysis

Secondary Immunological Endpoints/Estimands	Statistical Analysis Methods
RSV A neutralizing antibody titers at Day 31 (30 days post administration) Measured by ratio of GMT between group of RSVPreF3 vaccine co-administered with Flu D-QIV and RSVPreF3 vaccine alone (pooled lot 1,2,3) group in term of RSV A neutralizing antibody titers at Day 31 (30 days administration) Seroconversion rate to Flu D-QIVHI antibody titers against the ***3*** influenza strains at Day 31 Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone	**Secondary confirmatory immunogenicity analyses:** Non-inferiority of RSVPreF3 vaccine co-administered with Flu D-QIV vaccine compared to RSV alone group in terms of RSV A neutralizing antibody titers at Day 31 The 2-sided 95% CI for GMT ratio (RSV co-administered with Flu D-QIV group *versus* RSV group) will be computed based on the fact that the difference in the mean of log10 transformed RSV A neutralizing antibody titers at Day 31 between 2 groups follows a t-distribution. No interference on RSVPreF3 vaccine from quadrivalent seasonal influenza vaccine (Flu D-QIV) is demonstrated if lower bound of the 2-sided 95% CI of GMT ratio is above 0.67.Non-inferiority of Flu D-QIV co-administered with RSVPreF3 vaccine compared to Flu D-QIV vaccine alone with respect to each of the ***3*** Flu D-QIV strains at Day 31 in terms of Seroconversion rate (SCR) The 2-sided 95% CI for the difference of SCR (Flu D-QIV group *minus* RSV co-administered with Flu D-QIV group) will be calculated for each strain. Non-inferiority is demonstrated if the upper bound of 95% CI is less than or equal to the pre-defined clinical limit of 10% at Day 31 post vaccination.
RSV A, RSV B neutralizing antibody titers and RSVPreF3 IgG concentration at Day 1 and Day 31 GMT of RSV A and RSV B neutralizing antibody, GMC of RSVPreF3 IgG at Day 1 and Day 31, in the group of RSVPreF3 vaccine co-administered with Flu D-QIV and the group of RSVPreF3 vaccine alone. Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 1 and Day 31 HI GMT in the ***3*** influenza strains at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone Seroprotection rate to Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 1 and Day 31	**Descriptive immunogenicity analyses:** For each assay, descriptive immunogenicity analysis may include but not limited to the following: • GMT/GMCs will be tabulated with 95% CI at each timepoint and represented graphically by group. • Geometric mean of ratios of antibody titers/concentrations at Day 31 over pre-vaccination will be tabulated with 95% CI by group. • Number and percentage of participants achieving seroconversion for HI antibody at Day 31 will be tabulated with its 95% CI in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone. • Number and percentage of participants achieving HI antibody titer ≥ 1:40 at Day 1 and Day 31 will be tabulated with its 95% CI in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone.

Secondary Immunological Endpoints/Estimands	Statistical Analysis Methods
Measured by the proportion of participants achieving an HI antibody titer ≥1:40 at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone Seroconversion rate to Flu D-QIV HI antibody titers against the ***3*** influenza strains at Day 31 Measured by the proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone RSV A, RSV B neutralizing antibody titers and RSVPreF3 IgG antibody concentrations at pre-vaccination and Day 31 from each lot Geometric mean titer/concentration (GMT/GMC) in term of RSV A, RSV B neutralizing antibody and RSVPreF3 IgG antibody at Day 1 (pre-vaccination) and Day 31 in each of 3 lots of the investigational PreF3 vaccine.	Other descriptive analyses of immunogenicity if needed will be detailed in the SAP' **Exploratory immunogenicity between group analyses:** Exploratory comparisons between study groups will also be explored through statistical modeling for the applicable primary and secondary immunogenicity endpoints. The GMT/GMC ratio of involved study groups and the two-sided 95% CI will be computed by fitting an ANCOVA model on the logarithm10 transformation of the titers/concentrations, including the study group as fixed effect, age category at the time of vaccination (18-32 vs. 33-49) and pre-vaccination titers/concentrations as covariates, covariates in the model may be further adjusted when performing the analysis if appropriate and needed.

9.4.3. Tertiary endpoints/estimands analysis

The same statistical methods that are used to analyze the 3 strains in the primary and secondary endpoints will be used to analyze the A/Victoria/2570/2019 (H1N1) IVR-215 strain.

9.5. Conduct of analyses

9.5.1. Sequence of analyses *(Amended 26 May 2022)*

No interim analyses are planned.

The final analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion are available. A clinical study report (CSR) containing all available data will be written and made available to the investigators at that time.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses may be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

9.5.2. Statistical consideration for analysis *(Amended 26 May 2022)*

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF or Informed Assent Form, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators must provide the sponsor with full and accurate financial disclosure, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators must provide their financial interest information before initiation of the study center and again at the end of the study. Investigators are responsible for providing

a financial disclosure update if their financial interests change at any point during study participation and for 1 year after completion of the study.

10.1.3. Informed consent process

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

Participants must be informed that their participation is voluntary.

Freely given and written/witnessed/thumb printed informed consent must be obtained from each participant as appropriate, prior to participation in the study.

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

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

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

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

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants must be informed that:

- Her personal study-related data will be used by the sponsor in accordance with local data protection law.
- Her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

10.1.5. Committees structure

Safety oversight will be provided by a safety review team (SRT) composed of GSK RSV team members.

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

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

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

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

10.1.7. Data quality assurance

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

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

All participant data related to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

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

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

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

Quality tolerance limits (QTLs) will be pre-defined in the Study Management Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

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

10.1.8. Source documents

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

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests *(Amended 26 May 2022)*

10.2.1. Protocol required safety laboratory assessments

Assay descriptions could be subject to change, due to assay re-development and/or qualification.

RSV-A and RSV-B neutralization assays

The RSV-A and RSV-B neutralization assays are functional assays that measure the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

Virus neutralization is performed by incubating a fixed amount of RSV with serial dilutions of the test serum. Then, the serum-virus mixture is transferred onto a Vero cells culture and incubated for two days to allow infection of Vero cells. Thereafter, RSV-infected cells are detected by the visualization of the number of plaques.

RSVPreF3 IgG ELISA

The ELISA assay is based on an indirect ELISA allowing the detection and the quantification of specific IgG antibodies directed against RSVPreF3 in human serum samples and related to reference standard. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

FLU Hemagglutination-inhibition (HI) assay

Hemagglutination inhibition (HI) antibody titres are determined using the method derived from the WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5.

Measurements are conducted on thawed frozen serum samples with a standardized and comprehensively validated micro-method. Briefly, serum samples are treated with receptor destroying enzyme (RDE) overnight, diluted to 1:10, and serial diluted 2- fold in triplicate from 1:10 to 1:10240. After addition of an equal volume of standardized virus (4 HA / 25 µL), neutralization is performed for 1 hour at room temperature, followed by addition of the RBCs. After 30 minutes, plates are tilted and the titer is the reciprocal of the last dilution that fully inhibits hemagglutination as compared to a RBC control well. Each sera sample will be tested in triplicate within the same assay. The three titer results will be reported as will the geometric mean titer (GMT) for the triplicate.

The tests detailed in Table 20 will be performed by the local laboratory.

All clinical and safety laboratory tests will be performed by local laboratory(ies). All assessments of immune response will be performed centrally (by GSK or by a GSK designated laboratory).

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.

The investigator is not allowed to do extra testing on samples outside of what has been agreed upon by the ethics committees.

Table 20 Protocol required safety laboratory assessments

System	Discipline	Component	Method	Scale	Laboratory
Urine[1]		Pregnancy	As per local practice; dipstick provided by GSK Biologicals	Ordinal	At investigator's laboratory

The tests detailed in Table 20 will be performed by the local laboratory.

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

10.3.1. Definition of an AE

An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.

- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant before the study intervention. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Disease-related events (DRE), typically associated with the disease under study. These events will be recorded in the participant's eCRF and will be monitored by the SRT on a routine basis. However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 10.3.8):
  - The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
  - The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:
a. Results in death.
b. Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c. Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. The event will also be considered serious if a complication prolongs hospitalization or fulfills any other serious criteria. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Other situations Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 21 Solicited administration site events

Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 22 Solicited systemic events

Fever
Headache
GI Symptoms (Nausea, Vomiting, Diarrhea, Abdominal pain) *
Fatigue

* Nausea, vomiting, diarrhea and abdominal pain are collected individually.

Note: participants will be instructed to measure and record the axillary or oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the e-diary.

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

N/A

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

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to the Sections 10.3.1 and 10.3.2).

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

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to the Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, and pregnancies

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

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE instead of individual signs/symptoms.

An Electronic Diary (e-Diary), hereafter referred to as Participant Diary, will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the Participant Diary.

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

Collect and verify completed e-diary during discussions with the participant on Visit 2 (Day 31).

- Any unreturned e-diary device will be sought from the participant through telephone call(s) or any other convenient procedure.

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

Refer to the SPM for more information regarding the use of e-Diary including the occurrence of unsolicited AEs.

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

All solicited events that occur during 7 days following administration of the dose of study intervention (Day 1 to Day 7) must be recorded into the e-Diary, irrespective of intensity. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

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

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until end of study or until the participant is lost to follow-up.

10.3.8.2.1. Follow-up during the study

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

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

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE as fully as possible.

10.3.8.2.3. Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to GSK as described in the Section 10.3.10.

10.3.8.3. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to the Section 8.3.3.1 or to GSK VCSP department within the defined reporting time frames specified in the Table 12**.**

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

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.

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

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.

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

10.3.9.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the Summary of Product Characteristics and/or Prescribing Information for marketed products to assist in making his/her assessment.

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

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

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

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

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

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

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

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

10.3.9.4. Assessment of outcomes

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

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

10.3.10. Reporting of SAEs and pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 12 for the details on timeframes for reporting of SAEs/pregnancies.

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

Refer to the Section 10.3.10.2 for information on backup systems in case the electronic reporting system does not work.

10.3.10.2. Backup system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to the Sponsor Information) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

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

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not

using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 24).

Table 24 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable • ***oral***
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner)*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will be followed to determine the outcome of the pregnancy.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.6.1. Definition of medical device AE and adverse device effect (ADE)

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (i.e. user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

– A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

10.6.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Refer to paper 'Medical device or combination product with device deficiency/incident report form' for details on transmission of this information to the sponsor.
- GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting in Section 8.3.3.1

10.7. Appendix 7: Country-specific requirements

This appendix includes all applicable requirements of specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

10.7.1. South Korea

As per Ministry of Food and Drug Safety the following Prior/Concomitant Therapy Exclusion Criteria will be applicable »

- A participant who has participated in other clinical trial for healthy people within at least 6 months prior to enroll/study vaccination.
- A female between, and including, 19 and 49 years of age at the time of signing of the informed consent.

10.8. Appendix 8: Abbreviations and glossary of terms

10.8.1. List of abbreviations

AE:	Adverse Event
CLS:	Clinical Laboratory Sciences
COVID-19	Corona Virus Disease 2019
CSR	Clinical Study Report
DRE	Disease-related event
eCRF:	electronic Case Report Form
EoS:	End of Study
Flu D-QIV	(*Fluarix Quadrivalent*, *Fluarix Tetra*, *Fluarix Tetra*, α-*RIX-Tetra* and *Influsplit Tetra*)
GCP:	Good Clinical Practice
GSK:	GlaxoSmithKline
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
IDMC	***Independent Data Monitoring Committee (Amended 26 May 2022)***
LML	Local Medical Lead
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities

QTL	Quality Tolerance Limit
RRA:	Recruitment/Randomization Agreement
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomization
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
WOCBP	Woman of Childbearing Potential

10.8.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. In a single-blind study, the investigator and/or his staff are aware of the intervention assignment but the participant is not.
Caregiver	A ‘caregiver’ is someone who • lives in the close surroundings of a participant and has a continuous caring role or

	• has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g. a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product	Combination product comprises any combination of • drug • device • biological product Each drug, device and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS): (Synonym of End of Trial)	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (Visit X) or Last testing results released of samples collected at Visit X* * In this case EoS must be achieved no later than 8 months after LSLV.
Enrolled participant	'Enrolled' means a participant's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.2.4 of the protocol for the definition of 'enrolled set' applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant
Intervention number	A number identifying an intervention to a participant, according to intervention allocation
Investigational vaccine	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical trial. The terms legal representative or legally authorized representative are used in some settings
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study

Primary completion date	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated
Protocol administrative change	A protocol administrative change addresses changes to only logistical or administrative aspects of the study
Protocol amendment	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study
Randomization	Process of random attribution of intervention to participants to reduce selection bias
Self-contained study	Study with objectives not linked to the data of another study
Site Monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites
Solicited event	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical trial).

Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Unsolicited adverse event	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event

10.9. Appendix 9: Protocol Amendment

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

DOCUMENT HISTORY	
Document	Date of Issue
Original Protocol	21 April 2021
Amendment 1	24 May 2021
Amendment 2	17 November 2021
Amendment 3	26 May 2022

Detailed description of the Protocol amendment 1:

The protocol is being amended to align with the safety review team's recommended and approved safety oversight approach for this study. The committee structure provided in the previous version was described in error and this amendment corrects this error.

8.1.2 Laboratory Assays

Sampling time points	System	Component	Method	Unit	Groups	Laboratory
Visit 1	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	IU* **and/or ED60**	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus B Ab neutralizing	NEU	IU **and/or ED60**	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
Day 31	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	IU **and/or ED60**	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab
	Serum	Respiratory Syncytial Virus B Ab neutralizing	NEU	IU **and/or ED60**	RSV1 RSV2 RSV3 RSV1+Flu RSV2+Flu RSV3+Flu	GSK or GSK designated lab

***IU=international units ED60= serum dilution inducing 60% inhibition in plaque forming units (ED60)**

8.3.3.1 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Email address: ***ogm28723@gsk.com***~~PV.ICSRManagement@gsk.com~~

10.1.5 Committees structure

Safety oversight will be provided by a blinded safety review team (SRT) composed of GSK RSV team members. ~~and by an unblinded, internal safety review committee composed of GSK personnel not affiliated with the RSV program~~

Detailed description of the current Protocol amendment 2:

Other study intervention(s)	• Placebo (Saline solution [NaCl]) • Flu D-QIV vaccine ***[GSK2321138A]***
Title	A Phase III, randomized, ~~observer-blind~~, multi-country study to evaluate the lot-to-lot consistency of GSK's investigational RSV maternal vaccine and the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK's quadrivalent influenza D-QIV vaccine in healthy non-pregnant women 18-49 years of age.

1.2 Schema

~~The study is a~~ ***This*** Phase III, ~~observer-blind,~~ randomized, multi-country study ***is observer-blinded to*** evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine**,** ***and single-blinded*** to evaluate the immune response, safety and reactogenicity when co-administered with Flu D-QIV vaccine. A total ***of*** 1541 healthy non-pregnant women 18 to 49 YOA will be enrolled in the study.

All safety data will be reviewed by a ~~blinded~~ Safety Review Team (SRT) on an ongoing basis.

1.3 Schedule of Activities

Medical and vaccination history	●		**O**
Physical examination ~~and vital signs~~[2,4]	●		~~**O**~~
Vital signs[2,4]	●		O

[2] Physical examination including (height and weight) BMI as well as resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest.
At Day 1 (Visit 1) both physical exam and vital signs will be measured ~~while~~. ~~a~~***A***t Day 31 (Visit 2) ~~only~~ ***medical and vaccination history and*** vital signs ~~will~~ ***may*** be measured.

Table 2 Intervals between study visits

Interval	Optimal timing	Allowed interval (Study day)
Visit 1*→ Phone Contact 1	***Day*** 8 ~~days~~	***Day*** 7 – 10 ~~days~~
Visit 1→ Visit 2	***Day*** 31 ~~days~~	***Day*** 31 -38 ~~days~~
Visit 1 → Phone Contact 2	***Day*** 181 ~~days~~	***Day*** 165 - 195 ~~days~~

2.3 Benefit/Risk assessment

Safety monitoring will be conducted throughout this study by a ~~blinded~~ Safety Review Team.

4.1 Overall design

~~The study is a~~ ***This*** Phase III, randomized, multi-country study ***in healthy non-pregnant women 18-49 YOA is observer-blind*** to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine and ***single-blind*** to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with ~~GSK quadrivalent influenza (~~Flu D-QIV~~)~~ ~~vaccine in healthy non-pregnant women 18-49 YOA.~~

Blinding: This study will utilize an observer blinding ~~design~~ to ***evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine; and single-blinding design to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK quadrivalent influenza*** that is described in Section 6.3.5

5.2.2. Prior/Concomitant Therapy

- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before~~*~~ and ending 30 days after the vaccination dose*;

  * In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if, necessary for that vaccine, provided it is licensed and used according to its Product Information.

  (See Section 5.5 for more details on Criteria for Temporary Delaying Enrolment)

5.4 Screen failures

Screen failures are participants who consent to take part in this study but are determined ineligible and subsequently ~~randomly~~ not assigned to a study intervention.

5.5 Criteria for temporarily delaying enrolment

The standard time window for planned administration/administration of a vaccine not foreseen by the study protocol is 30 days before and after the day of vaccination with RSV vaccine. There may be an exception that can shorten the time window based on the local guidance, but it will not be less than 15 days before or after Visit 1.

6.1 Study intervention(s) administered

Study intervention formulation:	RSVPreF3(120 µg) Sodium Chloride (NaCl) (0.9%); Water for injections	~~A/(H1N1)~~ ***A/Victoria/2570/2019 (H1N1), IVR-215*** (15 µg HA); ~~A/(H3N2)~~ ***A/Tasmania/503/2020 (H3N2), IVR-221*** (15 µg HA**);** ~~B/(Victoria Lineage)~~ ***B/Phuket/3073/2013*** (15 µg HA); ~~B/(Yamagata Lineage)~~ ***B/Washington/02/2019 (15 µg HA);*** Water for injections q.s. 0.5 mL	Sodium Chloride (NaCl) (0.9%); Water for injections
Volume to be administered:**	whole content	~~Full volume~~ ***0.5mL******	whole content****

***Full volume (0.5mL) to be administered*.
******A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus)*.

6.3.5 Blinding and unblinding

Data will be collected in an observer-blind manner ***to evaluate the lot-to-lot consistency of GSK RSVPreF3 vaccine and single-blind manner to evaluate the immune response, safety and reactogenicity of RSV maternal vaccine when co-administered with GSK quadrivalent influenza.***

- ***This study will utilize a single blind design as described below:***
  - For the co-administration groups (Flu+RSV or Flu+P), the investigator and participant will both know that the participant is part of the co-administration study groups. However, ~~they~~ ***the participant*** will be blinded to the vaccine administration activities. Participant will be administered with either RSVPreF3 or Flu D-QIV on the left arm. On the right arm, participant will be administered with either Flu D-QIV or the placebo.

6.8 Concomitant therapy

- ***Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination) up to the first 30 days after vaccination***.

8.1.2 Laboratory Assays

Serum	Flu D-QIV * • ***A/Victoria/2570/2019 (H1N1) Ab*** ~~A/H1N1 vaccine strain Haemagglutinin Ab~~ • ***A/Tasmania/503/2020 (H3N2) Ab*** ~~A/H3N2 vaccine strain Haemagglutinin Ab~~ • ***B/Washington/02/2019 Ab*** ~~B/Yamagata vaccine strain (Hemagglutinin Ab)~~ • ***B/Phuket/3073/2013 Ab*** ~~*B/Victoria vaccine strain (Hemagglutinin Ab)*~~	HI assay	1/Dil	RSV1+Flu RSV2+Flu RSV3+Flu Flu+P	GSK designated lab

8.2.1.4 Physical Exam

- Perform a full physical examination of the participant at the ~~first visit~~ ***Visit 1 [Day 1]***, including assessment of oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest
- ~~Perform a~~ ***A*** history directed physical exam and vital signs at Visit ~~1~~***2*** [Day ***31***] ***may be performed***
- ~~Measure only vital sign at Visit 2[Day 31]~~

9.2.2 Primary objective: To demonstrate Non-inferiority of immune response of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine or administered alone at Day 31 post dose vaccination

The criteria to evaluate non-inferiority for ~~A/H1N1~~***A/Victoria/2570/2019 (H1N1) IVR-215***, ~~A/H3N2~~ ***A/Tasmania/503/2020 (H3N2) IVR-221***, ~~B/Victoria lineage~~ ***B/Washington/02/2019***, and ~~B/Yamagata lineage~~ ***B/Phuket/3073/2013*** is that the lower limits of the 95% CI on the GMT ratio (RSV PreF3 + Flu D-QIV divided by Flu D-QIV) is greater than ~~or equal to~~ 0.67 at Day 31 post vaccination.

Table 15: Power to demonstrate non-inferiority of immune response between Flu D-QIV vaccine co-administered with RSVPreF3 or administered alone in term of GMT for Flu D-QIV strains at Day 31 post 1st vaccination with assumed GMT ratio 1

Endpoint	NI criteria	Number of evaluable participants in each group	Reference*	Power
~~A/H1N1~~ ***A/Victoria/2570/2019 (H1N1) IVR-215*** GMT ratio	LL of 95% CI for GMT ratio ≥>0.67	400	0.60	98.56%
~~B/Victoria lineage~~ ***B/Washington/02/2019*** GMT ratio	LL of 95% CI for GMC ratio ≥>0.67	400	0.60	98.56%

Endpoint	NI criteria	Number of evaluable participants in each group	Reference*	Power
~~A/H3N2~~ ***A/Tasmania/503/2020 (H3N2)** IVR-221*** GMT ratio	LL of 95% CI for GMT ratio≧ >0.67	400	0.60	98.56%
~~B/Yamagata lineage~~ ***B/Phuket/3073/2013*** GMT ratio	LL of 95% CI for GMT ratio≧ >0.67	400	0.60	98.56%
Global power				94.24%

*****A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus).***

9.2.3 Secondary objectives

To control the global type I error, a hierarchical procedure will be used for confirmatory objectives assessment.

For instance, the secondary objective to demonstrate the non-inferiority of RSV A neutralizing antibodies using GMT ratios can only be assessed if the primary objective assessing the non-inferiority of GMT ratio for Flu D-QIV strains is met. As per the hierarchical procedure, secondary objective assessing the non-inferiority based on SCR difference of Flu D-QIV will only be assessed if the non-inferiority of RSV A neutralizing antibodies using GMT ratios is met.

~~In order to control the global type I error, the objectives will be assessed sequentially. The non-inferiority objective based on SCR difference of Flu D-QIV strains will only be assessed if the null hypothesis for the non-inferiority of GMT ratio for Flu D-QIV strains are rejected.~~

The criteria to evaluate non-inferiority for RSV A Nab is that the lower limits of the 95% CI on the GMT ratio (RSVPreF3+Flu D-QIV vaccine divided by RSV PreF3 vaccine (pooled RSV1, RSV2 and RSV3 group)) is greater ~~than or equal~~ to the pre-defined clinical limit of 0.67 at Day 31 post vaccination.

Table 16: Power to demonstrate non-inferiority of immune response of RSVPreF3 vaccine when co-administered with Flu D-QIV vaccine or administered alone at Day 31 post vaccination

Endpoint	NI criteria	N1:N2 (evaluable)	Reference*	Power
RSV A GMT ratio	LL of 95% CI for GMT ratio≧>0.67	400:600	0.40	99.99%

9.2.3.2 To demonstrate the non-inferiority of immune response between RSVPreF3 co-administered with Flu D-QIV and Flu D-QIV alone in term of SCR at Day 31 post 1st dose administration

Table 17: Powers to demonstrate non-inferiority in terms of HI antibody SCR for Flu D-QIV strains between Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and administered alone at Day 31 post vaccination

Endpoint	NI criteria	Anticipated SCR*	Number of participants per group (evaluable)	Power
A/Victoria/2570/2019 (H1N1) IVR-215 ~~A/H1N1~~ SCR	10%	60%	400	82.49%
B/Washington/02/2019 ~~B/Victoria lineage~~ SCR	10%	65%	400	84.39%
A/Tasmania/503/2020 (H3N2)** IVR-221 ~~A/H3N2~~ SCR	10%	65%	400	84.39%
B/Phuket/3073/2013 ~~B/Yamagata lineage~~ SCR	10%	65%	400	84.39%

*****A/Tasmania/503/2020 (H3N2) IVR-221 (an A/Cambodia/e0826360/2020 (H3N2)-like virus).***

9.4.1 Primary endpoints/estimands analysis

Primary Immunological Endpoints	Statistical Analysis Methods
RSVPreF3 IgG ELISA concentration at Day 31 (30 days post administration) Measured by ratio of GMC between lots in terms of RSVPreF3 IgG ELISA titers at Day 31 (30 days post administration) Flu D-QIV antibody titers against 4 influenza strains at Day 31 (30 days post administration) Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against 4 strains at Day 31 (30 days post administration)	**Primary confirmatory analyses:** Lot-to-lot consistency among 3 lots of RSV vaccine for RSVPreF3 IgG ELISA concentration at Day 31: The 2-sided 95% CI for GMC ratio (each pair of comparison is between 2 out of 3 lots) for RSVPreF3 IgG ELISA concentration at Day 31 will be computed based on the fact that the difference in the mean of log10 transformed RSVPreF3 IgG ELISA concentration on Day 31 between 2 lots follows t-distribution. Lot-to-lot consistency will be demonstrated if all 3 two-sided 95% CIs for GMC ratio fall within 0.67 and 1.5. Non-inferiority of Flu D-QIV co-administered with RSVPreF3 vaccine compared to Flu D-QIV group with respect to 4 Flu D-QIV strains at Day 31: The 2-sided 95% CIs for ***A/Victoria/2570/2019 (H1N1) IVR-215*** ~~A/H1N1~~ GMT ratio, ***A/Tasmania/503/2020 (H3N2) IVR-221*** ~~A/H3N2~~ GMT ratio, ***B/Washington/02/2019*** ~~B/Victoria lineage~~ GMT ratio and ***B/Phuket/3073/2013*** ~~B/Yamagata lineage~~ GMT ratio (RSVPreF3 co-administered with Flu D-QIV group versus Flu D-QIV group) will be computed based on the fact that the difference in the mean of log10 transformed titers on Day 31 between 2 groups follows a t-distribution. No interference on quadrivalent seasonal influenza vaccine (Flu D-QIV) from RSVPreF3 vaccine is demonstrated if lower bounds of all four 2-sided 95% CIs are above 0.67.

10.1.5 Committees Structure

Safety oversight will be provided by a ~~blinded~~ safety review team (SRT) composed of GSK RSV team members.

10.2.1 Protocol required safety laboratory assessments

Assay descriptions could be subject to change, due to assay re-development and/or qualification.

RSV-A and RSV-B neutralization assays

The RSV-A and RSV-B neutralization assays are functional assays that measure the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

Virus neutralization is performed by incubating a fixed amount of RSV with serial dilutions of the test serum. Then, the serum-virus mixture is transferred onto a Vero cells culture and incubated for two days to allow infection of Vero cells. Thereafter, RSV-infected cells are detected by the visualization of the number of plaques.

RSVPreF3 IgG ELISA

The ELISA assay is based on an indirect ELISA allowing the detection and the quantification of specific IgG antibodies directed against RSVPreF3 in human serum samples and related to reference standard. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

10.4.2 Contraception Guidance

Progestogen-only hormonal contraception associated with inhibition of ovulation

- injectable
- ***oral***

10.7.1, South Korea

- ***A female between, and including, 19 and 49 years of age at the time of signing of the informed consent.***

10.8.2 Glossary of Terms

Blinding:	***In a single-blind study, the investigator and/or his staff are aware of the intervention assignment but the participant is not.***

Trademarks

Trademarks of the GSK group of companies
Flu-DQIV, Fluarix Quadrivalent, Fluarix Tetra, Fluarix Tetra, α-RIX-Tetra and Influsplit Tetra

Generic description
~~A/H1/N1 vaccine strain (Hemagglutinin Ab)~~ ~~A/H3N2 vaccine strain (Hemagglutinin Ab)~~ ~~B/Yamagata vaccine strain (Hemagglutinin Ab)~~ ~~B/Victoria vaccine strain (Hemagglutinin Ab)~~ ***GSK's quadrivalent seasonal influenza vaccine***

Detailed description of the current Protocol amendment 3:

1.1. Synopsis

~~In the RSV maternal program to date, a~~ ***A*** Phase I/II, observer-blind study (RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 YOA, to determine the safety and immunogenicity of 3 dose levels of the RSVPreF3 vaccine (30, 60, and 120 µg) compared to placebo, has been completed. No safety concerns have been identified.

Based on preliminary results of RSV MAT-001 study, the 60 and 120 µg dose levels were selected for further evaluation in the following 2 additional studies, which are ~~ongoing~~***completed***:

Based on the final results of RSV MAT-001, on the Day 31 results of RSV MAT-004 and RSV MAT-011 studies, the 120µg dose level ~~has been~~***was*** selected for evaluation in RSV MAT-010 study. In addition, the 120µg dose level ~~is~~ ***was*** ~~currently~~ ***also*** administered ~~for~~ ***in*** pregnant women participating in the Phase III study RSV MAT-009.

2.1. Study rationale

~~In the GSK RSV maternal program to date, a~~***A*** Phase I/II study (study RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 YOA to determine the safety and immunogenicity of 3 dose levels of RSVPreF3 (30, 60 and 120µg) vaccine compared to placebo is now complete. The results from ~~these studies~~ ***this study*** demonstrated that the RSV maternal (RSVPreF3) vaccine is highly immunogenic and no safety concerns have been identified. Study results for safety and immunogenicity are now available in the Investigator Brochure.

In another ~~ongoing~~ ***completed*** Phase II randomized, observer-blinded study (RSV MAT-011) in non-pregnant women 18 to 45 YOA, two dose levels of the RSV maternal vaccine, 60 µg, and 120 µg, are being evaluated. The primary objectives are to evaluate the effects of *Boostrix* co-administration in terms of reactogenicity, safety and immune response to the RSV maternal vaccine at 1-month post study intervention (considering the US and outside the US data pooled). The effects of RSV maternal vaccine co-administration on the safety and immune response to *Boostrix* were evaluated as secondary objectives. Additional secondary objectives included safety assessment up to 6 months post-intervention, and evaluations of the safety and immune response considering the US and outside the US data both separately and pooled. Enrollment is complete and participant's follow-up is ongoing to examine the persistence of antibody 12-18 months post-1st dose and safety of a 2nd dose of RSV PreF3 vaccine given from 12 up to 18 months post 1st dose. Preliminary results are now available in the IB. Briefly, ~~an acceptable safety profile was observed for~~ both formulations ***and both dose levels*** of the investigational RSV maternal vaccine~~, and both dose levels~~ elicited an immune response, ***no safety concern was observed in the study population of non-pregnant women***. The safety and immunogenicity profile were also similar in another study (RSV MAT 004) examining RSV maternal vaccine in pregnant women.

This study (RSV MAT-010) will be the first to evaluate co-administration of 120 µg of the RSVPreF3 (RSV MAT) vaccine with Flu D-QIV in healthy non-pregnant women (see Figure 1). Selection of the RSVPreF3 antigen dose was based on preliminary results of the ~~completed (RSV MAT-001) and~~ ~~ongoing~~ ***completed studies*** (RSV MAT-001, RSV MAT-011 and RSV MAT-004) studies.

2.3. Benefit/Risk assessment

Following a recommendation from the Independent Data Monitoring Committee (IDMC), the Sponsor made the decision to pause the enrollment, randomization and vaccination of pregnant study participants in our active studies based on an observation of imbalance of the proportion of preterm births between the vaccine group and the placebo group in the RSV MAT-009 study in pregnant women. This pause was to allow for an evaluation of the available data in RSV MAT-009 to better understand the safety signal observed. Following a review of additional unblinded data from RSV MAT-009 trial in which a higher proportion of neonatal deaths reported in the treatment group compared to the placebo group was also observed, the Sponsor decided to STOP enrollment and vaccination in these studies.

The safety signals are being investigated and, although at this time a cause has not been determined, as a precautionary measure GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling both pregnant women on February 25, 2022. We also considered it not appropriate to enroll any additional participants in studies for the RSV maternal program and therefore also stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling non-pregnant women on March 1, 2022. The studies remain ongoing for safety follow-up. Participants already vaccinated will continue to be monitored until the end of the study.

At this time, the safety observation has been observed only among pregnant trial participants.

Table 3. Study objectives, endpoints and estimands

Objectives	Endpoints/Estimands
Primary	
Safety • To evaluate the safety and reactogenicity of RSVPreF3 when given alone (pooled lots) or co-administered with Flu D-QIV up to ~~Day 31~~***study end***~~. post administration~~.	The number and percentage of participants in each group reporting • Each solicited administration site AE collected during the 7 days follow-up period (Day 1 to Day 7) • Each solicited systemic events in the 7 days follow-up period • Unsolicited AEs collected during the 30 days follow-up period (Day 1 to Day 30) • SAEs in the 30 days follow-up period (Day 1 to Day 30) • ***SAEs in the 180 days follow-up period (Day 1 to Day 181)***
• To demonstrate non-inferiority of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine compared to Flu D-QIV given alone based on Geometric mean titer (GMT) of Flu D-QIV antibody titers against ~~4~~ 3 influenza strains at Day 31 post administration	Flu D-QIV antibody titers against ~~4~~ 3 influenza strains at Day 31 (30 days post administration) Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against 4-3 strains at Day 31 (30 days post administration)
Secondary	
*Confirmatory Immunogenicity***	
• To demonstrate the non-inferiority of Flu D-QIV vaccine co-administered with RSVPreF3 compared to given alone based on Seroconversion rate (SCR) of Flu D-QIV HI antibody titers against 4 ***3*** influenza strains at Day 31 post study intervention	• Seroconversion rate to Flu D-QIV* HI antibody titers against the 4 ***3*** influenza strains at Day 31 Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
Descriptive Immunogenicity	
• To evaluate the humoral immune response to the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine in terms of antibody titers against ***3*** influenza strains at Day 1 and Day 31	Flu D-QIV HI antibody titers against the 4 ***3*** influenza strains at Day 1 and Day 31 HI GMT in the 4 ***3*** influenza strains at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
• To evaluate seroprotection rate (SPR)* and Seroconversion rate (SCR)** of the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine	Seroprotection rate to Flu D-QIV HI antibody titers against the 4-3 influenza strains at Day 1 and Day 31 Measured by the proportion of participants achieving an HI antibody titer ≥1:40 at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone • Seroconversion rate to Flu D-QIV HI antibody titers against the 4-3 influenza strains‡ at Day 31 Measured by the proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of

	Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone
Tertiary ~~Objective~~	
To demonstrate non-inferiority of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine compared to Flu D-QIV given alone based on Geometric mean titer (GMT) of Flu D-QIV antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 post administration	***Flu D-QIV* antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 (30 days post administration)*** ***Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against the A/Victoria/2570/2019 (H1N1) strain at Day 31 (30 days post administration)***
To demonstrate the non-inferiority of Flu D-QIV vaccine co-administered with RSVPreF3 compared to given alone based on Seroconversion rate (SCR) of Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31 post study intervention	• ***Seroconversion rate to Flu D-QIV* HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31*** ***Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone***
To evaluate the humoral immune response to the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine in terms of antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31	***Flu D-QIVHI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31*** ***HI GMT in the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone***
To evaluate seroprotection rate (SPR)* and Seroconversion rate (SCR)** of the Flu D-QIV vaccine when given alone and co-administered with RSVPreF3 vaccine	***Seroprotection rate to Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 1 and Day 31*** ***Measured by the proportion of participants achieving an HI antibody titer ≥1:40 at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone*** • ***Seroconversion rate to Flu D-QIV HI antibody titers against the A/Victoria/2570/2019 (H1N1) influenza strain at Day 31*** ***Measured by the proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone***
CCI [redacted]	

~~*SPR is defined as the percentage of vaccines with a serum HI titer >1:40 that usually is accepted as indicating protection.~~

** The SCR is defined as the proportion of participants with:
A Day 1 (pre-vaccination) serum anti-HI titer <1:10 and a Day 31 (post-vaccination) serum anti-HI titer ≥1:40, or
A Day 1 (pre-vaccination) serum anti-HI titer ≥ 1:10 and a fold increase (post/pre) ≥ 4 at Day 31
*** Two confirmatory objectives will be tested sequentially.

6.3.5. Blinding and unblinding

- This blinding strategy will apply from Visit 1 to ~~Visit 2~~***study end (Day 181) (Amended 26 May 2022)***~~. after which the first analysis will be conducted and treatment-level unblinded summaries will be provided to GSK and regulatory agency for review. No individual treatment code will be shared with study participants, investigators, and the study team, except study statistician, until the end of the study.~~

9.2.2. Primary objective: To demonstrate Non-inferiority of immune response of Flu D-QIV vaccine when co-administered with RSVPreF3 vaccine or administered alone at Day 31 post dose vaccination

Possible interference of RSVPreF3 on influenza immune responses will be evaluated by using Flu D-QIV HI antibody titers against the ~~4~~ ***3*** influenza strains from RSVPreF3 + Flu (pooled of RSV1+Flu, RSV2+Flu, RSV3+Flu) and Flu+P group at Day 31. In the description of the subsequent analysis, the RSVPreF3+ Flu D-QIV vaccine group are RSV1+Flu, RSV2+Flu, RSV3+Flu groups pooled.

The criteria to evaluate non-inferiority for ~~A/Victoria/2570/2019 (H1N1) IVR-215,~~ A/Tasmania/503/2020 (H3N2) IVR-221, B/Washington/02/2019, and B/Phuket/3073/2013 is that the lower limits of the 95% CI on the GMT ratio (RSV PreF3 + Flu D-QIV divided by Flu D-QIV) is greater than 0.67 at Day 31 post vaccination.

Table 15 presents the power on the ratio of the GMT of Flu D-QIV ~~4~~ ***3*** strains. The power is at least ~~94~~***95***% when the sample size is 400 participants per group with standard deviation (SD) of 0.6 on its log10 transformation and non-inferiority margin of 0.67 between RSVPreF3 co-administrated with Flu D-QIV group and Flu D-QIV vaccine administered alone group.

Table 15 Power to demonstrate non-inferiority of immune response between Flu D-QIV vaccine co-administered with RSVPreF3 or administered alone in term of GMT for Flu D-QIV strains at Day 31 post 1st vaccination with assumed GMT ratio 1

Endpoint	NI criteria	Number of evaluable participants in each group	Reference*	Power
~~***A/Victoria/2570/2019 (H1N1) IVR-215*** GMT ratio~~	~~LL of 95% CI for GMT ratio >0.67~~	~~400~~	~~0.60~~	~~98.56%~~
B/Washington/02/2019 GMT ratio	LL of 95% CI for GMC ratio >0.67	400	0.60	98.56%
A/Tasmania/503/2020 (H3N2)** IVR-221 GMT ratio	LL of 95% CI for GMT ratio >0.67	400	0.60	98.56%
B/Phuket/3073/2013 GMT ratio	LL of 95% CI for GMT ratio >0.67	400	0.60	98.56%
Global power				~~94.24~~***95.68***%

9.2.3.2. To demonstrate the non-inferiority of immune response between RSVPreF3 co-administered with Flu D-QIV and Flu D-QIV alone in term of SCR at Day 31 post 1st dose administration

Potential interference of RSVPreF3 on influenza immune responses will be evaluated by comparing the Day 31 seroconversion rate of Flu D-QIV HI antibody titers against the ~~4~~ ***3*** influenza strains between RSVPreF3+ Flu D-QIV vaccine group and Flu D-QIV+P group.

The criteria to evaluate non-inferiority with respect to the SCR difference for Flu D-QIV antibody titers against ~~4~~ ***3*** influenza strains is that the upper limits of the 95% CI on the SCR difference (Flu D-QIV vaccine minus RSVPreF3+Flu D-QIV vaccine) is less than the pre-defined clinical limit of 10% at Day 31 post vaccination.

Table 17. Powers to demonstrate non-inferiority in terms of HI antibody SCR for Flu D-QIV strains between Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and administered alone at Day 31 post vaccination

Endpoint	NI criteria	Anticipated SCR*	Number of participants per group (evaluable)	Power
~~A/Victoria/2570/2019 (H1N1) IVR-215 SCR~~	~~10%~~	~~60%~~	~~400~~	~~82.49%~~
B/Washington/02/2019 SCR	10%	65%	400	84.39%
A/Tasmania/503/2020 (H3N2)** IVR-221 SCR	10%	65%	400	84.39%
B/Phuket/3073/2013 SCR	10%	65%	400	84.39%

9.4.1. Primary endpoints/estimands analysis

Primary Safety Endpoints	Statistical Analysis Methods
The number and percentage of participants in each group reporting • Unsolicited AEs collected during the 30 days follow-up period (Day 1 to Day 30) • SAEs in the 30 days follow-up period (Day 1 to Day 30). • ***SAEs in the 180 days follow-up period (Day 1 to Day 181)***	The number and percentage of participants reporting **unsolicited AEs** within 30 days after dosing with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, and for Grade 3 related unsolicited AEs. The number and percentage of participants reporting at least one SAE within 30 days after dosing with exact 95% CIs will be tabulated by group and by MedDRA terms. ***The number and percentage of participants reporting at least one SAE up to study end with exact 95% CIs will be tabulated by group and by MedDRA terms.*** By-subject listings of SAEs and AEs leading to study withdrawal will be prepared ~~(but will not be released until the final analysis has been completed)~~.
Primary Immunological Endpoints	**Statistical Analysis Methods**
RSVPreF3 IgG ELISA concentration at Day 31 (30 days post administration) Measured by ratio of GMC between lots in terms of RSVPreF3 IgG ELISA titers at Day 31 (30 days post administration) Flu D-QIV antibody titers against ~~4~~ ***3*** influenza strains at Day 31 (30 days post administration) Measured by ratio of Haemagglutinin inhibition (HI) GMT between group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and Flu D-QIV vaccine alone group against ~~4~~ ***3*** strains at Day 31 (30 days post administration)	**Primary confirmatory analyses:** Lot-to-lot consistency among 3 lots of RSV vaccine for RSVPreF3 IgG ELISA concentration at Day 31: The 2-sided 95% CI for GMC ratio (each pair of comparison is between 2 out of 3 lots) for RSVPreF3 IgG ELISA concentration at Day 31 will be computed based on the fact that the difference in the mean of log10 transformed RSVPreF3 IgG ELISA concentration on Day 31 between 2 lots follows t-distribution. Lot-to-lot consistency will be demonstrated if all 3 two-sided 95% CIs for GMC ratio fall within 0.67 and 1.5. Non-inferiority of Flu D-QIV co-administered with RSVPreF3 vaccine compared to Flu D-QIV group with respect to ~~4~~ ***3*** Flu D-QIV strains at Day 31: The 2-sided 95% CIs for ~~A/Victoria/2570/2019 (H1N1) IVR-215 GMT ratio,~~ A/Tasmania/503/2020 (H3N2) IVR-221 GMT ratio, B/Washington/02/2019 GMT ratio and B/Phuket/3073/2013 GMT ratio (RSVPreF3 co-administered with Flu D-QIV group versus Flu D-QIV group) will be computed based on the fact that the difference in the mean of log10 transformed titers on Day 31 between 2 groups follows a t-distribution. No interference on quadrivalent seasonal influenza vaccine (Flu D-QIV) from RSVPreF3 vaccine is demonstrated if lower bounds of all ~~four~~ ***three*** 2-sided 95% CIs are above 0.67.

9.4.2. Secondary endpoints/estimands analysis

~~**Secondary Safety Endpoints/Estimands**~~	~~**Statistical Analysis Methods**~~
~~The number and percentage of participants reporting SAEs from first vaccination up to study end. [Day 1 to Day 180]~~	~~The number and percentage of participants reporting at least one SAE from vaccination up to study end with exact 95% CIs will be tabulated by group and by MedDRA terms~~ ~~By participant listings of SAEs and(S)AEs leading to study withdrawal will be prepared but will not be released until the final analysis has been completed~~
Secondary Immunological Endpoints/Estimands	**Statistical Analysis Methods**
RSV A neutralizing antibody titers at Day 31 (30 days post administration) Measured by ratio of GMT between group of RSVPreF3 vaccine co-administered with Flu D-QIV and RSVPreF3 vaccine alone (pooled lot 1,2,3) group in term of RSV A neutralizing antibody titers at Day 31 (30 days administration) Seroconversion rate to Flu D-QIVHI antibody titers against the ~~4~~***3*** influenza strains at Day 31 Measured by the difference of proportion of participants achieving seroconversion for HI antibody at Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone	**Secondary confirmatory immunogenicity analyses:** Non-inferiority of RSVPreF3 vaccine co-administered with Flu D-QIV vaccine compared to RSV alone group in terms of RSV A neutralizing antibody titers at Day 31 The 2-sided 95% CI for GMT ratio (RSV co-administered with Flu D-QIV group *versus* RSV group) will be computed based on the fact that the difference in the mean of log10 transformed RSV A neutralizing antibody titers at Day 31 between 2 groups follows a t-distribution. No interference on RSVPreF3 vaccine from quadrivalent seasonal influenza vaccine (Flu D-QIV) is demonstrated if lower bound of the 2-sided 95% CI of GMT ratio is above 0.67.Non-inferiority of Flu D-QIV co-administered with RSVPreF3 vaccine compared to Flu D-QIV vaccine alone with respect to each of the ~~4~~***3*** Flu D-QIV strains at Day 31 in terms of Seroconversion rate (SCR) The 2-sided 95% CI for the difference of SCR (Flu D-QIV group *minus* RSV co-administered with Flu D-QIV group) will be calculated for each strain. Non-inferiority is demonstrated if the upper bound of 95% CI is less than or equal to the pre-defined clinical limit of 10% at Day 31 post vaccination.

RSV A, RSV B neutralizing antibody titers and RSVPreF3 IgG concentration at Day 1 and Day 31 GMT of RSV A and RSV B neutralizing antibody, GMC of RSVPreF3 IgG at Day 1 and Day 31, in the group of RSVPreF3 vaccine co-administered with Flu D-QIV and the group of RSVPreF3 vaccine alone. Flu D-QIV HI antibody titers against the ~~4~~***3*** influenza strains at Day 1 and Day 31 HI GMT in the ~~4~~***3*** influenza strains at Day 1 and Day 31 in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone Seroprotection rate to Flu D-QIV HI antibody titers against the ~~4~~***3*** influenza strains at Day 1 and Day 31 Seroconversion rate to Flu D-QIV HI antibody titers against the ~~4~~***3*** influenza strains at Day 1 and Day 31	**Descriptive immunogenicity analyses:** For each assay, descriptive immunogenicity analysis may include but not limited to the following: • GMT/GMCs will be tabulated with 95% CI at each timepoint and represented graphically by group. • Geometric mean of ratios of antibody titers/concentrations at Day 31 over pre-vaccination will be tabulated with 95% CI by group. • Number and percentage of participants achieving seroconversion for HI antibody at Day 31 will be tabulated with its 95% CI in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone. Number and percentage of participants achieving HI antibody titer ≥ 1:40 at Day 1 and Day 31 will be tabulated with its 95% CI in the group of Flu D-QIV vaccine co-administered with RSVPreF3 vaccine and the group of Flu D-QIV vaccine alone.

9.4.3. Tertiary endpoints/estimands analysis

The same statistical methods that are used to analyze the 3 strains in the primary and secondary endpoints will be used to analyze the A/Victoria/2570/2019 (H1N1) IVR-215 strain.

9.5.2. Statistical consideration for analysis

~~The first analysis will be performed when final immunogenicity data is available, therefore, no statistical adjustment for multiple analyses is required.~~***Not applicable***.

10.2.1. Protocol required safety laboratory assessments

FLU Hemagglutination-inhibition (HI) assay

Hemagglutination inhibition (HI) antibody titres are determined using the method derived from the WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5.

Measurements are conducted on thawed frozen serum samples with a standardized and comprehensively validated micro-method. Briefly, serum samples are treated with receptor destroying enzyme (RDE) overnight, diluted to 1:10, and serial diluted 2- fold in triplicate from 1:10 to 1:10240. After addition of an equal volume of standardized virus (4 HA / 25 µL), neutralization is performed for 1 hour at room temperature, followed by addition of the RBCs. After 30 minutes, plates are tilted and the titer is the reciprocal of the last dilution that fully inhibits hemagglutination as compared to a RBC

control well. Each sera sample will be tested in triplicate within the same assay. The three titer results will be reported as will the geometric mean titer (GMT) for the triplicate.

10.8.1. List of abbreviations

IDMC	***Independent Data Monitoring Committee***

11. REFERENCES

Beyer WEP, Palache AM., Baljet M *et al*. Antibody induction by influenza vaccines in elderly: a review of the literature. *Vaccine*. 1989; 7:385-394.

Brydak L, Machala M. Humoral immune response to influenza vaccination in patients from high risk groups. *Drugs*. 2000; 60:35-53.

Hannoun C, Megas F, and Piercy J. "ImmuFnogenicity and protective efficacy of influenza vaccination" *Virus Res*. 2004; 103:133-138.

Haralambieva IH, Ovsyannikova IG, Pankratz VS, Kennedy RB, Jacobson RM, Poland GA. The genetic basis for interindividual immune response variation to measles vaccine: new understanding and new vaccine approaches. *Expert Rev Vaccines*. 2013; 12(1):57–70.

Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 Criteria for Substance Use Disorders: Recommendations and Rationale. *The American journal of psychiatry*. 2013;170(8):834-851. Doi:10.1176/appi.ajp.2013.12060782.

Kollmann TR. Variation between Populations in the Innate Immune Response to Vaccine Adjuvants. *Front Immunol*. 2013; 4:81

Pérez-Losada M, Posada D, Arenas M, et al. Ethnic differences in the adaptation rate of HIV gp120 from a vaccine trial. *Retrovirology*. 2009; 6:67.

World Health Organization [WHO], Influenza (Seasonal) Fact sheet N°211, 2012; http://www.who.int/mediacentre/factsheets/fs211/en/.

World Health Organization [WHO]. Global Surveillance for COVID-19 caused by human infection with COVID-19 virus: Interim Guidance. March 2020. Available at: https://apps.who.int/iris/rest/bitstreams/1272502/retrieve. Accessed 8 May 2020.

Trademarks

The following trademarked products are referenced in the present protocol.

Trademarks of the GSK group of companies	Generic description
Flu-DQIV, Fluarix Quadrivalent, Fluarix Tetra, Fluarix Tetra, α-RIX-Tetra and Influsplit Tetra	GSK's quadrivalent seasonal influenza vaccine

Signature Page for 214709 TMF-14681251 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 01-Jun-2022 12:51:50 GMT+0000

Signature Page for TMF-14681251 v1.0