Protocol

A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above.

214488

Date of Document: 27 November 2020

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214488 (RSV OA=ADJ-007)
Protocol Amendment 1 Final

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

Primary study intervention and number	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other study interventions	GSK's *Fluarix Quadrivalent* or *Fluarix Tetra* (quadrivalent seasonal influenza vaccine)
eTrack study number and abbreviated title	214488 (RSV OA=ADJ-007)
Date of protocol	Final: 19 October 2020
Date of protocol amendment	Amendment 1 Final: 24 November 2020
Title	A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above.
Brief title	A study on the immune response and safety elicited by a vaccine against respiratory syncytial virus (RSV) when given alone and together with a vaccine against influenza in adults aged 60 years and above.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	214488 (RSV OA=ADJ-007)
Date of protocol	Final: 19 October 2020
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Title	A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above.
Sponsor signatory (Amended 24 November 2020)	***Marie Van Der Wielen***, MD Clinical and Epidemiology R&D Project Lead RSV Older Adults
Signature	_____
Date	_____

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (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	214488 (RSV OA=ADJ-007)
Date of protocol	Final: 19 October 2020
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Title	A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above.
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

Document history

Document	Date
Original Protocol	19 October 2020

Amendment 1: 24 November 2020

Overall Rationale for the Amendment:

The protocol is amended to address the comments from the Center for Biologics Evaluation and Research (CBER), United States Food and Drug Administration (US FDA). Specifically, the non-inferiority (NI) margins have been updated, and accordingly the power calculations associated with the co-primary objectives have been updated while the sample size remains the same. The formulation of the FLU vaccine has also been added based on WHO recommendations for the 2021 influenza season in the Southern Hemisphere, and a typographical error has been corrected, in Table 7 (Study interventions administered).

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study interventions administered	The formulation of the FLU vaccine has been added.	The formulation has been added based on WHO recommendations for the 2021 influenza season in the Southern Hemisphere.
Section 9.1 Statistical hypotheses	The NI margins associated with each co-primary objective have been changed from 2.0 to 1.5.	These changes are made to acknowledge CBER's recommendation of a NI margin of 1.5 for demonstrating NI based on influenza hemagglutinin inhibition and RSV-A neutralizing antibody geometric mean titers.
Section 9.2 Sample size determination	The power calculations have been updated to reflect the updated NI margin.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GSK is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in phase 3, and immunogenicity, safety and reactogenicity of the candidate vaccine when co-administered with an influenza vaccine are not known.

The current study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the seasonal quadrivalent influenza vaccine FLU-QIV in adults ≥60 YOA. The FLU-QIV vaccine is a quadrivalent inactivated split virion influenza vaccine manufactured in Dresden (Germany), containing 2 influenza A-like viruses (H1N1 and H3N2) and 2 influenza B-like viruses (1 from the Yamagata lineage and 1 from the Victoria lineage). The FLU-QIV vaccine is registered under the name *Fluarix Quadrivalent* or *Fluarix Tetra* (United States and other countries), *Influsplit Tetra* (Germany) and *Alpharix Tetra* (Belgium). It is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The vaccine is approved for use in individuals as of 6 months of age.

Note: for readability, at some places in this protocol, the "RSVPreF3 OA investigational vaccine" is also referred to as "RSV investigational vaccine".

Objectives and endpoints: Refer to Table 5**.**

1.2. Schema

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

1.3. Schedule of Activities (SoA)

Table 1 SoA for Co-Ad group

Type of contact	Visit 1	Visit 2*	Contact	Notes
Timepoints	Day 1	Day 31	Month 6[1]	
Informed consent	●			See Section 10.1.3 for details
Distribution of participant card	O			See Section 8.3.5 for details
Check inclusion/exclusion criteria	●			See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	O	O		See Sections 5.2.5 and 10.1.3 for details
Randomization	●			See Section 6.3 for more information
Baseline and demography assessments				
Collect demographic data	●			See Section 8.2.1.1 for more information
Recording of medical and vaccination history	●			See Sections 8.2.1.2 and 8.2.1.3 for more information
Perform history directed physical examination	O			See Section 8.2.1.4 for more information
Laboratory assessment				
Blood sampling from all participants for antibody determination (~10 mL)	●[2]	●[3]		See Section 8.1.1 for more information
Study interventions				
Check contraindications, warnings and precautions to study interventions administration	O			See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay of study interventions administration	O			See Section 5.5 for more information
Study group allocation	O			See Sections 6.3.2, 6.3.3 and 6.3.4 for more information
Recording of body temperature before study interventions administration[4]	●			The location for measuring temperature can be the oral cavity/axillary/tympanic membrane.
Study interventions administration (FLU vaccine + RSV investigational vaccine) (including 30-minute post-vaccination observation)	●			See Section 6.1 for more information
Recording of administered study interventions numbers	●			
Safety assessments				
Distribution of diary cards for solicited events and unsolicited adverse events	O			See Section 10.3.7 for more information
Return of diary cards		O		See Section 10.3.7 for more information
Recording of solicited events (Days 1–4 after study intervention administration)	●	●		See Sections 10.3.3 and 10.3.7 for more information
Recording of unsolicited adverse events (Days 1-30 after study intervention administration)	●	●		See Sections 10.3.4 and 10.3.7 for more information
Recording of concomitant medications/vaccinations	●	●	●	See Section 6.8 for more information

Type of contact	Visit 1	Visit 2*	Contact	Notes
Timepoints	**Day 1**	**Day 31**	**Month 6[1]**	
Recording of intercurrent medical conditions	●	●	●	See Section 9.3.1 for more information
Recording of SAEs and pIMDs	●	●	●	See Section 10.3.7 for more information
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[5]	●	●	●	See Section 10.3.7 for more information
Contact for safety follow-up			●	See Sections 8.2.2 and 10.3.7.2 for more information
Study Conclusion			●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to these time points.
● 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
AE = adverse event; pIMDs = potential immune-mediated diseases; SAE = Serious Adverse Event; eCRF = electronic case report form.
FLU vaccine = FLU-QIV.
* Visit 2 should preferably be done on site but if deemed necessary (during special circumstances such as Coronavirus Disease 2019 [COVID-19] pandemic), this study visit can be replaced by a home visit conducted by authorized staff . Any further information from the participant, not collected during the home visit, can be obtained by means of a phone call conducted by the site staff.
[1] Month 6 = 6 months after study interventions administration. For this contact, multiple formats can be proposed by the study site. Please refer to Section 8.2.2.1 for more details.
[2] Sample collected at Day 1 will be used as baseline for FLU and RSV vaccination.
[3] Sample collected at Day 31 will be used for the post-vaccination FLU vaccine- and RSV vaccine-related testing.
[4] The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C regardless of the location of measurement.
[5] SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study vaccine administration) up to study end.

Table 2 SoA for Control group

Type of contact	Visit 1	Visit 2	Visit 3*	Contact	Notes
Timepoints	**Day 1**	**Day 31**	**Day 61**	**Month 7[1]**	
Informed consent	●				See Section 10.1.3 for details
Distribution of participant card	O				See Section 8.3.5 for details
Check inclusion/exclusion criteria	●				See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	O	O	O		See Sections 5.2.5 and 10.1.3 for details
Randomization	●				See Section 6.3 for more information
Baseline and demography assessments					
Collect demographic data	●				See Section 8.2.1.1 for more information
Recording of medical and vaccination history	●				See Section 8.2.1.2 and 8.2.1.3 for more information
Perform history directed physical examination	O				See Section 8.2.1.4 for more information
Laboratory assessment					
Blood sampling from all participants for antibody determination (~10 mL)	●[3]	●[4]	●[5]		See Section 8.1.1 for more information
Study interventions					
Check contraindications, warnings and precautions to study intervention administration	O	O			See Sections 7.1.1 and 8.2.1.5 for more information
Check criteria for temporary delay of study intervention administration	O	O			See Section 5.5 for more information
Study group allocation	O				See Sections 6.3.2, 6.3.3 and 6.3.4 for more information
Recording of body temperature before study intervention administration[2]	●	●			The location for measuring temperature can be the oral cavity/axillary/tympanic membrane.
Study intervention administration: FLU vaccine (including 30-minute post-vaccination observation)	●				See Section 6.1 for more information
Study intervention administration: RSV investigational vaccine (including 30-minute post-vaccination observation)		●			See Section 6.1 for more information
Recording of administered study intervention number	●	●			
Safety assessments					
Distribution of diary cards for solicited events and unsolicited adverse events	O	O			See Section 10.3.7 for more information
Return of diary cards		O	O		See Section 10.3.7 for more information
Recording of solicited events (Days 1–4 after study intervention administration)	●	●	●		See Sections 10.3.3 and 10.3.7 for more information
Recording of unsolicited events (Days 1-30 after study intervention administration)	●	●	●		See Sections 10.3.4 and 10.3.7 for more information
Recording of concomitant medications/vaccinations	●	●	●	●	See Section 6.8 for more information

Type of contact	Visit 1	Visit 2	Visit 3*	Contact	Notes
Timepoints	Day 1	Day 31	Day 61	Month 7[1]	
Recording of intercurrent medical conditions	●	●	●	●	See Section 9.3.1 for more information
Recording of SAEs and pIMDs	●	●	●	●	See Section10.3.7 for more information
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	●	See Section10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[6]	●	●	●	●	See Section 10.3.7 for more information
Contact for safety follow-up				●	See Sections 8.2.2 and 10.3.7.2 for more information
Study Conclusion				●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to these time points.
● 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
AE = adverse event; pIMDs = potential immune-mediated diseases; SAE = Serious Adverse Event; eCRF = electronic case report form.
FLU vaccine = FLU-QIV.
*Visit 3 should preferably be done on site but if deemed necessary (during special circumstances such as COVID-19 pandemic), this study visit can be replaced by a home visit conducted by authorized staff. Any further information from the participant, not collected during the home visit, can be obtained by means of a phone call conducted by the site staff.
[1] Month 7 = 6 months after administration of RSV investigational vaccine. For this contact, multiple formats can be proposed by the study site. Please refer to Section 8.2.2.1 for more details
[2] The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C regardless the location of measurement.
[3]Sample collected at Day 1 will be used as baseline for the FLU vaccination in the Control group.
[4] Sample collected at Day 31 will be used for the post-vaccination FLU vaccine-related testing. This sample will also be used as baseline for the RSV vaccination in the Control group.
[5] Sample collected at Day 61 will be used for the post-vaccination RSV vaccine-related testing.
[6]SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study vaccine administration) up to study end.

Table 3 Intervals between study visits (Co-Ad group)

Interval	Planned visit interval	Allowed interval range
Visit 1 →Visit 2	30 days	30-42 days
Visit 1 → Contact	180 days	180-210 days

Table 4 Intervals between study visits (Control group)

Interval	Planned visit interval	Allowed interval range
Visit 1 → Visit 2	30 days	30-42 days
Visit 2 → Visit 3	30 days	30-42 days
Visit 2 → Contact	180 days	180-210 days

2. INTRODUCTION

2.1. Study rationale

GSK is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in phase 3, and immunogenicity, safety and reactogenicity of the candidate vaccine when co-administered with an influenza vaccine are not known.

The current study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the seasonal quadrivalent influenza vaccine FLU-QIV in adults ≥60 YOA. The FLU-QIV vaccine is a quadrivalent inactivated split virion influenza vaccine manufactured in Dresden (Germany), containing 2 influenza A-like viruses (H1N1 and H3N2) and 2 influenza B-like viruses (1 from the Yamagata lineage and 1 from the Victoria lineage). The FLU-QIV vaccine is registered under the name *Fluarix Quadrivalent* or *Fluarix Tetra* (United States and other countries), *Influsplit Tetra* (Germany) and *Alpharix Tetra* (Belgium). It is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The vaccine is approved for use in individuals as of 6 months of age.

Note: for readability, at some places in this protocol, the "RSVPreF3 OA investigational vaccine" is also referred to as "RSV investigational vaccine".

2.2. Background

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

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

There is currently no vaccine or other prophylactic treatment available against RSV in older adults. Currently available treatment for RSV in this age group is generally supportive in nature, as detailed in the IB.

Please refer to the current IB for information regarding pre-clinical and clinical studies of the RSVPreF3 OA investigational vaccine.

2.3. Benefit/Risk assessment

2.3.1. Risk Assessment

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

Important Potential/Identified Risk	Mitigation Strategy
RSV investigational vaccine	
Potential immune-mediated diseases (pIMDs) are considered a potential risk, as for all vaccines containing an adjuvant system.	Refer to Section 10.3.5.1 for details.
FLU-QIV	
Anaphylaxis, febrile seizures, Bell's palsy, Guillain-Barré syndrome (GBS), injection site hemorrhage in individuals with thrombocytopenia or any coagulation disorder, administration error due to mix-up of vaccine brands and narcolepsy are important potential risks under close monitoring for *Fluarix Tetra*.	All participants will remain under observation at the clinical center for at least 30 minutes after vaccination. pIMDs (including GBS, Bell's palsy and narcolepsy) will be monitored as described above and in Section 10.3.5.1
Study procedures	
Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	As a mitigation strategy, a topical analgesic may be applied to the site of injection.
Pain and bruising may occur at the site where blood is drawn.	As a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.
Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.

For details of study procedures, dose, and study design justification, refer to Sections 1.3 and 4.2.

2.3.2. Benefit Assessment

The participants may not directly benefit from vaccination with the RSVPreF3 OA investigational vaccine because vaccine efficacy has not been established yet. Hence it is not known whether the RSVPreF3 OA investigational vaccine is effective in protecting against RSV disease.

An indirect benefit is that the information obtained in this study will aid the development of an RSV investigational vaccine, which is intended to prevent disease associated with RSV infection in older adults.

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

All participants will receive the seasonal FLU vaccination as part of the study. By receiving FLU vaccine as part of standard medical care, the participant may have the benefit of being protected against circulating strains of influenza during the active season.

2.3.3. Overall Benefit/Risk Conclusion

The RSVPreF3 OA investigational vaccine is in clinical development. Considering the measures taken to minimize the risk to participants in this study, the potential risks are justified by the potential benefits linked to the development of this vaccine.

The benefits of *Fluarix Tetra* appear to outweigh its potential risks. The established favorable benefit-risk profile for *Fluarix Tetra* remains unchanged for the active immunization of individuals as of 6 months of age against influenza disease caused by influenza virus types A and B contained in the vaccine.

3. OBJECTIVES AND ENDPOINTS

Table 5 Study objectives and endpoints

Objectives	Endpoints
Co-Primary	
• To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralization antibody titers expressed as group GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose.
• To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• HI antibody titers for each of the FLU vaccine strains expressed as group GMT ratio, 1 month after the FLU vaccine dose.
Secondary	
• To evaluate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• HI seroconversion status for each of the FLU vaccine strains expressed as SCR, 1 month after the FLU vaccine dose.
• To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine or administered alone.	• RSV-A neutralization antibody titers expressed as MGI at 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing antibody titers expressed as group GMT ratio and MGI at 1 month after the RSVPreF3 OA investigational vaccine dose in a subset.

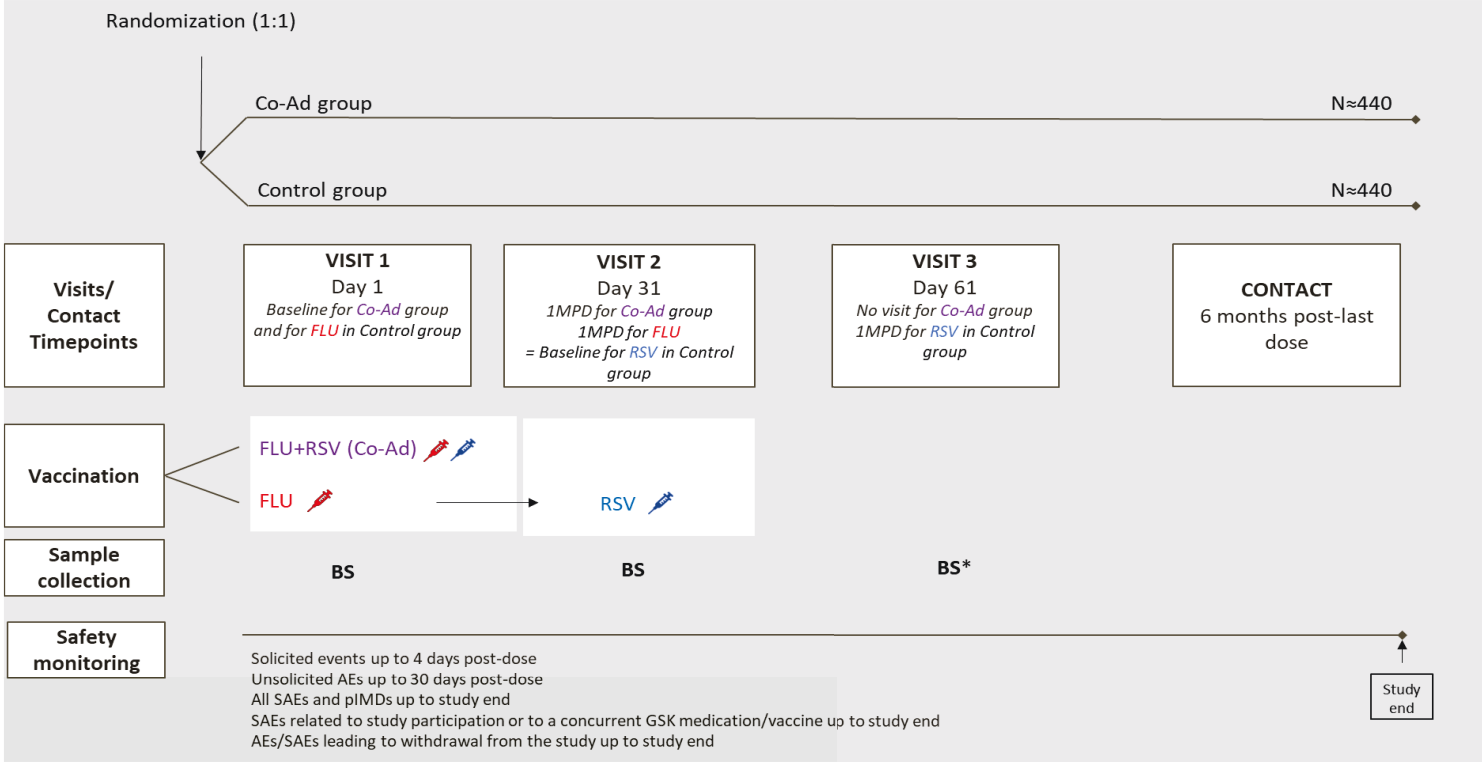
Objectives	Endpoints
• To evaluate the humoral immune response to the FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine or administered alone.	• HI antibody titers for each of the FLU vaccine strains expressed as GMT, at Day 1 and Day 31. • HI seroconversion status for each of the FLU vaccine strains expressed as SCR, from Day 1 to Day 31. • HI seroprotection status for each of the FLU vaccine strains expressed as SPR, at Day 1 and Day 31. • HI antibody titers for each of the FLU vaccine strains expressed as MGI, 1 month after the FLU vaccine dose.
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and FLU vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited event with onset within 4 days after vaccine administration (i.e. the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited adverse events (pIMD, non-serious AE or serious AE) within 30 days after vaccine administration (i.e. the day of vaccination and 29 subsequent days). • Percentage of participants reporting SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination). • Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination).
Tertiary	
• To further evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine or administered alone.	• RSVPreF3-specific IgG concentrations expressed as group GMC ratio and MGI at 1 month after the RSVPreF3 OA investigational vaccine dose in a subset.

FLU vaccine is referring to FLU-QIV; IgG: Immunoglobulin G; GMT: Geometric Mean Titer; GMC: Geometric Mean Concentration; HI: Hemagglutinin Inhibition; pIMD: potential immune-mediated disease. AE: adverse event; SAE: serious adverse event.
SCR: Seroconversion rate: the percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥ 1:40 or a pre-dose titer ≥ 1:10 and at least a four-fold increase in post-dose titer.
SPR: Seroprotection rate: The percentage of vaccinees with a serum HI titer ≥ 1:40 that usually is accepted as indicating protection.
MGI: The geometric mean of the within participant ratios of the post-dose titer over the pre-dose titer.

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



1MPD = 1 month post-dose.
* Blood sample only from participants in Control group.
FLU = FLU-QIV; RSV = RSVPreF3 OA investigational vaccine; BS = Blood sample from all participants (except for blood sample at Visit 3 which is only applicable for Control group).
Note: Unsolicited AEs will be collected from first dose to 30 days post-dose. SAEs and pIMDs will be collected from first dose through the entire study period. SAEs related to study participation will be collected from the time of consent.

- **Type of study**: self-contained.
- **Experimental design**: phase 3, randomized, open-label, multi-country study with 2 parallel groups (see Figure 1).
- **Duration of the study**: ~ 6 months for participants in Co-Ad group; ~ 7 months for participants in Control group.
- **Primary completion date**: Day 61 (1 month after the RSVPreF3 OA investigational vaccine dose in Control group).
- **Control**: active comparator, i.e. staggered administration of licensed FLU vaccine and RSVPreF3 OA investigational vaccine.
- **Blinding**: open-label. Refer to Section 6.3.5 for details.
- **Data collection**: standardized electronic Case Report Form (eCRF). Solicited events and unsolicited AEs will be collected using a participant Diary card (paper Diary card).
- **Study groups**: Refer to Figure 1 and Table 6 for an overview of the study groups.

Table 6 Study groups and intervention

Study groups	Number of participants	Age (Min-Max)	Study interventions
Co-Ad	~440	≥60 years	RSVPreF3 OA investigational vaccine
			FLU-QIV
Control	~440	≥60 years	RSVPreF3 OA investigational vaccine
			FLU-QIV

4.1.1. Overview of the recruitment plan

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

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

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

4.1.2. Enrolment rules

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

- Approximately 40% of participants 60-69 YOA, approximately 30% of participants 70-79 YOA and approximately 10% of participants ≥80 YOA. The remaining approximately 20% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining approximately 20% can be distributed freely between the 2 sexes.

4.2. Scientific rationale for study design

The influenza season coincides with the RSV season in temperate countries. Influenza vaccination begins at the start of the Flu season, at around the same time when the RSVPreF3 OA investigational vaccine may potentially be recommended for immunization against RSV infection. Till date, there is no data available on the safety and immunogenicity of the RSVPreF3 OA investigational vaccine when it is co-administered with an influenza vaccine.

The current study is therefore designed to assess the safety, reactogenicity and immunogenicity of the RSVPreF3 OA investigational vaccine when it is co-administered with a FLU vaccine, compared to administration of the vaccines separately. There are 2 parallel arms:

- **Co-Ad group:** Participants will receive a single dose of RSV investigational vaccine and a single dose of FLU vaccine at Visit 1 (Day 1).
- **Control group**: Participants will receive a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSV investigational vaccine at Visit 2 (Day 31).

The study will enroll older adults ≥60 YOA who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical conditions but should be medically stable in the opinion of the investigator.

As the RSVPreF3 OA investigational vaccine is adjuvanted, all participants will be followed up for safety for 6 months post-RSV investigational vaccine administration.

The 120µg RSVPreF3/AS01$_E$ vaccine formulation was selected in a previous study (RSV OA=ADJ-002), where the vaccine was administered intramuscularly according to a 0, 2-month vaccination schedule. Please refer to the IB for details.

4.3. Justification for dose

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

In the RSV OA=ADJ-002 study, the peak response for both IgG and neutralizing antibodies was observed at 1-month post-Dose 1. Comparisons of the mean responses 1 month post-Dose 2 versus 1 month post-Dose 1, in terms of neutralizing antibodies against RSV-A and in terms of frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers did not show any added value of the second dose.

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

In the current study, the FLU vaccine will be administered as a single dose (recommended standard of care).

4.4. End of Study definition

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

End of Study (EoS): Last subject last visit (LSLV) (Contact at 6 months post-last dose).

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 diary cards, return for follow-up visits, ability to access and utilize a phone or other electronic communications).

  Note: In case of physical incapacity that would preclude the self-completion of the diary cards, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no time will the site staff or caregiver evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. Refer to the Glossary of terms for the definition of caregiver.

- A male or female ≥60 YOA at the time of the first study intervention administration.
- Participants living in the general community or in an assisted-living facility that provides minimal assistance, such that the participant is primarily responsible for self-care and activities of daily living.
- Written or witnessed informed consent obtained from the participant prior to performance of any study-specific procedure.
- Participants who are medically stable in the opinion of the investigator at the time of first vaccination. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable.

5.2. Exclusion criteria

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

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

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Examination (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.
- Recurrent or un-controlled neurological disorders or seizures. Participants with medically-controlled active or chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol (e.g. completion of diary cards, attend regular phone calls/study site visits).
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival up to study end).

- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study interventions during the period beginning 30 days before the first dose of study vaccines and ending 30 days after the last vaccine administration, or planned use during the study period.
- Administration of an influenza vaccine during the 6 months preceding the study FLU vaccine administration.
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first study intervention administration and ending 30 days after the last study intervention administration.

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Previous vaccination with an RSV vaccine.
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. *infliximab*).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the first dose of study vaccine or planned administration during the study period.
- Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study vaccination or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.

5.2.3. Prior/Concurrent clinical study experience

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

  Note: EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.

5.2.4. Other exclusions

- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
- Planned move during the study conduct that prohibits participation until one month post-last vaccine administration.
- Bedridden participants.
- Participation of any study personnel or their immediate dependents, family, or household members.

5.2.5. Caregiver support

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

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

Caregivers may help the study participants with performing some practical study procedures such as receiving or making phone calls to site staff, planning study visits, transcribing responses to diaries, transportation to and from the study site etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. At the first study visit (Visit 1) the site staff should inform the participant of the possibility to appoint a caregiver. Then at subsequent study visit(s), the site staff should check again with the participant if he/she wishes to appoint a caregiver or if there were or will be changes of caregiver.

5.3. Lifestyle considerations

Not applicable for this study.

5.4. Screen failures

Not applicable for this study.

5.5. Criteria for temporarily delaying enrolment/ Study intervention administration

Study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of study intervention administration. Refer to Section 1.3 (SoA) for definition of fever and location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g. free of symptoms, COVID-19 negative testing, etc.).
- Participants with known COVID-19 positive contacts may be vaccinated at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study interventions administered

Table 7 Study interventions administered (Amended 24 November 2020)

Study intervention name:	RSVPreF3 OA investigational vaccine	FLU-QIV
Study intervention formulation:	RSVPreF3 (120 µg) AS01E: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injection q.s. 0.5 mL	FLU Quadrivalent Influenza vaccine, 15µg hemagglutinin (HA) per strain/dose**
Presentation:	RSVPreF3: Vial; Powder for suspension for injection AS01E: Vial; Suspension for suspension for injection	Syringe, suspension for injection
Type:	Biologic	Biologic
Route of administration:	Intramuscular (IM) injection	IM injection
Location	Deltoid	Deltoid
Directionality	Upper	Upper
Laterality	Non-Dominant	Co-Ad group: Dominant Control group: Non-Dominant
Number of doses to be administered:	1	1
Volume to be administered*:**	0.5 mL	0.5 mL
Packaging, labeling and TM: (when applicable)	Refer to the SPM for more details	Refer to the SPM for more details
Manufacturer:	GSK Biologicals	GSK Biologicals

* QS-21: *Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
The strains ***used in the FLU Quadrivalent Influenza vaccine are A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Hong Kong/2671/2019 (H3N2), NIB-121 (15 µg HA); B/Washington/02/2019, wild type (15 µg HA); B/Phuket/3073/2013, wild type (15 µg HA)*
*** Refer to the SPM for the volume after reconstitution

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

6.2. Preparation/Handling/Storage/Accountability

The study interventions 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 the individuals who have consented to participate in the study. Each study center will be allocated a range of participant identification numbers.

6.3.2. Randomization to study intervention

Approximately 880 eligible participants will be randomly assigned (1:1) to the study groups (Co-Ad or Control).

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

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

6.3.3. Intervention allocation to the participant

An automated Internet-based system, Source data Base for Internet Randomization (SBIR) will be used for randomization and for identification of intervention material. The randomization algorithm will use a minimization procedure accounting for age (60-69, 70-79 or ≥80 years), center, country and sex. Minimization factors will have equal weight in the minimization algorithm. Refer to Section 4.1.2 for the enrolment rules.

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. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR).

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

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

6.3.4. Allocation of participants to assay subsets

Testing of RSV-B neutralizing antibodies and RSVPreF3 IgG will be performed on a random subset of participants (approximately 220 participants each from the Co-Ad group and the Control group).

6.3.5. Blinding and unblinding

This is an open-label study

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 Internet-based system, such as SBIR.

The investigator may contact a GSK Helpdesk (refer to the Table 8) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the automated Internet-based system).

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 participant card provides contact information for the investigator, his/her back up and GSK Helpdesk.

Table 8 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Toll-free number: South Africa: 0800 984 003 Phone: New Zealand, Panama: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.4. Study intervention compliance

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

6.5. Dose modification

Not applicable for this study.

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

During the study conclusion contact, the investigator will ask each participant if they are interested in participating in 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 for this study.

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 medications and vaccinations, except vitamins and dietary supplements, administered during the 30-day period following each dose of study intervention.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to Sections 5.2.2 and 9.3.1 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Sections 8.3.1 and 10.3.2. These must also be recorded in the Expedited Adverse Event report.

The Local Medical Lead 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 interventions

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study interventions. A participant who discontinued subsequent study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

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

7.1.1. Contraindications to subsequent study intervention administration

The eligibility of participants in the Control group for subsequent study intervention administration must be confirmed before administering the RSV investigational vaccine at Visit 2.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive the RSV investigational vaccine at Visit 2. Such participants should be encouraged to continue other study procedures, at the investigators' discretion (Section 10.3.7.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to the first study intervention (FLU vaccine administered at Visit 1) and that, in the opinion of the investigator, may pose additional risk to the participant if he/she receives the second study intervention (RSV investigational vaccine).
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Anaphylaxis following the administration of study intervention(s) from Visit 1 onwards.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

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. Please refer to Section 10.3.9.1 for details.
- 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 he/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 10.3.7.2).

7.3. Lost to follow-up

A participant will be considered 'lost to follow-up' if he/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).

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

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

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit (from the site staff or from the home care service system), if appropriate.
- Diary cards may be transmitted from and to the site by electronic means and or conventional mail or collected at home.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 3, additional 30 days may be added to the Visit 2 interval (only for RSV investigational vaccine administration in the Control group).

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

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

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 9 Biological samples

Sample type	Quantity	Unit	Timepoint	Group
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31)	All participants in the Co-Ad group
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Day 61)	All participants in the Control group

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

- Co-Ad group: 2 x ~10 mL = ~20 mL
- Control group: 3 x ~10 mL = ~30 mL

8.1.2. Laboratory assays

Table 10 Laboratory assays

Assay type	System	Component	Method	Laboratory
Humoral Immunity (Antibody determination): RSV	Serum	Respiratory Syncytial Virus A antibody	Neutralization	GSK *
		Respiratory Syncytial Virus B Antibody	Neutralization	
		RSVPreF3-specific IgG antibody	ELISA	
Humoral Immunity (Antibody determination): FLU-QIV	Serum	H1N1 strain equivalent to vaccine strain (Hemagglutinin Ab)	Hemagglutination Inhibition	
		H3N2 strain equivalent to vaccine strain (Hemagglutinin Ab)		
		B/Yamagata strain equivalent to vaccine strain (Hemagglutinin Ab)		
		B/Victoria strain equivalent to vaccine strain (Hemagglutinin Ab)		

ELISA: Enzyme-linked immunosorbent assay.
*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy or to a contracted Contract Research Organization.

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

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

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

8.1.3. Immunological read-outs

Table 11 Immunological read-outs

Blood sampling timepoint		Subset tested	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Co-Ad group				
Visit 1 (Day 1)	Pre-dose 1	All participants	440	RSV-A neutralizing antibody
		Immunogenicity Subset	220	RSV-B neutralizing antibody
		Immunogenicity Subset	220	RSVPreF3-specific IgG antibody
		All participants	440	H1N1 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	H3N2 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Victoria strain equivalent to vaccine strain (Hemagglutinin Ab)

Blood sampling timepoint		Subset tested	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 2 (Day 31)	Post-dose 1	All participants	440	RSV-A neutralizing antibody
		Immunogenicity Subset	220	RSV-B neutralizing antibody
		Immunogenicity Subset	220	RSVPreF3-specific IgG antibody
		All participants	440	H1N1 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	H3N2 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Victoria strain equivalent to vaccine strain (Hemagglutinin Ab)
Control group				
Visit 1 (Day 1)	Pre-FLU dose	All participants	440	H1N1 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	H3N2 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Victoria strain equivalent to vaccine strain (Hemagglutinin Ab)
Visit 2 (Day 31)	Post-FLU dose	All participants	440	H1N1 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	H3N2 strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin Ab)
		All participants	440	B/Victoria strain equivalent to vaccine strain (Hemagglutinin Ab)
	Pre-RSV dose	All participants	440	RSV-A neutralizing antibody
		Immunogenicity Subset	220	RSV-B neutralizing antibody
		Immunogenicity Subset	220	RSVPreF3-specific IgG antibody
Visit 3 (Day 61)	Post-RSV dose	All participants	440	RSV-A neutralizing antibody
		Immunogenicity Subset	220	RSV-B neutralizing antibody
		Immunogenicity Subset	220	RSVPreF3-specific IgG antibody

8.1.4. Immunological correlates of protection

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

Although there is no accepted correlate of protection against influenza, either seasonal or pandemic, the protective role of antibodies against hemagglutinin (HA) and, to a lesser extent, neuraminidase, is well established and has been demonstrated both in experimentally infected animals and humans [Rimmelzwaan, 2008]. For this reason, the

induction of HA-specific antibodies is used as a marker of potential vaccine efficacy and the serum HI assay is 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 interventions.

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the participant's eCRF.

8.2.1.2. Medical history

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

8.2.1.3. Vaccination history

Obtain the participant's vaccination history by interviewing the participant and/or review of the participant's vaccination records.

Any vaccine administered up to 1 year before study vaccine administration should be recorded in the eCRF with date of vaccination. Any FLU vaccine administered up to 3 years before study intervention should be recorded with the date of vaccination and information about the vaccine formulation (e.g., adjuvanted or non-adjuvanted or high-dose).

8.2.1.4. History directed physical examination

- History directed physical examination will be performed for each participant.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to Section 5.5 for the list of criteria for temporary delay of study intervention administration.

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

8.2.1.5. 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.

8.2.1.6. Pre-vaccination body temperature

The body temperature of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. The route for measuring temperature can be oral, axillary or tympanic. If the participant has fever (fever is defined as temperature ≥38.0°C regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit, refer to Table 3.

8.2.2. Post-vaccination procedures

8.2.2.1. Safety contact at 6 months post-last vaccination

Six months after the last dose of study vaccine (i.e. Month 6 for participants in the Co-Ad group and Month 7 for participants of the Control group), each participant should be contacted to check if he/she has experienced any SAEs or any pIMDs since last study intervention administration, and to collect information on concomitant medications/vaccinations.

Multiple formats can be proposed by the site staff to organize these contacts. This contact may be done via email, text message, fax or phone call for example. The most appropriate format should be agreed between site staff and the study participant.

Text messages, email and fax may be used as a screening to check if the participant has anything to report. If the participant answers "Yes" for at least one of the items of interest, a phone call must be done to get the details on the event(s).

Data collected via phone calls and text messages will have to be recorded in source documents. E-mails and faxes can be archived in source documents. Receipt of the message must be confirmed by the participant or caregiver, as applicable.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

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

Table 12 Timeframes for collecting and reporting of safety information

Co-Ad group								
Event	Pre-Dose*	Vacc Co-Ad D1	D4	D31				6-months post-last dose ** Study conclusion
Administration site and systemic solicited events		■	■					
Unsolicited AEs		■	■	■				
Control group								
	Pre-Dose	Vacc FLU D1	D4	D31	Vacc RSV D31	D34	D61	6-months post last dose** Study conclusion
Administration site and systemic solicited events		■	■		■	■		
Unsolicited AEs		■	■	■	■	■	■	
All participants								
All SAEs		■	■	■	■	■	■	■
All pIMDs		■	■	■	■	■	■	■
SAEs related to study participation or concurrent GSK medication/ vaccine	■	■	■	■	■	■	■	■
AEs/SAEs leading to withdrawal from the study		■	■	■	■	■	■	■
Intercurrent medical conditions		■	■	■	■	■	■	■

D: day; AE: adverse event; SAE: serious adverse event; pIMD: potential immune-mediated disease; Vacc: Vaccination.
* i.e. consent obtained on Day 1 (prior to intervention administration).
** post-last dose = 6 months after Co-Ad vaccine administration (Co-Ad group) or 6 months after RSV investigational vaccine administration (Control group).
Note: COVID-19 cases will be collected during the same timeframes as those used for collecting and reporting the other safety information (unsolicited AEs/SAEs, etc.)

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.9. 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 12. 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 14.

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

Detection and recording of AE/SAE/pIMDs are detailed in Section 10.3.7.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.8.

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

8.3.3. Regulatory reporting requirements for SAEs and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 13. 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/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.8.2.

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/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 10.3.9 for further details regarding the reporting of SAEs/pIMDs.

Table 13 Timeframes for submitting SAE and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*, ⌗	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
pIMDs	24 hours**, ⌗	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

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

8.3.3.1. Contact information for reporting SAEs and pIMDs

Table 14 Contact information for reporting SAEs and pIMDs

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

8.3.4. Treatment of adverse events

Any medication, vaccine or products which may explain/cause/be used to treat an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.9.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to 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/caregiver/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.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in the current study.

8.6. Biomarkers

Not applicable for this study.

8.7. Immunogenicity

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses (Amended 24 November 2020)

The study includes 2 confirmatory co-primary objectives. The non-inferiority margins associated to each objective are provided in Table 15.

Table 15 Study objectives and null hypothesis (Amended 24 November 2020)

Objectives	Null hypothesis
Co-Primary	
• To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between RSVPreF3 OA investigational vaccine (Control group) divided by RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in RSV-A neutralization antibody titers 1 month after the RSVPreF3 OA investigational vaccine dose is above ***1.5***.
• To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• True Group GMT ratio between FLU vaccine (Control group) divided by RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in HI antibody titers for each of the FLU vaccine strains 1 month after the FLU vaccine is above ***1.5.***

FLU vaccine is referring to FLU-QIV; HI: Hemagglutinin Inhibition; GMT: Geometric Mean Titer.

The success of the study depends on the success of all co-primary objectives. Using a nominal alpha of 2.5% for each of them will ensure the global type I error for the co-primary objectives is controlled below 2.5%.

9.2. Sample size determination (Amended 24 November 2020)

The target enrolment will be 880 participants (440 in the group receiving the RSVPreF3 OA investigational vaccine co-administered with the FLU vaccine (Co-Ad group) and 440 in the Control group where RSVPreF3 OA investigational vaccine and FLU vaccine are administered staggered) to obtain at least 786 evaluable participants (393 in the Co-Ad group and 393 in Control group) for the evaluation of the primary objectives, assuming that approximately 10% of the enrolled participants will not be evaluable.

Each objective will be evaluated with a nominal type I error of 2.5%.

Table 16 Overall power to demonstrate co-primary objectives: non-inferiority of the immunogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU vaccine as compared to when administered alone- assuming 393 participants are available in each group (Amended 24 November 2020)

RSV Non-inferiority* (1-sided test with alpha = 2.5%)				
Endpoint	**Standard deviation of log10 concentration**	**Non-inferiority margin**	**Type II error**	**Power**
GMTs RSV-A neutralization antibody	0.45	***1.5***	***0.02%***	***99.98%***
FLU Non-inferiority* (1-sided test with alpha = 2.5%)				
Endpoint	**Standard deviation of log10 concentration**	**Non-inferiority margin**	**Type II error**	**Power**
GMTs HI H1N1 strain	0.6	***1.5***	***1.58%***	***98.42%***
GMTs HI H3N2 strain	0.6	***1.5***	***1.58%***	***98.42%***
GMTs HI B/***Washington*** strain	0.6	***1.5***	***1.58%***	***98.42%***
GMTs HI B/***Phuket*** strain	0.6	***1.5***	***1.58%***	***98.42%***
Global Type II error to show non-inferiority			***~6.3%***	
Global power				***~93.7%***

*Pass 2019 alpha = 2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean.

Considering identical true GMTs in both groups with a common population standard error of 0.45 for the RSV-A neutralization antigen and 0.6 for each of the FLU strains in log10 transformed concentration, the study has at least ***93.7%*** power to meet the co-primary objectives.

Nominal powers to evaluate secondary objective

The nominal power to evaluate the non-inferiority on seroconversion rate for each of the FLU strains is above 79%, depending on the plausible rates.

Table 17 Evaluation of non-inferiority in terms of HI antibody SCR when the FLU vaccine is co-administered with the RSVPreF3 OA investigational vaccine as compared to FLU when administered alone assuming 393 participants are available in each group for a range of plausible SCRs

N evaluable participants per group	Threshold	Plausible rates in Control group**	Type II error#	Nominal Power
		FLU vaccine: Non-inferiority* in terms of SCR		
393	10%	70%	13.4%	86.6%
393	10%	50%	20.4%	79.6%
393	10%	35%	16.1%	83.9%
393	10%	25%	10.1%	89.9%

SCR: Seroconversion Rate.
*Pass 2019 alpha = 2.5%, for SCR – Non-inferiority: Proportions – Two independent Proportions – Non-Inferiority Tests for the Difference Between Two Proportions.
** SCR observed in the Control group in Zoster-004 study range from 35.3% to 60.9%.
#The overall power for this secondary objective will be 100-sum of the type II error for each of the 4 strains.

9.3. Analysis sets

Table 18 Analysis sets

Analysis set	Description
Enrolled set	Participants who agreed to participate in a clinical study after completion of the informed consent process.
Exposed set (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered.
Per Protocol set (PPS)	All eligible participants who received all study interventions as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals (refer to Table 3) and contribution of participants to PPS at specific timepoint will be defined by timepoint, without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

9.3.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned in the Sections 7.1.1 (contraindication to subsequent vaccination) or 5.2.1 (medical conditions) or 5.2.2 (concomitant therapy), he/she may be eliminated from per-protocol analysis.

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

9.4. Statistical analyses (Amended 24 November 2020)

The Statistical Analysis Plan (SAP) will be developed and finalized before first subject first visit (FSFV). This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Supportive analyses***, safety*** and demography summaries will be described in the SAP.

9.4.1. Co-primary endpoints (Amended 24 November 2020)

The co-primary endpoints are described in Section 3. The confirmatory analyses of non-inferiority will be based on the per-protocol (PP) set.

- Method for non-inferiority of RSV investigational vaccine in terms of RSV-A neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e. at Day 31 for the Co-Ad group and at Day 61 for the Control group):

  The 2-sided 95% confidence interval (CI) for group GMT ratio between RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be derived from an ANCOVA model* on $\log_{10}$ transformed titer.

- Method for non-inferiority of FLU vaccine in terms of HI GMT ratio for each of the FLU vaccine strains at 1 month after the FLU vaccine (i.e. at Day 31 for both groups):

  The 2-sided 95% CI for group GMT ratio between FLU vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be derived from an ANCOVA model* on $\log_{10}$ transformed titer.

*The model will include the treatment group, the age category (age at vaccination: 60-69, 70-79 or ≥80 years), country and sex as fixed effects, and the pre-dose log10-transformed titer as covariate. Missing data will not be replaced. Titers below the assay cut-off will be replaced by half the assay cut-off, titers above the upper-limit of quantification (ULOQ) will be replaced by the ULOQ.

Success criteria for non-inferiority:

1. The upper limit of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for RSV investigational vaccine is ≤***1.5***.

   AND

2. The upper limit of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for each of the FLU vaccine strains are ≤***1.5***.

9.4.2. Secondary endpoints

- Method for evaluation of non-inferiority of FLU vaccine in terms of HI seroconversion rate for each of the FLU vaccine strains at 1 month after the FLU vaccine (i.e. at Day 31 for both groups):
  - The 2-sided 95% CI on group difference in seroconversion rate (Control group minus Co-Ad group) will be computed based on the method of Miettinen and Nurminen [Miettinen, 1985].
  - Reference criteria for evaluation of non-inferiority:

  The upper limit of the 2-sided 95% CI on the group difference (Control group minus Co-Ad group) in seroconversion rate is ≤10% for anti-HI antibodies.
- The other secondary endpoints are described in Section 3. Descriptive analyses of demography, immunogenicity and safety will be detailed in the SAP.

Table 19 Definitions of seroconversion rate, seroprotection rate and mean geometric increase

Abbreviation/term	Definition
HI SCR/ seroconversion rate	The percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥ 1:40 or a pre-dose titer ≥1:10 and at least a four-fold increase in post-dose titer.
HI SPR/ seroprotection rate	The percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.
MGI/ mean geometric increase	The geometric mean of the within participant ratios of the post-dose titer over the pre-dose titer.

- Additionally, the CBER and CHMP criteria for HI SPR and SCR will be assessed as follows:

CBER's criteria:

- The lower limit (LL) of the 95% CI for SCR should be ≥40% in participants aged 18-64* YOA or ≥30% in participants ≥65 YOA.
- The LL of the 95% CI for SPR should be ≥70% in participants aged 18-64* YOA or ≥60% in participants ≥65 YOA.

*In this study, only participants from 60 YOA and higher are included, hence we can expect only a small proportion of participants in this category of 60 to 64 years. Although the SCR will be estimated the criteria cannot be evaluated for this category.

CPMP / CHMP criteria (EMEA):

At least one of the 3 following criteria should be met:

- the point estimates of SPR >60%, SCR >30%, and MGI >2.0 for elderly > 60 years for each of the antigen strains.

9.5. Interim analyses

9.5.1. Sequence of analyses

A final analysis will be conducted once all the immunogenicity data are available for primary and secondary endpoints. This final analysis will include immunogenicity and safety data up to Visit 2 (Co-Ad group) or Visit 3 (Control group).

An EoS analysis with all data including the data obtained until 6 months post-last dose will be performed.

9.5.2. Statistical consideration for interim analysis

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 International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 informed consent must be obtained from each participant and/or each participant's witness, 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 requirements, where applicable, and the IRB/IEC or study center.

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

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

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

10.1.4. Data protection

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

- His/her personal study-related data will be used by the sponsor in accordance with local data protection law.
- His/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- GSK will 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

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

10.1.6. Dissemination of clinical study data

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

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

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

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

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Glossary of terms for the exact definition of essential and source documents). The 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, eCRF), the copy should fulfill the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All participant data related to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by 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 (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies 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 (see Glossary of terms for the exact definition of 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 state location(s) 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 Clinical Study Report (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 LSLV for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

10.2. Appendix 2: Clinical laboratory tests

RSV-A and RSV-B neutralization assays

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

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a monolayer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV-A/B IgG) and a secondary antibody conjugated to horse-radish peroxidase (HRP), allowing the visualization of plaques after coloration with *TrueBlue* peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software or equivalent). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014]. For the testing of phase 3 studies, secondary standards calibrated against the international reference (NIBSC 16/284) will be included in every run to allow conversion into international units.

RSVPreF3 protein IgG ELISA

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

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

Hemagglutination-inhibition assay

HI antibody titers are determined using the method derived from the World Health Organization (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 using 2 hemagglutinating units (2 HAU) of the appropriate antigens and a 0.50% fowl erythrocyte suspension. Non-specific serum inhibitors are removed by heat treatment and receptor-destroying enzymes.

Starting with an initial dilution of 1:10, a dilution series (by a factor of 2) is prepared up to an end dilution of 1:10240. The titration end-point is taken as the highest dilution step that shows complete inhibition of hemagglutination. All assays are performed in duplicate. The usual cut-off value is = 10 1/DIL.

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 Adverse Event (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).

- 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.

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.

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.	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 20 Solicited administration site events

Pain
Erythema/redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 21 Solicited systemic events

Fever
Headache
Fatigue
Myalgia
Arthralgia

Note: participants will be instructed to measure and record the temperature in the evening. The route for temperature measurement can be oral, axillary or tympanic. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited adverse events

An unsolicited AEs is an AE 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'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)

pIMDs are the only AESIs collected during this study.

10.3.5.1. Potential immune-mediated diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 22. Please refer to the Section 10.3.7.1 for reporting details.

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

Table 22 List of potential immune-mediated diseases (pIMDs)

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

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

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. Recording and follow-up of AEs, SAEs, and pIMDs

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.

A Paper Diary, hereafter referred to as Participant Diary, will be used in this study to capture solicited administration site or systemic events. The Participant Diary will be distributed to all participants at Visit 1, and additionally to participants in the Control group at Visit 2. 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. If any individual other than the participant is making entries in the Participant Diary, their identity must be documented in the Participant Diary.

- Collect and verify completed diary cards during discussions with the participant on Visit 2 (from all participants) and Visit 3 (only from participants in the Control group).
- Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure.

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

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

All solicited administration site and systemic events with onset during the 4 days following administration of the study interventions, and all unsolicited AEs that occur during the 30 days following administration of the study interventions must be recorded into the appropriate section of the eCRF, irrespective of their intensity.

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

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

10.3.7.2. Follow-up of AEs, SAEs, and pIMDs

After the initial AE/SAE/pIMDs or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs (as defined in Section 10.3.5.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

10.3.7.2.1. Follow-up during the study

AEs (serious or non-serious) or pIMDs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study or the participant is lost to follow-up.

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.

10.3.7.2.2. 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/pIMD 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/pIMD as fully as possible.

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

When additional SAE or pIMD information is received after 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 13.

10.3.8. Assessment of intensity and toxicity

10.3.8.1. Assessment of intensity

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

Table 23 Intensity scales for solicited events

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

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

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.

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

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.

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

10.3.8.3. Medically attended visits

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

10.3.8.4. 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).

10.3.9. Reporting of SAEs and pIMDs

10.3.9.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred, the investigator (or designee) must complete the 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 13 for the details on timeframes for reporting of SAEs/pIMDs.

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 10.3.9.2 for information on backup systems in case the electronic reporting system does not work.

10.3.9.2. 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: Abbreviations and glossary of terms

10.4.1. List of abbreviations

AE:	Adverse Event
AS01E:	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
COVID-19:	Coronavirus Disease 2019
CSR:	Clinical Study Report
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
FDA:	Food and Drug Administration, United States of America
FLU:	Influenza
FSFV:	First Subject First Visit
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
HA:	Hemagglutinin
HI:	Hemagglutinin inhibition
HRP:	Horse-Radish Peroxidase
IB:	Investigator Brochure
ICF:	Informed Consent Form

ICH:	International Council on Harmonisation
IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G
IRB:	Institutional Review Board
LSLV:	Last Subject Last Visit
MGI:	Mean Geometric Increase
OA:	Older Adults
pIMD:	Potential Immune-Mediated Disease
PP:	Per-Protocol
PPS:	Per-Protocol Set
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
QTL:	Quality Tolerance Limit
RSV:	Respiratory Syncytial Virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Source data Base for Internet Randomization
SCR:	Seroconversion Rate
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
SPR:	Seroprotection Rate
SUSAR:	Suspected Unexpected Serious Adverse Reactions
ULOQ:	Upper-Limit of Quantification
US:	United States
YOA:	Years of Age

10.4.2. 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 AEs In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Caregiver:	A ‘caregiver’ is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g. a relative of the participant including family members or friends). In the context of this study, a caregiver can be appointed by the participant to oversee and support the participant’s compliance with protocol-specific procedures (such as transcribing responses to diaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant’s health status while answering diaries or make decisions on behalf of the participant.
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.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant:	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 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.
Intercurrent medical condition:	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
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.
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.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
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.
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.

10.5. Appendix 5: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	**Date of Issue**
Original Protocol	19 October 2020

Overall Rationale for the Amendment

The protocol is amended to address the comments from CBER, US FDA. Specifically, the NI margins have been updated, and accordingly the power calculations associated with the co-primary objectives have been updated while the sample size remains the same. The formulation of the FLU vaccine has also been added based on WHO recommendations for the 2021 influenza season in the Southern Hemisphere, and a typographical error has been corrected, in Table 7 (Study interventions administered).

Detailed description of Protocol Amendment:

Sponsor Approval: The name of the Sponsor Signatory has been updated.

~~Narcisa Mesaros~~ ***Marie Van Der Wielen, MD.***
Clinical and Epidemiology R&D Project Lead, Older Adults project

Section 6.1: Study interventions administered: The formulation of the FLU vaccine has been added in the footnote for Table 7 based on WHO recommendations. A typographical error in the Vaccine Presentation has been corrected.

Table 7: Study interventions administered

Study intervention name:	RSVPreF3 OA investigational vaccine	FLU-QIV
Study intervention formulation:	RSVPreF3 (120 µg) AS01E: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injection q.s. 0.5 mL	FLU Quadrivalent Influenza vaccine, 15µg hemagglutinin (HA) per strain/dose**
Presentation:	RSVPreF3 ~~(120 µg)~~: Vial; Powder for suspension for injection AS01E: Vial; Suspension for suspension for injection	Syringe, suspension for injection
Type:	Biologic	Biologic
Route of administration:	Intramuscular (IM) injection	IM injection
Location	Deltoid	Deltoid
Directionality	Upper	Upper
Laterality	Non-Dominant	Co-Ad group: Dominant Control group: Non-Dominant
Number of doses to be administered:	1	1
Volume to be administered*:**	0.5 mL	0.5 mL

Packaging, labeling and TM: (when applicable)	Refer to the SPM for more details	Refer to the SPM for more details
Manufacturer:	GSK Biologicals	GSK Biologicals

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

The strains ~~will depend on the World Health Organization recommendation for the 2021 FLU season~~ ***used in the FLU Quadrivalent Influenza vaccine are A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Hong Kong/2671/2019 (H3N2), NIB-121 (15 µg HA); B/Washington/02/2019, wild type (15 µg HA); B/Phuket/3073/2013, wild type (15 µg HA)*

*** Refer to the SPM for the volume after reconstitution

Section 9.1 Statistical hypothesis: NI margins in Table 15 have been updated.

Table 15: Study objectives and null hypothesis

Objectives	Null hypothesis
Co-Primary	
• To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between RSVPreF3 OA investigational vaccine (Control group) divided by RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in RSV-A neutralization antibody titers 1 month after the RSVPreF3 OA investigational vaccine dose is above ~~2.0~~ ***1.5***.
• To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• True Group GMT ratio between FLU vaccine (Control group) divided by RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in HI antibody titers for each of the FLU vaccine strains 1 month after the FLU vaccine is above ~~2.0~~ ***1.5.***

FLU vaccine is referring to FLU-QIV; HI: Hemagglutinin Inhibition; GMT: Geometric Mean Titer.

Section 9.2 Sample size determination: The sample size consideration in Table 16 have been updated based on the NI margin of 1.5. The FLU strains have also been updated.

Table 16: Overall power to demonstrate co-primary objectives: non-inferiority of the immunogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU vaccine as compared to when administered alone- assuming 393 participants are available in each group

RSV Non-inferiority* (1-sided test with alpha = 2.5%)				
Endpoint	**Standard deviation of log10 concentration**	**Non-inferiority margin**	**Type II error**	**Power**
GMTs RSV-A neutralization antibody	0.45	~~2.0~~ ***1.5***	***0.02%*** ~~<0.1%~~	99.98% ~~>99.9%~~
FLU Non-inferiority* (1-sided test with alpha = 2.5%)				
Endpoint	**Standard deviation of log10 concentration**	**Non-inferiority margin**	**Type II error**	**Power**
GMTs HI H1N1 strain	0.6	~~2.0~~ ***1.5***	~~<0.1%~~ ***1.58%***	~~>99.9%~~ ***98.42%***

GMTs HI H3N2 strain	0.6	~~2.0~~ ***1.5***	~~<0.1%~~ ***1.58%***	~~>99.9%~~ ***98.42%***
GMTs HI B/***Washington*** ~~Yamagata~~ strain	0.6	~~2.0~~ ***1.5***	~~<0.1%~~ ***1.58%***	~~>99.9%~~ ***98.42%***
GMTs HI B/***Phuket*** ~~Victoria~~ strain	0.6	~~2.0~~ ***1.5***	~~<0.1%~~ ***1.58%***	~~>99.9%~~ ***98.42%***
Global Type II error to show non-inferiority			***~6.3%*** ~~~0.1%~~	
Global power				***~93.7%*** ~~~99.9%~~

*Pass 2019 alpha = 2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean.

Considering identical true GMTs in both groups with a common population standard error of 0.45 for the RSV-A neutralization antigen and 0.6 for each of the FLU strains in log10 transformed concentration, the study has at least ~~99.9%~~ ***93.7%*** power to meet the co-primary objectives.

Section 9.4: Statistical analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before first subject first visit (FSFV). This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Supportive analyses***, safety*** and demography summaries will be described in the SAP.

Section 9.4.1 Co-primary endpoints: The NI criteria have been updated.

Success criteria for non-inferiority:

1. The upper limit of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for RSV investigational vaccine is ≤***1.5*** ~~2.0~~.

   AND

2. The upper limit of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for each of the FLU vaccine strains are ≤***1.5*** ~~2.0~~.

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