Protocol Amendment 1

Phase I/II, observer-blind, safety, reactogenicity and immunogenicity study of GSK Biologicals' respiratory syncytial virus (RSV) vaccine GSK3844766A in subjects aged 18-40 or 60-80 years

NCT ID: NCT03814590
EudraCT Number: 2018-000849-38

Amendment 1 Final: 13 May 2020

CONFIDENTIAL

208851 (RSV OA=ADJ-002)
Protocol Amendment 1 Final

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

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A): • RSVPreF3 recombinant antigen, 30 µg • RSVPreF3 recombinant antigen, 30 µg adjuvanted with $AS01_E$ • RSVPreF3 recombinant antigen, 30 µg adjuvanted with $AS01_B$ • RSVPreF3 recombinant antigen, 60 µg • RSVPreF3 recombinant antigen, 60 µg adjuvanted with $AS01_E$ • RSVPreF3 recombinant antigen, 60 µg adjuvanted with $AS01_B$ • RSVPreF3 recombinant antigen, 120 µg • RSVPreF3 recombinant antigen, 120 µg adjuvanted with $AS01_E$ • RSVPreF3 recombinant antigen, 120 µg adjuvanted with $AS01_B$
Other Study vaccine/product	Control: Saline solution
eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
Investigational New Drug (IND) number	***18540***
EudraCT number	2018-000849-38
Date of protocol	Final Version 2: 11 September 2018
Date of administrative change / amendment	Administrative change 1 Final: 25 July 2019 ***Amendment 1 Final: 13 May 2020***
Title	Phase I/II, observer-blind, safety, reactogenicity and immunogenicity study of GSK Biologicals' respiratory syncytial virus (RSV) vaccine GSK3844766A in subjects aged 18-40 or 60-80 years.

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Co-ordinating authors ***(Amended, 13 May2020)***	PPD (XPE Pharma and Science, for GSK Biologicals) ***and*** PPD, Scientific Writer
Contributing authors ***(Amended, 13 May 2020)***	• PPD, Clinical Research and Development Lead • PPD Clinical ***Research and Development Lead*** • PPD, Project Statistician • PPD, Lead Statistician • PPD Study Delivery Leads • PPD Clinical Trial Supply Manager • PPD, Clinical Laboratory Sciences Study Manager (Business & Decision, for GSK Biologicals) • PPD, Clinical Read-out Team Leader • PPD, Safety Scientist • PPD, Oversight Data Manager • PPD, Global Regulatory Affairs • PPD, Global Patent • PPD, Clinical and Epidemiology R&D Project Lead • PPD, Clinical and Epidemiology R&D Project Lead

GSK Biologicals' Protocol DS v 15.0

Protocol Amendment 1 Sponsor Signatory Approval

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Sponsor signatory	Narcisa Mesaros Clinical and Epidemiology R&D Project Lead, Older Adults project
Signature	_____
Date	_____

Protocol Amendment 1 Rationale

Amendment number:	Amendment 1, 13 May 2020

Rationale/background for changes:

This Protocol Amendment 1 outlines measures that may be applicable during special circumstances (e.g., Coronavirus disease 2019 [COVID-19] pandemic). The purpose of the amendment is to protect subject's welfare and safety, and as far as possible ensure the potential benefit to the subject and promote data integrity. A new section has been added (Section 5.10) to provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic.

The measures include the following:

- **Instruction for the remaining scheduled visit (Visit 8):** Planned study visit can proceed, if the study subjects are healthy and allowed to come to the site to have the blood sample and safety information collected. If the visit is impacted due to the national guidelines and/or site restrictions linked to the special circumstances, and it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 8), the samples will be encoded as missing and encoded as protocol deviation. If the visit is impacted, the safety information (as per protocol: SAEs, pIMDs, concomitant medications/vaccinations and intercurrent medical conditions) will be collected by site staff via telephone contact or other means of virtual contact, and this will not be considered as protocol deviation.
- **Instruction for collection of home self-swabs in case study participant experiences suspected respiratory tract infection (RTI) symptoms:** In case the investigator determines this is not posing additional risk to the subjects or household members, the subjects will be instructed to perform the home self-swab and keep it in their freezer (preferred) or refrigerator until recovered, and able to bring it to the site. If there is a possibility, a healthy relative can bring the sample to the site to be processed. In case investigator judges this is not advisable due to the national guidelines and/or site restrictions linked to the special circumstances, the self-swab will not be collected and the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. The investigator and/or the site staff will provide these instructions to the subjects during the active surveillance contacts carried out every 2 weeks during the RSV season period.
- **Instructions for assessment visit for suspected respiratory tract infection (RTI):** Site staff will decide on the management of the cases (either having a site/different site location/home visit or by telephone contact) based on COVID-19 national guidelines and/or site restrictions linked to the special circumstances. If the nasal and throat samples cannot be collected at site, the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. Biological samples will not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

Additional changes:

- As per the request from the regulatory (Belgian) authorities, clarification has been added to the holding rule wording for non-life-threatening SAEs in Section 7.10.4. The paragraph has been modified to add clarification that SAEs that are not related to study vaccination will not be considered for safety holding rules.
- Blood collection and testing plan for samples arising at the last study visit (Visit 8) have been updated, following the formulation selection and based on data generated from the first analysis. At the last visit, blood samples will be collected for humoral and CMI determination from a subset of subjects (N≅460; from all subjects in part B1 [N≅100] and subjects who received a selected level of antigen dose and Placebo in part B2 [N≅360]).
- Blinding instructions have been updated to reflect the impact of the change in blood collection and testing plan at the last study visit (Visit 8). During the last study visit, the blood samples will be collected only from a subset of subjects (N≅460; from all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

  In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends.
- Missing cut-off values for some humoral assays have been included. The new naming for the competitive ELISA (RSVPreF3 RSB1 specific) has been implemented.

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.
- 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 Biologicals' study vaccine and other study-related duties and functions as described in the protocol.
- 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 Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

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Investigator name	_____
Signature	_____
Date	_____

Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 7.4.2.

5. GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 7.8.

SYNOPSIS

Detailed Title

A Phase I/II, randomized, placebo-controlled, observer-blind, multicenter study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_E$ or $AS01_B$ or unadjuvanted) when administered intramuscularly according to a 0, 2 month schedule in adults aged 18-40 or 60-80 years.

Indication

Active immunization in the prevention of moderate-to-severe lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in adults aged 60 years or above.

Rationale for the study and study design

Rationale for the study

Despite the significant medical need in older adults, there is currently no prophylactic vaccine approved for the prevention of LRTD caused by RSV.

GlaxoSmithKline (GSK) Biologicals is developing a new investigational RSV vaccine against moderate to severe RSV-associated (subtypes A and B) disease in adults aged 60 years or above.

Rationale for the study design

This study will evaluate 9 investigational RSV vaccine formulations, with different concentrations of pre-fusion conformation antigen RSVPreF3 (30, 60 or 120 µg), either unadjuvanted or adjuvanted with $AS01_E$ or $AS01_B$ when administered intramuscularly according to a 2-dose schedule at 0, 2 months in older adults (60-80 years). The main purpose will be to evaluate the safety, reactogenicity and immunogenicity of the vaccine candidates and select a formulation for further development of the RSV vaccine, based on those results. In terms of immunogenicity, the selection of the vaccine formulation will rely primarily on the levels of RSV-A neutralizing antibody titers and CD4+ T-cells response. Further assessment of immune responses, including the RSVPreF3 IgG antibody, might additionally guide the vaccine candidate selection.

As this dose ranging study will include the target population of older adults aged 60-80 years, it has been designed as a Phase I/II study.

- **Vaccine antigen and adjuvant selection:** The antigen which will be used in the investigational RSV vaccine is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation, resulting in the "RSVPreF3" pre-fusion molecule. The F protein has been selected because it is a major surface antigen of the RSV virus that is well conserved among RSV-A and RSV-B subtypes.

  In addition to boosting pre-existing neutralizing antibodies, another important element for the RSV candidate vaccine in older adults might be to boost or elicit RSV-specific T-cell responses. The use of an adjuvant may enable induction of CD4+ T-cells in addition to antibodies, leading to a stronger and persistent protection. Amongst the current GSK portfolio of adjuvants, AS01 has the potential to induce the targeted immune profile as it has been shown to improve antibody and T-cell response in older adults.

- **Dose regimen:** It is proposed to evaluate a 2-dose vaccination regimen with an interval of 2 months between doses.

- **Staggered design and safety monitoring:** As the RSVPreF3 antigen has not been administered to humans yet, this study will first evaluate the safety of 3 different dosages of RSVPreF3 (30, 60 and 120 μg, unadjuvanted) in healthy men and women aged 18-40 years in Part A (~12 subjects/group) before proceeding with vaccination of the target population in Part B (~100 subjects/group). To ensure the safety of the study participants, Part B will follow a staggered enrolment with 2 steps. For each part, study holding rules have been defined.

  After the first and second vaccine dose in Part A, safety evaluations will be performed by an Independent Data Monitoring Committee (IDMC). Only upon favorable outcome of the first IDMC evaluation, the vaccination in Part B of the study will be initiated. In this part, the safety and immunogenicity of 9 investigational RSV vaccine formulations (adjuvanted and unadjuvanted) will be evaluated in older adults aged 60-80 years. IDMC safety evaluations will be performed after each study vaccination step.

- **Study blinding:** Given the difference in reconstitution and visual appearance of the investigational RSV vaccine, double blinding is not possible and the study will be conducted in an observer-blind manner for the vaccination phases (up to one month post-Dose 2) of both study parts.

  A statistical analysis will be performed on data from vaccinated subjects up to one month post-Dose 2. Given that summary results may unblind some specific subjects, the persistence phase of Part B (Epoch 003) will be considered as single-blind, with subjects remaining blinded up to study end. The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

  During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

  In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends. (Amended, 13 May 2020)

Rationale for the use of placebo

As there is currently no licensed RSV vaccine available, a placebo group (receiving saline solution) will be used as control for the safety, reactogenicity and immunogenicity assessments in both study parts.

Objectives

Primary

For Part A and Part B

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

Secondary

For Part A and Part B

- To characterize the humoral immune responses (including dose-response) in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).
- To characterize the cell-mediated immune responses in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

For Part B

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccines administered IM according to a 0, 2 month schedule, up to the end of follow-up (Month 14, Visit 8).
- To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

Tertiary

For Part A and Part B

- To further characterize the cell-mediated immune responses to investigational RSV vaccine formulations.

For Part B

- To further characterize immune responses to investigational RSV vaccine formulations.
- To characterize persistence of immune responses to the investigational RSV vaccine formulations at Month 8 (Visit 7) and Month 14 (Visit 8).
- To further evaluate the occurrence of RSV-associated RTI (including co-infections with other respiratory viruses) during the RSV seasons in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.
- To evaluate the occurrence of RSV-associated RTI during the RSV season using self-collected nasal swabs.

Study design

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-country study with 2 parts (i.e., Part A in young adults aged 18-40 years with 4 parallel groups and Part B in older adults aged 60-80 years with 10 parallel groups).
- **Duration of the study:**

  Approximately 3 months per subject in Part A:

  – Epoch 001: Screening Visit (Day -30 to -3)
  – Epoch 002: Primary (vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 6 (Day 91)

  Approximately 14 months per subject in Part B:

  – Epoch 001: Screening Visit (Day -30 to -3)
  – Epoch 002: Primary (vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 6 (Day 91)
  – Epoch 003: Follow-up (persistence phase) starting after Visit 6 (Day 91) and ending at Visit 8 (Month 14)
- **Primary completion Date:** last visit of the vaccination phase in Part B (Visit 6 [Day 91]).
- **End of Study:** Last testing results released of samples collected up to Visit 8 in Part B (Month 14) (for assays related to primary and secondary endpoints only).
- **Treatment allocation:** Subjects will be randomized using a centralised randomization system on internet (SBIR) on Day 1.

  In Part A, the aim is to enrol approximately 48 subjects aged 18-40 years. The randomization algorithm will use a minimisation procedure accounting for center and gender.

  In Part B, the aim is to enrol approximately 700 subjects aged 60-69 years and approximately 300 subjects aged 70-80 years. The randomization algorithm will use a minimisation procedure accounting for age, center and gender in each step.
- **Study groups:** For the investigational RSV vaccine in Part A and Step 1 in Part B, the RSVPreF3 high-dose formulation containing 120 μg RSVPreF3 will be used for all groups. For Step 2 in Part B, the RSVPreF3 low-dose and mid-dose formulations will be used for the groups receiving 30 μg and 60 μg of RSVPreF3, respectively. As subjects enrolled in Step 1 and 2 of Part B will thus receive different vaccine formulations for the low-and mid-dose groups, separate study groups have been identified (referred to as B1 and B2).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
Part A					
30-PLAIN_A	12	18 - 40 years	x	x	
60-PLAIN_A	12	18 - 40 years	x	x	
120-PLAIN_A	12	18 - 40 years	x	x	
Placebo_A	12	18 - 40 years	x	x	
Part B - Step 1					
30-PLAIN_B1	10	60 - 80 years	x	x	x
30-AS01E_B1	10	60 - 80 years	x	x	x
30-AS01B_B1	10	60 -80 years	x	x	x
60-PLAIN_B1	10	60 - 80 years	x	x	x
60-AS01E_B1	10	60 - 80 years	x	x	x
60-AS01B_B1	10	60 - 80 years	x	x	x
120-PLAIN_B1	10	60 - 80 years	x	x	x
120-AS01E_B1	10	60 - 80 years	x	x	x
120-AS01B_B1	10	60 - 80 years	x	x	x
Placebo_B1	10	60 - 80 years	x	x	x
Part B - Step 2					
30-PLAIN_B2	90	60 - 80 years	x	x	x
30-AS01E_B2	90	60 - 80 years	x	x	x
30-AS01B_B2	90	60 - 80 years	x	x	x
60-PLAIN_B2	90	60 - 80 years	x	x	x
60-AS01E_B2	90	60 - 80 years	x	x	x
60-AS01B_B2	90	60 - 80 years	x	x	x
120-PLAIN_B2	90	60 - 80 years	x	x	x
120-AS01E_B2	90	60 - 80 years	x	x	x
120-AS01B_B2	90	60 - 80 years	x	x	x
Placebo_B2	90	60 - 80 years	x	x	x

Synopsis Table 2 Study groups and treatment foreseen in Part A

Treatment name	Vaccine/Product name	Study Groups			
		30-PLAIN_A	60-PLAIN_A	120-PLAIN_A	Placebo_A
30 µg RSVPreF3 plain	RSVPreF3 high dose	x			
	NaCl	x			
60 µg RSVPreF3 plain	RSVPreF3 high dose		x		
	NaCl		x		
120 µg RSVPreF3 plain	RSVPreF3 high dose			x	
	NaCl			x	
Placebo	NaCl				x

Synopsis Table 3 Study groups and treatment foreseen in Part B - Step 1

Treatment name	Vaccine/ Product name	Study Groups									
		30-PLAIN_B1	30-AS01E_B1	30-AS01B_B1	60-PLAIN_B1	60-AS01E_B1	60-AS01B_B1	120-PLAIN_B1	120-AS01E_B1	120-AS01B_B1	Placebo_B1
30 µg RSVPreF3 plain	RSVPreF3 high dose	x									
	NaCl	x									
30 µg RSVPreF3/AS01E	RSVPreF3 high dose		x								
	AS01E		x								
30 µg RSVPreF3/AS01B	RSVPreF3 high dose			x							
	AS01B			x							
60 µg RSVPreF3 plain	RSVPreF3 high dose				x						
	NaCl				x						
60 µg RSVPreF3/AS01E	RSVPreF3 high dose					x					
	AS01E					x					
60 µg RSVPreF3/AS01B	RSVPreF3 high dose						x				
	AS01B						x				
120 µg RSVPreF3 plain	RSVPreF3 high dose							x			
	NaCl							x			
120 µg RSVPreF3/AS01E	RSVPreF3 high dose								x		
	AS01E								x		
120 µg RSVPreF3/AS01B	RSVPreF3 high dose									x	
	AS01B									x	
Placebo	NaCl										x

Synopsis Table 4 Study groups and treatment foreseen in Part B - Step 2

Treatment name	Vaccine/ Product name	Study Groups									
		30-PLAIN_B2	30-AS01E_B2	30-AS01B_B2	60-PLAIN_B2	60-AS01E_B2	60-AS01B_B2	120-PLAIN_B2	120-AS01E_B2	120-AS01B_B2	Placebo_B2
30 µg RSVPreF3 plain	RSVPreF3 low dose	x									
	NaCl	x									
30 µg RSVPreF3/AS01E	RSVPreF3 low dose		x								
	AS01E		x								
30 µg RSVPreF3/AS01B	RSVPreF3 low dose			x							
	AS01B			x							
60 µg RSVPreF3 plain	RSVPreF3 mid dose				x						
	NaCl				x						
60 µg RSVPreF3/AS01E	RSVPreF3 mid dose					x					
	AS01E					x					
60 µg RSVPreF3/AS01B	RSVPreF3 mid dose						x				
	AS01B						x				
120 µg RSVPreF3 plain	RSVPreF3 high dose							x			
	NaCl							x			
120 µg RSVPreF3/AS01E	RSVPreF3 high dose								x		
	AS01E								x		
120 µg RSVPreF3/AS01B	RSVPreF3 high dose									x	
	AS01B									x	
Placebo	NaCl										x

- **Control:** placebo control.
- **Vaccination schedules:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Blinding:** observer-blind.

Synopsis Table 5 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	N/A
Epoch 002	observer-blind
Epoch 003	single-blind

N/A: Not applicable

- **RTI surveillance in Part B:** Active and passive surveillance will only be carried out during RSV seasons (approximately from October to March) throughout the entire Part B of the study:
- **Sampling schedule:**

  In Part A:

  – At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects.

  – At Day 1 (Visit 1), a blood sample for cytomegalovirus (CMV) status determination will be drawn from all subjects.

  – **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

  – **Blood samples for humoral immunogenicity** and **cell-mediated immunity (CMI)** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).

  In Part B:

  – At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects.

  – At Day 1 (Visit 1), a blood sample for CMV status determination will be drawn from all subjects.

  – **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects and on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

  - **Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91 **and** Month 8, ***and from a subset at*** Month 14 (Visits 1, 3, 4, 6, 7 and 8). ***(Amended, 13 May 2020)***
  - **Nasal/throat swabs:** In case of RTI symptoms during the RSV season (approximately from October to March), the study participants will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal swab and a throat swab by qualified staff from the study team.

- **Type of study:** self-contained.
- **Data collection:** eCRF. Solicited symptoms will be collected using an electronic subject Diary (eDiary). Unsolicited symptoms will be collected using a paper subject Diary.
- **Safety monitoring:** The study will be conducted in 2 parts with oversight by an IDMC. The investigator is not permitted to start vaccinating the subjects in the next step in each part until the Sponsor communicates the favorable outcome of the respective safety evaluations by the IDMC.

  Part A: Approximately 48 young adults aged 18-40 years will be enrolled and vaccinated with the first dose. If the IDMC evaluation is favorable, the Part A study participants will be vaccinated with the second dose and the vaccination in Part B of the study will be initiated.

  Part B: This part will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. In Step 1, 100 subjects will be enrolled and vaccinated. Safety evaluations based on unblinded data from those 100 subjects will be performed by the IDMC to allow the start of Step 2. In Step 2, the remaining study participants (N≅900) will be enrolled and vaccinated.

  In total, 6 IDMC meetings for safety evaluation are foreseen in the vaccination phase of the study (Epoch 002), i.e., 2 meetings in Part A and 4 meetings in Part B.

  During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

  If any safety concern is identified by the investigator or the sponsor, *ad-hoc* safety evaluations by the IDMC may be performed.

Number of subjects	A total of approximately 1048 participants are planned to be enrolled in this study, of whom 48 in Part A and 1000 in Part B.
Endpoints	**Primary** **For Part A and Part B:** • Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91): – Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination. – Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination. – Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68. – Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination. – Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91). **For Part B only:** – Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91). **Secondary** **For Part A and Part B:** • Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91): – Neutralizing antibody titers against RSV serotype A. – RSVPreF3-specific IgG antibody concentrations.

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro.

For Part B only:

- Occurrence of RSV-associated RTI (as measured by qRT-PCR in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
- Occurrence of SAEs from Dose 1 up to the end of follow-up.
- Occurrence of pIMDs from Dose 1 up to the end of follow-up.

(Amended, 13 May 2020)

Tertiary

For Part A and Part B:

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro.

For Part B only:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype B in all subjects.
  - RSVPreF3 ***RSB1*** specific antibody concentrations in a subset of subjects who received the selected vaccine formulation or placebo.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific memory B-cells in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.

- Persistence of the humoral immune response with respect to components of the investigational vaccine at Months 8 and 14:
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Persistence of the cell-mediated immune response profile with respect to components of the investigational vaccine:
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific memory B-cells at Month 14 in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:
  - Antibodies against specific protein F epitopes.
  - Potential new immunological markers for protection.
  - Cross-reactive neutralizing antibody titers against hMPV.
- Occurrence of RSV-associated RTI, including co-infections with other respiratory viruses (as measured by multiplex PCR in self-collected nasal swab samples and nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons.
- Occurrence of RSV-associated RTI as measured by qRT-PCR in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ALT:	Alanine Aminotransferase
ANCOVA:	Analysis of Covariance
ANOVA:	Analysis of Variance
$AS01_B$:	MPL, QS-21, liposome based Adjuvant System (50 µg MPL and 50 µg QS-21)
$AS01_E$:	MPL, QS-21, liposome based Adjuvant System (25 µg MPL and 25 µg QS-21)
AST:	Aspartate Aminotransferase
BUN:	Blood Urea Nitrogen
CD40L:	Cluster of Differentiation 40 Ligand
CDC:	Centers for Disease Control
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CMI:	Cell-Mediated Immunity
CMV:	Cytomegalovirus
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19	***Coronavirus Disease 2019 (Amended, 13 May 2020)***
eCRF:	electronic Case Report Form
EDD:	Estimated Date of Delivery
eDiary:	electronic Diary
EGA:	Estimated Gestational Age
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
eTDF:	Electronic Temperature excursion Decision Form
FDA:	Food and Drug Administration, United States of America
GCP:	Good Clinical Practice
gE:	glycoprotein E
GM:	Geometric Mean
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer

GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus
hMPV:	Human Metapneumovirus
HRP:	Horseradish Peroxidase
HZ/su:	Herpes Zoster subunit vaccine
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
ICS:	Intracellular Cytokine Staining
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IFN-γ:	Interferon Gamma
IgG:	Immunoglobulin G
IL:	Interleukin
IM:	Intramuscular(ly)
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB:	Institutional Review Board
LML:	Local Medical Lead
LMP:	Last Menstrual Period
LOC:	Local Operating Company
LRTD:	Lower Respiratory Tract Disease
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MedDRA:	Medical Dictionary for Regulatory Activities
PBMC:	Peripheral Blood Mononuclear Cells
PCR:	Polymerase Chain Reaction
pIMD:	Potential Immune-Mediated Disease
PPS:	Per Protocol Set
PT:	Preferred Term
Q:	Quartile
qRT-PCR:	Quantitative Reverse Transcription Polymerase Chain Reaction
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

RNA:	Ribonucleic Acid
RSV:	Respiratory Syncytial Virus
RTI:	Respiratory Tract Infection
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Randomization System on Internet
SDV:	Source Document Verification
SPM:	Study Procedures Manual
TNF-α:	Tumor Necrosis Factor Alpha
US:	United States
WBC:	White Blood Cells

GLOSSARY OF TERMS

Adequate contraception:

(Amended, 13 May 2020)

Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- Abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle;
- Combined estrogen and progesterone oral contraceptives;
- Injectable progestogen;
- Implants of ***etonogestrel*** or levonorgestrel;
- Contraceptive vaginal ring;
- Percutaneous contraceptive patches;
- Intrauterine device or intrauterine system;
- Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject;

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

Adverse event:

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable 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 one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 5.3 for details on observer-blinded studies).
Designate:	A person who helps the subject with performing some of the study procedures if the subject has difficulties to perform them alone (such as completion of the eDiary, receiving phone calls and planning of the study visits), e.g. a relative of the subject, a field worker who is linked to this study. Designates are appointed by the subject for help with the study procedures solely and cannot make decisions on behalf of the subject.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (Synonym of End of Trial)	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.

eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Sections 6.6.2 and 10.5 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
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 subject's initial immune status.
Investigational vaccine: (Synonym of Investigational Medicinal Product)	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation 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.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.

Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule,…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccines or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	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 subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
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.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Cervarix	Human Papillomavirus vaccine Types 16 and 18 (Recombinant, AS04 adjuvanted)
Shingrix	Zoster vaccine (Recombinant, adjuvanted)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Allplex Respiratory Panel (Seegene)	A multiplex one-step real-time RT-PCR assay to detect and identify 16 viruses, 7 bacteria and 3 Flu A subtypes
Fluad (Seqirus Inc.)	Influenza virus vaccine (Surface antigen, inactivated, adjuvanted with MF59)
MF59 adjuvant (Novartis)	Oil-in-water emulsion of squalene oil

1. INTRODUCTION

1.1. Background

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

According to the Centers for Disease Control and Prevention (CDC) website [CDC, 2017], RSV leads to 177 000 hospitalizations and 14 000 deaths on average each year among adults older than 65 years in the United States (US). As the global population ages, the morbidity and mortality of respiratory infections appear to be steadily increasing. In the US, the burden of the disease has been shown to be significant and data indicate that RSV is comparable to influenza (in an influenza vaccinated population) in terms of number of infections, hospitalization and deaths. 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 (≥ 65 years) with influenza-like illness is 7.4%, with values between 0% and 17.1% across countries [Falsey, 2014].

Previous infection with RSV does not prevent subsequent infections. Therefore, reinfection with RSV occurs throughout an individual's lifetime and is common in all age groups [Simoes, 1999; Krilov, 2011]. Generally, these re-infections go undiagnosed because they usually manifest as common acute upper RTIs. However, in more vulnerable individuals (e.g. immunocompromized subjects or older adults), re-infections can also lead to severe disease [Graham, 2011].

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Despite the significant medical need, there is currently no prophylactic vaccine approved for the prevention of lower respiratory tract disease (LRTD) caused by RSV. Several attempts have been made to develop an RSV vaccine but to date all have been unsuccessful. In the 1960's, a formalin-inactivated RSV vaccine not only failed to show protection, but it promoted more frequent and more severe clinical symptoms of LRTD after RSV natural infection in vaccinated children. In 2015, Novavax announced results of their Phase II Proof of Concept clinical trial showing the first ever demonstration of efficacy following the administration of an active RSV vaccine in older adults over 60 years of age. However, in September 2016, Novavax announced the vaccine candidate had failed the primary and secondary efficacy endpoints in its pivotal Phase III study.

GlaxoSmithKline (GSK) Biologicals is developing a new investigational RSV vaccine against moderate to severe RSV-associated (subtypes A and B) disease in adults aged 60 years or above.

Please refer to the current Investigator Brochure for information regarding the pre-clinical studies of the investigational RSV older adult vaccine formulations.

1.2.2. Rationale for the study design

This study will evaluate 9 investigational RSV vaccine formulations, with different concentrations of pre-fusion conformation antigen RSVPreF3 (30, 60 or 120 µg), either unadjuvanted or adjuvanted with $AS01_E$ or $AS01_B$ when administered intramuscularly according to a 2-dose schedule at 0, 2 months in older adults (60-80 years). The main purpose will be to evaluate the safety, reactogenicity and immunogenicity of the vaccine candidates and select a formulation for further development of the RSV vaccine. In terms of immunogenicity, the selection of the vaccine formulation will rely primarily on the levels of RSV-A neutralizing antibody titers and CD4+ T-cells response. Further assessment of immune responses, including the RSVPreF3 immunoglobulin G (IgG) antibody, might additionally guide the vaccine candidate selection.

As the RSVPreF3 antigen has not been administered to humans yet, the study will first evaluate the safety of 3 different dosages of RSVPreF3 (30, 60 and 120 µg) in healthy men and women aged 18-40 years according to a 2-dose regimen. As many safety data have already been generated with the $AS01_E$ and $AS01_B$ adjuvants in other GSK vaccine programs (Zoster and Malaria), the antigen and adjuvant dose ranging will be evaluated directly in the target population of older adults aged 60-80 years.

Hence, the study will follow a staggered design with the following 2 parts:

- Part A, including 48 healthy adults aged 18-40 years receiving either placebo or one of 3 unadjuvanted investigational RSV vaccines containing 30, 60 or 120 µg RSVPreF3 (~12 subjects/group).
- Part B, including 1000 older adults aged 60-80 years receiving either placebo or one of 9 investigational RSV vaccines containing 30, 60 or 120 µg RSVPreF3 unadjuvanted or adjuvanted with $AS01_E$ or $AS01_B$ (~100 subjects/group, enrolled in Steps 1 and 2 in a staggered manner).

As this dose ranging study will include the target population of older adults aged 60-80 years, it has been designed as a Phase I/II study.

1.2.2.1. Vaccine antigen and adjuvant selection

The antigen which will be used in the investigational RSV vaccine is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation, resulting in the "RSVPreF3" pre-fusion molecule. The F protein has been selected because it is a major surface antigen of the RSV virus that is well conserved among RSV-A and RSV-B subtypes. It was shown that most of the RSV neutralizing activity present in serum from previously infected individuals is directed to the pre-fusion

conformation of RSV F protein [Ngwuta, 2015]. In addition, antibodies specific for the RSV F pre-fusion conformation are typically more potent than those common to the post- and pre-fusion forms [Kwakkenbos, 2010]. Finally, an RSV F antigen in the prefusion conformation elicited higher levels of neutralizing antibodies than those observed with an RSV F protein in the post-fusion conformation [McLellan, 2013; Steff, 2017].

In addition to boosting pre-existing neutralizing antibodies, another important element for the RSV candidate vaccine in older adults might be to boost or elicit RSV-specific T-cell responses. The use of an adjuvant may enable induction of CD4+ T-cells in addition to antibodies, leading to a stronger and persistent protection. Amongst the current GSK portfolio of adjuvants, AS01 has the potential to induce the targeted immune profile as it has been shown to improve antibody and T-cell response in older adults [Chlibek, 2013; Chlibek, 2014; Chlibek, 2016; Schwarz, 2018]. Based on the available evidence, AS01 would be expected to boost the CD4+ T-cell as well as B-cell memory responses.

The $AS01_E$ and $AS01_B$ adjuvants have been evaluated in several GSK candidate vaccines. As of 30 June 2017, over 35 000 participants have been vaccinated with at least one dose of an AS01-containing vaccine in completed clinical trials. The population vaccinated with an AS01-adjuvanted vaccine consists in over 12 700 infants and toddlers participating in Malaria trials and over 22 500 adults and older adults mainly coming from Zoster trials. Clinical data from the efficacy trials of the Herpes Zoster subunit vaccine (HZ/su) in adults aged 50 years or above and adults aged 70 years or above have demonstrated the added value of AS01-based adjuvants for older adults. HZ/su (glycoprotein E [gE]/$AS01_B$) is able to induce strong and persistent gE-specific antibody and CD4+ T-cell responses up to 9 years in a population known for diminished immune response (immune-senescence) [Chlibek, 2016; Pauksens, 2017]. The HZ/su (gE/$AS01_B$) vaccine is currently licensed in several countries, including the United States, Canada, the European Union, Japan and Australia.

1.2.2.2. Dose regimen

It is proposed to evaluate a 2-dose vaccination regimen with an interval of 2 months between doses. This is supported by available data from several clinical studies in GSK's Herpes Zoster and chronic obstructive pulmonary disease (COPD) vaccine development programs conducted with an adjuvanted protein in older adults.

In the Phase II study ZOSTER-003 (Herpes Zoster vaccine program), conducted in older adults aged 60 years and above, a statistically significant higher cellular immune response (based on frequency of gE-specific CD4+ T-cells) and humoral immune response was observed in all groups who received 2 doses of the adjuvanted gE (gE/$AS01_B$) vaccine (at 3 different gE dosage levels tested) compared to a single dose of the highest concentration of gE/$AS01_B$ tested [Chlibek, 2014]. Descriptive data for persistence over 3 years further support this observation, as the median gE-specific CD4+ T-cell frequencies and anti-gE antibody concentrations remained higher in the 2-dose group as compared to the 1-dose group [Chlibek, 2014].

Similarly, in the Phase I study NTHI-003 (COPD vaccine development program) in older adults aged 50 to 70 years, a second dose of any of the adjuvanted non-typeable *Haemophilus influenzae* protein vaccine formulations administered 2 months following the first dose, induced higher antibody concentrations and cellular immune response (based on the frequency of antigen-specific CD4+ T-cells) as compared to one dose [Leroux-Roels, 2016].

1.2.2.3. Staggered design and safety monitoring

As the RSVPreF3 antigen has not been administered to humans yet, this study will first evaluate the safety of 3 different dosages of RSVPreF3 (30, 60 and 120 μg, unadjuvanted) in healthy adults aged 18-40 years in Part A (~12 subjects/group) before proceeding with vaccination of the target population of older adults aged 60-80 years in Part B (~100 subjects/group). For each part, study holding rules have been defined.

After the first and second vaccine dose in Part A, safety evaluations will be performed by an Independent Data Monitoring Committee (IDMC) based on data collected up to 30 and 7 days post-vaccination, respectively, based on all subjects (~12 group). Only upon favorable outcome of the first IDMC evaluation, the vaccination in Part B of the study will be initiated. In this part, the safety and immunogenicity of 9 investigational RSV vaccine formulations (adjuvanted and unadjuvanted) will be evaluated in older adults aged 60-80 years. To ensure the safety of the study participants, Part B will follow a staggered enrolment with 2 steps. The IDMC evaluations will be based on data after each study vaccine administration in the first 100 study participants enrolled in Step 1 (i.e., the first 10 study participants per group). In addition, holding rules for the whole population will be applied.

Holding rules for Phase I studies will be applied. The IDMC may recommend to stop vaccination in all groups or only in a specific study group while proceeding with vaccination in the other groups.

For more detailed information on the staggered design, study holding rules and safety monitoring, refer to Sections 7.10 and 7.10.5 for details).

1.2.2.4. Study blinding

Given the difference in reconstitution and visual appearance of the investigational RSV vaccines, double blinding is not possible and the study will be conducted in an observer-blind manner for the vaccination phases (up to one month post-Dose 2) of both study parts.

A statistical analysis will be performed when primary and secondary endpoint data from vaccinated subjects up to one month post-Dose 2 in both study parts will be available. Given that summary results may unblind some specific subjects, the persistence phase of Part B (Epoch 003, see Section 3) will be considered as single-blind, with subjects remaining blinded up to study end. The investigators will not be provided with the individual data listings or with the randomization listings until study end (Visit 8 [Month 14]).

During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends. (Amended, 13 May 2020)

Please refer to the glossary of terms for the definition of observer-blind and single-blind.

1.2.2.5. Rationale for the use of placebo

As there is currently no licensed RSV vaccine available, a placebo group (receiving saline solution) will be used as control for the safety, reactogenicity and immunogenicity assessments in both study parts.

1.3. Benefit : Risk Assessment

In total, approximately 936 subjects in this study will be exposed to the investigational RSV vaccine, whereas approximately 112 subjects will receive placebo.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Risks, Contraindications and Warnings	Data/Rationale for Risk	Mitigation Strategy
All Study Vaccines		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Ruggerberg, 2007].	Anaphylaxis following vaccine administration is a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination center for at least 60 minutes after vaccination.
Syncope	Syncope (fainting) can occur following or even before any vaccination as a psychogenic response to the needle injection.	All subjects will remain under observation at the vaccination center for at least 60 minutes after vaccination.
Intramuscular (IM) injection	Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling.	All subjects will remain under observation at the vaccination center for at least 60 minutes after vaccination. Solicited local adverse events (AE) will be collected and reviewed up to Day 8.
RSVPreF3		
Due to the lack of experience in human subjects to date, there is currently not enough information available to identify the risks of AEs related to the administration of the RSVPreF3 investigational vaccine.		Any untoward symptoms experienced by the subject after receiving the vaccine should be reported to the investigator. The study will be conducted in a staggered manner with safety evaluations by an IDMC. Holding rules that have been established will be applied.
Adjuvant Systems		
Potential immune-mediated diseases (pIMDs) are a theoretical concern with adjuvanted vaccines.	There are no safety findings suggesting a causal link between pIMDs and AS01-containing vaccines [Stassijns, 2016].	During the informed consent process, the subjects enrolling in Part B will be informed of this potential risk and the need to attend the clinic if they are unwell. pIMD is an AE of specific interest and will be collected up to 12 months after administration of the last dose of study vaccine (see Section 7.1.5). The occurrence of pIMD cases will be described.
Study Procedures – Blood sampling		
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be taken.
Syncope	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle injection.	Subject Monitoring (Section 7.10) All subjects will remain under observation at the clinical center for at least 60 minutes after vaccination.
Nerve Injury	There is a possibility that in the process of collecting blood a nerve may be injured.	Procedure to be performed by qualified personnel.

1.3.2. Benefit Assessment

The subjects receiving investigational RSV vaccine may not directly benefit from this vaccination because vaccine efficacy has not been assessed yet and it is hence not known whether the investigational RSV vaccine is effective in protecting against RSV infection.

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

Another benefit for all study participants may include gaining of information about their general health status through the medical evaluations/assessments associated with this study (i.e., physical examination, blood testing [hematology and biochemistry data]).

1.3.3. Overall Benefit : Risk Conclusion

The investigational RSV vaccine is currently in an early stage of clinical development. Taking into account the measures to minimise the risk to subjects participating in this study, the potential risks are justified by the potential benefits linked to the development of this RSV vaccine.

2. OBJECTIVES

2.1. Primary objective

For Part A and Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

For Part A and Part B:

- To characterize the humoral immune responses (including dose-response) in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).
- To characterize the cell-mediated immune responses in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

For Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccines administered IM according to a 0, 2 month schedule, up to the end of follow-up (Month 14, Visit 8).
- To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

Refer to Section 10.2 for the definition of the secondary endpoints.

2.3. Tertiary objectives

For Part A and Part B:

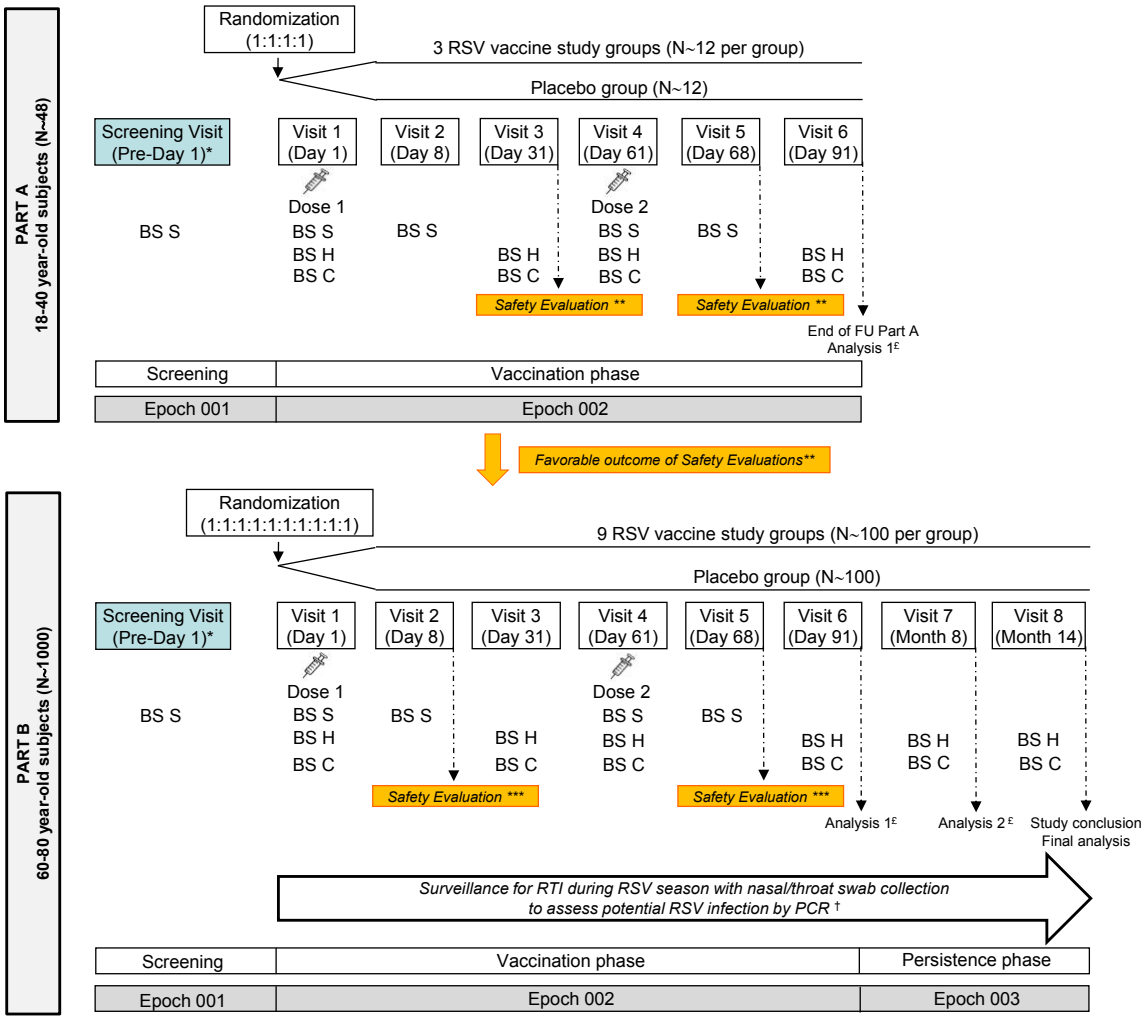
- To further characterize the cell-mediated immune responses to investigational RSV vaccine formulations.

For Part B:

- To further characterize immune responses to investigational RSV vaccine formulations.
- To characterize persistence of immune responses to the investigational RSV vaccine formulations at Month 8 (Visit 7) and Month 14 (Visit 8).
- To further evaluate the occurrence of RSV-associated RTI (including co-infections with other respiratory viruses) during the RSV seasons in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.
- To evaluate the occurrence of RSV-associated RTI during the RSV season using self-collected nasal swabs.

Refer to Section 10.3 for the definition of the tertiary endpoints.

3. STUDY DESIGN OVERVIEW



: Vaccination

BS S: Blood sample for safety (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
BS C: Blood sample for cell-mediated immune responses (for CD4+/CD8+ and/or memory B-cell testing)
FU: Follow-up; PCR: Polymerase Chain Reaction
* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.
** In Part A, a first IDMC evaluation of safety data up to Day 31 based on all subjects (~12 per group or at least 8 per group in case of slow recruitment, see Section 7.10.5) will be performed before proceeding with administration of Dose 2 in Part A and Dose 1 in Part B. A second IDMC evaluation will be performed based on safety data up to Day 68 for all subjects. Refer to Section 7.10 for details on the staggered design and safety evaluations.
*** In Part B, a third and fourth IDMC evaluation of safety data up to Day 8 and Day 68, respectively, for the first enrolled and vaccinated subjects (~10 per group or at least 8 per group in case of slow recruitment, see Section 7.10.5) will be performed. Additional IDMC evaluations will happen during the conduct of the study (see Section 7.10 for details on the staggered enrolment and safety evaluations).

† In case of RTI symptoms during the RSV seasons (approximately from October to March), the subject will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal swab and a throat swab at the site. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days; see Section 8).
£ Analysis 1 will be performed on all data collected up to Day 91 for at least primary and secondary endpoints based on both study parts (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). Analysis 2 will be performed when all safety data up to Month 8 (Visit 7) are available. The analyses will be based on data as clean as possible (refer to Section 10.12.1 for details on sequence of analyses).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct. ***Refer to Section 5.10 for study procedures to be considered during special circumstances (Amended, 13 May 2020).***

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-country study with 2 parts (i.e., Part A in young adults aged 18-40 years with 4 parallel groups and Part B in older adults aged 60-80 years with 10 parallel groups).
- **Duration of the study:**

  Approximately 3 months per subject in Part A:

  – Epoch 001: Screening Visit (Day -30 to -3)

  – Epoch 002: Primary (vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 6 (Day 91)

  Approximately 14 months per subject in Part B:

  – Epoch 001: Screening Visit (Day -30 to -3)

  – Epoch 002: Primary (vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 6 (Day 91)

  – Epoch 003: Follow-up (persistence phase) starting after Visit 6 (Day 91) and ending at Visit 8 (Month 14)
- **Primary Completion Date (PCD):** last visit of the vaccination phase in Part B (Visit 6 [Day 91]).

  Refer to glossary of terms for the definition of PCD.
- **End of Study (EoS):** Last testing results released of samples collected up to Visit 8 in Part B (Month 14) (for assays related to primary and secondary endpoints only).

  Refer to glossary of terms for the definition of EoS.
- **Treatment allocation:** Subjects will be randomized using a centralised randomization system on internet (SBIR) on Day 1.

  In Part A, the aim is to enrol approximately 48 subjects (~12 per group) aged 18-40 years. The randomization algorithm will use a minimisation procedure accounting for center and gender.

In Part B, the aim is to enrol approximately 700 subjects (~70 per group) aged 60-69 years and approximately 300 subjects (~30 per group) aged 70-80 years. The randomization algorithm will use a minimisation procedure accounting for age, center and gender in each step.

- **Study groups:**

  For the investigational RSV vaccines in Part A and Step 1 in Part B, the RSVPreF3 high-dose formulation containing 120 µg RSVPreF3 will be used to prepare the vaccines for all dose groups (i.e., 30 µg, 60 µg and 120 µg dose groups, see Table 2 and Table 3). For Step 2 in Part B, the RSVPreF3 low-dose and mid-dose formulations (containing 30 µg and 60 µg RSVPreF3, respectively) will be used for the groups receiving 30 µg and 60 µg of RSVPreF3, respectively, and the RSVPreF3 high-dose formulation will be used for the 120 µg dose groups (see Table 4). As the reconstitution methods for the vaccines administered to subjects enrolled in Step 1 and 2 of Part B will be different, separate study groups have been identified (referred to as B1 and B2). Throughout this document, the combined groups for Steps 1 and 2 are mentioned when referring to the number of groups in Part B (10 groups).

  In Part A:

  – **Group 30-PLAIN_A:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 30 µg RSVPreF3.

  – **Group 60-PLAIN_A:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 60 µg RSVPreF3.

  – **Group 120-PLAIN_A:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 120 µg RSVPreF3.

  – **Group Placebo_A:** subjects receiving 2 doses of placebo as control.

  In Part B (Steps 1 and 2):

  – **Groups 30-PLAIN_B1 and 30-PLAIN_B2:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 30 µg RSVPreF3.

  – **Groups 30-AS01E_B1 and 30-AS01E_B2:** subjects receiving 2 doses of the investigational RSV vaccine containing 30 µg RSVPreF3 adjuvanted with AS01E.

  – **Groups 30-AS01B_B1 and 30-AS01B_B2:** subjects receiving 2 doses of the investigational RSV vaccine containing 30 µg RSVPreF3 adjuvanted with AS01B.

  – **Groups 60-PLAIN_B1 and 60-PLAIN_B2:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 60 µg RSVPreF3.

  – **Groups 60-AS01E_B1 and 60-AS01E_B2:** subjects receiving 2 doses of the investigational RSV vaccine containing 60 µg RSVPreF3 adjuvanted with AS01E.

- **Groups 60-AS01B_B1 and 60-AS01B_B2:** subjects receiving 2 doses of the investigational RSV vaccine containing 60 µg RSVPreF3 adjuvanted with AS01B.
- **Groups 120-PLAIN_B1 and 120-PLAIN_B2:** subjects receiving 2 doses of unadjuvanted investigational RSV vaccine containing 120 µg RSVPreF3.
- **Groups 120-AS01E_B1 and 120-AS01E_*B2*:** subjects receiving 2 doses of the investigational RSV vaccine containing 120 µg RSVPreF3 adjuvanted with $AS01_E$ ***(Amended, 13 May 2020).***
- **Groups 120-AS01B_B1 and 120-AS01B_B2:** subjects receiving 2 doses of the investigational RSV vaccine containing 120 µg RSVPreF3 adjuvanted with $AS01_B$.
- **Groups Placebo_B1 and Placebo_B2:** subjects receiving 2 doses of placebo as control.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
Part A					
30-PLAIN_A	12	18 - 40 years	x	x	
60-PLAIN_A	12	18 - 40 years	x	x	
120-PLAIN_A	12	18 - 40 years	x	x	
Placebo_A	12	18 - 40 years	x	x	
Part B - Step 1					
30-PLAIN_B1	10	60 - 80 years	x	x	x
30-AS01E_B1	10	60 - 80 years	x	x	x
30-AS01B_B1	10	60 -80 years	x	x	x
60-PLAIN_B1	10	60 - 80 years	x	x	x
60-AS01E_B1	10	60 - 80 years	x	x	x
60-AS01B_B1	10	60 - 80 years	x	x	x
120-PLAIN_B1	10	60 - 80 years	x	x	x
120-AS01E_B1	10	60 - 80 years	x	x	x
120-AS01B_B1	10	60 - 80 years	x	x	x
Placebo_B1	10	60 - 80 years	x	x	x
Part B - Step 2					
30-PLAIN_B2	90	60 - 80 years	x	x	x
30-AS01E_B2	90	60 - 80 years	x	x	x
30-AS01B_B2	90	60 - 80 years	x	x	x
60-PLAIN_B2	90	60 - 80 years	x	x	x
60-AS01E_B2	90	60 - 80 years	x	x	x
60-AS01B_B2	90	60 - 80 years	x	x	x
120-PLAIN_B2	90	60 - 80 years	x	x	x
120-AS01E_B2	90	60 - 80 years	x	x	x
120-AS01B_B2	90	60 - 80 years	x	x	x
Placebo_B2	90	60 - 80 years	x	x	x

Table 2 Study groups and treatment foreseen in Part A

Treatment name	Vaccine/Product name	Study Groups			
		30-PLAIN_A	60-PLAIN_A	120-PLAIN_A	Placebo_A
30 µg RSVPreF3 plain	RSVPreF3 high dose	x			
	NaCl	x			
60 µg RSVPreF3 plain	RSVPreF3 high dose		x		
	NaCl		x		
120 µg RSVPreF3 plain	RSVPreF3 high dose			x	
	NaCl			x	
Placebo	NaCl				x

Table 3 Study groups and treatment foreseen in Part B - Step 1

Treatment name	Vaccine/ Product name	Study Groups									
		30-PLAIN_B1	30-AS01E_B1	30-AS01B_B1	60-PLAIN_B1	60-AS01E_B1	60-AS01B_B1	120-PLAIN_B1	120-AS01E_B1	120-AS01B_B1	Placebo_B1
30 µg RSVPreF3 plain	RSVPreF3 high dose	x									
	NaCl	x									
30 µg RSVPreF3/AS01E	RSVPreF3 high dose		x								
	AS01E		x								
30 µg RSVPreF3/AS01B	RSVPreF3 high dose			x							
	AS01B			x							
60 µg RSVPreF3 plain	RSVPreF3 high dose				x						
	NaCl				x						
60 µg RSVPreF3/AS01E	RSVPreF3 high dose					x					
	AS01E					x					
60 µg RSVPreF3/AS01B	RSVPreF3 high dose						x				
	AS01B						x				
120 µg RSVPreF3 plain	RSVPreF3 high dose							x			
	NaCl							x			
120 µg RSVPreF3/AS01E	RSVPreF3 high dose								x		
	AS01E								x		
120 µg RSVPreF3/AS01B	RSVPreF3 high dose									x	
	AS01B									x	
Placebo	NaCl										x

Table 4 Study groups and treatment foreseen in Part B - Step 2

Treatment name	Vaccine/ Product name	Study Groups									
		30-PLAIN_B2	30-AS01E_B2	30-AS01B_B2	60-PLAIN_B2	60-AS01E_B2	60-AS01B_B2	120-PLAIN_B2	120-AS01E_B2	120-AS01B_B2	Placebo_B2
30 µg RSVPreF3 plain	RSVPreF3 low dose	x									
	NaCl	x									
30 µg RSVPreF3/AS01E	RSVPreF3 low dose		x								
	AS01E		x								
30 µg RSVPreF3/AS01B	RSVPreF3 low dose			x							
	AS01B			x							
60 µg RSVPreF3 plain	RSVPreF3 mid dose				x						
	NaCl				x						
60 µg RSVPreF3/AS01E	RSVPreF3 mid dose					x					
	AS01E					x					
60 µg RSVPreF3/AS01B	RSVPreF3 mid dose						x				
	AS01B						x				
120 µg RSVPreF3 plain	RSVPreF3 high dose							x			
	NaCl							x			
120 µg RSVPreF3/AS01E	RSVPreF3 high dose								x		
	AS01E								x		
120 µg RSVPreF3/AS01B	RSVPreF3 high dose									x	
	AS01B									x	
Placebo	NaCl										x

- **Control:** placebo.
- **Vaccination schedule:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Blinding:** observer-blind.

  The vaccination phases of each study part (Epoch 002) will be observer-blind. A first statistical analysis will be performed on data available up to one month post-Dose 2 (Visit 6, Day 91) (see section 10.12.1 for details on the sequence of analyses). Given that summary safety results may unblind some specific subjects, the persistence phase of Part B (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Visit 8 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

  During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

  In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends. (Amended, 13 May 2020)

Table 5 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	N/A
Epoch 002	observer-blind
Epoch 003	single-blind

N/A: Not applicable

- **RTI surveillance in Part B:** Active and passive surveillance will only be carried out during RSV seasons (approximately from October to March) throughout the entire Part B of the study:
  - **Active surveillance:** study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience an RTI.
  - **Passive surveillance:** study participants are instructed to contact the investigator/study staff as soon as they experience an RTI.

  At the beginning of RSV seasons, study participants will be reminded of the start of the RTI surveillance.

- **Sampling schedule:**

  In Part A:

  – At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the electronic Case Report Form (eCRF). The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.

  – At Day 1 (Visit 1), a blood sample for cytomegalovirus (CMV) status determination will be drawn from all subjects.

  – **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

  – **Blood samples for humoral immunogenicity and cell-mediated immunity (CMI)** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).

  In Part B:

  – At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.

  – At Day 1 (Visit 1), a blood sample for CMV status determination will be drawn from all subjects.

  – **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects and on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

  – **Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91, Month 8 and ***from a subset at*** Month 14 (Visits 1, 3, 4, 6, 7 and 8). ***(Amended, 13 May 2020)***

  – **Nasal/throat swabs:** In case of RTI symptoms during the RSV season (approximately from October to March), the study participants will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal swab and a throat swab by qualified staff from the study team. The assessment visit should take place as

soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days; refer to Section 8 for further details).

- **Type of study:** self-contained.
- **Data collection:** eCRF. Solicited symptoms will be collected using an electronic subject Diary (eDiary). Unsolicited symptoms will be collected using a paper subject Diary.
- **Safety monitoring:** The study will be conducted in 2 parts with oversight by an IDMC. The investigator is not permitted to start vaccinating the subjects in the next step in each part until the Sponsor communicates the favorable outcome of the respective safety evaluations by the IDMC.
  - **Part A:** Approximately 48 young adults aged 18-40 years will be enrolled and vaccinated with the first dose. If the IDMC evaluation on data up to 30 days post Dose 1 is favorable, the Part A study participants will be vaccinated with the second dose and the vaccination in Part B of the study will be initiated.
  - **Part B:** This part will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. In Step 1, approximately 100 subjects will be enrolled and vaccinated. Safety evaluations based on unblinded data from those first 100 subjects will be performed by the IDMC to allow the start of Step 2. In Step 2, the remaining study participants (N≅900) will be enrolled and vaccinated.

  In total, 6 IDMC meetings for safety evaluation are foreseen in the vaccination phase of the study (Epoch 002), i.e., 2 meetings in Part A and 4 meetings in Part B.

  During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

  If any safety concern is identified by the investigator or the sponsor, *ad-hoc* safety evaluations by the IDMC may be performed.

  Interval for vaccination between study participants:

  Study participants enrolled in Part A and Step 1 of Part B should be vaccinated with an interval of at least 60 minutes between participants to allow efficient suspension of vaccination in case of any safety concern. This applies to first and second study vaccine doses. This safety measure is not applicable for study participants enrolled in Step 2 of Part B.

  Refer to Section 7.10 for details on the safety monitoring and holding rules.

4. STUDY COHORT

4.1. Number of subjects/centers

This will be a multicenter study planned to be conducted in multiple countries. A total of approximately 1048 participants are planned to be enrolled in this study, of whom 48 (approximately 12 in each group) in Part A and 1000 (approximately 100 in each group) in Part B. Refer to Section 10.4 for a detailed description of the criteria used in the estimation of sample size.

In the Part A, there will be 4 study groups, consisting of 3 groups receiving an investigational RSV vaccine formulation and one placebo group. The target is to enrol approximately 48 eligible participants (~12/group). Minimisation per gender and center will provide a good balance between the groups within each factor.

In the Part B, there will be 10 study groups, consisting of 9 groups receiving an investigational RSV vaccine formulation and one placebo group. The target is to enrol approximately 100 eligible participants in Step 1 (~10/group) and approximately 900 eligible participants in Step 2 (~90/group). Approximately 700 participants (~70 per group) aged 60-69 years and approximately 300 participants (~30 per group) aged 70-80 years will be enrolled. Minimisation per age, gender and center will provide a good balance between the groups within each factor in each step.

Overview of the recruitment plan

The study is planned to be conducted at sites in multiple countries.

In case a country would fall behind in subject recruitment (in a specific age group or overall), a redistribution of the enrolment target per country may be made to allow the other participating country(ies) to enrol additional participants in an effort to ensure full and timely enrolment of the overall targeted number of participants specified in this protocol. For more detailed information on the staggered enrolment, refer to Section 7.10.

The recruitment rate will be monitored and transfer of supplies will be tracked using SBIR. Monitoring visits frequency will be adapted to the pace of enrolment.

Vaccine doses will be distributed to each study site respecting the randomization block size.

Prior to Visit 1 (Day 1) in both study parts, a Screening Visit will be scheduled to screen potential study participants for eligibility. The purpose of the screening is to collect informed consent, check eligibility for study participation and collect a blood sample for eligibility evaluation.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the eDiaries, return for follow-up visits).
- Written informed consent obtained from the subject prior to performing any study specific procedure.

Specific inclusion criteria for Part A:

- A male or female between, and including, 18 and 40 years of age at the time of the first vaccination.

Specific inclusion criteria for Part B:

- A male or female between, and including, 60 and 80 years of age at the time of the first vaccination.
- Subjects with residence status allowing free mixing with general community or in an assisted-living facility that provides minimal assistance, such that the subject is primarily responsible for self-care and activities of daily living, may be enrolled.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity regulatory acceptability of the study, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked for all subjects at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make IM injection unsafe.
- Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 6 months prior to the first vaccine dose. For corticosteroids, this will mean prednisone (≥ 20 mg/day, or equivalent). Inhaled and topical steroids are allowed.
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab).
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of study vaccine administration, with the exception of inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each study vaccination.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.

- Hypersensitivity to latex.
- Serious or unstable chronic illness. Patients with chronic stable conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study.
- Any other condition (e.g. chronic obstructive pulmonary disease or severe respiratory condition) that, in the opinion of the investigator, might interfere with the evaluations required by the study.
- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

  For subjects with acute disease and/or fever at the time of enrolment/vaccination, Visit 1 may be re-scheduled within the allowed time-window.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by the investigator based on medical history, physical examination or laboratory screening tests.
- Hepatomegaly, right upper quadrant abdominal pain or tenderness.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential subject unable/unlikely to provide accurate safety reports.
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 2 years).
- Previous vaccination with an RSV vaccine.
- Lymphoproliferative disorder and malignancy within 5 years.
- Body mass index > 40 kg/m².
- Planned move to a location that will prohibit participating in the trial until study end.
- At screening: Hematology parameters (complete blood cell count [red blood cells, white blood cells], white blood cells differential count [lymphocytes, neutrophils and eosinophils], platelets count or hemoglobin level) and/or biochemistry parameters (creatinine, blood urea nitrogen or liver enzymes [alanine aminotransferase [ALT] or aspartate aminotransferase [AST]]) outside the normal laboratory ranges, unless the laboratory abnormalities are considered not clinically significant by the investigator.

Specific exclusion criteria for Part A:

- Pregnant or lactating female.
- Female subjects of childbearing potential, except if the subject:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

  Refer to glossary of terms for the definition of adequate contraception.

Specific exclusion criteria for Part B:

- Known previous administration of a vaccine containing MPL, QS-21 and/or *MF59* (e.g. GSK Biologicals' vaccine against human papillomavirus infection marketed as *Cervarix*, GSK Biologicals' Herpes Zoster vaccine marketed as *Shingrix*, an adjuvanted recombinant varicella zoster virus envelope gE subunit vaccine [HZ/su], or MF59 adjuvanted influenza vaccines [e.g. *Fluad*]).
- Planned administration of GSK Biologicals' Herpes Zoster vaccine marketed as *Shingrix* or an adjuvanted recombinant varicella zoster virus envelope gE subunit vaccine [HZ/su] within 180 days after the second dose of the study vaccine.
- Bedridden subjects.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for GCP, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable 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.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

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 and safety must be applied. For the duration of such special circumstances, additional measures may be implemented for enrolled participants. Refer to Section 5.10 for further details. (Amended, 13 May 2020).

5.2. Subject identification and randomization

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center.

5.2.2. Randomization of treatment

5.2.2.1. Randomization of supplies

The randomization of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centers /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multicenter study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 1048 eligible subjects who will be randomly assigned to the study groups in each study part as follows:

- In Part A, the target is to enrol approximately 48 eligible participants who will be randomly assigned to 4 study groups in a (1:1:1:1) ratio (approximately 12 subjects in each group).
- In Part B, the target is to enrol:
  - Approximately 100 eligible participants in Step 1 who will be randomly assigned to 10 study groups in a (1:1:1:1:1:1:1:1:1:1) ratio (approximately 10 subjects in each group);
  - Approximately 900 eligible participants in Step 2 who will be randomly assigned to 10 study groups in a (1:1:1:1:1:1:1:1:1:1) ratio (approximately 90 subjects in each group).

  The aim is to enrol approximately 700 participants (~70 per group) aged 60-69 years and approximately 300 participants (~30 per group) aged 70-80 years.

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The study part (Part A, Part B Step 1, Part B Step 2) will be used as stratification factor. For Part A, the randomization algorithm will use a minimisation procedure accounting for center and gender. For Part B, the randomization algorithm will use a minimisation procedure accounting for age, center and gender within each step (Step 1 and Step 2). Minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

During the vaccination phases of each study part (Epoch 002), data will be collected in an observer-blind manner. ***During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.***

In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends. (Amended, 13 May 2020)

By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety and reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

A first statistical analysis will be performed on primary and secondary endpoint data available up to one month post-Dose 2 (Visit 6, Day 91) (see Section 10.12.1 for details on the sequence of analyses). Given that summary safety results may unblind some specific subjects (e.g. an adverse event [AE] occurring only in a single group), anyone having access to this first analysis could become unblinded regarding that specific case. Therefore, the persistence phase of Part B (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Visit 8 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

The study will be conducted in 2 parts, i.e., Part A in young adults aged 18-40 years and Part B in older adults aged 60-80 years. Part B of the study will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects.

Study participants enrolled in Part A and Step 1 of Part B should be vaccinated with an interval of at least 60 minutes between participants to allow efficient suspension of vaccination in case of any safety concern. This applies to first and second study vaccine doses. This safety measure is not applicable for study participants enrolled in Step 2 of Part B.

All participants in each part and enrolment step will be closely observed for a minimum of 60 minutes after each vaccination.

Refer to Section 7.10 for information about the study holding rules, safety monitoring and safety evaluation by the IDMC.

5.5. Outline of study procedures

Table 6 List of study procedures for Part A

Epoch	*Screening (Epoch 001)*	*Vaccination phase (Epoch 002)*					
Type of contact	**screening visit** [1]	**visit 1**	**visit 2**	**visit 3**	**visit 4**	**visit 5**	**visit 6**
Time points		**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**
Sampling time points	**Pre-Day 1**	**Pre-Vacc**	**PI D8**	**PI D31**	**PI D61**	**PII D68**	**PII D91**
Informed consent	●						
Check inclusion/exclusion criteria	●	O					
Collect demographic data	O	●					
Medical history	O	●					
Vaccination history [2]	O	●					
Physical examination /Vital signs	O	●	O [3]	O [3]	O [3]	O [3]	O [3]
Check contraindications to vaccination		O			O		
Pre-vaccination body temperature		●			●		
Pregnancy test [4]	●	●			●		●
Vaccine							
Study group and treatment number allocation		O					
Treatment number allocation for subsequent doses					O		
Vaccine administration		●			●		
Recording of administered treatment number		●			●		
Laboratory assays							
Blood sampling for antibody determination (~20 mL)		●		●	●		●
Blood sampling for CMI response (~25 mL)		●		●	●		●
Blood sampling for hematology and biochemistry analysis (~5.5 mL)	● [1]	●	●		●	●	
Blood sampling for CMV status determination (~3.5 mL)		●					
Safety assessments							
Record any concomitant medications/vaccinations (as defined in Section 6.6)		●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●
Distribute and instruct subject on the use of eDiary devices for solicited AEs		O			O		
Return of eDiary devices							O
Distribution of paper diary cards for unsolicited AEs		O			O		
Return of paper diary cards			O	O		O	O

Epoch	***Screening (Epoch 001)***	***Vaccination phase (Epoch 002)***					
Type of contact	**screening visit [1]**	**visit 1**	**visit 2**	**visit 3**	**visit 4**	**visit 5**	**visit 6**
Time points		**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**
Sampling time points	**Pre-Day 1**	**Pre-Vacc**	**PI D8**	**PI D31**	**PI D61**	**PII D68**	**PII D91**
Recording of unsolicited AEs within 30 days post-vaccination (Days 1-30)		●	●	●	●	●	●
Recording of SAEs		●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●
Recording of pregnancy and pregnancy outcomes	O	●	●	●	●	●	●
Recording of AEs/SAEs leading to withdrawal from the study		●	●	●	●	●	●
Screening conclusion	●						
End of follow-up for Part A							●

Pre-Vacc: pre-vaccination; PI: Post-Dose 1; PII: Post-Dose 2; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X; D: Day

● is used to indicate a study procedure that requires documentation in the individual eCRF or on web-portal.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF or on web-portal.

[1] In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

[2] Any vaccination administered up to 5 years before administration of the first dose of study vaccine should be recorded in the eCRF.

[3] If deemed necessary by the investigator

[4] Only for women of childbearing potential. The results must be obtained and be confirmed negative before vaccination. A serum pregnancy test instead of a urine pregnancy test should only be considered if required by local or ethics committee regulations.

Table 7 List of study procedures for Part B

Epoch	*Screening (Epoch 001)*	*Vaccination phase (Epoch 002)*						*Persistence phase (Epoch 003)*		*RTI surveillance*	
Type of contact	**screening visit** [1]	**visit 1**	**visit 2**	**visit 3**	**visit 4**	**visit 5**	**visit 6**	**visit 7**	**visit 8**	**Regular contact for RTI surveillance**	**Assessment visit for potential RSV-RTI**
Time points		**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91**	**Month 8**	**Month 14**		
Sampling time points	**Pre-Day 1**	**Pre-Vacc**	**PI D8**	**PI D31**	**PI D61**	**PII D68**	**PII D91**	**PII M8**	**PII M14**		
Informed consent	●										
Check inclusion/exclusion criteria	●	O									
Collect demographic data	O	●									
Medical history	O	●									
Vaccination history [2]	O	●									
Physical examination /Vital signs	O	●	O [3]	O [3]	O [3]	O [3]	O [3]	O [3]	O [3]		●
Check contraindications to vaccination		O			O						
Pre-vaccination body temperature		●			●						
Vaccine											
Study group and treatment number allocation		O									
Treatment number allocation for subsequent doses					O						
Vaccine administration		●			●						
Recording of administered treatment number		●			●						
Laboratory assays											
Blood sampling for antibody determination (~20 mL)		●		●	●		●	●	●[4]		
Blood sampling for CMI response (~25 mL)		●		●	●		●	●	●[4]		
Blood sampling for hematology and biochemistry analysis (~5.5 mL)	● [1]	●	●		●	●					
Blood sampling for CMV status determination (~3.5 mL)		●									
RTI surveillance											
Instruct/remind subjects of RTI surveillance during RSV seasons										●	
Distribution of material for nasal swab collection at home (including instructions)		O									
Recording of nasal swab collection at home											●

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Epoch	*Screening (Epoch 001)*	*Vaccination phase (Epoch 002)*						*Persistence phase (Epoch 003)*		*RTI surveillance*	
Type of contact	screening visit [1]	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	Regular contact for RTI surveillance	Assessment visit for potential RSV-RTI
Time points		Day 1	Day 8	Day 31	Day 61	Day 68	Day 91	Month 8	Month 14		
Sampling time points	Pre-Day 1	Pre-Vacc	PI D8	PI D31	PI D61	PII D68	PII D91	PII M8	PII M14		
Nasal/throat swab sampling											●
Documentation of symptoms and signs of RTI											●
Safety assessments											
Record any concomitant medications/vaccinations (as defined in Section 6.6)		●	●	●	●	●	●	●	●		●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●		●
Distribute and instruct subject on the use of eDiary devices for solicited AEs		O			O						
Return of eDiary devices							O				
Distribution of paper diary cards for unsolicited AEs		O			O						
Return of paper diary cards			O	O		O	O				
Recording of unsolicited AEs within 30 days post-vaccination (Days 1-30)		●	●	●	●	●	●				
Recording of SAEs and pIMDs		●	●	●	●	●	●	●	●		●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●		●
Recording of AEs/SAEs leading to withdrawal from the study		●	●	●	●	●	●	●	●		●
Screening conclusion	●										
Study conclusion									●		

Note: The double-line borders following Day 91 and Month 8 indicate the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to these time points.

Pre-Vacc: pre-vaccination; PI: Post-Dose 1; PII: Post-Dose 2; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X; PII MX: Post-Dose 2 Study Month X; D: Day; M: Month

● is used to indicate a study procedure that requires documentation in the individual eCRF or on web-portal.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF or on web-portal.

[1] In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

[2] Any vaccination administered up to 5 years before administration of the first dose of study vaccine should be recorded in the eCRF.

[3] If deemed necessary by the investigator

[4] At Visit 8, blood samples for antibody and CMI determination will be collected from all subjects in part B1; and from a subset of subjects in part B2, who received a selected level of antigen dose and Placebo.

Refer to Section 5.10 for changes to study procedures to be considered during special circumstances (Amended, 13 May 2020).

Time intervals between visits related to study procedures performed on subjects participating in the study are presented in Table 8.

Table 8 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Part A		
screening visit → visit 1	3 - 30 days*	
visit 1 → visit 2	7 days	7 - 10 days
visit 1 → visit 3	30 days	30 - 37 days
visit 1 → visit 4	60 days	55 - 80 days
visit 4 → visit 5	7 days	7 - 10 days
visit 4 → visit 6	30 days	30 - 37 days
Part B		
screening visit → visit 1	3 - 30 days*	
visit 1 → visit 2	7 days	7 - 10 days
visit 1 → visit 3	30 days	30 - 37 days
visit 1 → visit 4	60 days	55 - 75 days
visit 4 → visit 5	7 days	7 - 10 days
visit 4 → visit 6	30 days	30 - 37 days
visit 4 → visit 7	180 days	170 - 190 days
visit 4 → visit 8	365 days	350 - 395 days

Grey shading indicates visit intervals that will be used to determine a subject's evaluability for the Per Protocol analysis (see Section 10.5.2).

* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

5.6. Detailed description of study procedures applicable for both study parts

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. In addition, the signed informed consent of the designate must be obtained, in case a designate is assigned by the subject. Refer to Section 5.1 for the requirements on how to obtain informed consent.

5.6.2. Screening procedures to check subject eligibility

5.6.2.1. Check inclusion and exclusion criteria

At the Screening Visit, the investigator will confirm strict adherence to all inclusion/exclusion criteria to ensure subjects are qualified for enrolment into the study, as described in Sections 4.2 and 4.3.

5.6.2.2. Collect demographic data, medical history, vaccination history and perform physical examination

The investigator will obtain the following information at the Screening Visit to confirm subject eligibility before enrolment: demographic data (such as age, gender, race and ethnicity), medical history and vaccination history. The investigator will also perform a physical examination of the subject, including assessment of oral body temperature and resting vital signs: systolic/diastolic blood pressure, pulse oximetry, heart rate and respiratory rate after at least 10 minutes of rest.

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

These procedures at the Screening Visit do not need to be recorded into the eCRF.

5.6.2.3. Blood sampling for eligibility assessment

At the Screening Visit, a blood sample for eligibility assessment will be drawn from all subjects.

In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.

5.6.2.4. Screening conclusion

Complete the Screening Conclusion screen in the eCRF, including the reason for screening failure, if applicable.

5.6.3. Procedures during the vaccination phases (Parts A and B) and/or persistence phase (Part B)

5.6.3.1. Check inclusion and exclusion criteria

Before randomization, the investigator should confirm strict adherence to all inclusion/exclusion criteria to ensure subjects are still qualified as described in Sections 4.2 and 4.3. This does not need to be recorded in the subject's eCRF.

5.6.3.2. Collect demographic data

Record demographic data such as age, gender, race and ethnicity in the subject's eCRF.

5.6.3.3. Medical history

Obtain the subject's medical history by interview and/or review the subject's medical records. Any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination should be recorded in the eCRF.

5.6.3.4. Vaccination history

Obtain the subject's vaccination history by interview and/or review the subject's vaccination records prior to the first study vaccination. Any vaccination administered up to 5 years before administration of the first dose of study vaccine should be recorded in the eCRF.

5.6.3.5. Physical examination

Perform a physical examination of the subject, including assessment of resting vital signs: systolic/diastolic blood pressure, pulse oximetry, heart rate and respiratory rate after at least 10 minutes of rest.

Physical examination at each study visit subsequent to the first vaccination visit will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

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

In addition, during the assessment visit for potential RSV-RTI, the investigator/study staff will evaluate the clinical signs and symptoms of the RTI and measure the subject's resting vital signs (systolic/diastolic blood pressure, pulse oximetry, heart rate, respiratory rate after at least 10 minutes of rest) and temperature (refer to Section 8.3 for the list of symptoms to be recorded).

5.6.3.6. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 for more details.

5.6.3.7. Assess pre-vaccination body temperature

The body temperature of each subjects needs to be measured prior to any study vaccine administration. The preferred location for measuring temperature in this study will be the oral cavity. If the subject has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 8).

5.6.3.8. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.6.3.9. Study vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered IM in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 8).
- Study participants enrolled in Part A and Step 1 of Part B should be vaccinated with an interval of at least 60 minutes between participants to allow efficient suspension of vaccination in case of any safety concern. This applies to first and second study vaccine doses. This safety measure is not applicable for study participants enrolled in Step 2 of Part B.

All subjects in each part and enrolment step will be observed closely for at least 60 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.3.10. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.3.11. Blood sampling for safety or immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures. Refer to the SPM for more details.

- A total volume of approximately 5.5 mL of blood should be drawn from all subjects for hematology and biochemistry analysis at each pre-defined time point. At Visit 1, an additional volume of approximately 3.5 mL should be drawn from all subjects for cytomegalovirus (CMV) status testing. After centrifugation, serum samples should be kept at room temperature (20 to 25°C/68 to 77°F) until shipment.
- A volume of approximately 20 mL of whole blood (to provide ~6.6 mL of serum) should be drawn from subjects for analysis of the humoral immune response at each pre-defined time point. After centrifugation, serum samples should be kept at -20°C/ –4°F or below until shipment.
- A volume of approximately 25 mL of whole blood should be drawn from subjects for analysis of the CMI response at each pre-defined time point. The blood should be stored at the investigator's site at room temperature. Samples will be shipped at room temperature (15 to 25°C/(59 to 77°F) to the designated laboratory for cell separation to be started within 24 hours.

- The overall volume of blood that will be collected from each subject during the entire duration of each study part is approximately 210 mL for Part A and approximately 300 mL for Part B ***(at Visit 8 blood will be collected from a subset of subjects)(Amended, 13 May 2020)***

5.6.3.12. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

5.6.3.13. Distribution of eDiary devices

- Subject eDiary assignment and use:
  - eDiaries will be distributed at Visit 1 for the collection of the body temperature and local and general solicited symptoms after each vaccination. They will be returned at the end of the unsolicited follow-up period after Dose 2 (at Visit 6 [Day 91]). Refer to Section 7.1.3 for guidelines.
  - Each subject will be shown how to use the device – this will include how to access the eDiary, performing test data entry on sample questions, and how to charge and store the device.
  - The subject will self-select a numeric access code secret to himself/herself. The same individual should make the assessments and complete the Subject eDiary throughout the course of the study.
  - The subject will select an alarm time that suits his/her daily routines whilst ensuring compliance with protocol requirements.
- Subject eDiary instructions provided by the site must ensure that the subject understands the following:
  - Timely completion of the Subject eDiary on a daily basis is a critical component to study participation.
  - The Subject eDiary will allow certain time windows for completion of each day's observations.
  - The Subject eDiary employs the use of audio-visual alarms to ensure timely completion of data entry.
  - The trained and assigned user of the Subject eDiary must not share access codes with anyone.
  - A helpdesk will be provisioned for users of Subject eDiary in case of technical issues, though it must be stressed that the helpdesk is not a replacement for normal medical care and no medical issues can be discussed with the agents.

– The Subject eDiary itself must never be considered a substitute for direct medical care and any concerns must be communicated to site staff as soon as possible.

5.6.3.14. Distribution of paper diary cards

Paper diary cards will be distributed at each vaccination visit for the subjects to note down any unsolicited symptom (i.e., any symptom not reported as solicited and already captured in the eDiary) they may have experienced as well as any medication taken in the 30-day period following each vaccination. Refer to Section 7.1.3 for guidelines.

5.6.3.15. Recording of AEs and SAEs

Solicited AEs will be recorded by the subjects in the eDiaries.

Non-serious unsolicited AEs will be recorded by the investigator in the Non-Serious Adverse Event section of the eCRF.

Any serious adverse event (SAE, solicited or unsolicited) will be recorded by the investigator in the Expedited Adverse Event report in the eCRF.

Refer to Section 7.3 for the detailed procedures for the investigator to record AEs and SAEs. Refer to Section 7.4 for guidelines and how to report SAE reports to GSK Biologicals.

5.6.3.16. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness.
- complete the Study Conclusion screen in the eCRF.

5.7. Detailed description of study procedures applicable for Part A only

5.7.1. Pregnancy test

Female subjects of childbearing potential are to have a pregnancy test at the Screening Visit, prior to any study vaccine administration (at Visits 1 and 4) and at the end of the study (Visit 6). The study vaccine may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.7.2. Recording of pregnancies

Refer to Section 7.3 for procedures for the investigator to record pregnancies. Refer to Section 7.4 for guidelines and how to report pregnancy reports to GSK Biologicals.

5.8. Detailed description of study procedures applicable for Part B only

5.8.1. Surveillance for RSV-RTI and nasal/throat swab sampling

Active and passive surveillance for RTI will be carried out during the RSV season period approximately from October to March throughout the entire duration of Part B of the study, i.e., from Visit 1 (after Dose 1) until the end of the study (Visit 8 [Month 14]).

- **Active Surveillance:** Study participants will be contacted by the investigator/study staff every 2 weeks to identify if they have experienced RTI symptoms (e.g., cough, runny nose, fever or difficulty to breath).
- **Passive surveillance (spontaneous referral):**
  - Subjects will be instructed to contact spontaneously the investigator/site staff and as soon as possible in case of RTI symptoms (e.g., cough, runny nose, fever or difficulty to breath) during the RSV season.
  - At each study visit during the RSV season period, subjects should be reminded to contact the investigator/study staff in case of RTI symptoms (e.g., cough, runny nose, fever or difficulty to breath).

In case of at least 3 RTI symptoms reported by the subject (refer to Section 8.3 for the list of symptoms):

- The subject will be asked to collect a nasal swab at home within 48 hours after the start of symptoms and contact the investigator/study staff.
- The self-collected nasal swab should be returned to the site staff. Refer to the SPM for details.
- The investigator/study staff will schedule an assessment visit for nasal and throat swab specimen collection by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).
- The swab samples will allow to assess the potential RSV infection by quantitative PCR at a sponsor or sponsor-designated laboratory. Episodes should be treated accordingly to local standard of care.
- In the event that it is not possible to schedule an assessment visit, the assessment visit page of the eCRF should be filled in as completely as possible using available medical records. Refer to Section 8 for further details on RTI surveillance during Part B.

Refer to the SPM for more details about nasal/throat swab sampling.

5.8.2. Recording of potential immune-mediated diseases (pIMDs)

PIMDs will be recorded by the investigator in the Expedited Adverse Event report in the eCRF.

Refer to Section 7.3 for the detailed procedures for the investigator to record pIMDs. Refer to Section 7.4.5 for guidelines and how to report pIMD reports to GSK Biologicals.

5.9. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment). ***Refer to Section 5.10 for measures for biological samples collection that may be implemented during special circumstances (Amended, 13 May 2020).***

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.9.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.9.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 10.5 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.9.2. Biological samples

Table 9 Biological samples

Sample type	Timepoint	Subset*	Quantity	Unit
Part A				
Blood for humoral immune response	visit 1 (Pre-Vacc) visit 3 (PI D31) visit 4 (PI D61) visit 6 (PII D91)	All enrolled subjects	~20	mL
Blood for CMI	visit 1 (Pre-Vacc) visit 3 (PI D31) visit 4 (PI D61) visit 6 (PII D91)	All enrolled subjects	~25	mL
Blood for hematology/biochemistry	screening (Pre-Day 1) visit 1 (Pre-Vacc) visit 2 (PI D8) visit 4 (PI D61) visit 5 (PII D68)	All screened subjects All enrolled subjects	~5.5	mL
Blood for serological status to CMV	visit 1 (Pre-Vacc)	All enrolled subjects	~3.5	mL
Urine**	screening (Pre-Day 1) visit 1 (Pre-Vacc) visit 4 (PI D61) visit 6 (PII D91)	All screened female subjects All enrolled female subjects	-	-
Total quantity of blood for each subject in Part A			**~ 211**	**mL**
Part B				
Blood for humoral immune response	visit 1 (Pre-Vacc) visit 3 (PI D31) visit 4 (PI D61) visit 6 (PII D91) visit 7 (PII M8) visit 8 (PII M14)	All enrolled subjects***	~20	mL
Blood for CMI	visit 1 (Pre-Vacc) visit 3 (PI D31) visit 4 (PI D61) visit 6 (PII D91) visit 7 (PII M8) visit 8 (PII M14)	All enrolled subjects***	~25	mL
Blood for hematology/biochemistry	screening (Pre-Day 1) visit 1 (Pre-Vacc) visit 2 (PI D8) visit 4 (PI D61) visit 5 (PII D68)	All screened subjects All enrolled subjects	~5.5	mL
Blood for serological status to CMV	visit 1 (Pre-Vacc)	All enrolled subjects	~3.5	mL
Nasal swab specimen collected by subject at home	-	Event-driven	-	-
Nasal/throat swab specimen collected by qualified staff	Assessment visit for potential RSV-RTI	Event-driven	-	-
Total quantity of blood for each subject in Part B			**~ 301**	**mL**

* Refer to Section 5.9.4.1 for a description of the subsets that will be used for testing of RSVPreF3 ***RSB1*** specific antibodies, CD4+/CD8+ CMI and memory B-cells at specific time points in Part B.

** A serum pregnancy test instead of a urine pregnancy test should only be considered if required by local or ethics committee regulations.

*** ***At Visit 8, blood samples for humoral and CMI determination will be collected from all subjects in part B1; and from a subset of subjects in part B2, who received a selected level of antigen dose and Placebo.***
See Section 5.10 for changes to study procedures to be considered during special circumstances. (Amended, 13 May 2020)

5.9.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

RSV humoral immune responses

Serological assays for the determination of functional antibodies against RSV-A and B will be performed by neutralization assays. Further characterization of the humoral immune response will be performed by use of enzyme-linked immunosorbent assays (ELISAs), including measurement of IgG antibodies binding to the RSVPreF3 protein and antibodies competing with monoclonal antibodies specific for binding to ***RSB1 site*** on RSVPreF3 (see Table 10). ***(Amended, 13 May 2020)***

The assays will be performed at a GSK Biologicals' laboratory or in a laboratory designated by GSK Biologicals.

Table 10 Humoral Immunity (Antibody determination) *(Amended, 13 May 2020)*

System	Component	Method	Kit / Manufacturer	Unit	Cut-off[§]	Laboratory
Serum	Respiratory Syncytial Virus A Ab	NEUTRALIZATION	In-house	ED60	18	GSK Biologicals* or NÉOMED-LABS
Serum	Respiratory Syncytial Virus B Ab	NEUTRALIZATION	In-house	ED60	***30***	GSK Biologicals* or NÉOMED-LABS
Serum	RSVPreF3-specific IgG antibody concentrations	ELISA	In house at Neomed Labs	ELU/mL	***25***	Neomed Labs
Serum	RSVPreF3 ***RSB1*** specific Ab	Competition ELISA	In-house	µg/mL	***2.11***	GSK Biologicals* or NÉOMED-LABS

Ab: antibody; ELISA: enzyme-linked immunosorbent assay; RSV: respiratory syncytial virus;
ED60: Estimated Dose: serum dilution giving a 60% reduction of the signal compared to a control without serum
* GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium;Marburg, Germany.

RSV cell-mediated immunity

Evaluation of the CD4+ and CD8+ T-cell responses will be performed by use of an Intracellular Cytokine Staining (ICS) assay performed on peripheral blood mononuclear cells (PBMC) samples at GSK Biologicals' laboratory or in a laboratory designated by GSK Biologicals (see Table 11). Evaluation of B memory cells will be performed by ELISpot.

Table 11 Cell-mediated Immunity (CMI)

System	Component	Challenge	Method	Unit	Laboratory
PBMC	IL-2, CD40L, 4-1BB, TNF-α, IFN-γ, IL-13, IL-17 secreting CD4+ and CD8+ T-cells	Peptide pool covering RSVPreF3	ICS	Events/10^6 cells	GSK Biologicals* or designated laboratory
PBMC	B-cell memory quantification	RSVPreF3	ELISPOT	Frequency of RSVPreF3-specific memory B-cells/10^6 B-cells	GSK Biologicals* or designated laboratory

PBMC: peripheral blood mononuclear cells; ICS: Intracellular cytokine staining
CD40L: cluster of differentiation 40 ligand; IFN-γ: interferon gamma, IL (IL-2; IL-13; IL-17): interleukin;
TNF-α: tumor necrosis factor alpha; 41BB (CD137)
* GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Hematology and biochemistry

Hematology and biochemistry assays for safety assessment will be performed in a central laboratory (see Table 12).

Table 12 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory
Whole blood	Hematology	Leukocytes (White Blood Cells)	As per central laboratory procedure	Quantitative	Q^2 Solutions
		Neutrophils*			
		Lymphocytes*			
		Basophils*			
		Monocytes*			
		Eosinophils*			
		Hemoglobin			
		Platelets			
		Erythrocytes (Red Blood Cells)			
Serum	Biochemistry	Alanine Aminotransferase (ALT)			
		Aspartate Aminotransferase (AST)			
		Creatinine			
		Blood Urea Nitrogen (BUN)			
		Uric Acid			

*For White Blood Cell (WBC) differential count.
**Grading of laboratory parameters will be based on the Food and Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to APPENDIX C). Basophils, monocytes, erythrocytes and uric acid are not included in the FDA Toxicity Grading Scale and will not be graded.

RSV molecular biology

For identified RTI cases under active or passive surveillance, the potential RSV infection will be assessed by quantitative reverse transcription PCR (qRT-PCR) testing of nasal/throat swab specimen (see Table 13). Swab samples that are positive by RSV qRT-PCR will be tested by a multiplex PCR (panel of viruses) for detection of potential viral co-infection. Further assessment of samples negative by RSV qRT-PCR may be performed with multiplex PCR if deemed necessary.

Table 13 Molecular Biology (PCR tests)

Component	Kit / Manufacturer	Method	Unit	Laboratory
System: Nasal/throat swab specimen				
Respiratory Syncytial Virus A RNA Respiratory Syncytial Virus B RNA	In-house	Quantitative RT-PCR	Copies/ml	GSK Biologicals* or designated laboratory
Influenza A virus (Flu A) Influenza B virus (Flu B) Human respiratory syncytial virus A (RSV A) Human respiratory syncytial virus B (RSV B) Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3) Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09) Human adenovirus (AdV) Human metapneumovirus (hMPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus 1/2/3/4 (HBoV) Human rhinovirus A/B/C (HRV) Human coronavirus 229E (229E) Human coronavirus NL63 (NL63) Human coronavirus OC43 (OC43)	Allplex Respiratory Panel or alternative	Multiplex PCR	Qualitative assay (positive/negative)	GSK Biologicals* or designated laboratory

Quantitative RT-PCR: quantitative reverse transcription polymerase chain reaction; RSV: respiratory syncytial virus
* GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Additional testing on blood or nasal/throat swab samples

Additional testing on serum and frozen PBMC samples to characterise the immune response to RSV/to the investigational RSV vaccine/vaccine components may be performed if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Additional viral/bacterial diagnosis testing on the nasal/throat swabs, such as (but not limited to) multiplex PCR, sequencing and/or high-throughput sequencing, may be done, if deemed necessary for accurate interpretation of the data and/or should such assays become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Additional testing may include, but is not limited to, the following:

- Further characterisation of the pathogens detected in the nasal/throat swabs (e.g. genotyping, strain identification).
- Further characterization of the immune response directed against different epitopes of RSV F proteins.

- Further characterization of the immune response by evaluation of cross-reactive neutralizing antibodies to human metapneumovirus (hMPV).
- Characterisation of the impact of vaccination on possible new immunological markers for protection (e.g. antibody affinity/avidity, ADCC).
- Host transcriptome signature: evaluation of mRNA and/or microRNA signatures by microarray and/or RNA sequencing.
- Translational research using next generation technologies.

Additional exploratory testing on the vaccine formulations and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals. These assays may not be represented in the objectives/endpoints of the study protocol and may be described in ancillary study protocol(s), as needed.

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

5.9.4. Biological samples evaluation

For blood sample collection, the following ranking applies:

1. Sample for hematology/biochemistry testing,
2. Sample for serological status to CMV testing (at Visit 1),
3. Sample for humoral immune responses,
4. Sample for CMI responses.

5.9.4.1. Immunological read-outs *(Amended, 13 May 2020)*

Testing of RSVPreF3 IgG antibodies will be performed on blood samples from all subjects, in both Part A and Part B, ***except at Month 14 (Visit 8)***.

Testing of RSV-A neutralizing antibodies will be performed on blood samples from all subjects, in both Part A and Part B, except at Month 8 (Visit 7) and Month 14 (Visit 8).

Testing of RSV-B neutralizing antibodies will be performed on blood samples from all subjects in Part B.

Testing of RSVPreF3 ***RSB1*** specific antibodies will be performed on blood samples from a subset of subjects ***at Day 31 or Day 91*** in Part B who received the selected vaccine formulation and placebo (N≅200).

Testing of CD4+/CD8+ CMI will be performed on blood samples from all subjects in both Part A and Part B, ***except at Month 8 (Visit 7) and Month 14 (Visit 8)***.

At Month 8 (Visit 7) blood sample testing for humoral response pertaining to RSV-A neutralizing antibodies and CMI response will be performed for all subjects in Part B1; and for a subset of subjects in Part B2, who received a selected level of antigen dose and Placebo (N≅460). Blood sample testing pertaining to the RSVPreF3 IgG antibodies will be performed for all subjects at Month 8 (Visit 7).

At Month 14 (Visit 8) humoral and CMI response testing will be performed for all subjects in Part B1; and for a subset of subjects in Part B2, who received a selected level of antigen dose and Placebo (N≅***460***)***.***

Testing of memory B-cells will be performed on blood samples from a subset of subjects in Part B who received the selected level of antigen dose or placebo (N≅400).

Testing of CMV IgG antibodies will be performed on blood samples from all subjects at Visit 1 (Day 1), in both Part A and Part B.

In case of insufficient blood sample volume to perform assays for all immunological read-out components, the samples will be analysed according to priority ranking provided in Table 14 for Part A and Table 15 for Part B.

Table 14 Immunological read-outs in Part A

Blood sampling time point		Sub-cohort	No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point				
Humoral immunity (on serum samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 48	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 3 (Day 31)	PI D31	All subjects	~ 48	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 4 (Day 61)	PI D61	All subjects	~ 48	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 6 (Day 91)	PII D91	All subjects	~ 48	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
Cell-mediated immunity (on PBMC samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 48	CD4+/CD8+	-
visit 3 (Day 31)	PI D31	All subjects	~ 48	CD4+/CD8+	-
visit 4 (Day 61)	PI D61	All subjects	~ 48	CD4+/CD8+	-
visit 6 (Day 91)	PII D91	All subjects	~ 48	CD4+/CD8+	-

Pre-Vacc: Pre-vaccination; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X; M: Month
PBMC: Peripheral Blood Mononuclear Cells

Table 15 Immunological read-outs in Part B *(Amended, 13 May 2020)*

Blood sampling time point*		Sub-cohort	No. subjects	Component	Components priority rank
Type of contact and time point	**Sampling time point**				
Humoral immunity (on serum samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3
		Subset	~ 200	RSVPreF3 ***RSB1*** specific antibody	4
visit 3 (Day 31)	PI D31	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 4 (Day 61)	PI D61	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 6 (Day 91)	PII D91	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3
		Subset	~ 200	RSVPreF3 ***RSB1*** specific antibody	4
visit 7 (Month 8)**	PII M8	***Subset***	~ ***460***	RSV-A neutralizing antibody	1
		All subjects	~1000	Anti-RSVPreF3-specific IgG antibody	2
visit 8 (Month 14)***	PII M14	***Subset***	~ ***460***	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
Cell-mediated immunity (on PBMC samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 3 (Day 31)	PI D31	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 4 (Day 61)	PI D61	All subjects	~ 1000	CD4+/CD8+	-
visit 6 (Day 91)	PII D91	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 7 (Month 8)**	PII M8	***Subset***	~ ***460***	CD4+/CD8+	-
visit 8 (Month 14)***	PII M14	Subset	~ ***460***	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2

Pre-Vacc: Pre-vaccination; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X; M: Month
PBMC: Peripheral Blood Mononuclear Cells

* Testing of additional time points for RSVPreF3 ***RSB1*** specific antibodies, RSV-B neutralizing antibodies and memory B-cells might be performed, should the results indicate that further investigation of the immune response is necessary.

***** At Visit 7, blood samples for RSV-A neutralizing antibody determination, and CMI determination will be tested from a subset of subjects (all subjects in part B1; and a subset of subjects in part B2, who received a selected level of antigen dose and Placebo).***

****** At Visit 8, blood samples for antibody and CMI determination will be collected and tested from all subjects in part B1; and from a subset of subjects in part B2, who received a selected level of antigen dose and Placebo.***

5.9.4.2. Haematology/Blood Chemistry and CMV serology

Table 16 Hematology and biochemistry read-outs and CMV serology testing

Blood sampling time point		Sub-cohort	No. subjects	Component
Type of contact and time point	Sampling time point			
Part A				
screening visit*	Pre-Day 1	All screened subjects	≥ 48	Hematology: leukocytes, neutrophils, lymphocytes, basophils, monocytes, eosinophils, hemoglobin, platelets, erythrocytes Biochemistry: ALT, AST, creatinine, BUN, uric acid
visit 1 (Day 1) visit 2 (Day 8) visit 4 (Day 61) visit 5 (Day 68)	Pre-Vacc PI D8 PI D61 PII D68	All enrolled subjects	~ 48	
visit 1 (Day 1)	Pre-Vacc	All enrolled subjects	~ 48	Anti-CMV IgG antibody
Part B				
screening visit*	Pre-Day 1	All screened subjects	≥ 48	Hematology: leukocytes, neutrophils, lymphocytes, basophils, monocytes, eosinophils, hemoglobin, platelets, erythrocytes Biochemistry: ALT, AST, creatinine, BUN, uric acid
visit 1 (Day 1) visit 2 (Day 8) visit 4 (Day 61) visit 5 (Day 68)	Pre-Vacc PI D8 PI D61 PII D68	All enrolled subjects	~ 1000	
visit 1 (Day 1)	Pre-Vacc	All enrolled subjects	~ 1000	Anti-CMV IgG antibody

Pre-Vacc: Pre-vaccination; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X
ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen
CMV = Cytomegalovirus
* In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

5.9.4.3. Molecular biology

Table 17 Molecular biology tests on nasal/throat swab specimen for Part B

Sampling time point		Sub-cohort	No. subjects	Component
Type of contact (time point)	Sampling time point			
Sampling of nasal swab by subject at home Assessment visit for potential RSV-RTI	Unscheduled	Event-driven*	Event-driven*	RSV-A/B RNA
		All RSV-A/B positive swab samples**	All RSV-A/B positive swab samples**	Influenza A virus (Flu A) Influenza B virus (Flu B) Human respiratory syncytial virus A (RSV A) Human respiratory syncytial virus B (RSV B) Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3) Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09) Human adenovirus (AdV) Human metapneumovirus (hMPV) Human enterovirus (HEV) Human parainfluenza virus 1 (PIV1) Human parainfluenza virus 2 (PIV2) Human parainfluenza virus 3 (PIV3) Human parainfluenza virus 4 (PIV4) Human bocavirus 1/2/3/4 (HBoV) Human rhinovirus A/B/C (HRV) Human coronavirus 229E (229E) Human coronavirus NL63 (NL63) Human coronavirus OC43 (OC43)

* RSV-A/B quantitative PCR (RSV-A/B RNA) will be performed on all specimen.
** Respiratory Viruses Panel (Multiplex PCR) will be performed on all swabs RSV-A/B positive by qRT-PCR. Further assessment of RSV-A/B RNA negative samples may be performed with Multiplex PCR if deemed necessary.

5.9.5. Immunological correlates of protection

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

5.10. Study procedures during special circumstances (Amended, 13 May 2020)

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 and safety must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Instruction for the remaining scheduled visit (Visit 8): Planned study visit can proceed, if the study subjects are healthy and allowed to come to the site to have the blood sample and safety information collected. If the visit is impacted due to the national guidelines and/or site restrictions linked to the special circumstances, and it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 8), the samples will be encoded as missing and encoded as protocol deviation. If the visit is impacted, the safety information (as per***

protocol: SAEs, pIMDs, concomitant medications/vaccinations and intercurrent medical conditions) will be collected by site staff via telephone contact or other means of virtual contact, and this will not be considered as protocol deviation.

- ***Instruction for collection of home self-swabs in case study participant experiences suspected respiratory tract infection (RTI) symptoms: In case the investigator determines this is not posing additional risk to the subjects or household members, the subjects will be instructed to perform the home self-swab and keep it in their freezer (preferred) or refrigerator until recovered, and able to bring it to the site. If there is a possibility, a healthy relative can bring the sample to the site to be processed. In case investigator judges this is not advisable due to the national guidelines and/or site restrictions linked to the special circumstances, the self-swab will not be collected and the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. The investigator and/or the site staff will provide these instructions to the subjects during the active surveillance contacts carried out every 2 weeks during the RSV season period.***
- ***Instructions for assessment visit for suspected respiratory tract infection (RTI): Site staff will decide on the management of the cases (either having a site/different site location/home visit or by telephone contact) based on COVID-19 national guidelines and/or site restrictions linked to the special circumstances. If the nasal and throat samples cannot be collected at site, the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. Biological samples will not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

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

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

All candidate vaccines to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Table 18 Study vaccine for Part A and Part B - Step 1

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered	Number of doses
30 µg RSVPreF3 plain	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
30 µg RSVPreF3/AS01$_E$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
30 µg RSVPreF3/AS01$_B$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
60 µg RSVPreF3 plain	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
60 µg RSVPreF3/AS01$_E$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
60 µg RSVPreF3/AS01$_B$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
120 µg RSVPreF3 plain	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
120 µg RSVPreF3/AS01$_E$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
120 µg RSVPreF3/AS01$_B$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
Placebo	NaCl	NaCl=150mM	Liquid in monodose ampule or vial	0.5 ml	2

AS01$_B$ = Adjuvant System AS01$_B$; AS01$_E$ = Adjuvant System AS01$_E$; MPL = 3-*O*-desacyl-4'-monophosphoryl lipid A

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

Table 19 Study vaccine for Part B - Step 2

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered	Number of doses
30 µg RSVPreF3 plain	RSVPreF3 low dose	RSVPreF3=30µg	Freeze-dried antigen (44 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
30 µg RSVPreF3/AS01$_E$	RSVPreF3 low dose	RSVPreF3=30µg	Freeze-dried antigen (44 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
30 µg RSVPreF3/AS01$_B$	RSVPreF3 low dose	RSVPreF3=30µg	Freeze-dried antigen (44 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
60 µg RSVPreF3 plain	RSVPreF3 mid dose	RSVPreF3=60µg	Freeze-dried antigen (87 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
60 µg RSVPreF3/AS01$_E$	RSVPreF3 mid dose	RSVPreF3=60µg	Freeze-dried antigen (87 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
60 µg RSVPreF3/AS01$_B$	RSVPreF3 mid dose	RSVPreF3=60µg	Freeze-dried antigen (87 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
120 µg RSVPreF3 plain	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	NaCl	NaCl=150mM	Liquid in monodose ampule or vial		
120 µg RSVPreF3/AS01$_E$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid in bidose vial		
120 µg RSVPreF3/AS01$_B$	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried antigen (174 µg/vial)	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in monodose vial		
Placebo	NaCl	NaCl=150mM	Liquid in monodose ampule or vial	0.5 ml	2

AS01$_B$ = Adjuvant System AS01$_B$; AS01$_E$ = Adjuvant System AS01$_E$; MPL = 3-*O*-desacyl-4'-monophosphoryl lipid A

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

6.2. Storage and handling of study vaccine

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s), there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

Table 20 Dosage and administration

Type of contact and time point	Study group	Treatment name	Volume to be administered	Route[1]	Site	
					Location	Laterality[2]
Part A						
visit 1 (Day 1) visit 4 (Day 61)	30-PLAIN_A	30 µg RSVPreF3 plain	0.5 ml	IM	Deltoid	Non-dominant
	60-PLAIN_A	60 µg RSVPreF3 plain				
	120-PLAIN_A	120 µg RSVPreF3 plain				
	Placebo_A	Placebo				
Part B - Step 1						
visit 1 (Day 1) visit 4 (Day 61)	30-PLAIN_B1	30 µg RSVPreF3 plain	0.5 ml	IM	Deltoid	Non-dominant
	30-AS01E_B1	30 µg RSVPreF3/AS01E				
	30-AS01B_B1	30 µg RSVPreF3/AS01B				
	60-PLAIN_B1	60 µg RSVPreF3 plain				
	60-AS01E_B1	60 µg RSVPreF3/AS01E				
	60-AS01B_B1	60 µg RSVPreF3/AS01B				
	120-PLAIN_B1	120 µg RSVPreF3 plain				
	120-AS01E_B1	120 µg RSVPreF3/$AS01_E$				
	120-AS01B_B1	120 µg RSVPreF3/$AS01_B$				
	Placebo_B1	Placebo				
Part B - Step 2						
visit 1 (Day 1) visit 4 (Day 61)	30-PLAIN_B2	30 µg RSVPreF3 plain	0.5 ml	IM	Deltoid	Non-dominant
	30-AS01E_B2	30 µg RSVPreF3/$AS01_E$				
	30-AS01B_B2	30 µg RSVPreF3/$AS01_B$				
	60-PLAIN_B2	60 µg RSVPreF3 plain				
	60-AS01E_B2	60 µg RSVPreF3/$AS01_E$				
	60-AS01B_B2	60 µg RSVPreF3/$AS01_B$				
	120-PLAIN_B2	120 µg RSVPreF3 plain				
	120-AS01E_B2	120 µg RSVPreF3/$AS01_E$				
	120-AS01B_B2	120 µg RSVPreF3/$AS01_B$				
	Placebo_B2	Placebo				

[1] Intramuscular (IM)
[2] The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

Refer to the SPM for detailed instructions on study vaccine administration.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 20% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement vial/syringe number. The replacement numbers will be allocated by dose. The system will ensure, in a blinded manner, that the replacement vial/syringe matches the formulation the subject was assigned to by randomization.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the investigational RSV vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 9.2.2).

Contraindications for ALL subjects:

- Anaphylaxis following the administration of vaccine(s).
- Hepatomegaly, right upper quadrant abdominal pain or tenderness.
- Decreased renal function since baseline, as defined by an increase in blood urea nitrogen or creatinine levels from values within normal range at pre-vaccination to Grade 2 abnormalities (based on the testing laboratory parameters) at 7 days post-vaccination.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- Any condition that in the judgment of the investigator would make IM injection unsafe.
- An SAE judged to be vaccine-related by the investigator.
- Hematology parameters (complete blood cell count [red blood cells, white blood cells], white blood cells differential count [lymphocytes, neutrophils and eosinophils], platelets count or hemoglobin level) and/or biochemistry parameters (creatinine, blood urea nitrogen or liver enzymes [ALT or AST]) outside the normal laboratory ranges that persist after the administration of a previous study vaccine, unless the laboratory abnormalities are considered not clinically significant by the investigator.

Specific contraindications for Part A:

- Pregnancy (see Section 7.2.1).

Specific contraindications for Part B:

- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, may expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 7.1.5 for the definition of pIMDs.

The following events constitute contraindications to administration of the investigational RSV vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Table 8 in Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 9.2.2).

Contraindications for ALL subjects:

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

6.6. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the subject about any medication/product taken and vaccination received by the subject.

6.6.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during the 30-day period following each dose of study vaccine (Day 1 to Day 30 and Day 61 to Day 90).
- Any concomitant vaccination administered in the period starting from the first dose of study vaccine and ending at the last study visit (Day 1 to 91 for Part A and Day 1 to Month 14 for Part B).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity.
- Any concomitant medications/products/vaccines listed in Section 6.6.2.
- For **Part A**, any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered during the study period for the treatment of an SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- For **Part B**, any concomitant medications/products/vaccines relevant to an SAE/pIMD to be reported as per protocol or administered during the study period for the treatment of an SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.5 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period (up to Day 91 for Part A and up to Month 14 for Part B).
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period (up to Day 91 for Part A and up to Month 14 for Part B). For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last vaccine dose*, except for inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each vaccination.

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised 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 licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period (up to Day 91 for Part A and up to Month 14 for Part B).

6.7. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition (refer to glossary of terms for the definition of intercurrent medical condition). If it is the case, the condition(s) must be recorded in the AE section of the eCRF.

At the time of analysis, subjects may be eliminated from the per-protocol cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

7. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

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

7.1. Safety definitions

7.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable 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.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 7.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- 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 subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

7.1.2. Definition of a serious adverse event

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 subject 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 subject 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. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   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, diarrhoea, 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 subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

7.1.3. Solicited adverse events

Solicited AEs (see Table 21 and Table 22) occurring during the 7-day follow-up period after each vaccination (day of vaccination and 6 subsequent days) will be recorded by the subjects in the eDiaries. The data will be made available for site follow-up on the eDiary web-portal.

The investigator will assess the causality of the general symptoms on the web-portal, after a discussion with the subject during a phone contact or a visit. The investigator should also enter on the portal the type of medical attention given for each of the solicited symptoms experienced by the subject.

7.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 21 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

7.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 22 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms†
Headache
Myalgia
Shivering
Arthralgia

† Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

Note: Subjects will be instructed to measure and record the oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the eDiary.

7.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology) or other abnormal assessments (e.g. physical examination signs or symptoms) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 7.1.1 and 7.1.2). 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.

The investigator will exercise his/ her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. As for other AEs/ SAEs, treatment for clinically significant abnormal laboratory findings or other assessments is at the sole discretion of the investigator and according to good medical practice.

In case of invalid or missing results or clinically significant grade 3 and above abnormal laboratory findings that cannot be reasonably explained (e.g. due to a pre-existing or current medical condition), the investigator will be recommended to recall the subject in a timely manner (preferably within 7 days after investigator's awareness/assessment of the abnormal findings, if applicable) for a repeat test to confirm the result.

7.1.5. Adverse events of specific interest (Potential immune-mediated diseases)

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 23.

However, the investigator will exercise his/her medical and scientific judgement in deciding 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 23 List of potential immune-mediated diseases

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. • Localised 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.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

7.2. Events or outcomes not qualifying as adverse events or serious adverse events

7.2.1. Pregnancy in Part A

In Part A, female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or an SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 7.4.1 and 7.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e., death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 7.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

7.3. Detecting and recording adverse events, serious adverse events and pregnancies

Electronic Diaries (eDiaries) will be used by the subjects to capture solicited AE data and to notify investigators if other (unsolicited) signs or symptoms were experienced.

Paper diary cards will be used by the subjects to capture the details of the unsolicited signs or symptoms. They will be reviewed by the investigator at the subsequent study visits (Day 8, Day 31, Day 68 or Day 91) and then reported as applicable in the AE section of the eCRF.

The subject should be trained on how and when to complete each field of the electronic and paper diary. If a subject is illiterate or unable or not willing to complete the electronic and/or the paper him/herself, he/she may be helped by a designate (refer to the glossary of terms for the definition of designate).

Subject Diary training should be directed at the individual(s) who will perform the measurements of AEs and who will enter the information into the Subject Diary. If a designate enters information into the Subject Diary, this person's identity must be documented in the subject's source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit when Subject Diary is dispensed. This training must be documented in the subject's source record.

The same individual should complete the Subject eDiary throughout the course of the study. The subject should be trained on how to self-measure local solicited AEs and body temperature. The measurement of solicited local AEs is to be performed using the ruler provided by the site.

7.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

For Part A and Part B:

All AEs starting within 30 days following administration of each dose of study vaccine (the day of vaccination and 29 subsequent days) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 1 month following administration of the last dose of study vaccine for each subject in Part A and 12 months following administration of the last dose of study vaccine for each subject in Part B. See Section 7.4 for instructions on reporting of SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e., protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

For Part A only:

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end 1 month following administration of the last dose of study vaccine. See section 7.4 for instructions on reporting of pregnancies.

For Part B only:

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine. See Section 7.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, pregnancies and/or pIMDs is given in

Table 24 for Part A and Table 25 for Part B.

Refer to Section 5.10 for measures for safety follow-up that may be implemented during special circumstances (Amended, 13 May 2020).

Table 24 Reporting periods for collecting safety information in Part A

Event	SCR Pre-D1*	Visit 1 Vacc 1	Visit 2	Visit 3	Visit 4 Vacc 2	Visit 5	Visit 6 End of FU for Part A
Solicited local and general AEs		Days 1-7			Days 61-67		
Unsolicited AEs		Days 1-30			Days 61-90		
AEs/SAEs leading to withdrawal from the study		Days 1-91					
SAEs		Days 1-91					
SAEs related to study participation or concurrent GSK medication/vaccine	Pre-Day 1* - Day 91						
Pregnancies		Days 1-91					
Intercurrent medical conditions		Days 1-91					

* i.e., consent obtained.
Pre-D1: Pre-vaccination Day 1; FU: Follow-up; Vacc: Vaccination; SCR: Screening Visit

Table 25 Reporting periods for collecting safety information in Part B

Event	SCR Pre-D1*	Visit 1 Vacc 1	Visit 2	Visit 3	Visit 4 Vacc 2	Visit 5	Visit 6	Visit 7	Visit 8 Study Conclusion
Solicited local and general AEs		Days 1-7			Days 61-67				
Unsolicited AEs		Days 1-30			Days 61-90				
AEs/SAEs leading to withdrawal from the study		Day 1 - Month 14							
SAEs		Day 1 - Month 14							
SAEs related to study participation or concurrent GSK medication/vaccine	Pre-Day 1* - Month 14								
pIMDs		Day 1 - Month 14							
Intercurrent medical conditions		Day 1 - Month 14							

* i.e., consent obtained.
Pre-D1: Pre-vaccination Day 1; Vacc: Vaccination
SCR: Screening Visit

7.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in

Table 24 for Part A and Table 25 for Part B. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

7.3.3. Evaluation of adverse events and serious adverse events

7.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

7.3.3.2. Assessment of adverse events

7.3.3.2.1. Assessment of intensity

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

Table 26 Intensity scales for solicited symptoms in adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia	0	Normal
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	Normal
	1	Mild: Shivering that is easily tolerated
	2	Moderate: Shivering that interferes with normal activity
	3	Severe: Shivering that prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity.

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

	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

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

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

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 7.1.2.

7.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccine and the occurrence of each AE/SAE using clinical judgement.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined as 'serious' (see Section 7.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

7.3.3.3. 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).

7.3.3.4. Medically attended visits

The subject will be asked if he/she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits.

7.4. Reporting of serious adverse events, pregnancies, and other events

7.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 7.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator determines that the event meets the protocol definition of an SAE.

Pregnancies that occur in the time period defined in Section 7.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 7.3 will be reported promptly to GSK within the timeframes described in Table 27, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 27 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy 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.
**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.

7.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

Study Contact for Reporting SAEs, pIMDs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US sites: Fax: PPD Email address: PPD US sites only: Fax: PPD

7.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that an SAE has occurred in a study subject, the investigator (or delegate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

7.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or delegate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or delegate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

7.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or delegate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

7.4.5. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or delegate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 7.4.3.1 for back-up system in case the electronic reporting system does not work.

7.4.6. Updating of SAE, pregnancy, and pIMD information after removal of write access to the subject's eCRF

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 27.

7.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 7.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for an SAE(s) that is both attributable to the study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

7.5. Follow-up of adverse events, serious adverse events, and pregnancies

7.5.1. Follow-up of adverse events and serious adverse events

7.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 27).

All SAEs and pIMDs (serious or non-serious) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the subject.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

7.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using an electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

7.5.2. Follow-up of pregnancies

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

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

7.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an SAE / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.6).

7.7. Unblinding

GSK Biologicals' policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccine, prior to regulatory reporting. The GSK Biologicals' Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 7.4.1).

7.8. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back-up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to Table 28) if he/she needs support to perform the unblinding (i.e., he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back-up process). Contact details of investigator and GSK Biologicals' Helpdesk are reported in the patient/subject card.

Table 28 Contact information for emergency unblinding

GSK Biologicals' Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email *(Amended, 13 May 2020)* Phone: PPD For US: ***Phone***: PPD Fax: PPD email:PPD

A subject may continue in the study if that subject's treatment assignment is unblinded.

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life threatening cases. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.9. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or delegate) must therefore provide a "subject card" to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

7.10. Holding rules and safety monitoring

The study will be conducted in 2 parts, i.e., Part A in young adults aged 18-40 years and Part B in older adults aged 60-80 years. Part B of the study will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. Figure 1 provides an overview of the IDMC safety evaluations in each study part and staggered enrolment in Part B.

The investigator is not permitted to start vaccinating the subjects in the next step in each part until the Sponsor communicates the favorable outcome of the respective safety evaluations by the IDMC. Screening procedures may however be performed to facilitate enrolment in Steps 1 and 2 of Part B.

The IDMC safety evaluations will be performed based on unblinded data up to the specific time point of the evaluation, including:

- Data as clean as possible;
- Hematology and biochemistry parameters post-vaccination;
- All safety data available by the time of a given safety evaluation.

In addition, if any safety concern is identified by the investigator (i.e., meeting of holding rules [see Section 7.10.4] or any other safety concern), he/she should inform GSK Biologicals immediately (within 24 hours), and vaccination may be put on hold at all sites as a consequence.

Refer to APPENDIX D for an overview of the communication flow in case a holding rule is met, as identified by the Investigator or IDMC.

7.10.1. Part A

- Approximately 48 young adults (~12 per group) aged 18-40 years will be enrolled and vaccinated with the first dose with an interval of at least 60 minutes between participants to allow efficient suspension of vaccination in case of any safety concern.
- If any safety concern is identified by the investigator (i.e., meeting of holding rules 1a-1d [see Table 29] or any other safety concern), he/she should inform GSK Biologicals immediately (within 24 hours), and vaccination may be put on hold at all sites as a consequence.
- All available data from Part A participants vaccinated with the first dose will be reviewed in a first IDMC meeting. This IDMC will perform a safety evaluation of all available data collected up to 30 days post-Dose 1. Holding rules described in Table 29 will apply.
- If the IDMC evaluation outcome is favorable, the participants in Part A will be vaccinated with the second dose with an interval of at least 60 minutes between participants, to allow efficient suspension of vaccination in case of any safety concern. The vaccination in Part B of the study will also be initiated in case of favorable outcome of this first IDMC meeting (see Section 7.10.2.1).
- All available data from participants in Part A who received the second vaccine dose will be reviewed in a second IDMC meeting. This IDMC will evaluate the safety data up to 7 days after Dose 2. Holding rules described in Table 29 will apply.
- All participants will be closely observed for a minimum of 60 minutes after each vaccination.

7.10.2. Part B

7.10.2.1. Part B - Step 1

- Upon favorable outcome of the first IDMC evaluation in Part A, a first wave of study participants aged 60-80 years (N≅100, approximately 10 per group, see Section 7.10.5) will be enrolled and vaccinated with the first dose with an interval of at least 60 minutes between participants, to allow efficient suspension of vaccination in case of any safety concern.
- All participants will be closely observed for a minimum of 60 minutes after each vaccination.
- If any safety concern is identified by the investigator (i.e., meeting of holding rules 1a-1d [see Table 29] or any other safety concern), he/she should inform GSK Biologicals immediately (within 24 hours), and vaccination may be put on hold at all sites as a consequence.
- All available data from those 100 participants vaccinated with the first dose will be reviewed in a third IDMC meeting. This IDMC will perform a safety evaluation of all available data collected up to 7 days post-Dose 1. Holding rules described in Table 29 will apply.

- If the outcome of the second IDMC evaluation in Part A as well as this third IDMC evaluation in Part B is favorable, participants from Step 1 of Part B who received the first vaccine dose will receive the second dose and Step 2 of Part B will follow (see Section 7.10.2.2).

  The second vaccine dose in Step 1 of Part B should be administered with an interval of at least 60 minutes between participants, to allow efficient suspension of vaccination in case of any safety concern.

7.10.2.2. Part B - Step 2

- Upon favorable outcome of the second IDMC evaluation in Part A as well as the third IDMC evaluation in Part B, the remaining study participants (N≅900, approximately 90 per group) will be enrolled and vaccinated with the first dose. The 60-minute interval for vaccination between participants does not apply at this step.
- If any safety concern is identified by the investigator (i.e., meeting of holding rules 1a-1c [see Table 30] or any other safety concern), he/she should inform GSK Biologicals immediately (within 24 hours), and vaccination may be put on hold at all sites as a consequence.
- A fourth IDMC meeting will review safety data collected up to 7 days post-Dose 2 from participants in Step 1 who received the second vaccine dose. Holding rules described in Table 29 will apply. In addition, the IDMC will review all available safety data up to 7 days post-Dose 1 of all study participants enrolled and vaccinated at the time of this IDMC analysis. Holding rules described in Table 30 will apply.

If this fourth IDMC evaluation outcome is favorable, the study participants enrolled in Step 2 will be administered the second vaccine dose.

All participants will be closely observed for a minimum of 60 minutes after each vaccination.

7.10.2.3. Additional safety monitoring in Part B

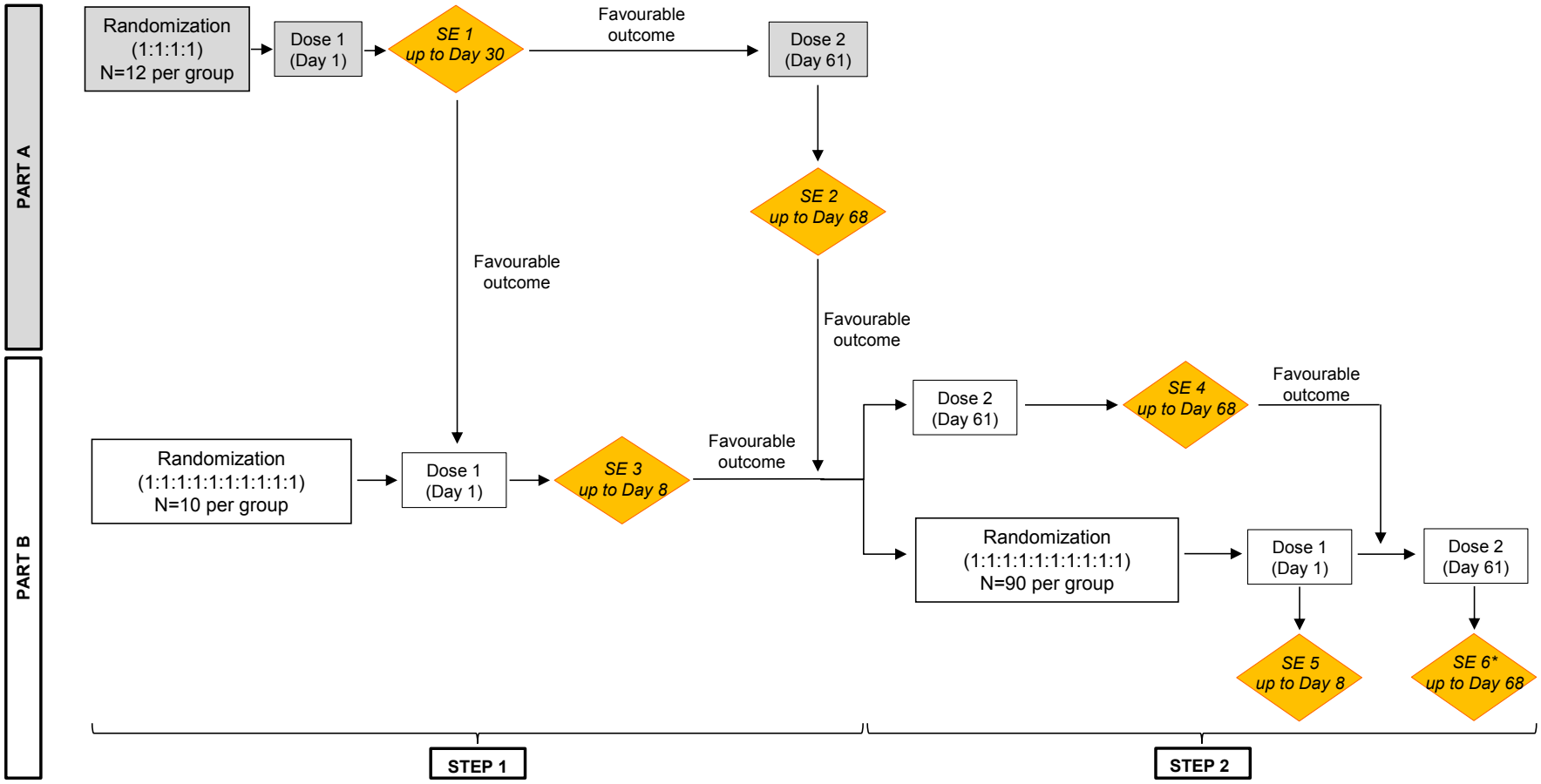
A fifth IDMC meeting will be performed after all subjects in Part B have received their first dose. All available safety data up to 7 days post-Dose 1 of all participants enrolled and vaccinated in Part B will be reviewed. Holding rules described in Table 30 will apply.

A sixth IDMC meeting will review all available safety data up to 7 days post-Dose 2 when at least 50% to 75% of participants enrolled in Part B have received the second vaccine dose. Holding rules described in Table 30 will apply.

If any safety concern is identified by the investigator or the sponsor, ad-hoc safety evaluations by the IDMC may be performed.

During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

Figure 1 Overview of IDMC safety evaluations in each study part and staggered enrolment in Part B



SE: Safety evaluation by IDMC
* The sixth IDMC evaluation will be based on all available safety data up to 7 days post-Dose 2 (data will be as clean as possible including Day 68 hematology and biochemistry parameters) when at least 50% to 75% of participants enrolled in Part B have received the second vaccine dose.

7.10.3. Safety evaluation by the IDMC

As the investigational RSV vaccine formulations will be administered for the first time in humans, an IDMC will be appointed and operating under a charter, in addition to the existing project's Safety Review Team. Safety holding rules have been defined. During the vaccination phase of the study (Parts A and B), there will be 6 planned IDMC meetings to review safety data. If considered as needed, ad hoc IDMC meetings between the planned meetings will be scheduled. During the persistence phase in Part B, the IDMC will meet at least every 6 months.

The IDMC will review the protocol and Statistical Analysis Plan (SAP). Meetings will be documented and minutes of open sessions of the IDMC meetings made available to the sponsor. The IDMC may, if deemed necessary, convene a meeting with, or request further information from GSK Biologicals' designated project representatives at any stage of the study.

The IDMC will conduct unblinded reviews of all available safety data (as clean as possible) from the present study, while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety signal that needs to be escalated to the sponsor.

In addition to the RSV program targeting older adults, GSK is also developing a RSV vaccine for infant immunization (RSV maternal program) using the same antigen. An RSV maternal study may be running at a time that can overlap with the conduct of this study. Any relevant safety information arising from this maternal study will be shared with the IDMC.

7.10.3.1. Outcome of the IDMC safety evaluation

If **no safety signal** is observed, the favorable outcome of the safety evaluations will be documented and provided in writing, authorizing the investigator to proceed with the next step as defined in Figure 1.

If a **safety signal** is observed during the safety evaluations or if any of the holding rules 2a-2c is met, the IDMC Chair (or his/her representative) is responsible for the urgent communication to the sponsor, including the rationale for the decision to put the vaccination on hold or not. The study CRDL will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

7.10.3.2. Process of suspension of vaccination and/ or study modification

In the event that a safety signal is observed, the sponsor might decide to cancel vaccination of all groups or selected groups.

In this case, for impacted groups:

- Subjects who were already vaccinated will not receive the second study vaccine dose (if not yet administered) and continue all other visits as planned.
- Subjects who signed an informed consent but did not receive any study vaccine will be informed that their study participation will be stopped.

7.10.4. Study holding rules for the vaccination phase

The safety holding rules for the vaccination phases of the study are defined in Table 29 and Table 30.

For subjects enrolled in Part A and in Step 1 of Part B, holding rules 1a-1d from Table 29 will be assessed by the investigator on a continuous basis and meeting any of these holding rules will trigger a hold of vaccination irrespective of number of subjects enrolled and/or timing of the event relative to vaccination. Holding rules 2a-2c from Table 29 will be assessed by the IDMC during the safety evaluations on unblinded data.

For subjects enrolled in Step 2 of Part B, holding rules 1a-1c from Table 30 will be assessed by the investigator on a continuous basis and meeting any of these holding rules will trigger a hold of vaccination, irrespective of the number of subjects enrolled and/or timing of the event relative to vaccination. For the overall safety data assessment after Dose 1 or 2 (in all the subjects who received the respective dose at that point), holding rules 1d, 2a-2c from Table 30 will be assessed by the IDMC during the safety evaluations on unblinded data.

The sponsor may decide to stop vaccination in all groups or only in a specific study group while proceeding with vaccination in the other groups.

Table 29 Study holding rules for Part A and Part B Step 1 (Dose 1 and Dose 2)

Holding Rule	Event	Number of subjects/group/dose	
		Part A	Part B - Step 1
1a	Death or any life-threatening **SAE**	≥ 1	≥ 1
1b	Any non-life-threatening **SAE** that cannot reasonably be attributed to a cause other than vaccination	≥ 1	≥ 1
1c	Any local or general solicited AE leading to **hospitalization**, or **fever > 40°C** (104°F) that cannot reasonably be attributed to a cause other than vaccination, or **necrosis** at the injection site, within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 1
1d	Any **withdrawal** from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1	≥ 1
2a	Any **Grade 3 solicited local** AE lasting 48h or more in an investigational RSV vaccine group, within the 7-day (Day 1-7) post-vaccination period	≥ 3/12 (≥ 25%)*	≥ 2/10**
2b	Any **Grade 3 solicited general** AE lasting 48h or more in an investigational RSV vaccine group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period	≥ 3/12 (≥ 25%)*	≥ 2/10**
2c	Any ≥ **Grade 3 unsolicited** AE in an investigational RSV vaccine group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period OR Any ≥ Grade 3 abnormality in pre-specified hematological or biochemical **laboratory parameters** in an investigational RSV vaccine group, up to the Day 8 post-vaccination visit.†	≥ 3/12 (≥ 25%)*	≥ 2/10**

† Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to APPENDIX C). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

* In case of slow recruitment of subjects enrolled in Part A, the IDMC evaluations after each dose can be performed before all 48 subjects reach their Day 31 visit but based on no less than a total of 32 subjects (at least 8 per group). In this situation, holding rules 2a-2c will be reached when 2/8 (or 3/9, 3/10, 3/11) subjects have reported the specific endpoint in one group.

** In case of slow recruitment of subjects enrolled in Step 1 of Part B, the IDMC evaluations after each dose can be performed before all 100 subjects reach their Day 8 visit but based on no less than a total of 80 subjects (at least 8 per group). In this situation, holding rules 2a-2c will be reached when 2/8 (or 2/9) subjects have reported the specific endpoint in one group.

The holding rules described in Table 29 for participants enrolled in Part A are applicable during the first and second planned IDMC meetings, where safety data after Dose 1 and 2 from these subjects are evaluated.

The holding rules described in Table 29 for participants enrolled in Step 1 of Part B are applicable during the third and fourth planned IDMC meetings, where safety data after Dose 1 and 2 from these subjects are evaluated. These holding rules have been written under the assumption that the safety data of all subjects enrolled in Step 1 of Part B will be available. If the data from all subjects are not available, the holding rules will be assessed on a pro-rata basis, however the IDMC evaluation will not be performed with data from less than 80 subjects.

Table 30 describes the holding rules applicable for the whole study population (overall safety data after each dose) during the fourth, fifth and sixth planned IDMC meetings.

Of note, no formal holding rules will be applied for other safety data such as:

- SAEs that are not life-threatening and are not attributed to the study vaccination,
- Missed visits due to vaccine-related AEs,
- Grade 1 and Grade 2 solicited, unsolicited AEs in the 7-day follow-up period, unsolicited AEs collected from Day 8 to Day 30 after vaccination.

However, these data, if available, will also be reviewed by the IDMC in order to allow for an overall assessment of the benefit/ risk ratio of vaccination ***(Amended, 13 May 2020).***

Table 30 Study holding rules for Part B (Steps 1 and 2 pooled)

Holding Rule	Event	Number of subjects/group/ dose
1a	Death or any life-threatening **SAE**	≥ 1
1b	Any non-life-threatening **SAE** that cannot reasonably be attributed to a cause other than vaccination	≥ 1
1c	Any local or general solicited AE leading to **hospitalization**, or **fever > 40°C** (104°F) that cannot reasonably be attributed to a cause other than vaccination, or **necrosis** at the injection site, within the 7-day (Day 1-7) post-vaccination period	≥ 1
1d	Any **withdrawal** from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 25%
2a	Any **Grade 3 solicited local** AE lasting 48h or more in an investigational RSV vaccine group, within the 7-day (Day 1-7) post-vaccination period	≥ 25%
2b	Any **Grade 3 solicited general** AE lasting 48h or more in an investigational RSV vaccine group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period	≥ 25%
2c	Any ≥ **Grade 3 unsolicited** AE in an investigational RSV vaccine group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period OR Any ≥ Grade 3 abnormality in pre-specified hematological or biochemical **laboratory parameters** in an investigational RSV vaccine group, up to the Day 8 post-vaccination visit.†	≥ 25%

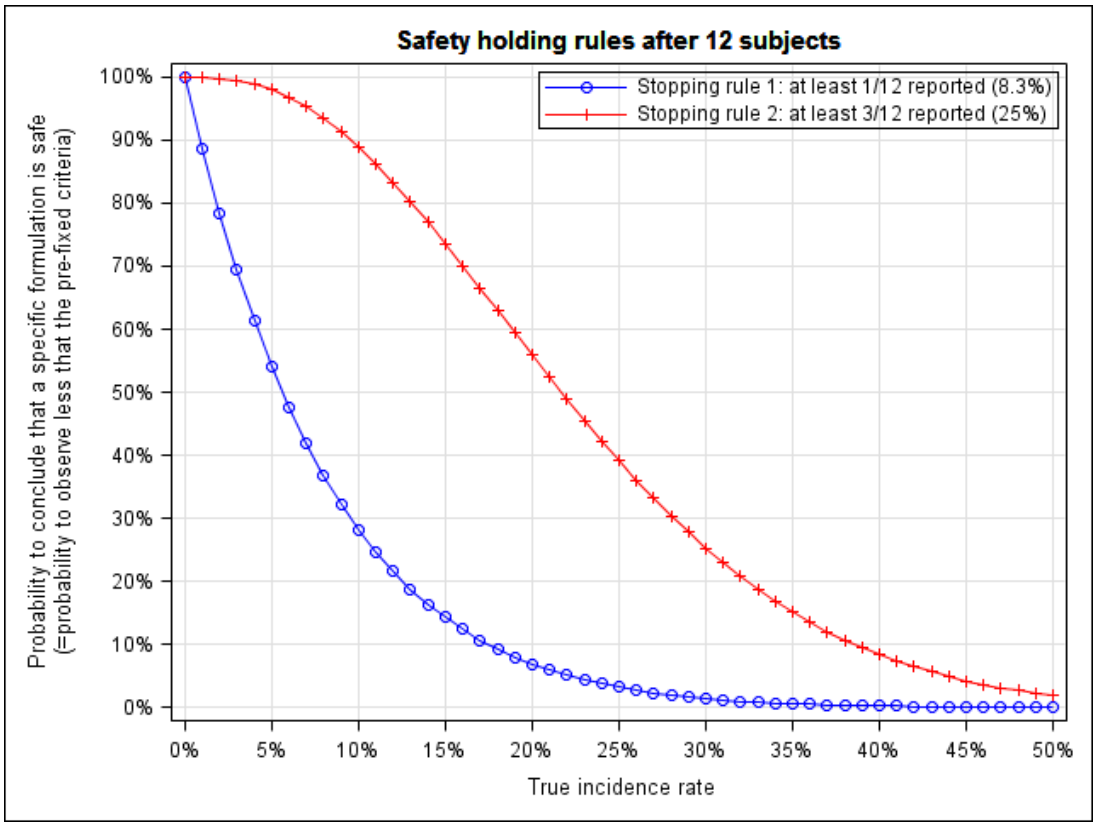
† Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to APPENDIX C). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

7.10.5. Risk assessment

7.10.5.1. Part A

Figure 2 gives the probability of not meeting holding rule 1 and 2 for 12 subjects per study group in Part A.

Figure 2 Evaluations based on 12 subjects - Risk assessment curves for Part A



The above figure illustrates that, with 12 subjects per study group:

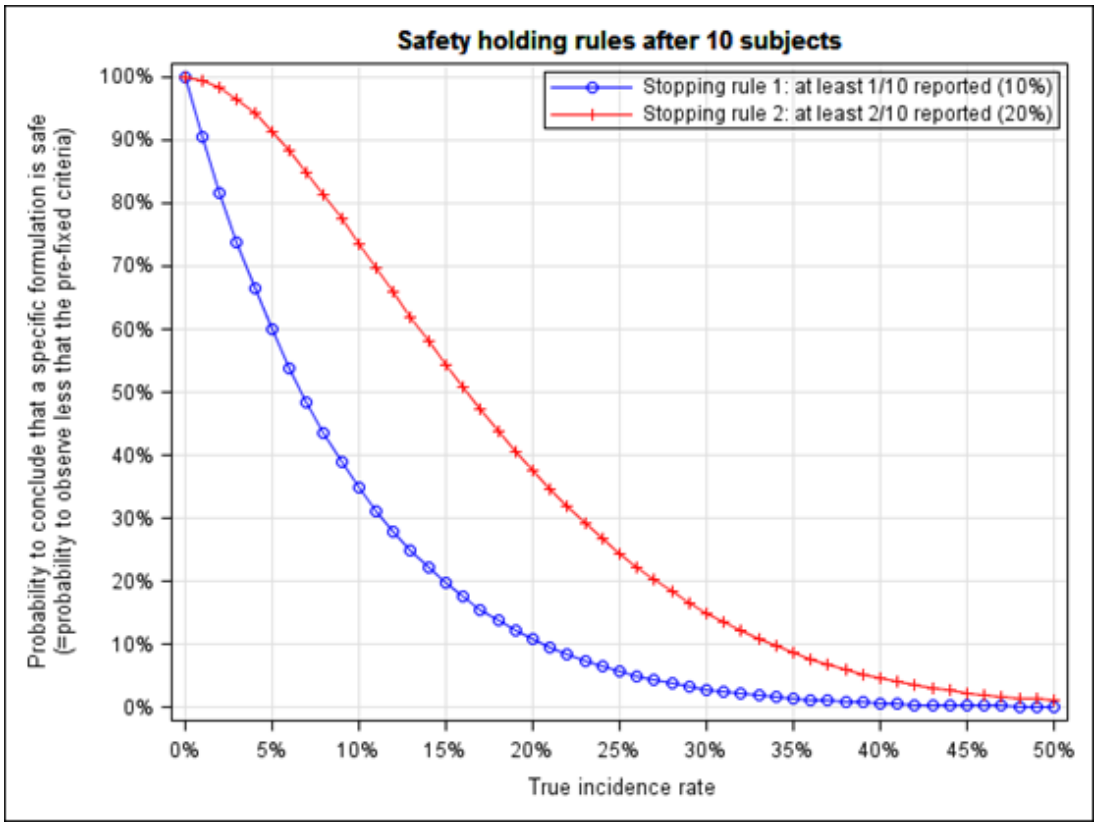
- Each holding rule 1a-1d has more than 89% chance of not being met for vaccination with a true incidence rate below 1% and has more than 70% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-2c has more than 89% chance of not being met for vaccination with a true incidence rate below 10% and more than 60% chance of being met for vaccination with a true incidence rate above 25%.

In case of slow recruitment of subjects enrolled in Part A, the IDMC evaluations after each dose can be performed before all 48 subjects reach their Day 31 visit but based on no less than a total of 32 subjects (approximately 8 per group). In this situation, holding rules 2a-2c will be reached when 2/8 (or 3/9, 3/10, 3/11) subjects have reported the specific endpoint in one group (see Figure 4).

7.10.5.2. Part B

Figure 3 gives the probability of not meeting holding rule 1 and 2 for 10 subjects per study group in Step 1 of Part B.

Figure 3 Evaluations based on 10 subjects - Risk assessment curve for one formulation based on the proposed safety holding rules for Part B - Step 1



The above figure illustrates that, with 10 subjects per study group:

- Each holding rule 1a-1d has more than 90% chance of not being met for vaccination with a true incidence rate below 1% and has more than 65% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-2c has more than 80% chance of not being met for vaccination with a true incidence rate below 8% and more than 75% chance of being met for vaccination with a true incidence rate above 25%.

In case of slow recruitment of subjects enrolled in Step 1 of Part B, the IDMC evaluations after each dose can be performed before all 100 subjects reach their Day 7 visit but based on no less than a total of 80 subjects (approximately 8 per group). In this situation, holding rules 2a-c will be reached when 2/8 (or 2/9) subjects have reported the specific endpoint in one group.

Figure 4 illustrates that, with 8 subjects per study group in Step 1 of Part B:

- Each holding rule 1a-1d has more than 90% chance of not being met for vaccination with a true incidence rate below 1% and has more than 55% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-2c has more than 80% chance of not being met for vaccination with a true incidence rate below 10% and more than 60% chance of being met for vaccination with a true incidence rate above 25%.

Figure 4 Evaluations based on 8 subjects - Risk assessment curve for one formulation based on the proposed safety holding rules for Part B - Step 1

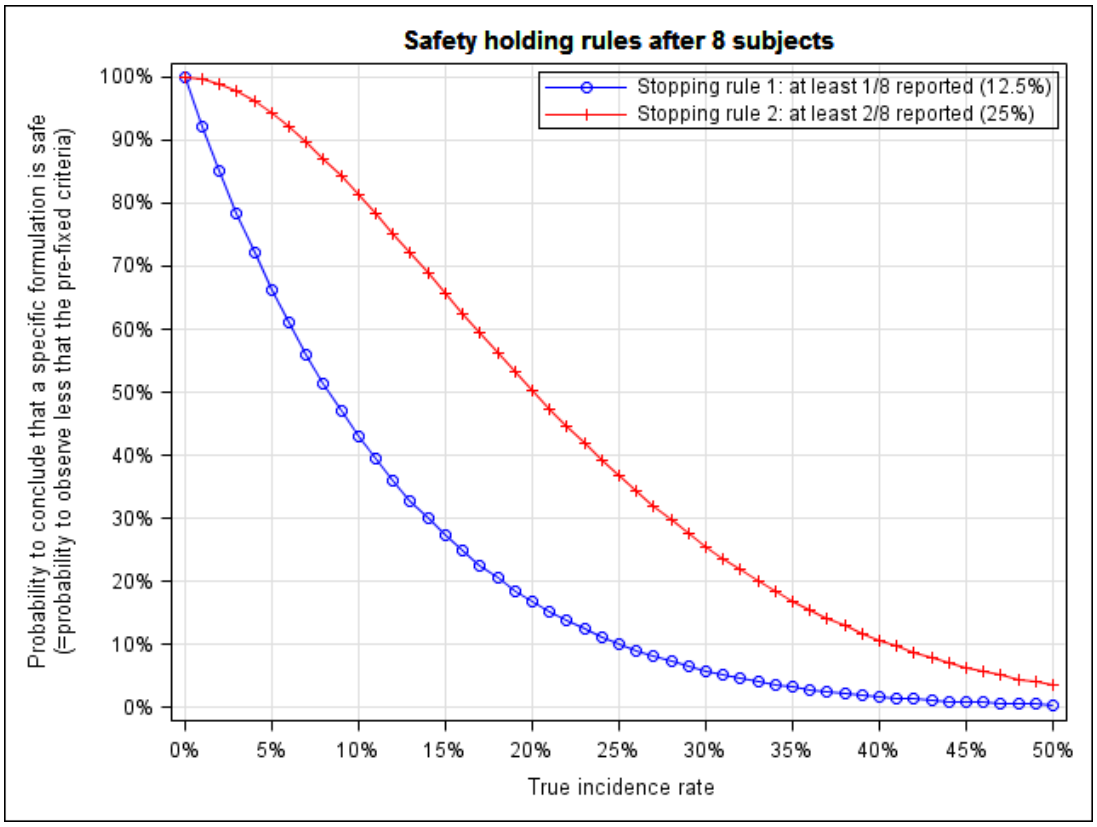
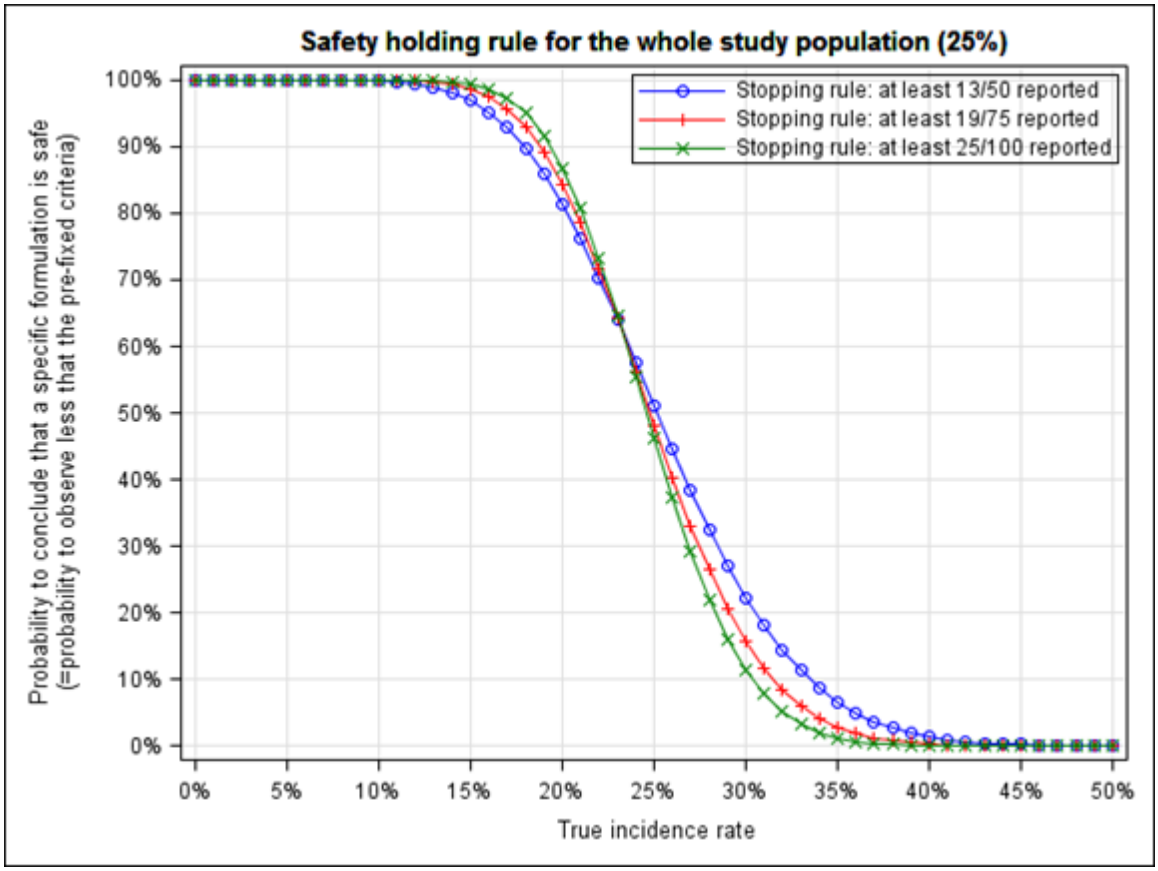


Figure 5 illustrates the chance of not meeting the holding rule during the entire enrolment phase in Part B (after 50, 75 and 100 subjects per group) depending on the true incidence rate.

Figure 5 **Risk assessment curve for the Part B study population for one formulation based on the proposed safety holding rules (25%)**



8. RTI SURVEILLANCE DURING PART B OF THE STUDY

RTI surveillance comprises active and passive surveillance and will only be carried out during Part B of the study.

8.1. Active surveillance

Active surveillance will only be carried out during the RSV seasons (approximately from October to March) throughout the entire Part B of the study. Study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience RTI symptoms (e.g., cough, runny nose, fever or difficulty to breath).

In case of RTI symptoms (at least 3) reported by the subject, the subject will be asked to collect a nasal swab at home within 48 hours after the start of symptoms and contact the investigator/study staff, who will schedule an assessment visit for nasal and throat swab specimen collection by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days). Episodes should be treated accordingly to local standard of care.

In the event that it is not possible to schedule an assessment visit, the assessment visit page of the eCRF should be filled in as completely as possible using available medical records.

8.2. Passive surveillance

Passive surveillance will only be carried out during the RSV seasons (approximately from October to March) throughout the entire Part B of the study. Study participants will be instructed to contact the investigator/study staff in case of RTI symptoms (e.g., cough, runny nose, fever or difficulty to breath).

In case of RTI symptoms (at least 3) reported by the subject, the subject will be asked to collect a nasal swab at home within 48 hours after the start of symptoms and contact the investigator/study staff, who will schedule an assessment visit for nasal and throat swab specimen collection by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days). Episodes should be treated according to local standard of care.

In the event that it is not possible to schedule an assessment visit, the assessment visit page of the eCRF should be filled in as completely as possible using available medical records.

8.3. Assessment Visit for potential RSV-RTI

The purpose of the Assessment Visit for potential RSV-RTI is to objectively document signs and symptoms (e.g., cough, runny nose, fever or difficulty to breath) by an appropriately qualified person (i.e., medical or nursing) and to take nasal and throat swabs for detection of RSV infection. The visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).

- Assessment visits may take place in the study participant's home, the investigator's clinical facility or a medical facility as appropriate to the circumstances in the judgment of the investigator.
- If the reported symptoms are already of a level of severity that urgent care is indicated, the study participant should be redirected to the proper location to receive this care (e.g. Emergency Room) and an assessment visit could be scheduled to take place there at a suitable time.
- For self-collection as well as staff-collection, swabs for analysis at sponsor laboratory should be collected when subjects show at least 3 of the following signs/symptoms:
  - Nasal congestion,
  - Sore throat,
  - Earache,
  - New or worsening cough,
  - New or worsening sputum,

- Dyspnea,
- Rhinorrhea,
- Wheezing (whistling, musical or puffing sound made on exhalation) or worsening of wheezing,
- Rales (crackles),
- Rhonchi (sound with musical pitch during inspiration or expiration),
- Fever (temperature of ≥ 37.5°C) or feeling feverish.

- During the assessment visit, the investigator/study staff will evaluate the clinical signs and symptoms of the RTI and measure the subject's resting vital signs (systolic/diastolic blood pressure, pulse oximetry, heart rate, respiratory rate after at least 10 minutes of rest) and temperature. RTI symptoms include, but may not be limited to, the following:
  - **Upper respiratory symptoms:** nasal congestion, sore throat, rhinorrhea, earache.
  - **Lower respiratory symptoms:** new or worsening cough, new or worsening of sputum production, dyspnea, wheezing or worsening of wheezing, rales (crackles), rhonchi.
  - **Systemic symptoms:** myalgia, arthralgia, fatigue, headache, decreased appetite, feverishness, pain (localized at chest or abdomen at respiration).

  Signs and symptoms and onset date of first symptom should be recorded within the RTI episode screen in the eCRF.
- Study participants will be instructed to contact the study staff if the severity of the already existing symptoms increases or if they develop difficulty in breathing or wheezing, and this may lead to a repeat assessment visit upon the judgment of the investigator.
- The status and evolution of the case will be followed until case resolution, as per routine practice.
- RTI data will be entered in the eCRF:
  - A new episode number and section will be created in the eCRF for each RTI episode.
  - All data pertaining to a same episode (including date of onset and end date) will be entered under the same eCRF episode number, even if observations are consolidated from several visits or contacts.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up (e.g., 3 telephone calls and a certified letter to the last known address).

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of an SAE/AE until resolution of the event (see Section 7.5.1.2).

9.2.2. Subject withdrawal from study vaccine

A 'withdrawal' from the study vaccine(s) refers to any subject who does not receive the complete treatment, i.e., when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the study vaccine(s) will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Unsolicited non-serious AE.
- Solicited AE.
- Not willing to be vaccinated
- Other (specify).

9.3. Screen and baseline failures

Screening failures are defined as subjects who are withdrawn from the study after giving informed consent, but who do not meet the inclusion and exclusion criteria.

The following information will be collected for screening failures:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographic data.
- Blood samples for hematology and biochemistry.
- SAEs related to study participation, or to a concurrent GSK medication/vaccine.
- Screening conclusion.

10. STATISTICAL METHODS

The analysis described in this section will be presented by RSV vaccine formulation (referred as "group", based on Steps 1 and 2 of Part B pooled), for Part A and Part B separately.

10.1. Primary endpoints

For Part A and Part B:

- Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91):
  - Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination.
  - Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination.
  - Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68.
  - Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination.
  - Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

For Part B only:

- Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

10.2. Secondary endpoints

For Part A and Part B:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro.

For Part B only:

- Occurrence of RSV-associated RTI (as measured by qRT-PCR in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
- Occurrence of SAEs from Dose 1 up to the end of follow-up.
- Occurrence of pIMDs from Dose 1 up to the end of follow-up.

10.3. Tertiary endpoints

For Part A and Part B:

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro.

For Part B only:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype B in all subjects.
  - RSVPreF3 ***RSB1*** specific antibody concentrations in a subset of subjects who received the selected vaccine formulation or placebo. ***(Amended, 13 May 2020)***
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific memory B-cells in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Persistence of the humoral immune response with respect to components of the investigational vaccine at Months 8 and 14:
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.

- Persistence of the cell-mediated immune response profile with respect to components of the investigational vaccine:
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific memory B-cells at Month 14 in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:
  - Antibodies against specific protein F epitopes.
  - Potential new immunological markers for protection.
  - Cross-reactive neutralizing antibody titers against hMPV.
- Occurrence of RSV-associated RTI, including co-infections with other respiratory viruses (as measured by multiplex PCR in self-collected nasal swab samples and nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons.
- Occurrence of RSV-associated RTI as measured by qRT-PCR in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

10.4. Determination of sample size

In Part A, the sample size of 12 subjects per group would provide a probability of 80% or 90% to observe at least one AE, if the true AE rate is 12.6% or 17.5%, respectively.

In Part B, the sample size of 100 subjects per group would provide a probability of 80% or 90% to observe at least one AE, if the true AE rate is 1.6% or 2.3%, respectively.

The study is designed as a factorial design with 2 factors resulting in 9 RSV formulations (~100 subjects per RSV formulation in Part B, Step 1 and Step 2 pooled, referred as "group" in text below) (see Table 31). In addition, a placebo group will be evaluated (~100 subjects, Step 1 and Step 2 pooled).

Table 31 Factorial design

		No adjuvant (Plain)	Factor B: Adjuvant	
			$AS01_E$	$AS01_B$
Factor A: Antigen dose	30 µg	100	100	100
	60 µg	100	100	100
	120 µg	100	100	100

Considering a 10% rate of non-evaluable subjects, it is assumed that approximately 90 subjects per group will be evaluable for the analysis of RSV-A neutralizing antibody titers and for the CD4+ T-cells response.

The 9 RSV formulations will be first compared to the Placebo in terms of RSV-A neutralizing antibody titers at Day 91 using the Dunnett's method via a one way ANOVA model. The sample size of 90 subjects per group (in 10 groups) achieves ≥ 90% power to detect a difference of at least 2.3-fold (alpha=0.025, SD=0.4, CV=115.6%, PASS 12.0.10 Multiple comparisons Analysis using Dunnett's adjustment for multiplicity).

The effect of the second vaccination will then be evaluated by comparing the response one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31) in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibodies. This comparison will be done on the groups pooled according to their adjuvant content (3 groups of 270 subjects: $AS01_B$, $AS01_E$ and Plain). Table 32 below presents the power and fold increase that can be detected with a sample size of 270 subjects per pooled group. The sample size of 270 subjects per group achieves 90% power to detect a difference of at least 1.2 fold between Dose 2 and Dose 1.

Table 32 Effect of second vaccination: Power and fold increase with a sample size of 270 subjects per pooled group

N/group	N evaluable/group	N Pooled groups	Power	Fold increase
100	90	270	90%	1.2
			80%	1.17

Power calculation done in PASS 12.0.10: Paired T-test with alpha=0.025, SD=0.4 (CV=115.6%).

The effect of the adjuvant will also be evaluated on the same pooled groups (according to adjuvant content: $AS01_B$, $AS01_E$, Plain) by comparing sequentially the 2 adjuvanted groups to the Plain group, in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibody titers at Day 91. Table 33 below presents the power and fold increase that can be detected with a sample size of 270 subjects per pooled group. The sample size of 270 subjects per group achieves 90% power to detect a difference of at least 1.3-fold between one adjuvanted group and the Plain group.

Table 33 Effect of adjuvant: Power and fold increase with a sample size of 270 subjects per pooled group

N/group	N evaluable/group	N Pooled groups	Power	Fold increase
100	90	270	90%	1.3
			80%	1.25

Power calculation done in PASS 12.0.10: Two-sample T-test assuming equal variance, with alpha=0.025, SD=0.4 (CV=115.6%).

Finally, the antigen dose-response will be evaluated in each adjuvanted group in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells at Day 91. Table 34 below presents the power and fold increase that can be detected with a sample size of 90 per group. The sample size of 90 subjects per group would provide 90% power to detect a difference of at least 1.56 between 2 groups.

Table 34 Antigen dose-response: Power and fold increase with a sample size of 90 subjects per group

N/group	N evaluable/group	Power	Fold increase
100	90	90%	1.56
		85%	1.51
		80%	1.47

Power calculation done in PASS 12.0.10: Two-sample T-test assuming equal variance, with alpha=0.025, SD=0.4 (CV=115.6%).

10.5. Cohorts for Analyses

10.5.1. Exposed Set

The Exposed Set (ES) will include all subjects with study vaccine administration documented.

A safety analysis based on the ES will include all vaccinated subjects.

An immunogenicity analysis based on ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered.

10.5.2. Per-protocol Set for analysis of immunogenicity

The Per Protocol set (PPS) for analysis of immunogenicity will be defined by time point (to include all eligible subjects' data up to the time of important protocol deviations). The PPS will include all evaluable subjects in the ES:

- Meeting all eligibility criteria.
- For whom the administration route of the vaccine was as according to protocol.
- For whom the study vaccine was administered as per protocol.
- Who did not receive a concomitant medication/ product leading to exclusion from a PP analysis, as described in Section 6.6.2, up to the considered time point.
- Who did not present with a medical condition leading to exclusion from a PP analysis, as described in Section 6.7, up to the considered time point.
- Who complied with the vaccination schedule, as specified in Table 8.
- Who complied with the timings of the post-vaccination blood sampling for immune response evaluation, as specified in Table 8.

- For whom post-vaccination immunogenicity results are available for at least one assay component at the corresponding time points.

10.6. Derived and transformed data

Demography

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

Safety

- For a given subject and the analysis of solicited symptoms during the 7-day follow-up period after vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the ES will include only vaccinated subjects with documented safety data (i.e., eDiary completed).
- For analysis of unsolicited AEs, SAEs, pIMDs, pregnancies and concomitant medications, all vaccinated subjects will be considered. Subjects who did not report an event or concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

Immunogenicity

- Any missing or non-evaluable immunogenicity measurement will not be replaced:
  - For the within-group assessment, the descriptive analysis performed for each assay at each time point will exclude subjects with a missing or non-evaluable measurement. Kinetics will be plotted on subjects with results available at all time points.
  - For the between group assessments, the Analysis of covariance (ANCOVA) model will be fitted based on the subjects having a result at both the baseline and the considered time point.
- The geometric mean titers (GMTs)/geometric mean concentrations (GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the $\log_{10}$ transformed titers/concentrations.
- A seronegative subject will be defined as a subject whose antibody titer/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titer/concentration is greater than or equal to the cut-off value of the assay.
- The description of the handling of data below the lower limit of quantification for GMT/GMC calculation and fold increase will be described in the SAP.

10.7. Analysis of demographics

Demographic characteristics (age at vaccination in years, gender, race and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error and range will be provided for continuous data such as age.

The distribution of subjects will be tabulated as a whole and per group and for each age category (60-69 years and 70-80 years in Part B only).

Withdrawal status will be summarized by group using descriptive statistics:

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

10.8. Analysis of safety

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 30-day follow-up period will be tabulated with exact 95% confidence interval (CI) after each dose and overall. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination, for Grade 3 AEs considered related to vaccination and for Grade 3 non-serious AEs.

The percentage of subjects with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will also be tabulated after each dose and overall.

The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for Grade 3 (> 39.0°C/102.2°F) causally related fever. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after each vaccination.

For each group and for each hematology and biochemistry parameter:

- The percentage of subjects having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
- The summary of grading post-vaccination will be tabulated versus baseline. (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX C. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. SAEs will also be described in details.

For Part A only, pregnancy and pregnancy outcomes will be listed (if applicable).

For Part B only, the percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. PIMDs will also be described in details.

The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group after each vaccine dose and overall.

The analysis of safety will also be performed by age category (60-69 years and 70-80 years in Part B only).

10.9. Analysis of immunogenicity

The primary analysis will be performed on the PPS for immunogenicity and, if in any study group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is at least 10%, a second analysis will be performed on the ES.

10.9.1. Within groups evaluation - humoral immune response

For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified):

In Part A and Part B:

- Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
- GMCs/GMTs and their 95% CI will be tabulated and represented graphically.
- Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.
- Antibody titer/concentration will be displayed using reverse cumulative curves.
- The ratio of the RSVPreF3 ELISA antibody concentrations over the RSV-A neutralizing antibody titers will be computed and tabulated using descriptive statistics (Ratio of fold increase Post- over Pre-vaccination).

In Part B only:

- The distributions of antibody titers/concentrations will be tabulated.
- Individual post-vaccination results (at Days 31, 61 and 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots. Results of the placebo group will be used as a reference.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers) will be tabulated.
- The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.

The immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years) in Part B only. The humoral immune response by CMV status before vaccination might be explored in Parts A and B.

10.9.2. Within groups evaluation - Cell-mediated immune response

The following parameters will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI:

In Part A and Part B:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, upon in vitro stimulation and background substracted, measured by ICS using PBMCs.

- Frequency of CD4+ and/or CD8+ T-cells expressing **any combination of immune marker(s)** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.
- Geometric mean ratios of frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ , at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.

In Part B only:

- Frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

This will be displayed overall and by pre-vaccination category: <Q1, Q1-Q3, >Q3, where Q1/Q3 are respectively the 25th and the 75th percentiles of the results at pre-vaccination computed on pooled groups.

In addition, vaccine response in terms of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ, will be explored and summarised by group.

The descriptive immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years) in Part B only. The cell-mediated immune response by CMV status before vaccination might be explored in Parts A and B.

10.9.3. Between groups evaluation (Part B only)

Statistical analyses will be performed to compare the 9 RSV investigational vaccine formulations in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells at Day 91.

Additional exploratory comparisons might also be performed on the RSVPreF3 ELISA antibody concentrations at Day 91.

The between-groups analysis will be performed in several steps as follows:

1. The 9 RSV formulations will be first compared to the Placebo in order to identify groups whose means are significantly different from the mean of the Placebo group, in terms of RSV-A neutralizing antibody titers at Day 91 (alpha=2.5%, Dunnett's adjustment test for multiplicity).
2. The effect of the second vaccination will be evaluated by comparing the means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31), on the groups pooled according to their adjuvant content ($AS01_B$, $AS01_E$ and Plain), in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibody titers.
3. The RSV formulations will be then compared using an ANCOVA model. Appropriate contrasts will be implemented:

- To demonstrate the adjuvant effect (on pooled groups according to their adjuvant content: $AS01_B$, $AS01_E$, Plain), by testing sequentially $AS01_B$ and $AS01_E$ versus Plain (alpha=2.5% for each test) in terms of CD4+ T-cells expressing at least 2 markers and RSV-A neutralizing antibodies at Day 91 and, if applicable, by comparing $AS01_B$ vs $AS01_E$.
- To demonstrate linearity of increase in immune response when increasing the antigen dose in each adjuvanted group in terms of RSV-A neutralizing antibody and/or RSVPreF3-specific CD4+ T-cells at Day 91.

Further ANCOVA t-tests would demonstrate superiority of 120 µg or 60 µg, should a quadratic effect be demonstrated.

10.10. Analysis of RTI for Part B

The analysis will be performed on the ES.

Any RTI episode for which a visit for the assessment of potential RSV-RTI has been performed (with nasal/throat swab sampling) will be considered for the analysis. The assessment of RSV infection will be performed using qRT-PCR on nasal/throat swabs separately for samples collected by the subject and those collected by an appropriately qualified person (i.e., medical or nursing) at the assessment visit.

The proportion of subjects with at least one RSV-associated RTI (with 95 % CI) will be calculated by group.

Descriptive analyses (mean, median, min, max) of viral load assessed by quantitative PCR (RSV-A/B) of RSV-RTI will be performed by study group.

The incidence rate of all-cause RTI (with 95% CI) will be calculated by group. These will also be presented by co-infection identified by multiplex PCR.

10.11. Interpretation of analyses

The analyses will be descriptive with the aim to characterize the difference in safety/reactogenicity or immunogenicity between groups.

Exploratory comparisons between groups/adjuvants/doses should be interpreted with caution considering that there will be no adjustment for multiplicity of endpoints.

10.12. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.12.1. Sequence of analyses

In preparation of the planned IDMC evaluations, analyses of all available safety data (as clean as possible) will be performed (see Section 7.10 for more information). The blinded analyses will be done by the GSK study statistician and distributed to the study team. The unblinded analyses will be done by an Independent External Statistician (IES) to maintain the study blind and will be shared with IDMC members through a secured folder (refer to the IDMC charter). Only the outcome of the IDMC reviews will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written at this stage.

The analyses will be performed stepwise:

- A first analysis will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 91 are available (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). This will include results from all subjects in Part A and Part B. This analysis will be considered as final for those endpoints. A clinical study report will be written.

  At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available), but no individual listings will be provided to the study team. Given that summary safety results may unblind some specific subjects, the study will be considered as single-blind from this point onwards, with subjects remaining blinded up to study end (Visit 8, Month 14). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

  During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

  In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends. (Amended, 13 May 2020)

- A second analysis will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:
  - The safety analysis of data up to 6 months post-Dose 2.
  - The analysis of all qPCR data available at that time.
  - The analysis of any additional laboratory results up to one month post-Dose 2 that may become available for all planned subjects in Part B.

- A third immunogenicity analysis will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 8 are available, to evaluate the persistence up to 6 months post-Dose 2 in Part B.
- A fourth analysis will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 14 (Visit 8) are available for the subjects enrolled in Step 1 of Part B. This analysis will include any additional laboratory results that may become available at that time.

  No individual listings will be provided before the final end of study analysis.
- The final end of study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion are available (Month 14). All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage. An integrated clinical study report containing all available data will be written and made available to the investigators.

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

10.12.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the

investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (Phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals 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 subjects, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

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13. APPENDICES

APPENDIX A LABORATORY ASSAYS

Assay descriptions are provided below. Assays may possibly be adapted during assay development and/or qualification.

RSV A/B neutralization assay

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize the cytopathic effects of RSV on the host cell line, hence RSV replication.

First, virus neutralization is performed by incubating a fixed amount of RSV (A long strain [ATCC No. VR-26] or B strain 18537 [ATCC N°. VR-1580]) with serial dilutions of the test serum. Then, the serum-virus mixture is transferred onto a monolayer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL-81) and incubated for 3 days to allow infection of Vero cells by non-neutralized viruses and the formation of plaques in the cell monolayer. Following the fixation period, RSV-infected cells are detected using a primary antibody directed against RSV (anti-RSV IgG) and a secondary antibody conjugated with 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 Axiovision software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in ED_{60} (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].

RSVPreF3 ELISA

The RSVPreF3 IgG ELISA is under development. The assay will be based on an indirect ELISA allowing the detection and the quantification of total IgG antibodies directed against RSVPreF3 in human serum samples.

The principle of this assay will be as follows. The RSVPreF3 antigen will be adsorbed onto a 96-well polystyrene microplate. After a washing and a blocking step, 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 conjugated to horseradish peroxidase (HRP). Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSV F3 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).

Epitope specific competition assays

Epitope specific competition assays are based on the competitive binding between a labelled epitope-specific monoclonal antibody and non-labelled antibodies present in serum samples and targeting the same epitope on a coated antigen. A competition assay specific for the ***RSB1*** epitope, using RSVPreF3 protein as coating antigen, is under development. ***(Amended, 13 May 2020)***

The principle of competition assays is as follows: The RSVPreF3 protein antigen will be coated onto an assay plate. After blocking, dilutions of control serum or sample, as well as labelled, epitope specific, monoclonal antibody, are added to the coated plate. If epitope-specific antibodies are present in serum samples, they will compete with the monoclonal antibody for binding to the epitope on the antigen-coated plate. After washing, the bound, labelled antibody is then quantitated using a validated chromogenic detection system. The intensity of the detected signal is inversely proportional to the concentration of the epitope-specific antibodies present in the sample.

The antibody concentrations are calculated for each control and sample by transforming the optical density values corresponding to the dilutions into a % competition value, and from this, the epitope-specific antibody concentration of the samples and controls is calculated.

Intracellular staining (ICS)

ICS has been used to assess CMI responses as previously described [Díez-Domingo, 2010; Moris, 2011].

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

- CD3: phenotyping CD4 and CD8 T-cells;
- CD40L (CD154), expressed on activated CD4 T-cells, and 41BB (CD137): expressed on activated CD4 or CD8 T-cells [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006];
- IL-2: key for the development, survival and function of T-cells [Boyman, 2012];
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014];

- IFN-γ: anti-viral factor, associated with the Th1-like profile and CD8 T-cells [Schoenborn, 2007];
- IL-13: associated with the Th2-like profile [Bao, 2015];
- IL-17: associated with the Th17-like profile [Korn, 2009].

The results are expressed as the frequency of CD4+ or CD8+ T-cells expressing, per million of CD4+ or CD8+ T-cells:

- At least one/two immune marker(s) (to detect and measure the CD4+ or CD8+ T-cell response).
- Any Th specific immune marker (to determine the Th profile of the CD4 response).

B-cell ELISpot (Memory B-cell detection assay)

Antigen-specific memory B-cells will be quantified using a B-cell ELISPOT assay adapted from Crotty *et al.* [Crotty, 2004]. Briefly, PBMCs are cultivated in the presence of a phosphorothioate oligonucleotide containing unmethylated CG motifs (CpG 7909) for 5 days to induce differentiation of circulating memory B lymphocytes into IgG secreting cells. These cells are then transferred onto plates coated with the relevant antigen, RSVPreF3, for the detection of antigen-specific antibody secreting cells. In addition, the total number of memory B cells, irrespective of their specificity, is established by plating cells onto anti-human IgG coated plates. Bound human IgG is then detected using enzyme coupled anti-human IgG antibody and the subsequent addition of enzymatic substrate. Spots in the form of coloured precipitate are counted to enumerate the antigen-specific and total antibody secreting cells. The results are expressed as the frequencies of antigen-specific memory B cells per million of total memory B cells.

PCR

- ***Quantitative PCR able to discriminate RSV-A and RSV-B subtypes***

  Briefly, RSV A and RSV B RNAs extracted from the nasal/throat swabs are detected in a duplex PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involves nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time PCR reaction using a calibration curve (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

- ***Qualitative multiplex PCR for detection of a panel of viruses:***

  A qualitative PCR multiplex assay is used for the detection and identification of multiple respiratory virus nucleic acids in the nasal/throat swabs. The following virus types and subtypes can be identified in the assay:

  – Influenza A virus (Flu A)
  – Influenza B virus (Flu B)
  – Human respiratory syncytial virus A (RSV A)

- Human respiratory syncytial virus B (RSV B)
- Human Influenza A virus subtype H1 (Flu A-H1)
- Human Influenza A virus subtype H3 (Flu A-H3)
- Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)
- Human adenovirus (AdV)
- Human metapneumovirus (MPV)
- Human enterovirus (HEV)
- Human parainfluenza virus 1 (PIV1)
- Human parainfluenza virus 2 (PIV2)
- Human parainfluenza virus 3 (PIV3)
- Human parainfluenza virus 4 (PIV4)
- Human bocavirus 1/2/3/4 (HBoV)
- Human rhinovirus A/B/C (HRV)
- Human coronavirus 229E (229E)
- Human coronavirus NL63 (NL63)
- Human coronavirus OC43 (OC43)

Following total nucleic acids extraction, viruses are detected by multiplex real-time RT-PCR assays targeting the above mentioned viruses. A comparative analysis of the fluorescence intensities of each target is performed to detect the viruses present in the sample.

APPENDIX B CLINICAL LABORATORIES

Table 35 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 36 Outsourced laboratories

Laboratory	Address
NÉOMED-LABS Inc.	525, Cartier Ouest Laval Quebec Canada H7V 3S8 NÉOMED-LABS Inc.
Q Squared Solutions (Quest) LLC (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q Squared Solutions Limited	The Alba Campus (Rosebank) Livingston West Lothian EH54 7EG Scotland, United Kingdom

APPENDIX C FDA GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS (SEPTEMBER 2007)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

i. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (*e.g.*, a certain number of AEs, as defined in the table, may call for stopping the study). Less extreme observations (*e.g.*, mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements

are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

ii. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

iii. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, and 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categories adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

a. Tables for Clinical Abnormalities

Note from the sponsor: The tables in this section of the guidance will not be used in this particular study. Instead, the parameters as provided in the current RSV OA=ADJ-002 protocol are to be used.

b. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Table 37 FDA toxicity grading scales for hematology/ biochemistry parameters evaluated in the current study RSV OA=ADJ-002

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

iv. REFERENCES for the APPENDIX C

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)
2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)
3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)
4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)
5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)
6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

APPENDIX D COMMUNICATION FLOW IN CASE HOLDING RULES ARE MET

In order to provide an effective study conduct, a proper communication plan will be set up between investigators, Local Operating Company (LOC) personnel, Central functions and the IDMC. This communication plan will allow an effective vaccination halt as well as restart or suspend of vaccination.

Holding rules identified by Investigators

If a holding rule is met at the site level, the study must be put on hold immediately in the respective center and the study Local Medical Lead (LML) in the LOC should be informed. The LOC will inform the central study team (study CRDL, Study Delivery Lead and Safety Physician), who will subsequently inform other LOCs and Investigators from all study centers. All vaccinations will cease as soon as possible, but all other procedures relating to safety and immunology will continue.

Following an internal review as well as review by the IDMC, the Sponsor will decide to continue the conduct of, suspend or modify the study. This decision will be documented and provided in writing to the investigators.

Holding rules identified by the IDMC

If a holding rule is met following safety evaluation by the IDMC, the IDMC Chairman must notify the primary GSK contact immediately. The central study team (study CRDL, Study Delivery Lead and Safety Physician) will subsequently inform the LOCs and Investigators from all study centers. All vaccinations will cease immediately, but all other procedures relating to safety and immunology will continue.

Following additional assessment by the IDMC, the Sponsor will decide to continue the conduct of, suspend or modify the study. This decision will be documented and provided in writing to the investigators.

APPENDIX E AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
IND number	Not available
EudraCT number	2018-000849-38
Administrative change number:	Administrative Change 1
Administrative change date:	25 July 2019
Co-ordinating author:	PPD

Rationale/background for changes:

- The toll-free number for Emergency Unblinding for US was not correct. This protocol administrative change provides the correct number.
- Study personnel has been updated.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Protocol cover page:

Contributing authors	PPD, ***Clinical and Epidemiology R&D Project Lead***

Protocol Administrative Change 1 Sponsor Signatory Approval:

Sponsor signatory	PPD Clinical and Epidemiology R&D Project Lead, Older Adults project

Section 7.8 Emergency unblinding:

GSK Biologicals' Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email Phone: PPD For US: Toll-free number : PPD Fax: PPD email: PPD

GlaxoSmithKline Biologicals SA

Vaccines R &D

Protocol Amendment 1

eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
IND number	***18540***
EudraCT number	2018-000849-38
Amendment number:	Amendment 1
Amendment date:	13 May 2020
Co-ordinating author:	PPD

Rationale/background for changes:

The protocol, dated 29 July 2019, is amended primarily to provide flexibility to certain study procedures in response to special circumstances (e.g., COVID-19 pandemic). Therefore, a new section (Section 5.10) has been added to provide guidance on adapting study procedures during special circumstances, such as nCOV19 pandemic.

The measures (as in Section 5.10) include the following:

- **Instruction for the remaining scheduled visit (Visit 8):** Planned study visit can proceed, if the study subjects are healthy and allowed to come to the site to have the blood sample and safety information collected. If the visit is impacted due to the national guidelines and/or site restrictions linked to the special circumstances, and it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 8), the samples will be encoded as missing and encoded as protocol deviation. If the visit is impacted, the safety information (as per protocol: SAEs, pIMDs, concomitant medications/vaccinations and intercurrent medical conditions) will be collected by site staff via telephone contact or other means of virtual contact, and this will not be considered as protocol deviation.
- **Instruction for collection of home self-swabs in case study participant experiences suspected respiratory tract infection (RTI) symptoms:** In case the investigator determines this is not posing additional risk to the subjects or household members, the subjects will be instructed to perform the home self-swab and keep it in their freezer (preferred) or refrigerator until recovered, and able to bring it to the site. If there is a possibility, a healthy relative can bring the sample to the site to be processed. In case investigator judges this is not advisable due to the national guidelines and/or site restrictions linked to the special circumstances, the self-swab will not be collected and the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. The investigator and/or the site staff will provide these instructions to the subjects

during the active surveillance contacts carried out every 2 weeks during the RSV season period.

- **Instructions for assessment visit for suspected respiratory tract infection (RTI):** Site staff will decide on the management of the cases (either having a site/different site location/home visit or by telephone contact) based on COVID-19 national guidelines and/or site restrictions linked to the special circumstances. If the nasal and throat samples cannot be collected at site, the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. Biological samples will not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

Additional changes:

- A**s** per the request from the regulatory (Belgian) authorities, clarification has been added to the holding rule wording for non-life-threatening SAEs in Section 7.10.4. The paragraph has been modified to add clarification that SAEs that are not related to study vaccination will not be considered for safety holding rules.
- Blood collection and testing plan for samples arising at the last study visit (Visit 8) have been updated, following the formulation selection and, based on data generated from the first analysis. At the last visit, blood samples will be collected for antibody and CMI determination from a subset of subjects (N≅460, from all subjects in part B1 [N≅100] and subjects who received a selected level of antigen dose and Placebo in part B2 [N≅360]).
- Blinding instructions have been updated to reflect the impact of the change in blood collection and testing plan at the last study visit (Visit 8). During the last study visit, the blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.

  In case there will be an extension study planned, with all or a subset of participants included, the investigators may be provided with the list of study subjects eligible to participate in such study, before the parent study ends. Therefore, the investigators, site and study staff will potentially receive an individual data listings for a subset. All subjects in this subset may be unblinded before the study ends.
- Missing cut-off values for some humoral assays have been included. The new naming for the competitive ELISA (RSVPreF3 RSB1 specific) has been implemented.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

- **Synopsis/Study Blinding, Section 1.2.2.4/Study Blinding, Section 3/Blinding, Section 5.3/Method of Blinding and Section 10.12.1/Sequence of Analyses, text added:** ***During the last study visit, blood samples will be collected only from a subset of subjects (N≅460, all subjects in part B1 and subjects who received a selected level of antigen dose and Placebo in part B2). Therefore, the investigators, site and study staff will be partially unblinded at group level, but not at the individual level.***
- Across the document, ~~site 0~~ has been be changed to ***RSB1*** for the site specific RSVPreF3 competitive ELISA.
- **Section 3, text added**: ***Refer to Section 5.10 for study procedures to be considered during special circumstances.***
  - **Text edited: Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91, Month 8 and ***from a subset at*** Month 14 (Visits 1, 3, 4, 6, 7 and 8).
  - **part B step was incorrectly mentioned for a group: Groups 120-AS01E_B1 and 120-AS01E_B~~1~~*2*:** subjects receiving 2 doses of the investigational RSV vaccine containing 120 μg RSVPreF3 adjuvanted with $AS01_E$
- **Section 5.1, text added*: 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 and safety must be applied. For the duration of such special circumstances, additional measures may be implemented for enrolled participants. Refer to Section 5.10 for further details.***
- **Section 5.6.3.11, text added*: (at Visit 8 blood will be collected from a subset of subjects). Deleted text 'all' as blood will be collected from a subset at Visit 8:*** A volume of approximately 20 mL of whole blood (to provide ~6.6 mL of serum) should be drawn from ~~all~~ subjects for analysis of the humoral immune response at each pre-defined time point. A volume of approximately 25 mL of whole blood should be drawn from ~~all~~ subjects for analysis of the CMI response at each pre-defined time point.
- **Section 5.9, text added:** ***Refer to Section 5.10 for measures for biological samples collection that may be implemented during special circumstances.***
- **Table 10 has been updated and assay cut-*off values been added.***

Table-10 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off[$]	Laboratory
Serum	Respiratory Syncytial Virus A Ab	NEUTRALIZATION	In-house	ED60	18	GSK Biologicals* or NÉOMED-LABS
Serum	Respiratory Syncytial Virus B Ab	NEUTRALIZATION	In-house	ED60	***30*** ~~TBD~~	GSK Biologicals* or NÉOMED-LABS
Serum	RSVPreF3-specific IgG antibody concentrations	ELISA	In house at Neomed Labs	ELU/mL	***25*** ~~TBD~~	Neomed Labs
Serum	RSVPreF3 ***RSB1*** ~~site 0~~ specific Ab	Competition ELISA	In-house	µg/mL	***2.11*** ~~TBD~~	GSK Biologicals* or NÉOMED-LABS

Ab: antibody; ELISA: enzyme-linked immunosorbent assay; RSV: respiratory syncytial virus;
ED60: Estimated Dose: serum dilution giving a 60% reduction of the signal compared to a control without serum
~~TBD: To be determined~~
* GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium;Marburg, Germany
[$] ~~Assay cut offs could be subject to change and will be defined in the Statistical Analysis Plan~~

- **Section 5.9.4.1, text added:**

Testing of ~~RSV-A neutralizing antibodies and~~ RSVPreF3 IgG antibodies will be performed on blood samples from all subjects, in both Part A and Part B, ***except at Month 14 (Visit 8)***.

Testing of RSV-A neutralizing antibodies ~~and RSVPreF3 IgG antibodies~~ will be performed on blood samples from all subjects, in both Part A and Part B, except at Month 8 (Visit 7) and Month 14 (Visit 8).

Testing of RSV-B neutralizing antibodies will be performed on blood samples from all subjects in Part B.

Testing of RSVPreF3 ***RSB1*** specific antibodies will be performed on blood samples from a subset of subjects ***at Day 31 or Day 91*** in Part B who received the selected vaccine formulation and placebo (N≅200).

Testing of CD4+/CD8+ CMI will be performed on blood samples from all subjects in both Part A and Part B, ***except at Month 8 (Visit 7) and Month 14 (Visit 8)***.

At Month 8 (Visit 7) blood sample testing for humoral response pertaining to RSV-A neutralizing antibodies and CMI response will be performed for all subjects in Part B1; and for a subset of subjects in Part B2, who received a selected level of antigen dose and Placebo (N≅460). Blood sample testing pertaining to the RSVPreF3 IgG antibodies will be performed for all subjects at Month 8 (Visit 7).

At Month 14 (Visit 8) humoral and CMI response testing will be performed for all subjects in Part B1; and for a subset of subjects in Part B2, who received a selected level of antigen dose and Placebo (N≅***460***). ~~testing might be performed only on blood samples from the subset of subjects who received the selected level of antigen dose or placebo (N≅400).~~

- ***New section added:***

Section 5.10 Study procedures during special circumstances

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 and safety must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Instruction for the remaining scheduled visit (Visit 8): Planned study visit can proceed, if the study subjects are healthy and allowed to come to the site to have the blood sample and safety information collected. If the visit is impacted due to the national guidelines and/or site restrictions linked to the special circumstances, and it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 8), the samples will be encoded as missing and encoded as protocol deviation. If the visit is impacted, the safety information (as per protocol: SAEs, pIMDs, concomitant medications/vaccinations and intercurrent medical conditions) will be collected by site staff via telephone contact or other means of virtual contact, and this will not be considered as protocol deviation.***
- ***Instruction for collection of home self-swabs in case study participant experiences suspected respiratory tract infection (RTI) symptoms: In case the investigator determines this is not posing additional risk to the subjects or household members, the subjects will be instructed to perform the home self-swab and keep it in their freezer (preferred) or refrigerator until recovered, and able to bring it to the site. If there is a possibility, a healthy relative can bring the sample to the site to be processed. In case investigator judges this is not advisable due to the national guidelines and/or site restrictions linked to the special circumstances, the self-swab will not be collected and the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. The investigator and/or the site staff will provide these instructions to the subjects during the active surveillance contacts carried out every 2 weeks during the RSV season period.***
- ***Instructions for assessment visit for suspected respiratory tract infection (RTI): Site staff will decide on the management of the cases (either having a site/different site location/home visit or by telephone contact) based on COVID-19 national guidelines and/or site restrictions linked to the special circumstances. If the nasal and throat samples cannot be collected at site, the sample will be encoded as missing. Samples that are not collected will be documented as protocol deviations. Biological samples will not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

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

- **Section 7.3.1, text added***: Refer to Section 5.10 for measures for safety follow-up that may be implemented during special circumstances.*

- **Table 7 footnote added:** ***[4] At Visit 8, blood samples for antibody and CMI determination will be collected from all subjects in part B1; and from a subset of subjects in part B2 who received a selected level of antigen dose and Placebo.*** To refer to this footnote, a numeric reference been added (4) to the blood sampling solid bullets at Visit 8.

  Refer to Section 5.10 for study procedures to be considered during special circumstances.

- **Table 9, footnote text added:**

  [***] At Visit 8, blood samples for antibody and CMI determination will be collected from all subjects in part B1; and from a subset of subjects in part B2 who received a selected level of antigen dose and Placebo. To refer to this footnote, a numeric reference been added (***) to the blood sampling solid bullets at Visit 8.

  Refer to Section 5.10 for study procedures to be considered during special circumstances.

- **Planned number of subjects for humoral and CMI testing has been updated in Table 15*:***

Table 15 Immunological read-outs in Part B

Blood sampling time point*		Sub-cohort	No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point				
Humoral immunity (on serum samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3
		Subset	~ 200	RSVPreF3 ***RSB1*** specific antibody	4
visit 3 (Day 31)	PI D31	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 4 (Day 61)	PI D61	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
visit 6 (Day 91)	PII D91	All subjects	~ 1000	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3
		Subset	~ 200	RSVPreF3 ***RSB1*** specific antibody	4
visit 7 (Month 8)**	PII M8	***Subset***	~ ***460***	RSV-A neutralizing antibody	1
		All subjects	~1000	Anti-RSVPreF3-specific IgG antibody	2
visit 8 (Month 14)***	PII M14	~~All subjects~~	~~~1000~~	RSV-A neutralizing antibody	1
		Subset	~***460***	Anti-RSVPreF3-specific IgG antibody	2
Cell-mediated immunity (on PBMC samples)					
visit 1 (Day 1)	Pre-Vacc	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 3 (Day 31)	PI D31	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 4 (Day 61)	PI D61	All subjects	~ 1000	CD4+/CD8+	-
visit 6 (Day 91)	PII D91	All subjects	~ 1000	CD4+/CD8+	1
		Subset	~ 400	Memory B-cells	2
visit 7 (Month 8)**	PII M8	~~All subjects~~	~~~1000~~	CD4+/CD8+	-
		Subset	~ ***460***		
	PII M14	Subset	~~~400~~	CD4+/CD8+	1

Blood sampling time point*		Sub-cohort	No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point				
visit 8 (Month 14)***			~ ***460***		
		Subset	~ 400	Memory B-cells	2

Pre-Vacc: Pre-vaccination; PI DX: Post-Dose 1 Study Day X; PII DX: Post-Dose 2 Study Day X; M: Month
PBMC: Peripheral Blood Mononuclear Cells
* Testing of additional time points for RSVPreF3 RSB1 specific antibodies, RSV-B neutralizing antibodies and memory B-cells might be performed, should the results indicate that further investigation of the immune response is necessary.
***** At Visit 7, blood samples for RSV-A neutralizing antibody determination, and CMI determination will be tested from a subset of subjects (all subjects in part B1; and a subset of subjects in part B2, who received a selected level of antigen dose and Placebo).***
****** At Visit 8, blood samples for antibody and CMI determination will be collected and tested from all subjects in part B1; and from a subset of subjects in part B2, who received a selected level of antigen dose and Placebo.***

- **Section 7.10.4, text deleted/added**: the text 'that ~~cannot reasonably~~ be attributed' has been edited to 'that ***are not*** attributed' to clarify that events that are not related to study vaccination will not be considered for safety holding rules. The paragraph has further been further structured using bullets:

Of note, no formal holding rules will be applied for other safety data such as:

  - SAEs that are not life-threatening and ~~cannot reasonably~~ ***are not*** attributed to the study vaccination,
  - Missed visits due to vaccine-related AEs,
  - Grade 1 and Grade 2 solicited, unsolicited AEs in the 7-day follow-up period, unsolicited AEs collected from Day 8 to Day 30 after vaccination.

- The list of abbreviations has been updated and COVID-19 has been included:

COVID-19 ***Coronavirus Disease 2019***

- The coordinating and contributing authors section has been updated to reflect the current contributor names in this amendment, the following names have been added: PPD (Scientific Writer), PPD (Study Delivery Lead), PPD (Project Statistician), PPD (Clinical Laboratory Sciences Study Manager) and PPD (Clinical Read-out Team Leader).
- Current role for PPD has been included: Clinical ~~and Epidemiology Scientist~~ ***Research and Development Lead***
- Typographical correction done for:
  - ~~etenogestrel~~ changed to ***etonogestrel*** in Glossary of Terms section for Adequate contraception.
  - **Groups 120-AS01E_B1 and 120-AS01E_~~B1~~*B2*:** subjects receiving 2 doses of the investigational RSV vaccine containing 120 µg RSVPreF3 adjuvanted with $AS01_{E,}$ in Section 3/Study design overview.

- Table 28, text edited: ~~Toll free number~~ ***Phone***
- ***The SMR database fields have been decoupled. The table with study intervention details has been updated based on GSK Vaccines' implementation of the IDMP ISO requirements and it does not impact, subject's safety, study conduct or study results.***