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

Primary study vaccine and number	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A): • RSVPreF3 recombinant antigen, 120 µg adjuvanted with $AS01_B$
Other study vaccine/product	Control: Saline solution
eTrack study number and abbreviated title	209699 (RSV OA=ADJ-003)
Date of protocol	Final Version 1: 30 April 2019
Title	Phase I, observer-blind, safety, reactogenicity and immunogenicity study of GSK's respiratory syncytial virus (RSV) vaccine GSK3844766A in Japanese subjects aged 60-80 years.
Short title	A phase I, randomized, placebo-controlled, observer-blind study to evaluate the safety, reactogenicity and immunogenicity of GSK's investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_B$) when administered intramuscularly according to a 0, 2-month schedule in Japanese adults 60-80 years of age.
Co-ordinating author	PPD, Scientific Writer (XPE Pharma and Science, for GSK)
Contributing authors	• PPD, Clinical Research and Development Lead • PPD, Project Statistician • PPD, Lead Statistician • PPD, Study Delivery Lead • PPD and PPD, Clinical Trial Supply Managers • PPD and PPD, Clinical Laboratory Sciences Study Manager (Business & Decision, for GSK)

eTrack study number and abbreviated title	209699 (RSV OA=ADJ-003)
Short title	A phase I, randomized, placebo-controlled, observer-blind study to evaluate the safety, reactogenicity and immunogenicity of GSK's investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_B$) when administered intramuscularly according to a 0, 2-month schedule in Japanese adults 60-80 years of age.
Contributing authors	• PPD, Clinical Read-out Team Leader • PPD, Safety Scientist • PPD, Safety Physician • PPD, Oversight Data Manager • PPD, Study Data Manager • PPD, Global Regulatory Affairs • PPD, Global Patent Representative • PPD and PPD, Local Delivery Leads • PPD, Clinical and Epidemiology R&D Project Lead

GSK Protocol WS v 16.0.1

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209699 (RSV OA=ADJ-003)
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Sponsor signatory	Narcisa Mesaros, Clinical and Epidemiology R&D Project Lead
	_____
Signature	_____
Date	_____

Protocol Investigator Agreement

I agree:

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

Hence, I:

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

eTrack study number and Abbreviated Title	209699 (RSV OA=ADJ-003)
Date of Protocol	Final Version 1: 30 April 2019
Short Title	A phase I, randomized, placebo-controlled, observer-blind study to evaluate the safety, reactogenicity and immunogenicity of GSK's investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_B$) when administered intramuscularly according to a 0, 2-month schedule in Japanese adults 60-80 years of age.
Investigator name	
Signature	
Date	
GSK Japan study representative name, function and title	
Signature	
Date	

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart, Belgium

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 Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.8.3.

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

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

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.5.4.1.

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1. SYNOPSIS

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:

RSV is a ribonucleic acid (RNA) virus of which 2 antigenically distinct subgroups exist, referred to as RSV-A and RSV-B. RSV is a highly contagious human pathogen that causes respiratory tract infections (RTI) in people of all ages. According to the 'Centers for Disease Control and Prevention' (CDC) website, 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). The current studies available in Japan are on a smaller scale when compared to the current abundance of data obtainable for RSV disease burden globally and in the US. Although a limited amount of information is currently available, recent studies suggest that the burden of disease for RSV infections is high, and can conclude that RSV is an important and underreported disease in the older adult population in Japan.

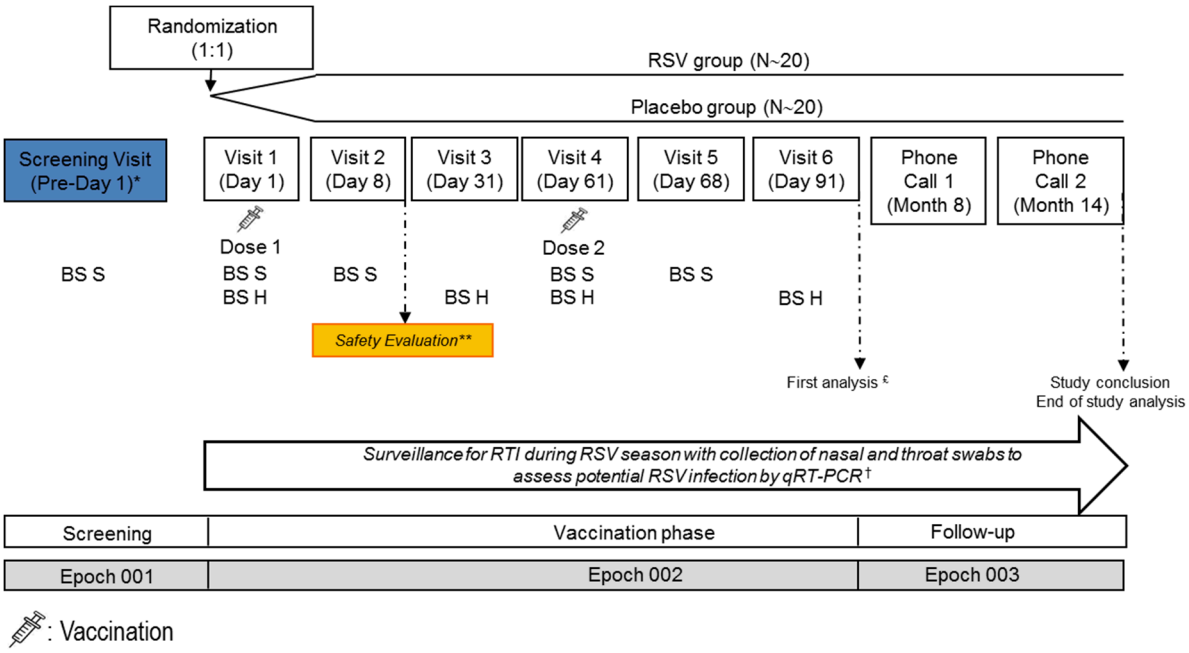
Despite the significant medical need, there is currently no prophylactic vaccine approved for the prevention of LRTD caused by RSV. GlaxoSmithKline Biologicals SA (GSK) is developing a new investigational RSV vaccine against moderate to severe RSV-associated (subtypes A and B) disease in adults aged 60 years or above.

This study in Japan will evaluate an investigational RSV vaccine formulation, with 120 μg of pre-fusion conformation antigen RSVPreF3 adjuvanted with $AS01_B$ 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 GSK's investigational RSV vaccine in ethnic Japanese adults 60-80 years of age, for further development of the RSV vaccine based on those results.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
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).	• 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). – Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).
Secondary	
To evaluate the humoral immune responses 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).	• 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-A. – RSVPreF3-specific IgG antibody concentrations.
To evaluate the safety of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 -month schedule, up to the end of follow-up (Month 14, Phone call 2).	• 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.
To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV seasons in combined nasal and throat swab samples collected during the assessment visit for potential RSV-RTI.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in the combined nasal and throat swabs collected during the assessment visit for potential RSV-RTI during the RSV seasons, up to the end of follow-up.
Tertiary	
To further characterize immune responses to investigational RSV vaccine formulation.	• 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. • 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.
To evaluate the occurrence of RSV-associated RTI during the RSV seasons using self-collected nasal swabs.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

Overall Design:



BS S: Blood sample for safety evaluation (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
qRT-PCR: quantitative reverse transcription 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.
** An internal Safety Review Committee (iSRC) evaluation of safety data up to Day 8 from all subjects will be performed before proceeding with administration of Dose 2. Additional iSRC evaluations will happen during the conduct of the study.
† In case of RTI symptoms during the RSV seasons (from August until end of February), 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).
£ A first analysis will be performed on all data collected up to Day 91 for at least primary and secondary endpoints (except for the occurrence of RSV RTI). The analysis will be based on data as clean as possible.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of activities

Epoch	Screening *(Epoch 001)*	Vaccination phase *(Epoch 002)*						Follow-up *(Epoch 003)*		RTI surveillance		Notes
Type of contact	Screening Visit [1]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Phone call 1	Phone call 2	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					
Informed consent	●											[See Section 12.4.3 for details]
Check inclusion/exclusion criteria	●	O										[See Section 6.1 and 6.2 for Inclusion and Exclusion criteria] [See Section 8.2.1 for more information]
Collect demographic data	O	●										[See Section 8.2.2 for more information]
Medical history	O	●										[See Section 8.3.3 for more information]
Vaccination history [2]	O	●										[See Section 8.3.4 for more information]
Physical examination /Vital signs	O	●	O [3]	O [3]	O [3]	O [3]	O [3]				●	[See Section 8.3.5 for more information]
Check contraindications to vaccination		O			O							[See Section 7.7 for more information]
Pre-vaccination body temperature		●			●							[See Section 8.3.7 for more information]
Vaccine												
Study group and treatment number allocation		O										[See Section 7.2.2.2.1 for more information]
Treatment number allocation for subsequent doses					O							[See Section 7.2.2.2.2 for more information]
Vaccine administration		●			●							[See Section 8.3.9 for more information]

Epoch	Screening *(Epoch 001)*	Vaccination phase *(Epoch 002)*						Follow-up *(Epoch 003)*		RTI surveillance		Notes
Type of contact	Screening Visit [1]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Phone call 1	Phone call 2	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					
Recording of administered treatment number		●			●							[See Section 7.2.2 for more information]
Laboratory assay												
Blood sampling for antibody determination (~10 mL)		● [4]		●	● [4]		●					[See Section 8.4.2.1 for more information]
Blood sampling for hematology and biochemistry analysis (~5.5 mL)	● [1]	● [4]	●		● [4]	●						[See Section 8.4.2.1 for more information]
RTI surveillance												
Instruct/remind subjects of RTI surveillance during RSV seasons										●		[See Section 8.6 for more information]
Distribution of material for nasal swab collection at home (including instructions)		O									O	
Recording of nasal swab collection at home											●	[See Section 8.6.3 for more information]
Nasal and throat swab samplings											●	[See Section 8.4.2.2 and 8.6.3 for more information]
Documentation of symptoms and signs of RTI											●	See Section 8.6.3 for more information
Safety assessments												
Recording of any concomitant medications/vaccinations		●	●	●	●	●	●	●	●		●	[See Section 7.5.1 for more information]
Recording of any intercurrent medical conditions		●	●	●	●	●	●				● [6]	[See Section 7.6 for more information]
Distribute and instruct subject on the use of eDiary devices for solicited AEs		O			O [5]							[See Sections 8.3.11 and 12.5.7 for more information]

Epoch	Screening *(Epoch 001)*	Vaccination phase *(Epoch 002)*						Follow-up *(Epoch 003)*		RTI surveillance		Notes
Type of contact	**Screening Visit** [1]	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Phone call 1**	**Phone call 2**	**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**					
Return of eDiary devices							O					
Distribution of paper diary cards for unsolicited AEs		O			O							[See Section 8.3.12 for more information]
Return of paper diary cards			O	O		O	O					
Recording of unsolicited AEs within 30 days post-vaccination (Days 1-30)		●	●	●	●	●	●					[See Section 8.3.13 for more information]
Recording of SAEs and pIMDs		●	●	●	●	●	●	●	●		●	[See Sections 12.5.7, 12.5.8 and 12.5.5.1 for more information]
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●		●	
Recording of AEs/SAEs leading to withdrawal from the study		●	●	●	●	●	●	●	●		●	
Recording of causality assessment for solicited general AEs on eDiary web-portal			●			●						
Screening conclusion	●											
Study Conclusion									●			[See Section 5.4 for more information]

Note: The double-line borders following Day 91 indicate the analysis which will be performed. See Section 10.4 for all details.
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] Blood sampling to be performed before vaccination.

[5] Only re-instruction on the use of eDiary device at Visit 4.

[6] Intercurrent medical conditions will only be collected up to Visit 6 (Day 91); thus, not during Assessment visits for potential RSV-RTI occurring after Visit 6.

Whenever possible, the investigator should arrange study visits within the intervals described in Table 2.

Table 2 Intervals between study visits

Interval	Length of interval	Allowed interval
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 - 65 days
Visit 4→Visit 5	7 days	7 - 10 days
Visit 4→Visit 6	30 days	30 - 37 days
Visit 4→Phone call 1	180 days	180 - 200 days
Visit 4→Phone call 2	365 days	365 - 395 days

* 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.

3. INTRODUCTION

3.1. Study rationale

Despite the significant medical need, there is currently no prophylactic vaccine approved for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (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 Biologicals SA (GSK) 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.

The purpose of this study in Japan is to evaluate the safety, reactogenicity and immunogenicity of GSK's investigational RSV vaccine in ethnic Japanese adults 60-80 years of age, for further development of the RSV vaccine based on those results.

The rationale for the study design is presented in Section 5.1.

3.2. Background

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, re-infection 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. immunocompromised subjects or older adults), re-infections can also lead to severe disease [Graham, 2011].

The current studies available in Japan are on a smaller scale when compared to the current abundance of data obtainable for RSV disease burden globally and in the US. Although a limited amount of information is currently available, recent studies [Ikematsu, 2012; Morimoto, 2015; Doi, 2014; Kanou, 2018; Takahashi, 2016; Kurai, 2016] suggest that the burden of disease for RSV infections is high, and can conclude that RSV is an important and under-reported disease in the older adult population in Japan.

Data on hospitalization rates, co-morbidity and mortality rate for RSV in older adults in Japan are limited. One study assessing the burden of community-onset pneumonia (COP) in Japan found RSV to be the third leading viral pathogen found in COP cases. Out of 1201 cases who underwent Multiplex-PCR in sputum specimens, 51 (4%) tested positive for RSV and 64 (5%) with Influenza; 23% of all pneumonia cases were found to be associated with respiratory viruses. The majority (75%) of the patients with COP were ≥65 years of age [Morimoto, 2015]. In another study [Takahashi, 2016], 5.3% (43/817) of the adult cases with pneumonia during two consecutive winter seasons were diagnosed as having RSV-related illness, while 3.1% (25/817) had influenza-related illness. For the 43 patients with RSV-related pneumonia, the mean age was 81.0 years (range: 24–95). In terms of co-morbidity in patients with RSV-related pneumonia, the same study found respiratory disorders in 30.2% (13 patients), house oxygen therapy in 7% (3 patients), and other systemic disorders in 72.1% (31 patients). Finally, the 30-day mortality rate for RSV-related pneumonia was found to be 7.0% compared to 8.0% for influenza-related pneumonia. The overall hospital mortality rates for RSV-related pneumonia were found to be 11.6%, compared to 8.0% for influenza-related pneumonia [Takahashi, 2016].

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

3.3. Benefit/Risk assessment

In total, approximately 20 subjects in this study will be exposed to the investigational RSV vaccine, whereas approximately 20 subjects will receive placebo.

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

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the investigational RSV older adult vaccine.

3.3.1. Risk assessment

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine		
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 limited 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. Safety evaluations will be performed by an iSRC. Holding rules that have been established will be applied (refer to Section 8.7).
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 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 12.5.5.1). The occurrence of pIMD cases will be described.

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 insertion.	Subject Monitoring 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.

3.3.2. 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]).

3.3.3. Overall Benefit: Risk conclusion

The investigational RSV vaccine is currently in an early stage of clinical development. Taking into account the measures to minimize 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.

4. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints

Objectives	Endpoints
Primary	
• 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).	• 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). – Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).
Secondary	
• To evaluate the humoral immune responses 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).	• 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-A. – RSVPreF3-specific IgG antibody concentrations.
• To evaluate the safety of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 -month schedule, up to the end of follow-up (Month 14, Phone call 2).	• 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.
• To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV seasons in combined nasal and throat swab samples collected during the assessment visit for potential RSV-RTI.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in the combined nasal and throat swabs collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
Tertiary	
• To further characterize immune responses to investigational RSV vaccine formulation.	• 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. • Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:

Objectives	Endpoints
	– Antibodies against specific protein F epitopes. – Potential new immunological markers for protection. – Cross-reactive neutralizing antibody titers against hMPV.
• To evaluate the occurrence of RSV-associated RTI during the RSV seasons using self-collected nasal swabs.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

IM: intramuscular; RSV: respiratory syncytial virus; AE: adverse event; WBC: white blood cells; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; SAE: serious adverse event; pIMD: potential immune-mediated disease; RTI: respiratory tract infection; qRT-PCR: quantitative reverse transcription polymerase chain reaction.

5. STUDY DESIGN

5.1. Scientific rationale for study design

This study will evaluate an investigational RSV vaccine formulation, 120 µg of pre-fusion conformation antigen RSVPreF3 adjuvanted with $AS01_B$, when administered intramuscularly (IM) 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 GSK's investigational RSV vaccine in ethnic Japanese adults 60-80 years of age, for further development of the RSV vaccine based on those results.

5.1.1. 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 pre-fusion 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 $AS01_B$ adjuvant has 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]/$AS01_B$) can 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; Schwarz, 2018]. The HZ/su (gE/$AS01_B$) vaccine is currently licensed in several countries, including the US, Canada, the European Union, Japan and Australia.

5.1.2. 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 AS01-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].

5.1.3. Safety monitoring

Safety evaluations post-Dose 1 will be performed by an internal Safety Review Committee (iSRC) based on data collected up to 7 days post-vaccination from all subjects. Only upon favorable outcome of the iSRC evaluation, administration of Dose 2 will be initiated. For more detailed information on the study holding rules and safety monitoring, refer to Section 8.7.

5.1.4. Study blinding

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

A statistical analysis will be performed on data up to one month post-Dose 2. Given that summary results may unblind some specific subjects, the follow-up phase (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.

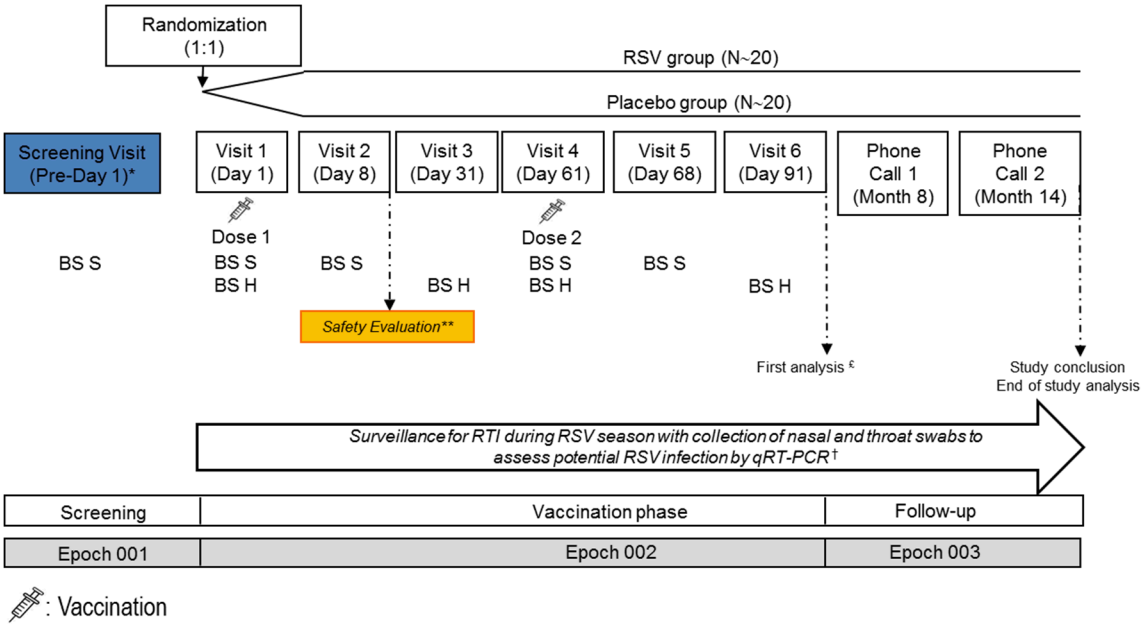
Please refer to the Section 12.1.2 (Glossary of Terms) for the definition of observer-blind and single-blind.

5.1.5. 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.

5.2. Overall design

Figure 1 Study design overview



BS S: Blood sample for safety evaluation (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
qRT-PCR: quantitative reverse transcription 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.
** An internal Safety Review Committee (iSRC) evaluation of safety data up to Day 8 from all subjects will be performed before proceeding with administration of Dose 2. Additional iSRC evaluations will happen during the conduct of the study.
† In case of RTI symptoms during the RSV seasons (from August until end of February), 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).
£ A first analysis will be performed on all data collected up to Day 91 for at least primary and secondary endpoints (except for the occurrence of RSV RTI). The analysis will be based on data as clean as possible.

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 SoA (Section 2), are essential and required for study conduct.

- **Type of study**: self-contained.
- **Experimental design**: a phase I, observer-blind, randomized, placebo-controlled, single-country study with 2 parallel groups (see Figure 1):
- **Duration of the study:** Approximately 14 months per subject.
  - 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 starting after Visit 6 (Day 91) and ending at Phone call 2 (Month 14)
- **Primary completion Date (PCD):** last visit of the vaccination phase (Visit 6 [Day 91]).

  Refer to Section 12.1.2 (Glossary of Terms) for the definition of PCD.
- **End of Study (EoS):** Last testing results released of samples collected up to Phone call 2 (Month 14) (for assays related to secondary endpoints only), or Last subject last Phone Call, whichever comes last.

  While no samples will be collected at Phone calls 1 and 2, nasal and throat swabs may be collected in case of RTI symptoms up to the Phone call 2 (Month 14) timepoint, if this timepoint falls within the RSV season.

  Refer to Section 12.1.2 (Glossary of Terms) for the definition of EoS.
- **Study groups:**
  - **RSV Group**: subjects receiving 2 doses of the investigational RSV vaccine containing 120 µg RSVPreF3 adjuvanted with $AS01_B$.
  - **Placebo**: subjects receiving 2 doses of placebo as control.

Table 4 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)		
				Epoch 001 (N/A)	Epoch 002 (observer-blind)	Epoch 003 (single-blind)
RSV Group	~20	60 - 80 years	120 µg RSVPreF3/$AS01_B$	x	x	x
Placebo	~20	60 - 80 years	Placebo	x	x	x

N/A: Not applicable

- **Control**: placebo control.
- **Vaccination schedule:** Two vaccine doses administered IM at Day 1 and Day 61.
- **Treatment allocation:** Subjects will be randomized using a centralized randomization system on internet (SBIR) on Day 1.

  A total of approximately 40 participants are planned to be enrolled in this study in a 1:1 ratio. The target is to enroll approximately 28 eligible participants aged 60-69 years (approximately 14 per group) and approximately 12 (and minimum 10) eligible participants aged 70-80 years (approximately 6 per group). The randomization algorithm will use a minimization procedure accounting for age, center and gender.

  For a detailed description of the randomization method, refer to Section 7.2.2**.**
- **Blinding:** observer-blind.

  The vaccination phase (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 10.4 for details on the sequence of analyses). Given that summary safety results may unblind some specific subjects, the follow-up phase (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Phone Call 2 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

  Refer to Section 7.3 for details on blinding and unblinding procedures.
- **RTI surveillance:** Active and passive surveillance will only be carried out during RSV seasons (from August until end of February) throughout the entire study:
  - **Active surveillance:** study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experienced 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:**
  - At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects (Section 8.2.3). 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).
  - **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** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).
  - **Nasal and throat swabs:** In case of RTI symptoms during the RSV season (from August until end of February), 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 8.6 for further details).

- **Data collection:** standardized electronic Case Report Form (eCRF). Solicited symptoms will be collected using an electronic Diary (eDiary). Unsolicited symptoms will be collected using a paper Diary.
- **Safety monitoring:** The study will be conducted with oversight by an iSRC. An iSRC evaluation of safety data up to Day 8 from all subjects will be performed before proceeding with administration of Dose 2. Additional iSRC evaluations will happen during the conduct of the study (see Section 8.7). If any safety concern is identified by the investigator or the sponsor, ad-hoc safety evaluations by the iSRC may be performed.

The investigator is not permitted to start the administration of the next dose until receipt of the favorable outcome of the safety evaluation, documented and provided in writing (scanned and emailed), authorizing the investigator to proceed. Moreover, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (refer to Table 17 and Table 18 for holding rules, and Section 8.7.2 for flow of communication related to holding rules)**.**

Refer to Section 8.7 for detailed description of holding rules and safety monitoring.

5.3. Number of subjects

Approximately 40 subjects will be randomized such that about 36 evaluable subjects complete the study, considering a 10% rate of non-evaluable subjects.

Withdrawals will not be replaced.

Refer to Section 10.1 for further information on sample size determination.

Overview of the recruitment plan

The study is planned to be conducted in Japan. 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 respecting the randomization block size.

Prior to Visit 1 (Day 1), 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.

5.4. Subject and study completion

A subject is considered to have completed the study if he/she is available for the concluding contact (Phone call 2) as described in the protocol.

6. STUDY POPULATION

6.1. 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 performance of any study specific procedure.
- 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.
- Japanese ethnic origin (defined as having been born in Japan with four ethnic Japanese grandparents and able to speak Japanese).
- Subject satisfying screening requirements.

6.2. 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 at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study.

6.2.1. Medical conditions

- Any medical condition that in the judgment of the investigator would make IM injection unsafe.
- 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 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.
- 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).
- Lymphoproliferative disorder and malignancy within 5 years.
- 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.

6.2.2. Prior/Concomitant therapy

- 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.
- 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.
- Previous vaccination with an RSV vaccine.
- Known previous administration of a vaccine containing MPL, QS-21 and/or MF59 (e.g. GSK's vaccine against human papillomavirus infection marketed as Cervarix, GSK's 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's 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.

- 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).
- 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.

6.2.3. Prior/Concurrent clinical study experience

- 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).

6.2.4. Other exclusions

- 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.
- Body mass index > 40 kg/m².
- Planned move to a location that will prohibit participating in the trial until study end.
- Bedridden subjects.

6.3. Criteria for temporary delay for screening and vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

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

  For subjects with acute disease and/or fever at the time of screening/vaccination, the visit may be re-scheduled within the allowed time-window.

6.4. 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.

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

7.1. Treatments administered

Table 5 Treatments administered

Study Treatment Name:	120 µg RSVPreF3/AS01B	Placebo
Study group	RSV Group	Placebo
Vaccine name	RSVPreF3 high dose *	NaCl
	AS01B	
Presentation	Freeze-dried antigen (174 µg/vial)	Liquid in monodose vial
	Liquid in monodose vial	
Vaccine formulation:	RSVPreF3=120µg	NaCl=150mM
	MPL=50µg; QS21=50µg; Liposomes	
Route of Administration	IM injection	IM injection
– **Location**	Deltoid	Deltoid
– **Laterality****	Non-dominant	Non-dominant
Number of doses to be administered:	2	2
Type of contact and timepoint	Visit 1 (Day 1) Visit 4 (Day 61)	Visit 1 (Day 1) Visit 4 (Day 61)
Volume to be administered	0.5 ml	0.5 ml
Packaging and Labelling	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	Hollister-Stier Laboratories

AS01B = Adjuvant System AS01B; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; SPM: Study Procedures Manual, QS-21: Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
* Corresponding to the highest dose of antigen evaluated in the RSV OA=ADJ 002 dose selection study.
** 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 Study Procedures Manual (SPM) for detailed instructions on study vaccine reconstitution.

After completing all prerequisite procedures prior to vaccination, 1 dose of study vaccine will be administered IM in the deltoid of the non-dominant arm (refer to Table 5 for details regarding the treatment administered). If the investigator or delegator 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 2; Section 6.2). Please refer to Section 12.1.2 (Glossary of Terms) for the definition of delegator.

The subjects 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 and syncope.

7.2. Method of treatment assignment

7.2.1. 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.

7.2.2. Randomization of treatment

7.2.2.1. Randomization of supplies

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

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

7.2.2.2.1. Study group and treatment number allocation

The target will be to enroll approximately 40 eligible subjects who will be randomly assigned to 2 study groups in a 1:1 ratio. The aim is to enroll approximately 28 eligible participants aged 60-69 years (approximately 14 per group) and approximately 12 (and minimum 10) eligible participants aged 70-80 years (approximately 6 per group).

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimization procedure accounting for age, center and gender. Minimization factors will have equal weight in the minimization algorithm.

After obtaining the signed and dated Informed Consent Form (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 age category (60-69 or 70-80 years) and the gender, 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 SPM for specific instructions.

7.2.2.2.2. 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.

7.3. Blinding and unblinding

During the vaccination phase, data will be collected in an observer-blind manner. 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 authorized medical personnel who will not participate in any of the study clinical evaluation assays.

A first statistical analysis will be performed on data available up to one-month post-Dose 2 (Visit 6, Day 91) (See Section 10.4 for details on the sequence of analyses). Given that summary safety results may unblind some specific subjects (e.g. an AE occurring only in a single group), anyone having access to this first analysis could become unblinded regarding that specific case. Therefore, the follow-up phase (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Phone call 2 [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.

GSK's 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 Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 12.5.8.1).

7.3.1. 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 Helpdesk (refer to Table 6) 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 Helpdesk (back up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

Table 6 Contact information for emergency unblinding

GSK Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email 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 1 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.

7.4. Handling, storage and replacement of study vaccine

The candidate vaccine to be used has been developed and manufactured by GSK.

The Quality Control Standards and Requirements for the 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.

For information on dosage and administration of the study vaccine, refer to Table 5. Administration will occur on Visit 1 (Day 1) and Visit 4 (Day 61).

7.4.1. 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.

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccine(s)/product(s) must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccine(s)/product(s) that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor).

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, storage and accountability of the study vaccine.

7.4.2. 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 10% additional vaccine doses will be supplied to replace those that are unusable.

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

7.5. Concomitant medications/products and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

At each study contact, the investigator or delegator should question the subject about any medications/products taken and vaccinations received by the subject.

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 period of 30 days post-vaccination (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 Month 14).
- 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 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 7.5.2
- Any concomitant medications/products/vaccines relevant to an SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMDs need to be recorded on the expedited Adverse Event report.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.2. 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 10.2 for populations to be analyzed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period (up to Month 14).
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period (up to Month 14). 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 organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or 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 Month 14).

7.6. 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 that may lead to elimination from per protocol analysis (refer to Section 12.1.2 (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. Intercurrent medical conditions will not be collected during the follow-up phase.

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.

7.7. Contraindications to subsequent vaccine administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination.

If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, the subjects should be encouraged to continue other study procedures at the discretion of the investigator (Section 9.2).

- 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.
- 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 12.5.5.1 for the definition of pIMDs.
- Subjects who experience any serious adverse event judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.

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 2 in Section 2), or the subject may be withdrawn at the discretion of the investigator (see Section 9.2).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C. 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.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. 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.

A schedule of activities is provided in Table 1. Time intervals between visits related to study procedures performed on subjects participating in the study are presented in Table 2.

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

Refer to Section 8.7 for information about the study holding rules, safety monitoring and safety evaluation by the iSRC.

8.1.1. Informed consent

The signed informed consent of the subject must be obtained before study participation. In addition, the signed informed consent of the designee must be obtained, in case a designee is assigned by the subject. Refer to Section 12.4.3 for the requirements on how to obtain informed consent. Please refer to Section 12.1.2 (Glossary of Terms) for the definition of designee.

8.2. Screening procedures to check subject eligibility

8.2.1. Check inclusion and exclusion criteria

When all data from the Screening Visit are available, 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 6.1 and 6.2.

8.2.2. 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.

8.2.3. 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.

8.2.4. Screening conclusion

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

8.3. Pre-vaccination procedures

8.3.1. 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 6.1 and 6.2. This does not need to be recorded in the subject's eCRF.

8.3.2. Collection of demographic data

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

8.3.3. Medical history

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

8.3.4. 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.

8.3.5. 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 (to be recorded in the eCRF at Visit 1 and at the Assessment visit for potential RSV-RTI).

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 8.6.3 for the list of symptoms to be recorded).

8.3.6. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Section 7.7 for more details.

8.3.7. Pre-vaccination body temperature

The body temperature of each subjects needs to be measured prior to any study vaccine administration and recorded in the eCRF. 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 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 2).

8.3.8. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 7.2.2. The number of each administered treatment must be recorded in the eCRF.

8.3.9. 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. If the investigator or delegator 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 2).

All subjects 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.

8.3.10. 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 7.5.

Intercurrent medical conditions must be checked (up to Visit 6) and recorded in the eCRF as described in Section 7.6.

8.3.11. Distribution of eDiary devices

eDiary devices will be distributed at Visit 1 (Day 1). At this timepoint, the subjects or designees will be instructed on the use of the eDiaries for the capture of solicited AEs (re-instructions will be provided at Visit 4). Refer to Section 12.5.7 for details regarding the completion of the eDiary devices. The devices need to be returned at Visit 6 (Day 91).

8.3.12. 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 in the eDiary) they may have experienced as well as any medication taken in the 30-day period following each vaccination. Refer to Section 12.5.4 for guidelines.

8.3.13. Recording of AEs and SAEs

Solicited AEs will be recorded by the subjects or their designee 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 12.5.7 for the detailed procedures for the investigator to record AEs and SAEs. Refer to Section 12.5.8 for guidelines and how to report SAE reports to GSK.

8.3.14. 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 12.5.5.1 for the detailed procedures for the investigator to record pIMDs. Refer to Section 12.5.8.4 for guidelines and how to report pIMD reports to GSK.

8.3.15. Study conclusion

The investigator will:

- Review data collected to ensure accuracy and completeness.
- Complete the Study Conclusion screen in the eCRF.

8.4. Efficacy assessments

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

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 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 Japan 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.

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 8.4.4 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.

8.4.1. Use of specified study materials

When materials are provided by GSK, 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 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK 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.

8.4.2. Biological samples

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

Table 7 Biological samples

Sample type	Timepoint	Subset	Quantity	Unit
Blood for humoral immune response	Visit 1 (Pre-Vacc) Visit 3 (PI D31) Visit 4 (PI D61) Visit 6 (PII D91)	All enrolled subjects	~10	ml
Blood for hematology/biochemistry	Screening Visit (Pre-Day 1)	All screened subjects	~5.5	ml
	Visit 1 (Pre-Vacc) Visit 2 (PI D8) Visit 4 (PI D61) Visit 5 (PII D68)	All enrolled subjects		
Nasal swab specimen collected by subject at home	Assessment visit for potential RSV-RTI	Event-driven	-	-
Combined nasal and throat swab specimen collected by qualified staff	Assessment visit for potential RSV-RTI	Event-driven	-	-
Total quantity of blood for each subject			**~ 67.5**	**mL**

8.4.2.1. Blood sampling for safety or immunogenicity response assessments

Blood samples will be taken during certain study visits as specified in Section 2. Refer to the SPM for more details. Blood sampling at vaccination visits needs to be performed before vaccination.

- 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. After centrifugation, serum samples should be kept at room temperature (20 to 25°C) until shipment.
- A volume of approximately 10 mL of whole blood (to provide ~3.3 mL of serum) should be drawn from all subjects for analysis of the humoral immune response at each pre-defined time point. After centrifugation, serum samples should be kept at -20°C or below until shipment.
- The overall volume of blood that will be collected from each subject during the entire duration of the study is approximately 67.5 mL.

8.4.2.2. Other biological samples

During the assessment visit for potential RSV-RTI, one swab will be collected from both nostrils of each subject and another swab will be collected from the throat. Both swabs will be placed together in one M4RT medium tube and sent for testing. Refer to the SPM for more details about nasal and throat swab sampling.

In case of RTI symptoms (at least 3) reported by the subject, the subject will be asked to collect a nasal swab from both nostrils at home within 48 hours after the start of symptoms.

8.4.3. Laboratory assays

Please refer to Section 12.2 (Appendix 2) for a detailed description of the assays performed in the study. Please refer to Section 12.3 (Appendix 3) 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 (see Table 8).

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

Table 8 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* or NÉOMED-LABS
SERUM	Respiratory Syncytial Virus B Ab	NEUTRALIZATION	In-house	ED60	TBD	GSK* or NÉOMED-LABS
Serum	RSVPreF3-specific IgG antibody concentrations	ELISA	In house at Neomed Labs	ELU/mL	TBD	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 laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.
**Refer to Section 12.3 (Appendix 3) for the laboratory addresses.
[$] Assay cut-offs could be subject to change and will be defined in the Statistical Analysis Plan.

Hematology and biochemistry

Hematology and biochemistry assays for safety assessment will be performed in a central laboratory (see Table 9).

Table 9 Hematology/biochemistry

System	Discipline	Component	Method	Scale**	Laboratory***
Whole blood	Hematology	Leukocytes (White Blood Cells)	As per central laboratory procedure	Quantitative	Q² 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 Section 12.7, Appendix 7). Basophils, monocytes, erythrocytes and uric acid are not included in the FDA Toxicity Grading Scale and will not be graded.
***Refer to Section 12.3 (Appendix 3) for the laboratory addresses.

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 swabs (see Table 10).

Table 10 Molecular biology (qRT-PCR tests)

Component	Kit / Manufacturer	Method	Unit	Laboratory**
System: Self-collected nasal swab, and combined nasal and throat swab specimen				
Respiratory Syncytial Virus A RNA Respiratory Syncytial Virus B RNA	In-house	Quantitative RT-PCR	Copies/mL	GSK * or designated laboratory

Quantitative RT-PCR: quantitative reverse transcription polymerase chain reaction; RSV: respiratory syncytial virus
* GSK laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.
**Refer to Section 12.3 (Appendix 3) for the laboratory addresses.

Additional testing on blood or swab samples

Additional testing on serum to characterize 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's laboratory or a laboratory designated by GSK.

Additional viral/bacterial diagnosis testing on the 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's laboratory or a laboratory designated by GSK.

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

- Further characterization of the pathogens detected in the 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).
- Characterization 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 testing on the vaccine formulation 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. These assays may not be represented in the objectives/endpoints of the study protocol.

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

8.4.4. Biological samples evaluation

For blood sample collection, the following ranking applies:

1. Sample for hematology/biochemistry testing
2. Sample for humoral immune responses

8.4.4.1. Immunological read-outs

Testing of RSV-A neutralizing antibodies and RSVPreF3 IgG antibodies will be performed on blood samples from all subjects.

In case of insufficient blood sample volume to perform assays for all immunological read-out components, the samples will be analyzed according to priority ranking provided in Table 11.

Table 11 Immunological read-outs

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-Day 1	All subjects	~ 40	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3
Visit 3 (Day 31)	PI D31	All subjects	~ 40	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
Visit 4 (Day 61)	PI D61	All subjects	~ 40	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
Visit 6 (Day 91)	PII D91	All subjects	~ 40	RSV-A neutralizing antibody	1
				Anti-RSVPreF3-specific IgG antibody	2
				RSV-B neutralizing antibody	3

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

8.4.4.2. Hematology/blood chemistry

Table 12 Hematology and biochemistry read-outs

Blood sampling time point		Sub-cohort	No. subjects	Component
Type of contact and time point	Sampling time point			
Screening Visit *	Pre-Day 1	All screened subjects	≥ 40	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	~ 40	

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
* 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.

8.4.4.3. Molecular biology

Table 13 Molecular biology tests on combined nasal and throat swab specimen

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

* RSV-A/B quantitative RT-PCR (RSV-A/B RNA) will be performed on all specimen.

8.4.5. 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.

8.5. Safety Assessments

The investigator and any delegators are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE or pIMD. After the initial report of AE, SAE or pIMD (serious or non-serious), the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs or pIMDs (serious or non-serious) will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up.

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Time period and frequency for collecting AE, serious adverse event (SAE), and pIMD information

An overview of the protocol-required reporting periods for AEs, SAEs and pIMDs is given in Table 14. Refer to the Section 12.5.7.1 for details on the time period for recording safety information.

Table 14 Reporting periods for collecting safety information

Event	SCR Pre-D1*	Visit 1 Vacc 1	Visit 2	Visit 3	Visit 4 Vacc 2	Visit 5	Visit 6	Phone call 1	Phone call 2 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 - Day 91							

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

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or its delegator immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Section 12.5.8. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.5.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.7 and Section 12.5.8.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjects is the preferred method to inquire about AE occurrence.

8.5.4. Reporting of serious adverse events and other events

SAEs that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of an SAE.

pIMDs that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 15 Timeframes for submitting serious adverse event, and other events reports to GSK

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

* Timeframe allowed after receipt or awareness of the information.
**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 causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE or pIMD.

8.5.4.1. Contact information for reporting of serious adverse events (SAEs), pIMDs and study holding rules

Table 16 Contact information for reporting of serious adverse events (SAEs), pIMDs and study holding rules

Study contact for questions regarding SAEs and pIMDs
Refer to the local study contact information document.
Study Contact for Reporting of study holding rules
As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the Local Medical Lead (LML).
Back-up Study Contact for Reporting SAEs and pIMDs
24/24 hour and 7/7 day availability: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD

8.5.4.2. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Follow-up of AEs and SAEs

After the initial report of AE, SAE or pIMD (serious or non-serious), the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs or pIMDs (serious or non-serious), will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.10.

8.5.6. 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 or pIMD should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.5.7. Clinical safety laboratory assessments

Refer to Section 12.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- All laboratory tests with values considered clinically significant abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. Refer to the Section 12.5.6 for clinical laboratory abnormal assessments qualified as AEs or SAEs.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory safety assessments, as defined in Section 12.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA (Section 2).

8.5.8. 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 delegator) 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.

8.5.9. Safety follow-up calls

At the Month 8 and Month 14 telephone contacts, subjects will be queried in accordance with a template script provided separately by GSK. The subjects will be queried about concomitant medications and the occurrence of pIMDs, SAEs, concurrent vaccination, SAEs related to study participation or to a concurrent GSK medication/vaccine, and AEs or SAEs leading to withdrawal. Information collected will be documented in the source document and will be recorded in the eCRF.

8.6. RTI Surveillance

RTI surveillance comprises active and passive surveillance. Both active and passive surveillance will only be carried out during the RSV seasons (from August until end of February), as based on local data. According to a surveillance study assessing the seasonality in 19 different countries, the RSV season from 2010 to 2017 in Japan specifically was found to start between late July and early November and continue through February with a peak seen between early October to early December. Information regarding the regional variability was not available [Obando-Pacheco, 2018]. These findings are similar to that reported by the Infectious Agents Surveillance Report (IASR) in their weekly report detecting RSV from 2007 onward in Japan [IASR, 2014] with a seasonality which approximates that of North America [Saijo, 1994]. In most recent seasons, RSV epidemics have been observed as beginning earlier, accompanied with a rapid increase in the number of reports since early July, 2018 [IDWR, 2018].

8.6.1. Active surveillance

During the RSV seasons, study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience RTI symptoms (i.e., cough, runny nose, fever [≥ 37.5°C] or difficulty to breathe). A template script will be provided separately by GSK.

In case of RTI symptoms (at least 3; see Section 8.6.3) reported by the subject, the subject will be asked to collect a nasal swab at home ideally within 48 hours after the start of symptoms. An assessment visit for nasal and throat swab specimen collection by qualified staff from the study team will be scheduled. 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.

8.6.2. Passive surveillance

Study participants will be instructed to contact the investigator/study staff in case of RTI symptoms during the RSV seasons (e.g., cough, runny nose, fever [≥ 37.5°C] or difficulty to breathe).

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.

8.6.3. 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 [≥ 37.5°C] or difficulty to breathe) 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, resting vital signs, temperature and onset date of first symptom should be recorded within the RTI episode screen in the eCRF.
- Following the assessment visit, 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.

8.7. Holding rules and safety monitoring

An iSRC will be appointed and operating under a charter, in addition to the existing project's Safety Review Team. Safety holding rules have been defined (Table 17, Table 18). The iSRC will review the protocol and Statistical Analysis Plan (SAP). Meetings will be documented and in case open sessions are held at the iSRC meetings, the minutes from these open sessions will be made available to the study team. The iSRC may, if deemed necessary, convene a meeting with, or request further information from GSK's designated project representatives at any stage of the study.

The iSRC 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.

Other GSK studies evaluating the same antigen in the RSV older adults or RSV maternal program may be running at a time that can overlap with the conduct of this study. Any relevant safety information from these other GSK studies with the same antigen will be shared with the iSRC of the Japan study; the holding rules of these other studies might also impact the Japan study, and vice versa.

Overview of safety monitoring:

- All participants will be closely observed for a minimum of 60 minutes after each vaccination.
- All available data from the participants vaccinated with the first dose will be reviewed in a first iSRC meeting. This iSRC will perform a safety evaluation of all available data collected up to 7 days post-Dose 1. Holding rules described in Table 18 will apply.
- If the outcome of the first iSRC evaluation is favorable, participants will receive the second dose.
- A second iSRC meeting will review all available safety data up to 30 days post-Dose 2.
- During the follow-up phase, 2 iSRC meetings will be planned with an interval of approximately 6 months. For the last of these iSRC evaluations, the end-of-study Clinical Study Report will be provided to the iSRC for review.
- If any safety concern is identified by the investigator (i.e., meeting of holding rules 1a-1c [see Table 17] or any other safety concern), he/she should hold vaccination and inform GSK immediately (within 24 hours). GSK will confirm the hold of the vaccination and call for an ad-hoc iSRC if needed.

8.7.1. Outcome of 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 start vaccination of subjects with the subsequent dose.
- If a **safety signal** is observed during the safety evaluations or if any of the holding rules 2a-d is met, the iSRC Chair (or his/her representative) is responsible for the urgent communication to GSK, including the rationale for the decision to put the vaccination on hold or not.
- The study Clinical Research and Development Lead (CRDL) will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study.

Refer to Section 8.7.2 for an overview of the communication flow in case a holding rule is met, as identified by the Investigator or iSRC.

8.7.1.1. Process of stopping the vaccination

In the event that a safety signal is observed, the sponsor might decide to cancel vaccination.

In this case:

- 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.

8.7.2. Study holding rules

The safety holding rules are defined in Table 17 and Table 18.

Holding rules 1a-1c from Table 17 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. The safety holding rules 2a – 2d from Table 18 will be assessed by iSRC during the first safety evaluation on unblinded data. These holding rules have been written under the assumption that the safety data from all subjects will be available. If the data from all subjects are not available (i.e. in case a subject is lost to follow-up), then the holding rules will be assessed by the iSRC on a pro-rata basis.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs that cannot reasonably be attributed to the study vaccination (non-life-threatening non-related SAEs), 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 iSRC in order to allow for an overall assessment of the benefit/ risk ratio of vaccination.

Table 17 Study holding rules identifiable by the investigator

Holding Rule	Event	Number of subjects
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 (non-life-threatening related SAEs)	≥ 1
1c	Any local or general solicited AE leading to **hospitalization**, or **fever > 40°C** 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

Table 18 Study holding rules identifiable by the iSRC

Holding Rule	Event	Percentage (number of subjects/group/ dose)
2a	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% (5/20)
2b	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% (5/20)
2c	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% (5/20)
2d	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% (5/20)

† 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 Section 12.7, Appendix 7). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

The investigator is not permitted to start the administration of the next dose until receipt of the favorable outcome of the safety evaluation, documented and provided in writing, authorizing the investigator to proceed.

Moreover, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. meeting of holding rules 1a-c).

The below flow of communication has to be followed:

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 iSRC. 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, vaccination must be put on hold immediately in each study 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). All other procedures relating to safety and immunology will continue.

Following an internal review as well as review by the iSRC, 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 iSRC

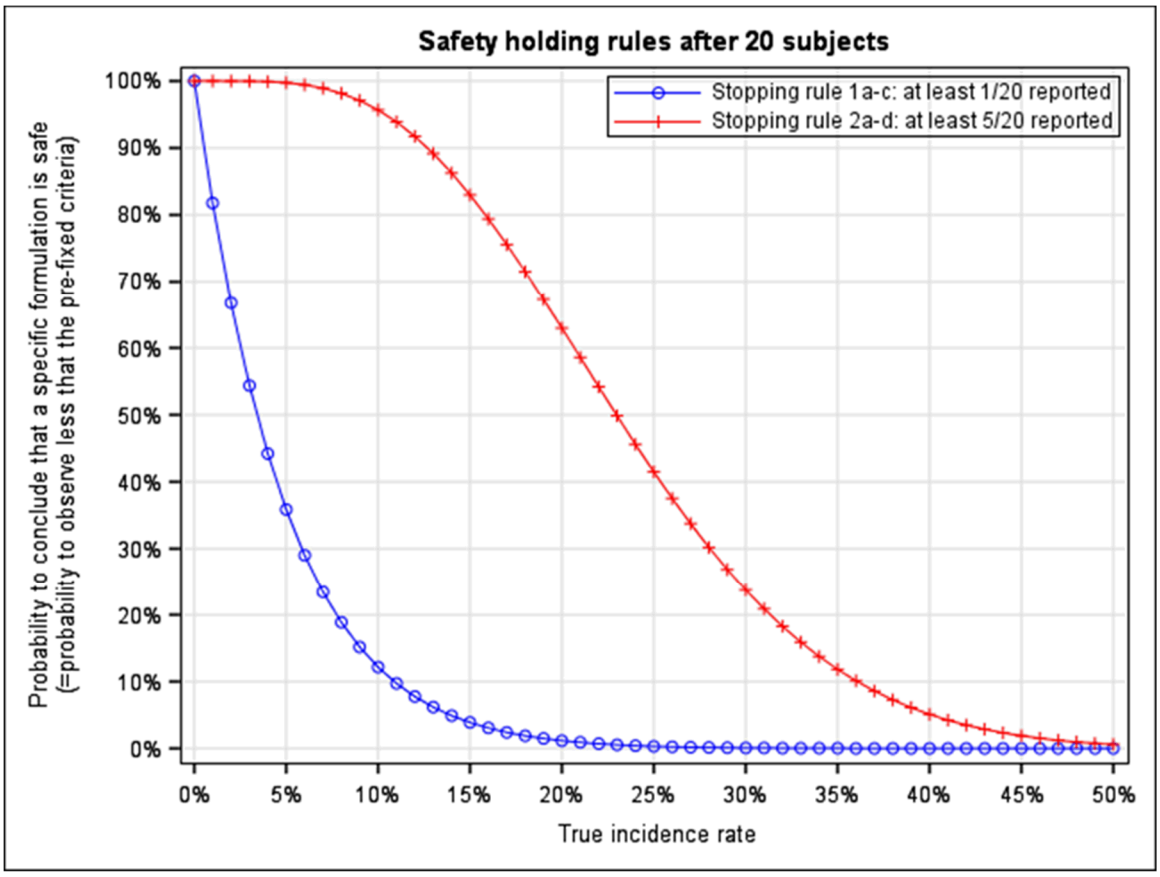
If a holding rule is met following safety evaluation by the iSRC, the iSRC Chairman must notify the primary GSK contact immediately. The central study team (study CRDL, Study Delivery Lead, or Safety Physician) will subsequently inform the LOC and Investigators from each study center. All vaccinations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

Following additional assessment by the iSRC, 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.

8.7.3. Risk assessment

Figure 2 gives the probability of not meeting each holding rule 1 and 2 for 20 subjects per group.

Figure 2 Evaluations based on 20 subjects per group - risk assessment curve for 1 group based on the proposed safety holding rules



The above figure illustrates that, with 20 subjects per study group:

- Each holding rule 1a-c has more than 90% chance of not being met for vaccination with a true incidence rate below 1% and has more than 88% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-d has more than 80% chance of not being met for vaccination with a true incidence rate below 16% and more than 60% chance of being met for vaccination with a true incidence rate above 25%.

8.8. Genetic Research (Pharmacogenetics)

Genetics are not evaluated in this study.

9. DISCONTINUATION CRITERIA

- Refer to the Section 7.7 for contraindications to subsequent vaccination.
- All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first study vaccine (refer to Section 12.5, Appendix 5).

9.1. Discontinuation from the study

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

All data and samples 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).

Primary reason for study 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:

- Adverse events requiring expedited reporting (refer to Section 12.5.8.2 for details)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation (specify)
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- 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 12.5.10).

9.2. Discontinuation of 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 continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

Primary reason 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:

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

9.3. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or delegator must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

10.1.1. Sample size calculation

A sample size of 20 subjects per group would provide a probability of 80% or 90% to observe at least one AE, if the true AE rate is 7.8% or 10.9%, respectively.

Considering a sample size of 20 subjects per group, Table 19 below illustrates the exact 95% Confidence Intervals (CIs) for the different possible numbers of AEs within each group.

Table 19 Two-sided 95% exact confidence intervals based on the percentage of subjects with adverse events following vaccination of 20 subjects per group

Number (%) of subjects with an AE	Exact 95% Confidence Interval (CI)	
	Lower Limit (%)	Upper limit (%)
0 (0%)	0.00	16.84
1 (5%)	0.13	24.87
2 (10%)	1.23	31.70
3 (15%)	3.21	37.89
4 (20%)	5.73	43.66
5 (25%)	8.66	49.10
6 (30%)	11.89	54.28
7 (35%)	15.39	59.22
8 (40%)	19.12	63.95
9 (45%)	23.06	68.47
10 (50%)	27.20	72.80
11 (55%)	31.53	76.94
12 (60%)	36.05	80.88
13 (65%)	40.78	84.61
14 (70%)	45.72	88.11
15 (75%)	50.90	91.34
16 (80%)	56.34	94.27
17 (90%)	62.11	96.79
18 (95%)	68.30	98.77
19 (95%)	75.13	99.87
20 (100%)	83.16	100.00

Exact 95% CI computed based on Clopper/Pearson formula.

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	All subjects who sign informed consent.
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Per Protocol	All subjects who received at least 1 dose of the study treatment to which they are randomized and have post-vaccination data minus subjects with protocol deviations that lead to exclusion.

10.3. Statistical analyses

The analyses will be descriptive with the aim to characterize the safety/reactogenicity and immunogenicity of the vaccine group with respect to the placebo.

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.

10.3.1. Demography and baseline characteristics analyses

The demography analysis will be performed on the Exposed Set (ES) and on the Per Protocol (PP) set.

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 deviation 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).

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.

10.3.2. Safety analyses

The primary analysis will be performed on the ES.

Endpoint	Statistical Analysis Methods
Primary	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) 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 section 12.7 (Appendix 7). The 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 qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported from Dose 1 up to 30 days after the second vaccine dose (Day 91) will be tabulated with exact 95% CI. The percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported from Dose 1 up to 30 days after the second vaccine dose (Day 91) will be tabulated with exact 95% CI.
Secondary	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 detail. 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 detail.
Tertiary	N/A

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 might also be performed by age category (60-69 years and 70-80 years).

10.3.3. Immunogenicity analyses

The primary analysis will be based on the PP set for analysis of immunogenicity. If, in any study group and at any timepoint, the percentage of vaccinated subjects with serological results excluded from the PP set for analysis of immunogenicity is 10% or more, a second analysis based on the ES will be performed to complement the PP analysis.

Endpoint	Statistical Analysis Methods
Primary	N/A
Secondary	For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated. • Geometric mean concentrations (GMCs)/ geometric mean titers (GMTs) and their 95% CI will be tabulated and represented graphically. • Antibody titer/concentration will be displayed using reverse cumulative curves. • The distributions of antibody titers/concentrations will be tabulated. • Geometric mean of ratios of antibody titer/concentrations at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI. • 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 ratio of the fold-increase of RSVPreF3 ELISA antibody concentrations over the fold-increase of RSV-A neutralizing antibody titers will be computed and tabulated using descriptive statistics (Ratio of fold increase Post- over Pre-vaccination). The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.
Tertiary	Will be described in a Statistical Analysis Plan finalized before database unblinding/freezing

The immunogenicity analysis might also be performed by age category (60-69 years and 70-80 years).

10.3.4. Other analyses

10.3.4.1. Analysis of RTI

The analysis will be performed on the ES.

Endpoint	Statistical Analysis Methods
Primary	N/A
Secondary/Tertiary	A listing of RTI cases and their respective viral load results assessed by qRT-PCR will be provided by group.

10.3.5. Interim analyses

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

10.4. Sequence of analyses

In preparation of the planned iSRC evaluations, analyses of all available safety data (as clean as possible) will be performed. The blinded analyses will be distributed to the study team. The unblinded analyses will be done by an Independent External Statistician to maintain the study blind and will be shared with iSRC members through a secured folder (refer to the iSRC charter). Only the recommendations of the iSRC reviews will be communicated to the RSV OA study team. No clinical study report will be written at this stage.

The following 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 the occurrence of RSV RTI). This analysis will be considered as final for those endpoints. A statistical 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 (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 end of study analysis will be performed when all data for primary and secondary endpoints up to study conclusion are available (Month 14). 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.

The final study report will contain at least the final analyses of all primary and secondary endpoints. If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in annex(es) to the study report and will be made available to the investigators at that time**.**

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

AE:	Adverse Event
ALT:	Alanine Aminotransferase
$AS01_B$:	MPL, QS-21, liposome based Adjuvant System (50 μg MPL and 50 μg QS-21)
AST:	Aspartate Aminotransferase
BUN:	Blood Urea Nitrogen
CDC:	Centers for Disease Control
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CoP:	Correlate of Protection
COP:	Community-Onset Pneumonia
COPD:	Chronic Obstructive Pulmonary Disease
eCRF:	electronic Case Report Form
eDiary:	electronic Diary
ELISA:	Enzyme-Linked Immunosorbent Assay
eTDF:	Electronic Temperature excursion Decision Form
EoS:	End of Study
ES:	Exposed Set
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
HZ/su:	Herpes Zoster subunit vaccine
IASR:	Infectious Agents Surveillance Report
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G
IL:	Interleukin
IM:	Intramuscular(ly)
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
LML:	Local Medical Lead
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

PCD:	Primary Completion Date
PCR:	Polymerase Chain Reaction
PP:	Per protocol
PT:	Preferred Term
pIMD:	Potential Immune-Mediated Disease
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:	Source data Base for Internet Randomization
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SoA	Schedule of Activities
SPM:	Study Procedures Manual
US:	United States
WBC:	White Blood Cells

12.1.2. Glossary of terms

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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the 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 7.3 for details on observer-blinded studies).
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Designee:	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. Designees are appointed by the subject for help with the study procedures solely and cannot make decisions on behalf of the subject.
Delegator:	A qualified person appointed by the investigator or sponsor to take over a specific part of their trial-related duties or responsibilities.

Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) (Synonym of End of Trial)	For studies with collection of human biological samples, the EoS is defined as Last subject last visit (Phone Call 2), or Last testing results released of samples collected up to Phone Call 2* * In this case EoS must be achieved no later than 8 months after LSLV.
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardized term to replace: period, cycle, phase, stage.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.2 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 authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Pharmacogenomics	The International Council on Harmonization (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.
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 etiology.
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.
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 1 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.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
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 vaccine 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.

12.1.3. Trademarks

Trademark Information

The following trademarks are used in the present protocol.

Note: In the body of the protocol, the names of the vaccines/products and/or medications and/or assays are written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GSK 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 GSK group of companies	Generic description
Fluad (Seqirus Inc.)	Influenza virus vaccine (Surface antigen, inactivated, adjuvanted with MF59)
MF59 adjuvant (Novartis)	Oil-in-water emulsion of squalene oil
TrueBlue peroxidase substrate (SeraCare)	Chromagenic substrate for visualization of horseradish peroxidase-labeled reporter reagents

12.2. Appendix 2: Clinical and safety laboratory tests

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

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

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

Table 20 Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters
Hematology	Platelet Count
	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils RBC Count Hemoglobin
Clinical Chemistry	Alanine Aminotransferase (ALT)
	Blood Urea nitrogen (BUN)
	Aspartate Aminotransferase (AST)
	Creatinine
	Uric Acid

12.2.1. Laboratory assays

Assay descriptions for RSV-specific read-out 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 2 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).

qRT-PCR

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

  Briefly, RSV A and RSV B RNAs extracted from the nasal and 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.

12.3. Appendix 3: Clinical laboratories

Table 21 GSK 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
GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

Table 22 Outsourced laboratories

Laboratory	Address
NÉOMED-LABS Inc.	525, Cartier Ouest Laval Quebec Canada H7V 3S8 NÉOMED-LABS Inc.
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Tan Tock Seng Hospital	Dept of Laboratory Medicine Level 2, Podium Block Tan Tock Seng Hospital 11 Jalan Tan Tock Seng Singapore 308433
DDL Diagnostic Laboratory B.V.	Fonteijnenburghlaan 7 Voorburg Netherland

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF), Investigator, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the center and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.4.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each subject, prior to participation in the study.

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

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

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

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

The ICF contains a specific section that addresses the use of remaining leftover samples for future use. The investigator or authorized delegator will inform each subject of the possibility of future use of left-over samples not related to the study/disease. Subjects will be told that they are free to refuse and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a subject's agreement to allow any remaining leftover samples to be used for future use not related to the study/disease. Subjects who decline the use of left-over samples for objectives not related to the study/disease will tick the corresponding box.

12.4.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the frame and for the purpose of the study.

12.4.5. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.6. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

In addition, for studies that are in scope of the EU Clinical Trial Directive, summaries of the results of GSK interventional studies (phase I-IV) in adult population will be posted within defined timelines on the publicly available EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines 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.

	Clinicaltrial.gov	EU
Protocol summary	Before enrolment of subjects	As per CTA submission/Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 6 months (for pediatric population studies)/Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymized patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

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

12.4.7. Data quality assurance

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

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

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

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

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

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

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

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

12.4.8. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

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

Definition of what constitutes source data and source documents can be found in the Section 12.1.2 (Glossary of Terms).

12.4.9. Study and site closure

GSK or its delegator reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

The investigator will:

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

12.5. Appendix 5: Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE definition

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

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.5.1.2. Events meeting the AE definition

- 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 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 or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine 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).
- Signs, symptoms that require medical attention (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as solicited AEs are described in Section 12.5.3. All other AEs within 30 days post-vaccination will be recorded as unsolicited AEs.

12.5.1.3. Events NOT meeting the AE definition

- 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.

12.5.2. Definition of SAE

An SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study 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 jeopardize 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.

12.5.3. Solicited adverse events

Solicited AEs (see Table 23 and Table 24) occurring during the 7-day follow-up period after each vaccination (day of vaccination and 6 subsequent days) will be recorded by the subjects or designees 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.

a. Solicited local (injection-site) adverse events

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

Table 23 Solicited local adverse events

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

b. Solicited general adverse events

The following general AEs will be solicited:

Table 24 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms†
Headache
Myalgia
Shivering
Arthralgia

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

Note: subjects will be instructed to measure and record the body temperature (preferably oral) 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.

12.5.4. Unsolicited adverse events

An unsolicited AE is 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. Unsolicited adverse events will be collected up to 30 days after each vaccination. Note that solicited symptoms with onset in the specified period of follow-up, but continuing until after the 7-day follow-up period after vaccination, do not become unsolicited AEs but should continue to be reported as solicited AE until resolved.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subjects. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

All unsolicited AEs up to 30 days after each vaccination have to be reported via paper diary or orally, and detailed information about the reported unsolicited AEs will be collected by the qualified site personnel and will be documented in the subject's records.

12.5.5. Adverse events of special interest (AESIs)

12.5.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 25 (Please refer to section 12.5.8.2 for reporting details).

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 25 List of potential immune-mediated diseases (pIMDs)

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

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: • Giant Cell Arteritis (Temporal Arteritis), • Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: • Polyarteritis nodosa, • Kawasaki's disease, • Microscopic Polyangiitis, • Wegener's Granulomatosis (granulomatosis with polyangiitis), • Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), • Buerger's disease (thromboangiitis obliterans), • Necrotising 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.

12.5.6. 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, urinalysis) 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 12.5.1 and 12.5.2). 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement 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 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.

12.5.7. Detecting and recording adverse events and serious adverse events

Electronic Diaries (eDiaries) will be used to capture solicited adverse events.

Paper diary cards will be used by the subjects or their designee 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 subjects should be trained on how and when to complete each field of the electronic and paper diary. If a subject is unable or not willing to complete the electronic and/or the paper diary him/herself, he/she may be helped by a designee (refer to the Section 12.1.2 (Glossary of Terms) for the definition of designee). This person's identity must then be documented in the subject's source record and be trained. The training will be given at the visit when the electronic and paper diaries are dispensed and will be documented in the subject's source record. This person also needs to sign an ICF.

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

- The same individual should complete the eDiary throughout the course of the study.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature.
- The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- Subjects will be instructed to measure and record the body temperature (preferably oral) 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.

eDiary assignment and use:

- Each subject or designee will be assigned a eDiary and shown how to use the device – this will include how to access the diary, performing test data entry on sample questions, and how to charge and store the device.
- The subject or designee will self-select a numeric access code secret to themselves. The same individual should make the assessments and complete the eDiary throughout the course of the study.
- The subject or designee will select an alarm time that suits their daily routines whilst ensuring compliance with protocol requirements.

eDiary instructions must ensure that the subject understands the following:

- Timely completion of the eDiary on a daily basis is a critical component to study participation.
- The eDiary will allow certain time windows for completion of each day's observations.
- The eDiary employs the use of audio-visual alarms to ensure timely completion of data entry.
- The trained and assigned user of the eDiary must not share access codes with anyone.
- A helpdesk will be provisioned for users of 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 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.
- Any new safety information reported during the safety follow-up phone call or site visits (including a solicited adverse event) cannot be entered into the eDiary. Such information must be described in the source documents as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered into the eCRF.

12.5.7.1. Time period for detecting and recording adverse events and serious adverse events

All solicited AEs during 7 days following administration of each dose of study vaccine (the day of vaccination and 6 subsequent days) must be recorded in the eDiary, irrespective of intensity or whether or not they are considered vaccination-related.

All unsolicited AEs during 30 days following administration of each dose of study vaccine (the day of vaccination and 29 subsequent days) recorded by the subjects on their paper diary cards or reported orally must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine for each subject. See Section 12.5.8 for instructions on reporting of SAEs to GSK.

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

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.

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 12.5.8.4 for instructions on reporting of pIMDs.

12.5.7.2. Evaluation of adverse events and serious adverse events

12.5.7.2.1. 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 instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

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

12.5.7.2.2. Assessment of adverse events

Assessment of intensity

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

Table 26 Intensity scales for solicited symptoms in adults

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 (with 1 decimal)
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, diarrhea 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 to be reported as AE is defined as temperature ≥38.0°C. 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 as follows:

	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C
1:	> 20 - ≤ 50 mm	≥ 38.0°C - ≤ 38.5°C
2:	> 50 - ≤ 100 mm	> 38.5°C - ≤ 39.0°C
3:	> 100 mm	> 39.0°C

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 1 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 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 1 of the pre-defined outcomes as described in Section 12.5.2.

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. 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. 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 12.5.2), 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).

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).

12.5.7.2.3. Medically attended visits

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

12.5.8. Reporting of serious adverse events, and other events

12.5.8.1. Prompt reporting of serious adverse events, and other events to GSK

SAEs that occur in the time period defined in Section 12.5.7 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of an SAE.

pIMDs that occur in the time period defined in Section 12.5.7 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a pIMD.

12.5.8.2. SAEs requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study subject, the investigator (or delegator) 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.

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

If the electronic reporting system does not work, the investigator (or delegator) 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 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 delegator) 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.

12.5.8.4. Reporting of pIMDs to GSK

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or delegator) 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 AESIs standard questionnaire provided. Even if the investigator does not have all information regarding an 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 12.5.8.3 for back-up system in case the electronic reporting system does not work.

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

When additional SAE 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 Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

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

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

12.5.10.1.1. 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 (within 24 hours for SAEs; refer to Table 15).

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 contact with the subject in the context of the study. In case any SAEs or pIMDs remain not resolved at this last contact, these SAEs or pIMDs will continue to be followed after study end (refer to section 12.5.10.1.2).

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.

12.5.10.1.2. 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, stabilized, 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 using a paper/electronic Expedited Adverse Events Report as applicable.

GSK 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 recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

12.6. Appendix 6: Country-specific requirements

12.6.1. Regulatory and ethical considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

The statement "I agree to assume responsibility for the proper conduct of the study at this site." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

GSK Japan will submit the CTN to the regulatory authorities in accordance with Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Device before conclusion of any contract for the conduct of the study with study sites.

12.6.2. Informed consent

Prior to participation in the study, the investigator (or sub-investigator) should fully inform the potential subject or designee including the written approval given by the IRB. The investigator (or sub-investigator) should provide the subject or designee ample time and opportunity to inquire about details of the study. The subject or designee should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. The investigator (or delegator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject or designee

12.6.3. Study administrative structure

Sponsor Information and List of Medical Institutions and Investigators are included in Exhibit 1 and Exhibit 2, respectively.

12.6.4. Unapproved medical device

If unapproved medical devices are used in the study, further details will be added in Exhibit 3. In case no unapproved medical devices are used, Exhibit 3 will not be attached.

12.7. Appendix 7: FDA guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007) - 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 27 FDA toxicity grading scales for hematology/ biochemistry parameters evaluated in the current study RSV OA=ADJ-003

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).
*** "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.