Protocol Amendment 1

Study ID: 213569

Official Title of Study: A phase 2b, open-label, multi-center, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the RSV OA=ADJ-002 study

EudraCT number: 2020-000692-21

Date of Document: 04-11-2020

CONFIDENTIAL

213569 (RSV OA=ADJ-011 EXT:002 MTH20)
Protocol Amendment 1 Final

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

Primary Study vaccines and numbers	GlaxoSmithKline (GSK) Biologicals' investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other Study vaccine(s)/product(s)	Not applicable
eTrack study number and abbreviated title	213569 (RSV OA=ADJ-011 EXT:002 MTH20)
EudraCT number	2020-000692-21
Date of protocol	Final: 2 July 2020
Date of protocol amendment	Amendment 1 Final: 4 November 2020
Title	A phase 2b, open-label, multi-center, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the RSV OA=ADJ-002 study.
Short title	Extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 OA investigational vaccine in adults 60 years and older who participated in the RSV OA=ADJ-002 study.

Based on GSK Biologicals' Protocol WS v17.0

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	213569 (RSV OA=ADJ-011 EXT:002 MTH20)
EudraCT number	2020-000692-21
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Sponsor signatory (Amended 4 November 2020)	***Marie Van Der Wielen***, MD Clinical and Epidemiology R&D Project Lead, Older Adults project
Signature	_____
Date	_____

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccines and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representatives of GSK Biologicals 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 vaccines, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information for the 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	213569 (RSV OA=ADJ-011 EXT:002 MTH20)
EudraCT number	2020-000692-21
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Investigator name	_____
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 the protocol section 8.3.3.1.

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

5. GSK Helpdesk for Emergency Unblinding

Refer to the protocol Section 6.3.3.1**.**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history

Document	Date
Original Protocol	2 July 2020

Amendment 1: 4 November 2020

Overall Rationale for the Amendment:

The protocol is amended to address the comments from the United States Food and Drug Administration (US FDA). Specifically, instructions to delay enrolment or vaccination of participants with symptoms suggestive of Coronavirus Disease 2019 (COVID-19) infection or with known COVID-19 positive contacts have been updated. In addition, the requirement to obtain written approval from the Sponsor for a participant to receive a vaccine as part of mass vaccination for an unforeseen public health threat (e.g., pandemic) if the vaccine to be used according to the local governmental recommendations has been amended. Other changes have been made to align the protocol with the parent RSV OA=ADJ-002 study and other phase 3 studies in the project.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 5.2.2 Prior/ Concomitant therapy	Wording for mass vaccination during a pandemic is updated.	This change is made to acknowledge the FDA's request to remove the requirement to obtain written approval from the Sponsor for a participant to receive a vaccine as part of mass vaccination for an unforeseen public health threat (e.g., pandemic) if the vaccine to be used according to the local governmental recommendations.
Section 7.1.1 Criteria for temporary delay for enrolment and/or vaccination	Wording for COVID-19-related delay of vaccination is updated.	This change is made to acknowledge the FDA's recommendation about the temporary delay of enrolment of vaccination of participants with symptoms suggestive of COVID-19 infection or known COVID-19 positive contacts.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GlaxoSmithKline Biologicals SA (GSK) is developing an RSV Prefusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV) -associated (subtypes A and B) disease in adults aged ≥ 60 years.

Different formulations of the RSVPreF3 OA investigational vaccine were administered intramuscularly for the first time to adults aged 60 – 80 years according to a 0, 2 months schedule in the parent study, RSV OA=ADJ-002 (208851). Based on safety and immunogenicity data from the parent study, the selected vaccine formulation is composed of RSVPreF3 recombinant antigen dose 120 µg adjuvanted with $AS01_E$ (hereafter referred to as 120 µg RSVPreF3/$AS01_E$). The participants who received 2 doses of the selected formulation, as well as the participants who received vaccine formulations with the same adjuvant (RSVPreF3 recombinant antigen doses 30 µg and 60 µg adjuvanted with $AS01_E$) in the parent study will be invited to participate in this study.

All participants enrolled in the current study will receive a single dose of the selected RSVPreF3 OA investigational vaccine (120 µg RSVPreF3/$AS01_E$) at approximately 18 months after they received Dose 2 in the parent study, RSV OA=ADJ-002 (208851).

The purpose of this study is to:

i. evaluate the safety and reactogenicity of the third dose of the RSVPreF3 OA investigational vaccine in adults previously vaccinated in RSV OA=ADJ-002, Part B with formulations containing the same, selected adjuvant, and

ii. evaluate the immunological response (boostability) of the third dose of the RSVPreF3 OA investigational vaccine in adults previously vaccinated with the same antigen (120 µg RSVPreF3/$AS01_E$ recipients in parent study receiving a third dose of the same vaccine). In addition, this study will also evaluate the immunogenicity of the vaccine in adults previously vaccinated in RSV OA=ADJ-002, Part B with the same, selected formulation of the RSVPreF3 OA investigational vaccine.

Objectives and Endpoints: Please refer to Table 3.

1.2. Schema

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

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Type of contact Timepoints	Visit 1 Day 1*	Visit 2 Day 31	Contact Month 6	Notes
Informed consent	●			See Section 10.1.3 for details
Check inclusion/exclusion criteria	●			See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●			See Section 8.2.1.1 for more information
Medical and vaccination history**	●			See Section 8.2.1.2 for more information
Physical examination	●	O		See Section 8.2.1.3 for more information
Vaccine(s)/product(s)				
Check contraindications, warnings and precautions to vaccination	O			See Section 8.2.1.4 for more information
Check criteria for temporary delay for enrolment and vaccination	O			See Section 7.1.1 for more information
Study group and intervention number allocation	O			See Section 6.3.2 for more information
Pre-vaccination body temperature	●			The preferred location for measuring temperature will be the oral cavity. Fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement.
Recording of administered intervention number	●			
Vaccine(s)/product(s) administration	●			See Section 6.1 for more information
Distribution of diary cards	O			
Laboratory assessments				
Blood sampling for antibody determination (~20 mL)***	●	●		See Section 8.1.1 for more information
Blood sampling for CMI response (~25 mL)***	●	●		See Section 8.1.1 for more information
Safety assessments				
Record concomitant medication/vaccination	●	●	●	See Section 6.5 for more information
Record any intercurrent medical conditions	●	●	●	See Section 9.3.1.1 for more information
Recording of solicited events (Days 1–4 post-vaccination)	●	●		See Section 10.3.7 for more information
Return of diary cards		O		
Diary card transcription by investigator		O		

Type of contact	Visit 1	Visit 2	Contact	Notes
Timepoints	**Day 1***	**Day 31**	**Month 6**	
Recording of unsolicited adverse events (Days 1-30 post-vaccination)	●	●		See Section 10.3.7 for more information
Recording of SAEs, pIMDs	●	●	●	See Section 10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	See Section 10.3.7 for more information
AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.7 for more information
Contact for safety follow-up			●	See Section 10.3.7.2 for more information
Study Conclusion			●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to those time points.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
CMI = Cell- Mediated Immunity; pIMDs = potential Immune-Mediated Diseases
AE = Adverse Event; SAE = Serious Adverse Event
*Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study
** Only for the transition period between the RSV OA=ADJ-002 parent study and the current extension study. Note that administration of *Shingrix* during the transition period and throughout the duration of the current study should be recorded in the eCRF (refer to Section 8.2.1.2).
***Only for the group 120-AS01E_B: Selected formulation revaccinated with the same formulation

Table 2 Intervals between study visits

Interval	Length of interval	Recommended interval	Allowed interval***
RSV OA=ADJ 002 Visit 4 (Month 2*) → Visit 1 (Day 1**)	540 days	525-555 days	510-570 days
Visit 1 → Visit 2	30 days	30-42 days	30-42 days
Visit 1 → Contact	180 days	165-195 days	165-195 days

*Dose 2 in parent study RSV OA=ADJ-002
**Dose 3 in current study RSV OA=ADJ-011 EXT:002 MTH20; 18 months post-Dose 2 in RSV OA=ADJ-002 study
***During special circumstances if site visits are restricted (e.g., COVID-19 pandemic-related national restrictions)

2. INTRODUCTION

2.1. Study rationale

GlaxoSmithKline Biologicals SA (GSK) is developing an RSV Prefusion Protein F3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV) -associated (subtypes A and B) disease in adults aged ≥ 60 years.

Different formulations of the RSVPreF3 OA investigational vaccine were administered intramuscularly for the first time to adults aged 60 – 80 years according to a 0, 2 months schedule in the parent study, RSV OA=ADJ-002 (208851). Based on safety and immunogenicity data from the parent study, the selected vaccine formulation is composed of RSVPreF3 recombinant antigen dose 120 µg adjuvanted with $AS01_E$ (hereafter referred to as 120 µg RSVPreF3/$AS01_E$). The participants who received 2 doses of the selected formulation, as well as the participants who received vaccine formulations with the same adjuvant (RSVPreF3 recombinant antigen doses 30 µg and 60 µg adjuvanted with $AS01_E$) in the parent study will be invited to participate in this study.

All participants enrolled in the current study will receive a single dose of the selected RSVPreF3 OA investigational vaccine (120 µg RSVPreF3/$AS01_E$) at approximately 18 months after they received Dose 2 in the parent study, RSV OA=ADJ-002 (208851).

The purpose of this study is to:

i. evaluate the safety and reactogenicity of the third dose of the RSVPreF3 OA investigational vaccine in adults previously vaccinated in RSV OA=ADJ-002, Part B with formulations containing the same, selected adjuvant, and

ii. evaluate the immunological response (boostability) of the third dose of the RSVPreF3 OA investigational vaccine in adults previously vaccinated with the same antigen (120 µg RSVPreF3/$AS01_E$ recipients in parent study receiving a third dose of the same vaccine). In addition, this study will also evaluate the immunogenicity of the vaccine in adults previously vaccinated in RSV OA=ADJ-002, Part B with the same, selected formulation of the RSVPreF3 OA investigational vaccine.

2.2. Background

RSV is a ribonucleic acid virus of the *Pneumoviridae* family of which 2 antigenically distinct subgroups, referred to as RSV A and RSV B, exist [Rima, 2017]. RSV is a highly contagious human pathogen that causes respiratory tract infections in people of all ages. In temperate climates throughout the world, RSV predictably causes fall-winter epidemics [Simões, 2008], whereas viral activity is more endemic in (sub-) tropical regions and outbreaks are less temporally focused [Borchers, 2013].

According to the 'Centers for Disease Control and Prevention' (CDC) website [CDC], RSV leads to 177 000 hospitalizations and 14 000 deaths on average each year among adults ≥ 65 YOA 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 OA (≥ 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 [Simões, 1999; Krilov, 2011]. Generally, these re-infections go undiagnosed because they usually manifest as common acute upper respiratory tract infections. However, in more vulnerable individuals (e.g. immunocompromised persons or OA), re-infections can also lead to severe disease despite the presence of serum RSV neutralizing antibodies, as very similar levels of RSV antibody response can be found in both OA and young adults [Graham, 2011; Cherukuri, 2013].

Despite the significant medical need in OA aged 60 years or above, there is currently no prophylactic vaccine approved for the prevention of lower respiratory tract disease (LRTD) caused by RSV. Additionally, no prophylactic treatments against RSV are available for this age population. Several attempts have been made to develop an RSV vaccine but to date all have been unsuccessful.

Currently available treatment for RSV in OA is generally supportive in nature, consisting of supplemental oxygen, intravenous fluids and bronchodilators. Inhaled and systemic corticosteroids are often prescribed in patients with asthma or chronic obstructive pulmonary disease (COPD) [Falsey, 2000].

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies of RSVPreF3 OA investigational vaccine.

2.3. Benefit/Risk assessment

2.3.1. Risk Assessment

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

All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema, and swelling.

In addition to risks related to the vaccine, there may be risks related to the blood sampling planned in the study:

- Pain and bruising may occur at the site where blood is drawn; as a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.
- Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.

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

2.3.2. Benefit Assessment

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

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

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

2.3.3. Overall Benefit/Risk Conclusion

The RSVPreF3 OA investigational vaccine is in clinical development.

Considering the measures taken to minimize risk to participants in this study, the potential risks are justified by the potential benefits linked to the development of this vaccine.

3. OBJECTIVES AND ENDPOINTS

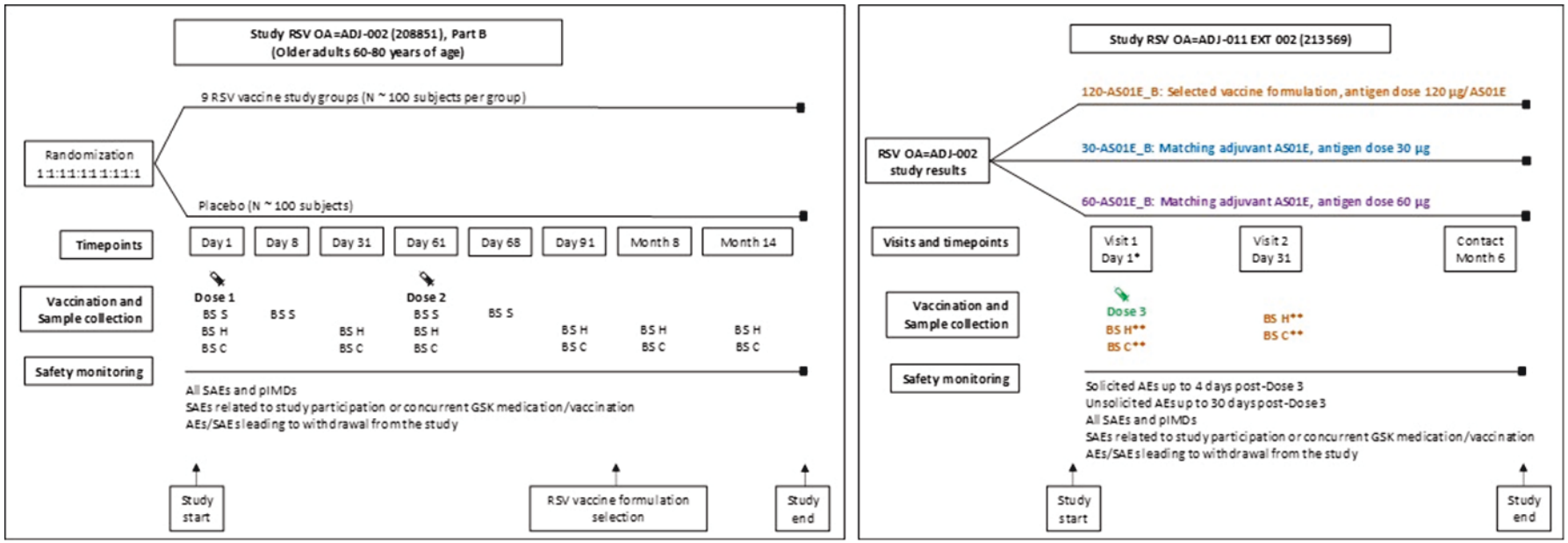
Table 3 Study objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity following intramuscular (IM) administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for all participants.	• Occurrence of solicited adverse events (AEs) up to 4 days post-Dose 3 (Day 4). • Occurrence of unsolicited AEs up to 30 days post-Dose 3 (Day 31). • Occurrence of serious adverse events (SAEs)/ Potential immune mediated diseases (pIMDs) up to 30 days post-Dose 3 (Day 31).
• To evaluate the humoral immune response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: – Neutralizing antibody titers against Respiratory Syncytial Virus (RSV)-A – Neutralizing antibody titers against RSV-B
Secondary	
• To evaluate the humoral and cell-mediated immune (CMI) response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: – RSVPreF3-specific Immunoglobulin G (IgG) antibody concentrations • CMI response at 1 month post-Dose 3: – Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α , IFN-γ
• To evaluate the safety and reactogenicity following IM administration of RSVPreF3 OA investigational vaccine up to the study end, for all participants.	• Occurrence of SAEs from vaccination (Day 1) up to study end (Month 6). • Occurrence of pIMDs from vaccination (Day 1) up to study end (Month 6).
Tertiary	
• To further characterize immune responses following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Any further exploratory immunology such as, but not limited to: – Antibodies against specific protein F epitopes. – Potential new immunological markers for protection. – Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing one or any combination of immune marker(s) in vitro.

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



= Vaccination with one of 9 RSVPreF3 OA investigational vaccine formulations or placebo, in RSV OA=ADJ-002 study

= Vaccination of all study participants with RSVPreF3 OA investigational vaccine in current study

N = number of participants; BS S = Blood sample for safety (hematology/biochemistry); BS H = blood sample for humoral immune responses; BS C = blood sample for CMI response

AE = adverse event; SAE = serious adverse event; pIMD = potential immune mediated disease

*Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study

**Only for the 120-AS01E_B group that received the same, selected formulation of RSVPreF3 OA investigational vaccine in RSV OA=ADJ-002 study

At the time of initiation of this extension study, the investigator will contact ONLY those participants who received the vaccine formulations with RSVPreF3 recombinant antigen doses 120 µg, 30 µg and 60 µg adjuvanted with $AS01_E$ in the parent study RSV OA=ADJ-002 and who expressed a willingness to participate when questioned during the primary study. The reason for non-participation in the extension study will be documented in the site's screening log, provided that the participant is willing to specify a reason.

- ***Type of study:*** Extension of study RSV OA=ADJ-002 (208851)
- ***Experimental design:*** Phase 2b, open-label, multi-center study with 3 parallel groups (Table 4).
- ***Duration:*** Approximately 6 months per participant.
- ***Primary completion date:*** One month post vaccination , i.e., Day 31 (Visit 2)
- ***Control:*** None
- ***Blinding:*** Open-label study
- ***Data collection:*** electronic case report form (eCRF)

Table 4 Study groups, intervention and blinding foreseen in the study

Study Groups	Number of participants	Age* (Min-Max)	Intervention	Blinding
120-AS01E_B	~100	60-80 years	RSVPreF3 OA investigational vaccine	Open
30-AS01E_B	~100	60-80 years	RSVPreF3 OA investigational vaccine	Open
60-AS01E_B	~100	60-80 years	RSVPreF3 OA investigational vaccine	Open

*Age at the time of Dose 1 in the parent study RSV OA=ADJ-002

Overview of the recruitment plan

The study is planned to be conducted at sites in the US and Belgium.

The participants who received RSVPreF3 recombinant vaccine formulations containing different doses of the same antigen (120 µg, 30 µg and 60 µg) adjuvanted with $AS01_E$ in the parent study will be invited to participate in the current extension study.

4.2. Scientific rationale for study design

4.2.1. Rationale for study design

The study has been designed as a phase 2b extension study to assess the safety and reactogenicity of a revaccination dose of the RSVPreF3 OA investigational vaccine in adults aged 60 years and above previously vaccinated in RSV OA=ADJ-002, Part B. There are 3 groups in this study:

- Participants in group 120-AS01E_B had received the RSVPreF3 OA investigational vaccine (120 µg RSVPreF3/$AS01_E$) in the parent study RSV OA=ADJ-002
- Participants in group 30-AS01E_B had received the vaccine formulation RSVPreF3 recombinant antigen dose 30 µg adjuvanted with $AS01_E$ in the parent study RSV OA=ADJ-002
- Participants in group 60-AS01E_B had received the vaccine formulation RSVPreF3 recombinant antigen dose 60 µg adjuvanted with $AS01_E$ in the parent study RSV OA=ADJ-002

In addition, this study will also evaluate the immunogenicity of a revaccination dose of the RSVPreF3 OA investigational vaccine in participants previously vaccinated in RSV OA=ADJ-002, Part B with the same, selected formulation of the RSVPreF3 OA investigational vaccine (i.e. group 120-AS01E_B).

4.3. Justification for dose

Different formulations and a 2-dose vaccination regimen with an interval of 2 months between doses of the RSVPreF3 OA investigational vaccine were administered intramuscularly for the first time to adults aged 60 – 80 years according to a 0, 2 months schedule in the parent study, RSV OA=ADJ-002 (208851). Based on safety/reactogenicity and immunogenicity data (humoral and cellular immune responses) from the RSV OA=ADJ-002 study, the 120 µg RSVPreF3/$AS01_E$ vaccine formulation was selected for further clinical development. All participants in the current study will receive this selected formulation of the vaccine.

4.4. End of Study definition

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

End of Study (EoS): Last subject last visit (LSLV) (i.e. contact at Month 6).

5. STUDY POPULATION

5.1. Inclusion criteria for enrolment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety.

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

- Male or female participants, who received 2 doses of RSVPreF3 OA investigational vaccine and formulations with matched adjuvant in part B of the parent study RSV OA=ADJ-002: recombinant RSVPreF3 antigen doses 120 µg, 30 µg and 60 µg adjuvanted with $AS01_E$
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for the follow-up visit, be available for contact)
- Written informed consent obtained from the participant prior to performance of any study specific procedure.

5.2. Exclusion criteria for enrolment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

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

5.2.1. Medical conditions

- Significant underlying illness or administered therapy that in the opinion of the investigator would be expected to prevent participation in the study.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on information on concomitant medication/vaccination collected prior to the study start and physical examination (no laboratory testing required).
- Serious or unstable chronic illness that developed during or after the parent study. Patients with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study if considered by the investigator as clinically stable.
- Recurrent or un-controlled neurological disorders or seizures that developed during or after the parent study. Participants with medically-controlled active or chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol (e.g. completion of diary cards, attend phone calls/study site visits).

- Significant underlying illness that developed during or after the parent study, 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 6 months).
- Lymphoproliferative disorder and malignancy developed during or after the parent study.
- Any medical condition that developed during or after the parent study, that in the judgment of the investigator would make intramuscular injection unsafe.
- Previous vaccination with RSV vaccine, other than the one in the parent study.

5.2.2. Prior/Concomitant therapy (Amended 4 November 2020)

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine during the period beginning 30 days before the dose of study vaccine, or planned use during the study period.
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study vaccine administration, with the exception of inactivated, split virion and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after the study vaccination.

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

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or invasive medical device). Refer to the Glossary of terms for the definition of invasive medical device.

5.2.4. Other exclusions

- Bedridden participants.
- Planned move to a location that will prohibit participating in the trial.
- History of chronic alcohol consumption and/or drug abuse that developed during or after the parent study as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.

5.3. Lifestyle considerations

Not applicable.

5.4. Screen failures

Not applicable.

6. STUDY INTERVENTION

A 'study intervention' is defined as a set of investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

Refer to the Study Procedures Manual (SPM) for additional details (including vaccine reconstitution).

6.1. Study intervention administered

Table 5 Study intervention administered

Study intervention name:	RSVPreF3 OA interventional vaccine
Vaccine(s)/Product(s) name *	RSVPreF3 (120 µg)
	AS01E
Presentation	RSVPreF3 (120 µg): Vial; Powder for suspension for injection
	AS01E: Vial; Suspension for injection
Vaccine formulation:	RSVPreF3 (120 µg) AS01E: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injection q.s. 0.5 mL
Route of administration	Intramuscular
Location	Deltoid
Laterality **	Non-dominant
Number of doses to be administered:	1 dose
Volume to be administered	0.5 mL
Packaging, labelling and TM	Refer to SPM for more details
Manufacturer	GSK Biologicals

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

The participants must be observed closely for at least 30 minutes after the administration of the vaccine. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

Refer to Section 4 for the schedule of vaccine administration.

6.2. Preparation/Handling/Storage/Accountability

The study vaccine must be stored in a safe, locked place at the temperature specified on the vaccine label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Only authorized study personnel should be allowed access to the study vaccine. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participants will receive the same identification number as in the parent study RSV OA=ADJ-002.

6.3.2. Intervention allocation to the participant

Intervention allocation to the participants will be performed using an automated, Internet-based system (SBIR). After obtaining the signed and dated ICF from the participant and having checked the eligibility of the participant, the site staff in charge of the intervention administration will access SBIR. Upon providing the participant identification number, the system will provide the treatment number to be used. The number of each administered intervention must be recorded in the eCRF.

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

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

6.3.3. Blinding and unblinding

This is an open-label study, as all participants will receive the same RSVPreF3 OA investigational vaccine.

6.3.3.1. Emergency unblinding

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

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via an automated Internet-based system e.g. SBIR.

The investigator may contact a GSK Helpdesk (refer to the Table 6) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the SBIR).

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

Table 6 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Toll-free numbers: Belgium: PPD United States: PPD Fax: PPD Email: PPD

6.4. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date of the dose administered in the clinic will be recorded in the source documents and in the eCRF. The study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant therapy

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

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

- All concomitant medications/products/vaccines, except vitamins and dietary supplements, administered during the 30-day period following vaccination (Day 1 to Day 31).
- Any concomitant medications/products/vaccines leading to study participation/intervention non-eligibility, or an elimination from the analysis (refer to Section 5.2.2 for details).
- Any prophylactic medication (e.g. analgesics, antipyretics) administered on the day of study vaccination (Day 1) and in the absence of ANY symptom and in anticipation of a reaction to the vaccination.
- 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. Concomitant medications relevant to SAEs and pIMDs must be recorded on the Expedited Adverse Event Report.
- *Shingrix* or any AS01-containing vaccine throughout the entire study.

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

6.6. Dose modification

Not applicable.

6.7. Intervention after the end of the study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable, as only one dose of the RSVPreF3 OA investigational vaccine will be administered in the study.

7.1.1. Criteria for temporary delay for enrolment and/or vaccination (Amended 4 November 2020)

Enrolment/vaccination may be postponed within the permitted time interval until transient circumstances cited below are resolved:

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

7.2. Participant discontinuation/withdrawal from the study

A participant 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 participant from the date of withdrawal/last contact.

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

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

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

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

- Adverse events requiring expedited reporting to GSK (please refer to Section 10.3.9.1 for the details)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of an SAE/AE until the event is resolved. (see Section 10.3.7.2).

7.3. Lost to follow-up

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Adherence to the protocol is required for study conduct.

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

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the IEC/IRB.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team is aware of them.

Participants who received 2 doses of RSVPreF3 OA investigational vaccine and formulations with matched adjuvant in part B of the parent study RSV OA=ADJ-002: recombinant RSVPreF3 antigen doses 120 µg, 30 µg and 60 µg adjuvanted with $AS01_E$ will be invited to participate in this extension study.

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

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

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.
- Diary cards may be transmitted from and to the site by electronic means and/ or conventional mail.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to vaccinate the participants within the recommended interval predefined in the protocol (see Table 2, recommended interval), then the interval may be extended up to a maximum length of 30 days only for vaccination (see Table 2, allowed interval).

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

Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

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

Before implementing any study procedures, the investigator should confirm strict adherence to all inclusion/exclusion criteria (refer to Table 1). The criteria for temporary delay for enrolment and/or vaccination to ensure participants are still qualified for enrolment in the study should be checked, but this does not need to be recorded in the participant's eCRF.

8.1. Efficacy and/or immunogenicity assessments

Collected biological 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.

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. Therefore, all participants in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

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

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

If additional testing is performed, the marker priority ranking given in the Section 8.1.3 may be changed.

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally to, and discussed and agreed with GSK.

8.1.1. Biological samples

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

Table 7 Biological samples*

Sample type	Quantity	Unit	Timepoint
Blood for CMI	Approximately 25	mL	Visit 1 (Day 1**) Visit 2 (Day 31)
Blood for humoral immune response	Approximately 20	mL	Visit 1 (Day 1**) Visit 2 (Day 31)

*Samples taken only from the group 120-AS01E_B: Selected formulation revaccinated with the same formulation
** Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study

The approximate overall volume that will be collected per participant in the 120-AS01E_B group during the entire study period will be ~90 mL.

8.1.2. Laboratory assays

Table 8 Laboratory assays

Assay type	System	Component	Challenge	Method	Laboratory*
Cell-mediated Immunity (CMI)	PBMC	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17, 4-1BB secreting CD4+ and CD8+ T-cells	Peptide pool covering RSVPreF3	ICS	GSK ** or designated laboratory
Humoral Immunity (Antibody determination)	Serum	Respiratory Syncytial Virus A Ab		NEUTRALIZATION	GSK ** or designated laboratory
	Serum	Respiratory Syncytial Virus B Ab		NEUTRALIZATION	GSK ** or designated laboratory
	Serum	RSVPreF3-specific IgG antibody concentrations		ELISA	GSK ** or designated laboratory

Ab: antibody; ELISA: enzyme-linked immunosorbent assay; RSV: respiratory syncytial virus; PBMC: peripheral blood mononuclear cells; ICS: Intracellular cytokine staining; CD40L: cluster of differentiation 40 ligand; IFN-γ: interferon gamma, IL (IL-2, IL-13, IL-17): interleukin; TNF-α: tumor necrosis factor alpha; 4-1BB (CD137).
*Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy or to a contracted CRO.

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

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

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

8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint Type of contact and timepoint	No. participants*	Component	Components priority rank
Humoral immunity (serum samples)			
Visit 1 (Day 1**)	~100	RSV-A neutralizing antibody	1
		RSV-B neutralizing antibody	2
		RSVPreF3-specific IgG antibody	3
Visit 2 (Day 31)	~100	RSV-A neutralizing antibody	1
		RSV-B neutralizing antibody	2
		RSVPreF3-specific IgG antibody	3
Cell-mediated immunity (on PBMC samples)			
Visit 1 (Day 1)	~100	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17, 4-1BB secreting CD4+ and CD8+ T-cells	-
Visit 2 (Day 31)	~100	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17, 4-1BB secreting CD4+ and CD8+ T-cells	-

*Samples taken only from the group 120-AS01E_B: Selected formulation revaccinated with the same formulation
**Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study
PBMC = peripheral blood mononuclear cells; CD40L: cluster of differentiation 40 ligand; IFN- γ : interferon gamma, IL (IL-2, IL-13, IL-17): interleukin; TNF- α : tumor necrosis factor alpha; 4-1BB (CD137).

8.1.4. Immunological correlates of protection

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

8.2. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study.

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

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

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history for the transition period between the parent study RSV OA=ADJ-002 and the current study by interviewing the participant and/or review of the participant's medical records. Record any pre-existing participant conditions, signs and/or symptoms present during the transition period between the parent study RSV OA=ADJ-002 and the current study, or that worsened from the parent study, in the eCRF.

Administration of *Shingrix* during the transition period between the parent study RSV OA=ADJ-002 and the current study, and throughout the duration of the current study should be recorded in the eCRF. The date of vaccination should be collected and recorded in the eCRF.

8.2.1.3. Physical examination (Amended 4 November 2020)

At minimum, vital signs (e.g., heart rate, respiratory rate, blood pressure) must be collected.

Vital signs are to be taken before blood collection for laboratory tests and/or vaccination. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

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

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.

8.2.1.4. Warnings and precautions to vaccination

Warnings and precautions to vaccination must be checked at the beginning of the vaccination visit.

8.2.1.5. Pre-vaccination body temperature

The oral body temperature of each participant needs to be measured prior to any study vaccine administration and recorded in the eCRF. If the participant has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 2).

8.2.1.6. Distribution of paper diary cards

Paper diary cards will be distributed at the vaccination visit (Visit 1) for the participants to record any solicited event and any unsolicited AE they may have experienced as well as any medication taken in the 30-day period following the vaccination. Refer to Section 10.3.7 for guidelines.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other events of interest

8.3.1. Time period and frequency for collecting AEs, SAEs and other safety information (Amended 4 November 2020)

Table 10 Timeframes for collecting and reporting of safety information

	Pre-Dose 3* V1 (D1)	Dose 3 V1 (D1)	D4	V2 (D31)	Phone contact (M6, study conclusion)
Solicited administration site and systemic events					
Unsolicited AEs					
All SAEs/pIMDs					
SAEs/pIMDs related to study vaccination					
SAEs related to study participation or concurrent GSK medication/vaccine					
Intercurrent medical conditions					
AEs/SAEs leading to withdrawal from the study					

* i.e. consent obtained. V: visit, M: Month; D: Day

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the ***Adverse Events Form and the corresponding*** Expedited Adverse Event Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.9. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 10. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to vaccination, the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in the Table 12.

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

Methods of detecting and recording AEs/SAEs/pIMDs are detailed in the Section 10.3.7. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.8.

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

8.3.3. Regulatory reporting requirements for SAEs and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD, he/she must report it to GSK using the required documentation, and within the timeframes, mentioned in the Table 11. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.8.2.

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

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

Please refer to Section 10.3.9 for further details regarding the reporting of SAEs/pIMDs.

Table 11 Timeframes for submitting serious adverse events and other events reports to GSK (Amended 4 November 2020)

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

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
⌗ The investigator will be required to review the SAE/pIMD causality within 72 hours of submission of the SAE/pIMD. ***Date/time of the causality review should be entered in the eCRF.***

8.3.3.1. Contact information for reporting of SAEs and pIMDs

Table 12 Contact information for reporting of SAEs and pIMDs

Study contact for questions regarding SAEs and pIMDs Refer to the local study contact information document
Back-up study contact for reporting SAEs and pIMDs Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.9.1).

8.3.5. Participant card

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

8.4. Treatment of overdose

This section is not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in the current study.

8.8. Biomarkers

Biomarkers for pharmacogenetics are not evaluated in this study.

8.9. Health outcomes

Economic outcome measures such as health care resource utilization data associated with healthcare encounters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Not applicable as this study is descriptive.

9.2. Sample size determination

No sample size is calculated for this study. Potentially eligible participants who received 2 doses of the RSVPreF3 OA investigational vaccine and formulations with matched adjuvant in part B of the parent study RSV OA=ADJ-002: recombinant antigen doses 120 μg , 30 μg and 60 μg adjuvanted with $AS01_E$ will be invited to participate in this extension study. An estimate of the maximum number of participants to be potentially enrolled can therefore be obtained by considering all currently enrolled participants in study RSV OA=ADJ-002 who received both doses in the groups considered for this extension study.

Withdrawals will not be replaced.

9.3. Populations for analyses

Table 13 Populations for analyses

Analysis Set	Description
Enrolled	Participants who agreed to participate in the clinical study after **completion of the informed consent process.**
Exposed	All participants who received Dose 3 of the study intervention.
Per Protocol	All participants who received Dose 3 of the study intervention and have post-vaccination data minus participants with protocol deviations that lead to exclusion.

The primary analysis for immunogenicity will be performed on the Per Protocol set (PPS) for immunogenicity. If in any study group the percentage of participants with serological results excluded from the PPS for immunogenicity is at least 10%, a second analysis will be performed on the Exposed Set (ES).

9.3.1. Criteria for elimination from analysis

9.3.1.1. Intercurrent medical conditions and concomitant medications/products/vaccines that may lead to elimination of a participant from per-protocol analyses

If the participant meets one of the criteria mentioned in the Sections 5.2.1 (medical conditions) or 5.2.2 (prior/concomitant therapy), he/she may be eliminated from per protocol analysis. Refer to Glossary of terms for the definition of intercurrent medical conditions.

9.4. Statistical analyses

The statistical analysis plan (SAP) will be finalized prior to First Participant First Visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General considerations

9.4.1.1. Demography

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

9.4.1.2. Immunogenicity

- Any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each time point will exclude participants with a missing or non-evaluable measurement.
- The geometric mean titers/concentrations (GMTs/GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the $\log_{10}$ transformed titers/concentrations.

- A seronegative participant will be defined as a participant whose antibody titer/concentration is below the cut-off value of the assay. A seropositive participant is a participant whose antibody titer/concentration is greater than or equal to the cut-off value of the assay.
- Antibody titers/concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMT/GMC calculation.
- Antibody titers/concentrations above the assay upper limit of quantification (ULOQ) will be given the value of the ULOQ for the purpose of GMT/GMC calculation.

9.4.1.3. Reactogenicity/Safety

- For a given participant and the analysis of solicited events within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of solicited events will include only vaccinated participants with documented solicited safety data (i.e., paper diary completed).
- For analysis of unsolicited AEs, SAEs, pIMDs and concomitant medications, all vaccinated participants will be considered. Participants who did not report an event or concomitant medication will be considered as participants without the event or the concomitant medication, respectively.

9.4.2. Demographics and participants disposition

Demographic characteristics (age in years, sex) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as sex.
- Mean, median, standard deviation and range will be provided for continuous data such as age.

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

9.4.3. Primary endpoint

9.4.3.1. Safety analysis

The safety analysis will be performed on the ES. A descriptive analysis by group and overall will present a summary of:

- The number and percentage of participants with at least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE during the 4-day or 30-day follow-up period will be tabulated with exact 95% CI after Dose 3. The same computations will be done for Grade 3 and related AEs.
- The number and percentage of participants with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will be tabulated after Dose 3.
- The number and percentage of participants reporting each individual solicited administration site event (any grade, Grade 3) and solicited systemic event (any grade, Grade 3) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- The number and percentage of participants 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. The same 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 number and percentage of participants with at least one report of SAE/pIMD classified by the MedDRA Preferred Terms and reported during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be tabulated with exact 95% CI. The same tabulation will be done for related SAEs/pIMDs.
- The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 4-day follow-up period (i.e., on the day of vaccination and 3 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.

9.4.3.2. Humoral immune response up to 1 month post-Dose 3

At each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified), the analyses below will be performed:

- Percentage of participants with antibody titers/concentrations above the positivity cut-off and their exact 95% CI will be tabulated.
- GMTs/GMCs and their 95% CI will be tabulated and represented graphically. Antibody titers/concentrations will be displayed using reverse cumulative curves.
- Distributions of antibody titers/concentrations will be tabulated.
- The mean geometric increase (MGI) i.e. geometric mean of ratios of antibody titers/concentrations of each post-vaccination time point over pre-vaccination, will be tabulated with 95% CI.
- Individual post-vaccination results versus pre-vaccination results will be plotted using scatter plots.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers/concentrations) will be tabulated.
- The ratio of fold increase (pre to post) of anti-RSVPreF3-specific antibody concentrations over the fold increase (pre to post) of anti-RSV-A neutralizing antibody titers will be tabulated using descriptive statistics and displayed graphically using scatter plots.
- The fold increase of post-dose 3 (in RSV OA=ADJ-011 EXT:002 MTH20 study) over post-dose 1 (in RSV OA=ADJ-002 study) antibody titers/concentrations will be tabulated using descriptive statistics.

As pre-vaccination will be considered both pre-Dose 1 in RSV OA=ADJ-002 and pre-Dose 3 in RSV OA=ADJ-011 EXT:002 MTH20.

The immunogenicity analysis might also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

9.4.4. Secondary endpoints

9.4.4.1. Humoral immune response up to 1 month post-Dose 3

See Section 9.4.3.2.

9.4.4.2. CMI response up to 1 month post-Dose 3

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

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

- Fold increase of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers among IL-2, CD40L, TNF-α, IFN-γ, at each post-vaccination time point over pre-vaccination.
- Distribution of the fold increase: the percentage of participants with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

The immunogenicity analysis might also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

9.4.4.3. SAEs and pIMDs up to 6 months post-Dose 3

- The number and percentage of participants 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. The same tabulation will be done for causally related and fatal SAEs. SAEs will also be described in detail.
- The number and percentage of participants 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. The same tabulation will be done for causally related pIMDs. pIMDs will also be described in detail.

9.4.5. Tertiary endpoints

The statistical analyses concerning tertiary endpoints will be described in the SAP.

9.5. Interim analyses

All analyses will be conducted on final data, as clean as possible.

9.5.1. Sequence of analyses

The analyses will be performed stepwise:

- A first analysis will be performed when all data as clean as possible are available for at least primary and secondary endpoints up to Visit 2 (Day 31).
- The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion (Month 6) are available. All available tertiary endpoints will also be analyzed in this step. Individual listings will only be provided at this stage.

If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

9.5.2. Statistical consideration for interim analysis

All analyses will be conducted on final data (all planned results available for the time points of interest) and therefore no statistical adjustment for interim analyses is required.

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/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.

10.1.2. 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 interests during the course of the study and for 1 year after completion of the study. Investigators are responsible for providing a Financial Disclosure update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

10.1.3. Informed consent process

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

Participants must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant, as appropriate, prior to participation in the study. In addition, the signed informed consent of the designate must be obtained, in case a designate is assigned by the participant.

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 participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

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

10.1.4. Data protection

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

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

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

The participants 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 protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Committees structure

10.1.6. Dissemination of clinical study data

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

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

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

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

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. 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 trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

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

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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). The safety and rights of participants 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.

10.1.8. Source documents

Source documents provide evidence for the existence of the participant 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 Glossary of terms.

10.1.9. Study and site start and closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at 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 occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and 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 participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Laboratory assays

RSV-A and RSV-B neutralization assays

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

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

RSVPreF3 protein IgG ELISA

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

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

Intracellular cytokine staining (ICS)

The ICS is used to assess RSVPreF3-specific CD4+ and/or CD8+ T-cells expressing CD40L and/or IL2 and/or IFN-γ and/or TNF-α (secondary endpoint). Additional markers might be used to further characterize the cellular immune response (exploration analysis in tertiary endpoint): 4-1BB, IL-13, IL-17.

As previously described [Moris, 2011], thawed peripheral blood mononuclear cells (PBMCs) are stimulated in vitro in the presence of anti-CD28 and anti-CD49d antibodies either with pools of 15-mer peptides overlapping by 11 amino acids and spanning the sequence of the RSVPreF3 protein, or with medium. After 2 hours of incubation at 37°C, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation at 37°C. Cells are subsequently harvested, stained for surface markers (CD4+ and CD8+) and then fixed. Fixed cells are then permeabilized and stained with labeled antibodies specific for the following immune markers (7 parameters assay):

- CD3+: phenotyping T-cells;
- CD40L (CD154), expressed on activated CD4+ T-cells, [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006];
- IL-2: key for the development, survival and function of T-cells [Boyman, 2012];
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014];
- IFN-γ: anti-viral factor, associated with the Th1-like profile [Schoenborn, 2007];

And potentially integrating as well (10 parameters assay):

- 4-1BB (CD137), expressed on activated CD4+ and CD8+ T-cells [Wölfl, 2008];
- IL-13: associated with the Th2-like profile [Bao, 2015];
- IL-17: associated with the Th17-like profile [Korn, 2009].

After staining with the markers above, the cellular samples are analyzed by flow-cytometry allowing to determine the frequency of CD4+ T-cells expressing the marker(s) of interest per million of CD4+ T-cells.

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

10.3.1. Definition of an Adverse Event (AE)

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after 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 or symptoms temporally associated with study vaccine administration.
- Signs or symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits)
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

10.3.1.2. Events NOT Meeting the AE Definition
• Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Pre-existing conditions or signs and/or symptoms present in a participant prior to the study vaccination. These events will be recorded in the medical history Section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline. • 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 participant's condition, or that are present or detected at the start of the study and do not worsen. • Disease/Population -related events (DRE/PRE), typically associated with the disease/population under study. These events will be recorded in the participant's eCRF and will be monitored on a routine basis. However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 10.3.7): • The event is, in the investigator's opinion, of greater intensity, frequency or duration than expected for the individual participant, or • The investigator considers that there is a reasonable possibility that the event was related to the administration of the study vaccine

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:	
a.	Results in death
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered as 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.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant
f.	Other situations Medical or scientific 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 participant 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.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 14 Solicited administration site events

Pain at the injection site
Erythema at the injection site
Swelling at the injection site

b. Solicited systemic events

The following systemic events will be solicited:

Table 15 Solicited systemic events

Fever

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

10.3.4. Unsolicited AEs

An unsolicited AE is an AE that was not solicited using a Participant Diary and that was spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

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

Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

10.3.5.1. Potential immune-mediated diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 16.

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

Table 16 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. • Localised Scleroderma (Morphoea).

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

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

Not applicable.

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

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

When an AE/SAE/pIMD 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/pIMD in the eCRF. The investigator is not allowed to send photocopies of the participant'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 participant 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/pIMD and not the individual signs/symptoms.

A Paper Diary (pDiary), hereafter referred to as Participant Diary will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete each field of the Participant Diary.

Any individual(s) (including the designate; refer to the Glossary of terms for the definition of the term "designate") who performs the measurements of administration site or systemic events and who will enter the information into the Participant Diary should be trained on the use of the Diary. This training must be documented in the participant's source record. If any other individual than the participant is making entries in the Participant Diary, their identity should be documented in the participant's source record.

- Collect and verify completed diary cards during discussion with the participant on Visit 2.
- Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure.

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

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

All AEs that occur during 30 days following administration of the dose of study vaccine (Day 1 to Day 31) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

10.3.7.2. Follow-up of AEs, SAEs, pIMDs

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

Other non-serious AEs must be followed until 30 days after the last vaccination or until the participant is lost to follow-up.

10.3.7.2.1. Follow-up during the study

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

If participant 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.

10.3.7.2.2. Follow-up after the participant is discharged from the study (Amended 4 November 2020)

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

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

When additional SAE, pIMD information is received after removal of write access to the participant'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 Section 8.3.3.1 or to GSK Clinical Safety and Pharmacovigilance department within the defined reporting time frames specified in the Table 11).

10.3.8. Assessment of intensity and toxicity

10.3.8.1. Assessment of intensity

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

Adults		
Event	**Intensity grade**	**Parameter**
Pain at the 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.
Erythema at the injection site		Record greatest surface diameter in mm
Swelling at the injections site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F

* Refer to the Section 1.3 (SoA) for the definition of fever and the preferred location for temperature measurement.

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

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

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

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

1 (mild) = An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities
In adults such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

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

10.3.8.2. Assessment of causality (Amended 4 November 2020)

All solicited administration-site and systemic events will be considered causally related to vaccination. The complete list of these events is provided in the Table 14 and Table 15.

The investigator must assess the relationship between the study vaccine and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

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.

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

Is there a reasonable possibility that the unsolicited AE may have been caused by the study 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 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

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

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

10.3.8.3. Assessment of outcomes

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

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

10.3.9. Reporting of SAEs, pIMDs

10.3.9.1. Events requiring expedited reporting to GSK (Amended 4 November 2020)

Once an investigator becomes aware that an SAE/pIMD has occurred in a study participant, the investigator (or designee) must ***report the SAE/pIMD*** WITHIN 24 HOURS ***by completing an Adverse Events Form and a corresponding Expedited Adverse Event Form***. The***se forms*** 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/pIMD, the ***forms*** 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.

Refer to the Table 11 for the details on timeframes for reporting of SAEs/pIMDs.

The investigator will be required to review the SAE/pIMD causality within 72 hours of submission of the SAE/pIMD. ***Date/time of the causality review should be entered in the eCRF.***

Refer to the Section 10.3.9.2 for the back-up system in case the electronic reporting system does not work.

10.3.9.2. Back-up system in case facsimile or electronic reporting system does not work (Amended 4 November 2020)

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax completed, dated and signed paper Expedited Adverse Event Report to the Study Contact for Reporting SAEs/pIMDs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

Investigator (or designee) must complete the electronic ***Adverse Events Form and the corresponding*** Expedited Adverse Event ***Form*** within 24 hours upon electronic reporting system is resumed. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Abbreviations and glossary of terms

10.4.1. List of abbreviations

AE:	Adverse Event
AESI:	Adverse Event of Specific Interest
AS01$_E$:	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19:	Coronavirus Disease 2019
CMI:	Cell Mediated Immunity
DRE:	Disease-related event
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
ICS:	Intracellular Cytokine Staining
IEC:	Independent Ethics Committee

IgG:	Immunoglobulin G
IRB:	Institutional Review Board
LML:	Local Medical Lead
LRTD:	Lower Respiratory Tract Disease
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
MGI:	Mean Geometric Increase
OA:	Older Adults
PBMC:	Peripheral Blood Mononuclear Cells
pIMD:	Potential Immune-Mediated Disease
PP:	Per protocol
PRE:	Population-related event
PT:	Preferred Term
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RSV:	Respiratory Syncytial Virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Source data Base for Internet Randomisation
SoA:	Schedule of Activities
SPM:	Study Procedures Manual
US:	United States

10.4.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An 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 intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
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.
Designate:	A person who helps the subject with performing some of the study procedures if the subject has difficulties to perform them alone (such as completion of the Diary, receiving phone calls and planning of the study visits), e.g. a relative of the subject, a field worker who is linked to this study. Designates are appointed by the subject for help with the study procedures solely and cannot make decisions on behalf of the subject.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Enrolled:	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 for the definition of 'enrolled' applicable to the study.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 9.3 for details on criteria for evaluability).
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical condition:	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the subject's initial immune status.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product

Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine or as a control. Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified 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 legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, 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.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.5. Appendix 5: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	Date of Issue
Original Protocol	2 July 2020

Overall Rationale for the Amendment

The protocol is amended to address the comments from the United States Food and Drug Administration (US FDA). Specifically, instructions to delay enrolment or vaccination of participants with symptoms suggestive of Coronavirus Disease 2019 (COVID-19) infection or with known COVID-19 positive contacts have been updated. In addition, the requirement to obtain written approval from the Sponsor for a participant to receive a vaccine as part of mass vaccination for an unforeseen public health threat (e.g., pandemic) if the vaccine to be used according to the local governmental recommendations has been amended. Other changes have been made to align the protocol with the parent RSV OA=ADJ-002 study and other phase 3 studies in the project.

Detailed description of Protocol Amendment:

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

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

Section 5.2.2: Prior/ Concomitant therapy: Updated to acknowledge the FDA's request to remove the requirement to obtain written approval from the Sponsor for mass vaccination.

Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is ~~licensed and~~ used according to the local governmental recommendations and provided ~~a written approval of the Sponsor is obtained~~ ***that the Sponsor is notified accordingly***.

Section 7.1.1 Criteria for temporary delay for enrolment and/or vaccination: Updated to acknowledge FDA feedback.

~~Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to vaccination.~~

Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (i.e. fever, cough, etc.) ~~until they are free of symptoms for at least 14 days~~. ***The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g. free of symptoms, COVID-19 negative testing, etc.). until they are free of symptoms for at least 14 days.***

~~Enrolment and/or vaccination of subjects with known COVID-19 positive contacts within the past 14 days should be delayed for at least 14 days since the exposure and if the subject remains symptom free.~~ ***Participants with known COVID-19 positive contacts within the past 14 days may be vaccinated at the discretion of the investigator at least 14 days after the exposure if the participant remains symptom free.***

Section 8.2.1.3 Physical examination: Updated to avoid duplication of temperature measurement.

At minimum, ~~temperature,~~ vital signs (e.g., heart rate, respiratory rate, blood pressure) must be collected.

Sections 8.3.1, 8.3.3 (Table 11), 10.3.7.2.2, 10.3.8.2, 10.3.9.1, 10.3.9.2: Throughout the document, in applicable sections, the wording is updated to account for both Adverse Events Form and the Expedited Adverse Event Form.

…***Adverse Events Form and the corresponding*** Expedited Adverse Event~~s Report~~ ***Form***.

Sections 8.3.3 (Table 11), 10.3.9.1: Wording is updated to align with the eCRF.

The investigator will be required to ~~confirm~~ review ~~of~~ the SAE/pIMD causality ~~by ticking the "reviewed" box in the electronic Expedited Adverse Events report~~ within 72 hours of submission of the SAE/pIMD. ***Date/time of the causality review should be entered in the eCRF.***

11. REFERENCES (AMENDED 4 NOVEMBER 2020)

Bao K, Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. *Cytokine* 2015;75(1):25-37.

Barbas CF, Crowe JE, Cababa D, *et al*. Human monoclonal Fab fragments derived from a combinatorial library bind to respiratory syncytial virus F glycoprotein and neutralize infectivity. *Proc Natl Acad Sci USA*. 1992; 89(21):10164-8.

Bates JT, Keefer CJ, Slaughter JC, *et al*. Escape from neutralization by the respiratory syncytial virus-specific neutralizing monoclonal antibody palivizumab is driven by changes in on-rate of binding to the fusion protein. *Virology*. 2014;454-455:139-44.

Borchers AT, Chang C, Gershwin ME, et al. Respiratory syncytial virus – a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45:331-79.

Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. *Nat Rev Immunol.* 2012;12(3):180-90.

Centers for Disease Control and Prevention. Respiratory Syncytial Virus Infection (RSV): Trends and Surveillance. RSV | Trends and Surveillance | Respiratory Syncytial Virus | CDC ***2018***, Accessed ***November*** 2020. [CDC website]. **(Amended 4 November 2020)**

Chattopadhyay PK, Yu J, Roederer M. A live-cell assay to detect antigen-specific CD4+ T cells with diverse cytokine profiles. *Nat Med.* 2005;11(10):1113-7.

Cherukuri A, Patton K, Gasser Jr RA, et al. Adults 65 years old and older have reduced numbers of functional memory T-cells to respiratory syncytial virus fusion protein. *Clin Vaccine Immunol.* 2013;20:239-47.

Falsey AR and Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev.* 2000;13:371–84.

Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *J Infect Dis.* 2014;209:1873-81.

Frentsch M, Arbach O, Kirchhoff D, et al. Direct access to CD4+ T cells specific for defined antigens according to CD154 expression. *Nat Med/* 2005;11(10):1118-24.

Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. *Immunol Rev.* 2011;239:149-66.

Korn T, Bettelli E, Oukka M *et al*. IL-17 and Th17 Cells. *Annu Rev Immunol.* 2009;27:485-517.

Krilov LR. Respiratory syncytial virus disease: update on treatment and prevention. *Expert Rev. Anti. Infect. Ther.* 2011;9:27–32.

Moris P, Van Der Most R, Leroux-Roels I *et al*. H5N1 influenza vaccine formulated with AS03 A induces strong cross-reactive and polyfunctional CD4 T-cell responses. *J Clin Immunol.* 2011; 31(3):443-54.

Rima B, Collins P, Easton A, et al. ICTV Virus Taxonomy Profile: Pneumoviridae. *J Gen Virol.* 2017;98:2912-3.

Samten B, Thomas EK, Gong J, Barnes PF. Depressed CD40 ligand expression contributes to reduced gamma interferon production in human tuberculosis. *Infect Immun* 2000;68(5):3002-6.

Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. *Adv Immunol.* 2007; 96:41-101.

Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. *Cytokine Growth Factor Rev.* 2014;25(4):453-72.

Simões EA. Respiratory syncytial virus infection. *Lancet*. 1999;354:847–52.

Simões EA. RSV disease in the pediatric population: epidemiology, seasonal variability, and long-term outcomes. *Manag Care*. 2008;17(11 Suppl 12):3-6, discussion 18-9.

Stubbe M, Vanderheyde N, Goldman M *et al*. Antigen-specific central memory CD4+ T lymphocytes produce multiple cytokines and proliferate in vivo in humans. *J Immunol.* 2006;177(11):8185-90.

Wölfl M, Kuball J, Eyrich M, Schlegel PG, Greenberg PD. Use of CD137 to study the full repertoire of CD8+ T cells without the need to know epitope specificities. *Cytometry A.* 2008 Nov;73(11):1043-9.

TRADEMARKS

The following trademarked products are referenced in the present protocol.

Trademarks of the GSK group of companies	Generic description
Shingrix	Zoster vaccine (Recombinant, adjuvanted)

Trademarks not owned by the GSK group of companies	Generic description
TrueBlue peroxidase substrate (SeraCare)	Chromagenic substrate for visualization of horseradish peroxidase-labeled reporter reagents