Protocol

Official Title of Study: A phase 3, randomized, double blind, multi country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above

Study ID: 217131

Approval Date of Document: 10-MAY-2021

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

Primary study intervention(s) and number(s)	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
eTrack study number and abbreviated title	217131 (RSV OA=ADJ-009)
EudraCT number	2021-002225-18
Date of protocol	Final: 10 May 2021
Title	A phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above.
Brief title	A study of 3 lots of an investigational vaccine against respiratory syncytial virus (RSV) in adults aged 60 years and above.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

Protocol Sponsor Signatory Approval

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Date of protocol	Final: 10 May 2021
Title	A phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above.
Sponsor signatory	Veronica Hulstrøm Senior Clinical Research and Development Lead RSV Older Adults
Signature	_____
Date	_____

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

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

Hence, I:

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

eTrack study number and abbreviated title	217131 (RSV OA=ADJ-009)
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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

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

GSK central back up study contact for reporting SAEs: refer to 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 Section 6.3.4.1.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GSK is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥ 60 years of age (YOA). The vaccine development is currently in phase 3.

The current study will assess lot-to-lot consistency in terms of immunogenicity and evaluate safety and reactogenicity of the 3 RSVPreF3 OA investigational vaccine lots in adults ≥ 60 YOA. The study is designed as a randomized, double-blind study with 3 parallel groups. The 3 investigational groups (hereafter referred to as RSVPreF3_Grp1, RSVPreF3_Grp2, and RSVPreF3_Grp3) will be vaccinated with 1 of the 3 lots of RSVPreF3 OA investigational vaccine, each composed of unique randomized combinations of antigen and adjuvant lots (for details see Table 6 and Section 6.3.3).

Note: for readability, hereafter, the "RSVPreF3 OA investigational vaccine" is also referred to as "RSV investigational vaccine".

Objectives and endpoints:

Refer to Table 4 for an overview of the study objectives and endpoints.

1.2. Schema

Refer to Figure 1 for an overview of the study design.

1.3. Schedule of activities (SoA)

Table 1 Schedule of activities (SoA)

Type of contact Timepoints	Visit 1 Day 1	Visit 2* Day 31	Contact Month 6[1]	Notes
Informed consent	●			See Section 10.1.3
Distribution of participant cards	○			See Section 8.3.5
Check inclusion/exclusion criteria	●			See Sections 5.1 and 5.2
Check if the participant will appoint a caregiver and distribute caregiver information letter, when applicable	○	○		See Sections 4.1.3 and 10.1.3
Baseline and demography assessments				
Collect demographic data	●			See Section 8.2.1.1
Recording of medical and vaccination history	●			See Sections 8.2.1.2 and 8.2.1.3
History directed physical examination	○			See Section 8.2.1.4 for more information
Laboratory assessment				
Blood sampling for antibody determination (~10 mL)	●[2]	●		See Section 8.1.1 for more information
Study intervention				
Check warnings and precautions to study intervention administration	○			See Section 8.2.1.5 for more information
Check criteria for temporary delay for enrolment and study intervention administration	○			See Section 5.5 for more information
Study group and study intervention number allocation	○			See Sections 6.3.2 and 6.3.3 for more information
Recording of body temperature before study intervention administration[3]	●			The location for measuring temperature can be the oral cavity/axillary/tympanic membrane
Study intervention administration (including 30 minutes observation after study intervention administration)	●			See Section 6.1 for more information
Recording of administered study intervention number	●			
Safety assessments				
Distribution of Paper Diary cards	○			See Section 10.3.7 for more information
Return of Paper Diary cards		○		See Section 10.3.7 for more information
Recording of solicited adverse events (Days 1 - 4 after study intervention administration)	●	●		See Sections 10.3.3 and 10.3.7 for more information
Recording of unsolicited adverse events AEs (Day 1 - 30 after study intervention administration)	●	●		See Sections 10.3.4 and 10.3.7 for more information
Recording of any concomitant medications/vaccinations	●	●	●	See Section 6.8 for more information
Recording of any intercurrent medical conditions	●	●	●	See Section 9.2.1 for more information
Recording of SAEs and pIMDs	●	●	●	See Section 10.3.7 for more information
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[4]	●	●	●	See Section 10.3.7 for more information
Contact for safety follow-up			●	See Sections 8.2.2 and 10.3.7.2 for more information
Study conclusion			●	See Section 4.4 for more information

Note: The double-line border indicates the analyses which will be performed on all data (i.e. data that are as clean as possible).
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF
AE: adverse event; pIMDs: potential immune-mediated diseases; RSV: respiratory syncytial virus, SAE: serious adverse event; eCRF: electronic Case Report Form
* Visit 2 should preferably be performed on site, but if deemed necessary (during special circumstances such as Coronavirus Disease 2019 [COVID-19] pandemic), this study visit can be replaced by a home visit conducted by qualified staff. Any information from the participant required according to study procedures and not collected during the home visit, can be obtained by means of a phone call conducted by the site staff.
[1]. Month 6: 6 months after study intervention administration. For this contact multiple formats can be proposed by the study site.
[2]. The blood sample on Day 1 should be drawn prior to study intervention administration.
[3]. Fever is defined as temperature ≥ 38.0°C/100.4°F regardless of the location of measurement.
[4]. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study intervention administration) up to study end.

Table 2 Intervals between study visits

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

2. INTRODUCTION

2.1. Study rationale

GSK is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in phase 3.

The current study will assess lot-to-lot consistency in terms of immunogenicity and evaluate safety and reactogenicity of the 3 RSVPreF3 OA investigational vaccine lots in adults ≥60 YOA. The study is designed as a randomized, double-blind, multi-country study with 3 parallel groups. The 3 investigational groups (hereafter referred to as RSVPreF3_Grp1, RSVPreF3_Grp2, and RSVPreF3_Grp3) will be vaccinated with 1 of the 3 lots of RSVPreF3 OA investigational vaccine, each composed of unique randomized combinations of antigen and adjuvant lots (for details see Table 6 and Section 6.3.3).

Note: for readability, hereafter, the "RSVPreF3 OA investigational vaccine" is also referred to as "RSV investigational vaccine".

The rationale for the study design is presented in Section 4.2.

2.2. Background

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

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

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

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

2.3. Benefit/Risk assessment

2.3.1. Risk assessment

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

Table 3 Important risks and mitigation strategy

Potential/Identified Risk	Mitigation Strategy
RSV investigational vaccine	
Potential immune-mediated diseases (pIMDs) are considered a potential risk, as for all vaccines containing an adjuvant system.	Refer to Section 10.3.5.1 for details.
Syncope and hypersensitivity.	All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.
Study procedures	
Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	As a mitigation strategy, a topical analgesic may be applied to the site of injection.
Pain and bruising may occur at the site where blood is drawn.	As a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.
Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.

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

2.3.2. Benefit assessment

The participants receiving the RSVPreF3 OA investigational vaccine may not directly benefit from this vaccination because the 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 OA.

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

2.3.3. Overall Benefit/Risk conclusion

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

3. OBJECTIVES AND ENDPOINTS

Table 4 Study objectives and endpoints

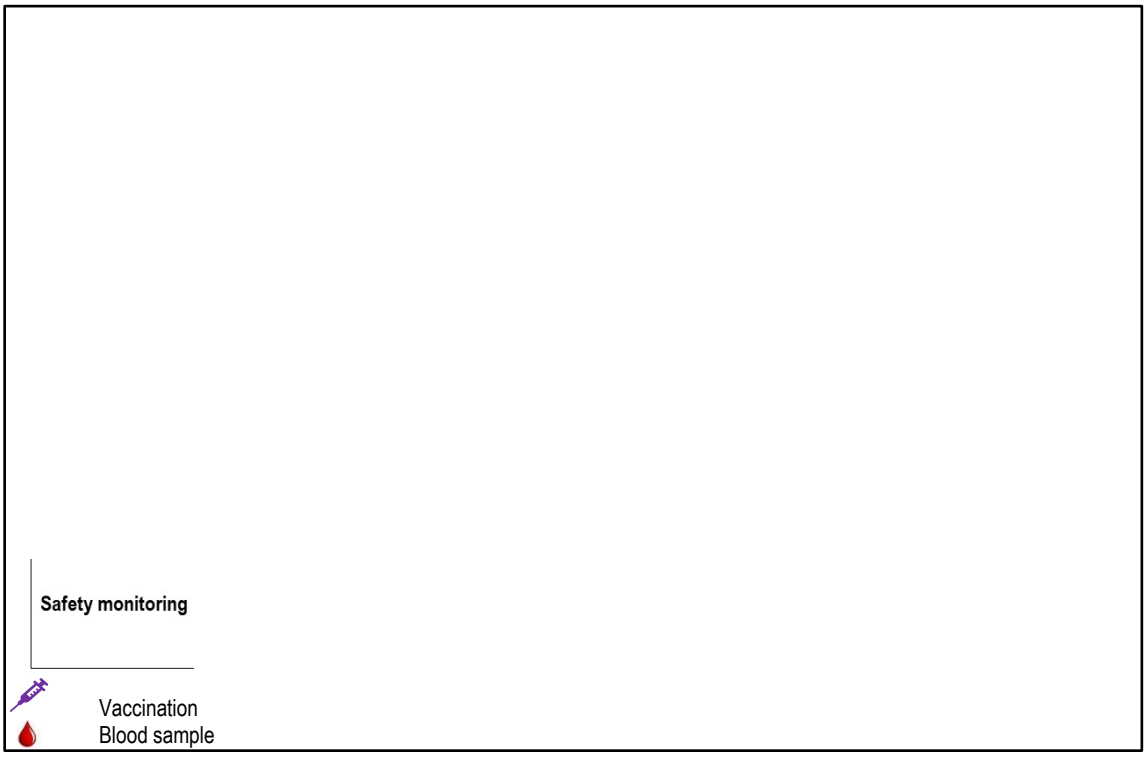
Objectives	Endpoints
Primary	
• To demonstrate the lot-to-lot consistency of 3 lots of the RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine in terms of immunogenicity.	• RSVPreF3-specific immunoglobin (Ig)G antibody concentrations expressed as group geometric mean concentration (GMC) ratio at 30 days post-vaccination (Day 31).
Secondary	
• To evaluate the humoral immune response of the 3 lots of the RSVPreF3 OA investigational vaccine.	• RSVPreF3-specific IgG antibody concentrations expressed as mean geometric increase (MGI) at 30 days post-vaccination (Day 31).
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine.	• Percentage of participants reporting each solicited event with onset within 4 days after study intervention administration (i.e. the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited adverse events (AE) within 30 days after study intervention administration (i.e. the day of vaccination and 29 subsequent days). • Percentage of participants reporting serious AEs after study intervention administration (Day 1) up to study end (6 months after vaccination). • Percentage of participants reporting potential immune-mediated diseases after study intervention administration (Day 1) up to study end (6 months after vaccination).
Tertiary	
CCI [redacted]	

RSV: respiratory syncytial virus.

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



AE: adverse event; Grp: group; N: number of participants; pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
BS: blood samples. Blood samples will be collected from all participants at Visit 1 and Visit 2 to assess humoral immune response.
Note: All SAEs related to study participation or a GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study (prior to study vaccination) up to study end.

- **Study type:** Self-contained.
- **Experimental design**: Phase 3, randomized, double-blind, multi-country study with 3 parallel groups (see Figure 1).
- **Duration of the study**: ~ 6 months for each participant.
- **Method of study intervention allocation:** Randomized.
  - Participants will be randomly assigned (1:1:1) to the 3 study groups (250 participants in each study group: RSVPreF3_Grp1, RSVPreF3_Grp2, and RSVPreF3_Grp3) at Visit 1 (Day 1) (see 6.3.2 for details of randomization procedures).
- **Level of blinding:** Double-blind (blinded to the study intervention lots). The study will be conducted in a double-blind manner from study start-up to final analysis (see Section 9.4.1 for details), beyond which the study will be considered single-blind.

Refer to Table 5 and Section 6.3.4 for details on blinding and unblinding procedures.

- **Data Collection:** Standardized electronic Case Report Form (eCRF). Solicited events and unsolicited AEs will be collected using a Participant Diary card (Paper Diary card). Concomitant medications/vaccinations will be collected in the Diary card on the day of vaccination and for 29 subsequent days (Days 1 to 30).
- **Safety monitoring:** The study will be conducted with oversight by the project Safety Review Team (SRT). Please refer to Section 10.1.5 for the SRT structure.
- **Study groups:** Refer to Figure 1 and Section 6.3.2 for an overview of the study groups.
- **Vaccination schedule:** A single dose of RSVPreF3 OA investigational vaccine on Day 1.
- **Timepoint for reaching the Primary Completion Date milestone:** Day 31 (30 days post-study intervention administration).

Table 5 Study groups, intervention and blinding

Study groups	Number of participants	Age	Study intervention	Blinding
RSVPreF3_Grp1	~ 250	≥ 60 years	RSVPreF3 OA investigational vaccine	The study will be conducted in a double-blind manner from study start-up to final analysis, beyond which the study will be considered single-blind.
RSVPreF3_Grp2	~ 250	≥ 60 years	RSVPreF3 OA investigational vaccine	
RSVPreF3_Grp3	~ 250	≥ 60 years	RSVPreF3 OA investigational vaccine	

Grp: Group
*GSK central study team will be unblinded to the data at the time of final analysis in order to prepare the Clinical Study Report of the final analysis. The study participants will remain blinded until the study end.

4.1.1. Overview of recruitment plan

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

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

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

4.1.2. Study enrolment rules

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

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

4.1.3. Care giver support

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

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

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

4.2. Scientific rationale for study design

The current study is designed as a phase 3, double-blind study to assess lot-to-lot consistency in terms of immunogenicity and evaluate safety and reactogenicity of the 3 RSVPreF3 OA investigational vaccine lots in adults ≥ 60 YOA. There are 3 parallel investigational groups (see Table 6):

- RSVPreF3_Grp1
- RSVPreF3_Grp2
- RSVPreF3_Grp3

All participants will receive a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1). The 3 investigational groups will be vaccinated with 1 of the 3 lots of RSVPreF3 OA investigational vaccine, each composed of unique randomized combinations of antigen and adjuvant lots (see Table 6). Details of blinding and unblinding procedures are provided in Section 6.3.4.

The study will enroll OA ≥ 60 YOA who are primarily responsible for self-care and activities of daily living. Participants may have 1 or more chronic medical conditions but should be medically stable in the opinion of the investigator.

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

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

4.3. Justification for dose

Based on the results up to 1-month post-Dose 2 from study RSV OA=ADJ-002, a single dose regimen (0.5 mL) and the formulation of 120 µg RSVPreF3/AS01$_E$ were selected for further evaluation in the phase 3 clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01$_E$-adjuvanted or unadjuvanted RSVPreF3 vaccine administered according to a 0-, 2-month schedule with the aim to maximize the immune response against RSV and vaccine efficacy over several seasons. Based on the data from clinical development programs for AS01-adjuvanted protein antigen vaccines in OA, such as *Shingrix* and the chronic obstructive pulmonary disease investigational vaccine, it was expected that immunological responses would reach higher levels 1 month post-Dose 2 as compared with 1 month post-Dose 1. However, the RSV OA=ADJ-002 results demonstrated that the second dose given 2 months after the first dose had no added value in terms of humoral and/or cellular immune responses. The humoral response, both in terms of RSV A neutralizing antibody geometric mean titers and RSVPreF3 IgG geometric mean concentrations (GMCs), peaked 1 month after the first dose, and the second dose did not increase the levels observed after the first dose.

The results from study RSV OA=ADJ-002 demonstrated statistically significant superiority of the 120 µg formulations in terms of RSV A neutralizing titers over at least 1 of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. The data demonstrated an immunologic benefit of any AS01$_E$ or AS01$_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 markers. Importantly, despite lower baseline observed in OA, the AS01-containing formulations induced CD4+ T cells frequencies at a close or similar level as in young adults, that is not observed with the unadjuvanted formulations.

There was no safety concern detected in unadjuvanted groups to be linked to the RSVPreF3 antigen assessed for the first time in OA. The acceptable safety/reactogenicity profile in all 120 µg groups, together with the immunological benefit demonstrated for the 120 µg antigen dose, supports the selection of a 120 µg based formulation. The results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the AS01$_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the AS01$_E$-based formulation is considered adequate for a RSVPreF3 OA candidate 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 6 months post-study intervention administration).

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visit, ability to access and utilize a phone or other electronic communications).

  Note: In case of physical incapacity that would preclude the self-completion of the diary cards, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no time will the site staff or caregiver evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. Refer to the Glossary of terms for the definition of caregiver.
- A male or female ≥ 60 YOA at the time of first study intervention administration.
- Participants living in the general community or in an assisted-living facility that provides minimal assistance, such that the participant is primarily responsible for self-care and activities of daily living.
- Written or witnessed informed consent obtained from the participant prior to performance of any study specific procedure.
- Participants who are medically stable in the opinion of the investigator at the time of vaccination. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, can participate in this study if considered by the investigator as medically stable.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

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

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

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before study intervention administration and ending 30 days after study intervention administration, 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 study intervention administration, with the exception of inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 14 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 that the Sponsor is notified accordingly.

- Previous vaccination with an RSV vaccine.
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the administration of the study intervention 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 study intervention administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day or equivalent. Inhaled and topical steroids are allowed.

5.2.3. Prior/Concurrent clinical study experience

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

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

5.2.4. Other exclusions

- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
- Planned move during the study period that will prohibit participating in the study until study end.
- Bedridden participants.
- Participation of any study personnel or their immediate dependents, family, or household members.

5.3. Lifestyle considerations

No lifestyle restrictions are applicable for this study.

5.4. Screening failures

Not applicable for this study.

5.5. Criteria for temporarily delaying enrolment/Study intervention administration

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

- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA (Table 1) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g. free of symptoms, COVID-19 negative testing, etc.).
- Participants with known COVID-19 positive contacts may be vaccinated at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.
- In case of administration of inactivated and subunit influenza vaccines: Postponement of study vaccine administration within given protocol timelines to allow respect of the 14-days interval between flu vaccination and study vaccine administration.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study interventions administered

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

Table 6 Study intervention(s) administered

Study group	RSVPreF3_Grp1	RSVPreF3_Grp2	RSVPreF3_Grp3
Study intervention name:	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine
Study intervention formulation:	RSVPreF3 (120 µg) (Lot 1)	RSVPreF3 (120 µg) (Lot 2)	RSVPreF3 (120 µg) (Lot 3)
	AS01E (Lot A): QS-21* (25 µg), MPL (25 µg), liposomes; water for injections q.s. 0.5 mL	AS01E (Lot B): QS-21* (25 µg), MPL (25 µg), liposomes; water for injections q.s. 0.5 mL	AS01E (Lot C): QS-21* (25 µg), MPL (25 µg), liposomes; water for injections q.s. 0.5 mL
Presentation:	RSVPreF3: Vial; powder for suspension for injection	RSVPreF3: Vial; powder for suspension for injection	RSVPreF3: Vial; powder for suspension for injection
	AS01E: Vial; suspension for suspension for injection	AS01E: Vial; suspension for suspension for injection	AS01E: Vial; suspension for suspension for injection
Type:	Biologic	Biologic	Biologic
Route of administration:	IM	IM	IM
Administration site:			
• **Location**	Deltoid	Deltoid	Deltoid
• **Directionality**	Upper	Upper	Upper
• **Laterality****	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered:	1	1	1
Volume to be administered by dose *:**	0.5 mL	0.5 mL	0.5 mL
Packaging, labeling and TM:	Refer to the SPM for more details	Refer to the SPM for more details	Refer to the SPM for more details
Manufacturer:	GSK Biologicals	GSK Biologicals	GSK Biologicals

Grp: group; IM: Intramuscular; SPM: Study Procedures Manual

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

** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.

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

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

6.2. Preparation, handling, storage, and accountability

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

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

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

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

6.3.2. Randomization to study intervention

Approximately 750 eligible participants will be randomly assigned (1:1:1) to the 3 study groups (250 participants in each study group: RSVPreF3_Grp1, RSVPreF3_Grp2, and RSVPreF3_Grp3) at Visit 1 (Day 1).

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

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

6.3.3. Intervention allocation to the participant

An automated Internet-based system, Source data Base for Internet Randomization (SBIR) will be used for randomization and for identification of intervention material.

The randomization algorithm will use a minimization procedure accounting for age (60 to 69, 70 to 79 or ≥ 80 years) and center. Minimization factors will have equal weight in the minimization algorithm. Refer to Section 4.1.2 for the enrolment rules.

The 3 study groups for the lot-to-lot evaluation will receive adjuvanted vaccine consisting of unique combinations of RSVPreF3 antigen lots, i.e., Lot 1, Lot 2, or Lot 3, and extemporaneously reconstituted with $AS01_E$ adjuvant lots, i.e., Lot A, Lot B, and Lot C.

One of the combinations of the $AS01_E$ adjuvant lot and RSVPreF3 antigen lot will be in alignment with the RSV OA=ADJ-006 study (efficacy study). The 2 remaining adjuvant lots will be randomly combined with the 2 RSVPreF3 antigen lots. The random assignment will be done using the RAND function, that uses the Mersenne-Twister algorithm. Details of the study groups and antigen/adjuvant lots are presented in Table 5 and Table 6.

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

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

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

6.3.4. Blinding and unblinding

Data will be collected in a double-blind manner. The investigator and the participant will not know which lot of the study intervention is administrated.

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

The study will be conducted in a double-blind manner from study start-up to final analysis, beyond which the study will be considered single-blind. The study participants will remain blinded up to study end, however, the investigators will receive a copy of the Clinical Study Report (CSR) with results of the final analyses on immunogenicity and safety data up to Day 31. As a consequence, the investigators could become unblinded to some specific participants through summary results. The individual data listings and participant treatment assignments will not be provided to the investigators until after the conclusion of the study (completion of Month 6 contact [study end]).

Note that the GSK central study team (Clinical Research and Development Lead [CRDL], Statistician, Safety Representative, etc.) will be unblinded to the study intervention lot assignment at the time of final analysis in order to prepare the CSR of the final analysis.

6.3.4.1. 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.

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via an automated Internet-based system (e.g. SBIR). The investigator may contact a GSK Helpdesk (refer to Table 7) if he/she needs help to access participant's study intervention information (i.e. if the investigator is unable to access SBIR).

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

Table 7 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email **Toll-free phone number(s):** Canada +1 833 541 0263 USA +1 844 446 3133 Sweden: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.3.4.2. Unblinding prior to regulatory reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.9.1).

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

6.4. Study intervention compliance

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

6.5. Dose modification

Section is not applicable.

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

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

6.7. Treatment of overdose

Not applicable for this study.

6.8. Concomitant therapy

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

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

- All concomitant medications and vaccinations, except vitamins and dietary supplements, administered during the 30-day period following study intervention administration.
- All concomitant medications leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to the Sections 5.2.2 and 9.2.1for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Sections 8.3.1 and 10.3.7. These must also be recorded in the Expedited Adverse Event Report.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study vaccination (Day 1) in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable

7.2. Participant discontinuation/withdrawal from the study

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

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

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

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

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

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

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

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

7.3. Lost to follow-up

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit (from the site staff or from the home care service system), if appropriate.
- Diary cards may be transmitted from and to the site by electronic means and or conventional mail or collected at home.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets International Council on Harmonisation (ICH) GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to European Medicines Agency 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 (PPS) for immunogenicity will be determined on a case by case basis.

8.1. Immunogenicity assessments

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

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

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

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

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

8.1.1. Biological samples

Table 8 Biological samples

Sample type	Quantity	Unit	Timepoint	Group
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31)	RSVPreF3_Grp1
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31)	RSVPreF3_Grp2
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31)	RSVPreF3_Grp3

Grp: Group

8.1.2. Laboratory assays

Table 9 Laboratory assays

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	RSVPreF3-specific IgG antibody	ELISA	GSK

CRO: Contract Research Organization; ELISA: enzyme-linked immunosorbent assay; Ig: immunoglobin
*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 10 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-dose	All participants	~ 750	RSVPreF3-specific IgG antibody
Visit 2 (Day 31)	Post-dose	All participants	~ 750	RSVPreF3-specific IgG antibody

Ig: immunoglobin

If necessary, additional testing such as but not limited to RSV neutralization assays may be performed for all participants to further characterize the immune response to the RSV investigational vaccine.

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 study intervention.

8.2. Safety assessments

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

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

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

8.2.1.2. Medical history

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

8.2.1.3. Vaccination history

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

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

8.2.1.4. History directed physical examination

- History directed physical examination will be performed for each participant.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to Section 5.5 for the list of criteria for temporary delay of study intervention administration.
- Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.1.5. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked before the planned administration of study intervention.

8.2.1.6. Pre-vaccination body temperature

The body temperature of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. The route for measuring temperature can be oral, axillary or tympanic. If the participant has fever (fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled.

8.2.2. Post-vaccination procedures

8.2.2.1. Safety contact at 6 months post-vaccination (Month 6)

Six months after the study intervention administration (i.e. Month 6), each participant should be contacted to check if he/she has experienced any SAEs or any pIMDs since study intervention administration, and to collect information on concomitant medications/vaccinations.

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

Text messages, email and fax may be used as a screening to check if the participant has anything to report. If the participant answers "Yes" for at least 1 of the items of interest, a phone call must be done to get the details on the event(s).

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

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

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

Table 11 Timeframes for collecting and reporting of safety information

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

AE: adverse event; D: Day; M: Month; pIMD: potential immune-mediated disease; SAE: serious adverse event; V: Visit
* After informed consent, prior to intervention administration.
Note: COVID-19 cases will be collected during the same timeframes as those used for collecting and reporting the other safety information (unsolicited AEs/SAEs, etc.)

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

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

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

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

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

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

8.3.3. Regulatory reporting requirements for SAEs and other events

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

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

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

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

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

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

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

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

8.3.3.1. Contact information for reporting SAEs and pIMDs

Table 13 Contact information for reporting SAEs and pIMDs

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

8.3.4. Treatment of adverse events

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

8.3.5. Participant card

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

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Not applicable for this study.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The assumptions, statistical hypotheses and success criteria associated to the primary objective to demonstrate the lot-to-lot consistency of 3 lots of the RSVPreF3 OA investigational vaccine in terms of immunogenicity at 30 days post-vaccination are described hereafter.

- **Endpoint:** RSVPreF3 IgG-specific antibody concentration at 1-month post-vaccination (Day 31).
- **Group level summary:** Antibody GMC per group.
- **Reference for the sample size calculation:** A standard deviation (SD) of the $\log_{10}$ transformed concentrations of 0.45 is used as reference. It is the highest SD observed in the RSV OA=ADJ 002 (208851) study among all treatment groups and humoral assays.
- **Success criteria for consistency:** the 2 sided 95% confidence interval (CI) of the GMC ratios between each pair of the 3 lots is within the pre-defined clinical limit of [0.67, 1.5].
- **Null hypothesis:** At least 2 of the 3 vaccine lots differ by more than 1.5-fold (1 sided non-inferiority limit) with respect to their GMC.
- **Alternative hypothesis:** Clinical equivalence (consistency) between each pair of the 3 lots with respect to their GMCs.
- **Type I error:** a 1-sided alpha of 2.5% will be used for the 6 non-inferiority tests.
- **Type II error:** Considering a Bonferroni correction for multiplicity, the global Type II error will be equal to 6 time the nominal Type II error calculated for 1 non-inferiority test. The sample size is determined to reach a global power of at least 90%.

9.2. Analysis sets

Table 14 Analysis sets

Analysis Set	Description
Enrolled Set	Participants who agreed to participate in a clinical study after completion of the informed consent process. *
Exposed Set (ES)	All participants who received the study intervention. The analysis per group will be performed according to the administered study intervention.
Per Protocol Set (PPS)	All eligible participants who received the study intervention as per-protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals (Table 2), without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis per group will be performed according to the administered study intervention.

*All participants enrolled and included in the database will be part of the Enrolled Set.

9.2.1. Criteria for elimination from analysis

If the participant meets 1 of the criteria mentioned Sections 5.2.1 (medical conditions) or 5.2.2 (concomitant therapy), he/she may be eliminated from per-protocol analysis.

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

9.3. Statistical analyses

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

9.3.1. Primary endpoint analysis

The primary analysis of lot-to-lot consistency will be performed on the PPS for immunogenicity (PPSi).

If in any study group the percentage of vaccinated participants with serological results excluded from the PPSi is more than 5%, a second analysis based on the Exposed Set (ES) will be performed to complement the PPSi analysis.

The 3 RSVPreF3 OA investigational vaccine lots will be compared in terms of RSVPreF3 IgG-specific antibody concentrations at 1-month post-vaccination, with a 1-sided alpha of 2.5%. The 95% CIs of the GMC ratios will be computed for each pair of RSVPreF3 OA investigational vaccine lots (RSVPreF3_Grp1 versus RSVPreF3_Grp2, RSVPreF3_Grp1 versus RSVPreF3_Grp3, RSVPreF3_Grp2 versus RSVPreF3_Grp3) using an analysis of covariance (ANCOVA) model on the log transformation of the RSVPreF3 IgG concentrations. The ANCOVA model will include the vaccine group and the age category (60 to 69 years, 70 to 79 years, ≥ 80 years) as fixed effect and the baseline antibody concentration as covariates.

9.4. Interim analyses

There is no interim analysis planned for this study.

9.4.1. Sequence of analyses

A final analysis will be conducted once all the immunogenicity data are available for the primary endpoint. This final analysis will include immunogenicity and safety data up to Visit 2 (Day 31). The individual data listings and participant treatment assignments will not be provided at this time.

An end-of-study analysis with all data including the data obtained until 6 months post-vaccination will be performed.

Please see Section 6.3.4 for details of blinding and unblinding procedures.

Note that the GSK central study team (Clinical Research and Development Lead [CRDL], Statistician, Safety Representative, etc.) will be unblinded to the details of the study intervention lots at the time of final analysis in order to prepare the CSR of the final analysis.

9.4.2. Statistical considerations for interim analysis

Not applicable.

9.5. Sample size determination

Table 15 shows that the probability (global power) to reach the lot-to-lot consistency criterion (Section 9.1) with 225 evaluable participants in each vaccine lot group is at least 91%, with a 1-sided alpha = 0.025.

Table 15 Power to demonstrate consistency between each pair of the 3 lots in terms of RSVPreF3 IgG GMCs with 225 evaluable participants per group

Vaccine component	Endpoints	Reference SD*	Clinically acceptable bounds for consistency	N per group	1-sided alpha	Power	Type II error
RSVPreF3 IgG-specific	GMC	0.45	[0.67, 1.5]	225	0.025	91%	9%

GMC: geometric mean concentration; Ig: immunoglobin; N = number of participants; SD: Standard Deviation (of the log_{10} transformed concentration)
Pass 2019 (Non-Inferiority test of 2 independent means). Power = 100-the Type II error (Beta). The Type II error (Beta) has been adjusted using Bonferroni's method (overall Type II error = sum of the individual Type II errors) since 6 non-inferiority tests are needed for lot-to-lot consistency (nominal Beta for each non-inferiority test is 1.5%).
* SD = 0.45 was selected based on the results from the RSV OA=ADJ-002 study. A conservative approach was used by selecting the highest value observed for SD across groups and humoral assays.

The primary objective analysis will be performed on the PPSi. Assuming a 10% non-evaluable rate up to Day 31 (participants dropped-out or excluded from the PPSi), a total of approximately 750 participants (250 per group) will have to be enrolled in order to reach 225 participants evaluable for the primary objective.

Participants who withdraw from the study will not be replaced.

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

10.1.2. Financial disclosure

Investigators and sub-investigators 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 study and for 1 year after completion of the study.

10.1.3. Informed consent process

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

Participants must be informed that their participation is voluntary.

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

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

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

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

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

10.1.4. Data protection

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

The participants must be informed that:

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

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

10.1.5. Committees structure

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

Safety oversight will be provided by a blinded SRT composed of GSK RSV OA project team members.

10.1.6. Dissemination of clinical study data

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

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

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

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

GSK intends to make anonymized patient-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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

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

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

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

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

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see Glossary of terms for the exact definition of source data).

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

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

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

10.1.8. Source documents

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

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

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

10.1.9. Study and site start and closure

First act of recruitment

Start of study is defined as FSFV at a country-level.

Study/Site termination

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

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 horse-radish peroxidase (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).

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

10.3.1. Definition of an adverse event (AE)

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
  - Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).

- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant before the study intervention administration. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:

a. Results in death

b. Is life-threatening

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is 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 judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 16 Solicited administration site events

Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 17 Solicited systemic events

Fever
Headache
Myalgia
Arthralgia
Fatigue

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

10.3.4. Unsolicited adverse events

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

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

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

10.3.5. Adverse events of special interest (AESIs)

Potential-immune-mediated diseases are the only AESIs collected for this study.

10.3.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest, which may or may not have an autoimmune etiology. Adverse events that need to be recorded and reported as pIMDs include those listed in the Table 18 (Please refer to the Section 10.3.7.1 for reporting details).

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

Table 18 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 Spondylarthritis – Psoriatic Arthritis – Enteropathic arthritis • Relapsing Polychondritis • Mixed Connective Tissue disorder • Gout	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Lichen planus • Sweet's syndrome • Localized Scleroderma (Morphea)

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

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

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

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

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

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

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

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

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

A Paper Diary will be used in this study to capture solicited administration site or systemic events. The Participant Diary will be distributed to all participants at Visit 1. The participant should be trained on how and when to complete the Paper Diary. If a participant is unable or not willing to complete the Paper Diary him/herself, he/she may be helped by a caregiver (refer to Glossary of terms for the definition of caregiver).

Anyone who measures administration site or systemic events and who will record the event in the Paper Diary, e.g. the study caregiver, should have received a caregiver information letter explaining the role of the caregiver prior to completing the diary card. This training must be documented in the participant's source record.

If any individual other than the participant is making entries in the Paper Diary, their identity must be documented in the participant's Diary.

Collect and verify completed Paper Diary during discussions with the participant on Visit 2.

Any unreturned Paper Diary 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

Refer to Table 11 in Section 8.3.1 for an overview of the protocol-required reporting periods for AEs, SAEs and pIMDs.

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

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

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

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

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

10.3.7.2.1. Follow-up during the study

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

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

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

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

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

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

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**:**

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

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

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

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

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

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

10.3.8.2. Assessment of causality

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

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

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

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

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

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

Possible contributing factors include:

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

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

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

10.3.8.3. Medically attended visits

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

10.3.8.4. Assessment of outcomes

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

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

10.3.9. Reporting of SAEs and pIMDs

10.3.9.1. Events requiring expedited reporting to GSK

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

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

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

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

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

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

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

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

10.4. Appendix 5: Abbreviations and glossary of terms

10.4.1. List of abbreviations

AE:	Adverse Event
ANCA:	Anti-neutrophil Cytoplasmic Antibody
ANCOVA:	Analysis of Covariance
AS01$_E$:	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
CI:	Confidence Interval
CIOMS:	Council for International Organizations of Medical Sciences
CLS:	Clinical Laboratory Sciences
COVID-19:	Coronavirus Disease 2019
CSR:	Clinical Study Report
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
FLU:	Influenza
FSFV:	First Subject First Visit
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline
HIPAA:	Health Insurance Portability and Accountability Act
HRP:	Horse-Radish Peroxidase
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors

IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G
IM	Intramuscular
IRB:	Institutional Review Board
LSLV:	Last Subject Last Visit
MGI:	Mean Geometric Increase
MoCA	Mini-Cog or Montreal Cognitive Assessment
OA:	Older Adults
pIMD:	Potential Immune-Mediated Disease
PP:	Per-Protocol
PPS:	Per-Protocol Set
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
QTL:	Quality Tolerance Limit
RSV:	Respiratory Syncytial Virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SBIR:	Source data Base for Internet Randomization
SPM:	Study Procedures Manual
SRT:	Safety Review Team
SUSAR:	Suspected Unexpected Serious Adverse Reactions
US:	United States
YOA:	Years of Age

10.4.2. Glossary of terms

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding: A procedure in which 1 or more parties to the study 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 study, 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 AE.

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

In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.

Caregiver: A ‘caregiver’ is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g. a relative of the participant including family members or friends).

In the context of this study, a caregiver can be appointed by the participant to oversee and support the participant’s compliance with protocol-specific procedures (such as transcribing responses to diaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant’s health status while answering diaries or make decisions on behalf of the participant.

Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant:	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.2 of the protocol for the definition of 'Enrolled Set' applicable to the study.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical condition:	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical study, 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 study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study 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 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 follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

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