Statistical Analysis Plan Amendment 3

Study ID: 217848

Official Title of Study: A Phase 3, open-label, randomized, controlled study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine (Omicron XBB.1.5) in adults aged 50 years and above

NCT number: NCT06374394

Note: The title page of this document presents an incorrect EudraCT number as an official clinicaltrials.gov registry identifier and therefore it is masked. For all references and purposes, the NCT ID mentioned above on this cover page is the official clinicaltrials.gov identifier for this study.

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TITLE PAGE

Protocol Title: A Phase 3, open-label, randomized, controlled study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine (Omicron XBB.1.5) in adults aged 50 years and above.

Study Number: 217848

Compound Number: GSK3844766A

Abbreviated Title: RSV OA=ADJ-013

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
eCRF	electronic Case Report Form
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean Geometric Increase
NI	Non-inferiority
OA	Older Adults
pIMD	Potential Immune-Mediated Disease
PPS	Per-Protocol Set
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRR	Seroresponse rate
SRT	Safety Review Team
ULOQ	Upper Limit Of Quantification
YOA	Years of Age

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	18 April 2024	Protocol v4.0 (09 January 2024)	Not Applicable	Original version
SAP Amendment 1	23 July 2024	Protocol v4.0 (09 January 2024)	Section 4.2.2: Add precision that the RSV-A/RSV-B primary analysis will be based on ED60 units. Section 4.3.1: Addition of RSV-A/RSV-B secondary analysis based on IU/mL units. Remove graph for MGI. Section 4.4.1: Removal of tables for demyelinating disorder AEs Reformatting the paragraph and clarifying the analyses performed by	Section 4.2.2: Clarification on the unit used for RSV-A/RSV-B primary endpoints. Section 4.3.1: Addition of RSV-A/RSV-B immunogenicity analysis on IU/mL to align at Project level. No graph will be produced for MGI. Section 4.4.1: Demyelinating disorder AEs will be part of overall AE tables showing different SMQs. Clarification of safety analyses performed by dose and overall.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			dose and overall. Section 6.1.2: Add age category, ≥ 60 YOA & ≥ 80 YOA. Add sentence on potential requirement for de-identified displays. Section 6.2: Appendix added for eCOA compliance	Section 6.1.2: To align age category presented in demography table with age category used in subgroup analyses. De-identification of public disclosure to ensure data privacy of clinical trials participants. Section 6.2: Updated SAP template – Not applicable as assessment collected via paper diary
SAP Amendment 2	12 December 2024	Protocol v4.0 (09 January 2024)	Section 3.1.3: Change elimination code 2080 to eliminate from the specific visit at which the condition is met onwards. Section 6.3.5: Modify	Section 3.1.3: Correction for elimination code Section 6.3.5: Alignment with project specific definition for missing/partial dates.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			imputation rule for AE end dates with missing day and month	
SAP Amendment 3	24 Mar 2025	Protocol v4.0 (09 January 2024)	Section 4.1.1: Modify the imputation rule for values below LLOQ in the reverse cumulative curves Section 4.6.1: Modify the sequence of analysis Section 4.7: Including the modifications in the sequence of analysis	Section 4.1.1: Alignment with project specific imputation rules for the reverse cumulative curves Section 4.6.1: Add the possibility of performing a combined analysis in case of delay in lab data availability Section 4.7: Add the possibility of performing a combined analysis not considered in the protocol

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses to be included in the clinical study report (CSR) for Study RSV-OA=ADJ-013 (217848).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate non-inferiority* of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralization titers expressed as group GMT ratio 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralization titers expressed as group GMT ratio 1 month after the RSVPreF3 OA investigational vaccine dose.
• To demonstrate non-inferiority* of humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to COVID-19 mRNA vaccine administered alone.	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers against pseudovirus bearing S protein expressed as group GMT ratio 1 month after the COVID-19 mRNA vaccine.
Secondary	
• To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine or administered alone.	• RSV-A neutralization titers expressed as GMT, MGI and SRR at 1 month after the RSVPreF3 OA investigational vaccine dose. • Percentage of participants having RSV-A neutralizing titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralization titers expressed as GMT, MGI and SRR at 1 month after the RSVPreF3 OA investigational vaccine dose. • Percentage of participants having RSV-B neutralizing titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose.
• To evaluate the humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine or administered alone.	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers against pseudovirus bearing S protein expressed as GMT and MGI at 1 month after the COVID-19 mRNA vaccine. • Percentage of participants having SARS-CoV-2 Omicron XBB.1.5 neutralization titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the COVID-19 mRNA vaccine dose.

Objectives	Endpoints
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and a COVID-19 mRNA vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited administration site event and systemic event within 4 days post study intervention administration (i.e., the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days post study intervention administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration). • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration).

AE: adverse event; GMT: Geometric Mean Titer; MGI: Mean Geometric Increase; pIMD: potential immune mediated disease; SAE: serious adverse event, SRR: Seroreponse rate. MGI and SRR are defined in Section 4.1.1

* Non-inferiority criteria are defined in Section 4.2.2

1.1.1. Estimands

1.1.1.1. Immunogenicity Objectives

The primary question of interest is to demonstrate the non-inferiority of the humoral immune response after RSVPreF3 OA investigational vaccine co-administered with a dose of COVID-19 mRNA vaccine when compared to RSVPreF3 OA investigational vaccine administered alone and COVID-19 mRNA vaccine administered alone, in adults aged 50 years vaccinated as per protocol.

The secondary objectives are the following:

- To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a dose of COVID-19 mRNA vaccine or when administered alone.
- To evaluate the humoral immune response to a dose of COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine or when administered alone.

Attributes						Summary measure
Objectives	Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
				Description	Handling strategy	
Primary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• RSV-A and RSV-B neutralizing titers measured at 1 month (at Day 61 for Control group, at Day 31 for Co-ad group) after RSVPreF3 OA investigational vaccine administration). • SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at 1 month (at Day 31 for both groups) after COVID-19 mRNA vaccine administration.	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• Ratio of GMTs with 95% CI for RSV-A and RSV-B neutralizing titers 1 month after RSVPreF3 OA investigational vaccine administration between the Control group versus Co-ad group. • Ratio of GMTs with 95% CI for SARS-CoV-2 Omicron XBB.1.5 titers 1 month after COVID-19 mRNA vaccine administration between the Control group versus Co-ad group.
Secondary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• RSV-A and RSV-B neutralizing titers measured at pre-vaccination (at Day 1 for Co-ad group and at Day 31 for Control group) and at 1 month (at Day 31 for Co-ad group and at Day 61 for Control group) after RSVPreF3 OA investigational vaccine administration. • Fold increase in RSV-A and RSV-B neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• GMTs with 95% CI for RSV-A and RSV-B neutralizing titers at pre-vaccination and at 1 month after RSVPreF3 OA investigational vaccine dose administration. • MGI with 95% CI for RSV-A and RSV-B neutralizing titers at 1 month after RSVPreF3 OA investigational vaccine dose administration • Percentage of participants having RSV-A and RSV-B neutralizing titers ≥ cut-off and 95% CI at pre-vaccination and 1 month

Attributes						Summary measure
Objectives	Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
				Description	Handling strategy	
			investigational vaccine administration. • RSV-A and RSV-B neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose administration. • Seroresponse in RSV-A and RSV-B, defined as a fold increase in neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration ≥4.			after the RSVPreF3 OA investigational vaccine dose administration. • Seroresponse rate (SRR) with 95% CIs for RSV-A and RSV-B, defined as the proportion of participants having a fold increase in neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration ≥4.
Secondary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at pre-vaccination (at Day 1) and at 1 month (at Day 31) after COVID-19 mRNA vaccine administration. • Fold increase in SARS-CoV-2 Omicron XBB.1.5 neutralization titers from pre-vaccination to 1-Month post COVID-19 mRNA vaccine administration.	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• GMTs with 95% CI for SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at pre-vaccination and at 1 month after COVID-19 mRNA vaccine dose administration. • MGI with 95% CI for SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at 1 month after COVID-19 mRNA vaccine dose administration.

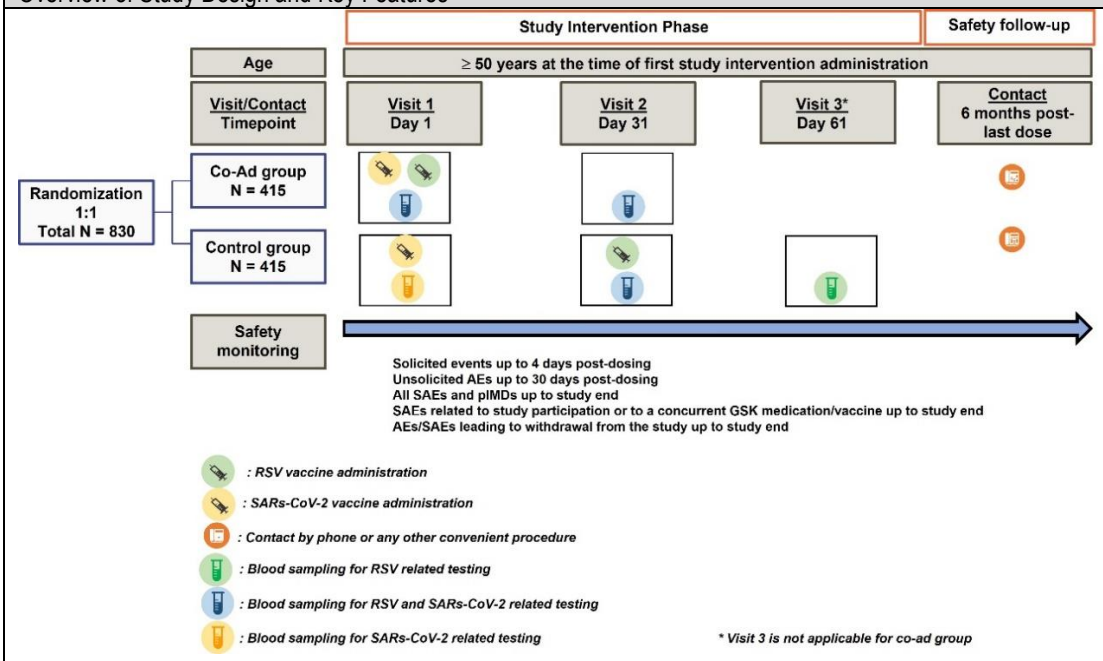
Attributes						Summary measure
Objectives	Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
				Description	Handling strategy	
			• SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the COVID-19 mRNA vaccine vaccine dose administration.			• Percentage of participants having SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ cut-off and 95% CI at pre-vaccination and 1 month after the COVID-19 mRNA vaccine dose administration.

1.1.1.2. Safety Objectives

The secondary question of interest is to evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and a dose of COVID-19 mRNA vaccine, co-administered or administered alone.

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥50 years at the time of first vaccination	• Occurrence of each solicited administration site event with onset within 4 days after study intervention administration. • Occurrence of each solicited systemic event with onset within 4 days after study intervention administration. • Occurrence of unsolicited AEs within 30 days after study intervention administration. • Occurrence of SAEs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration).	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	All the data collected for the variable of interest are used regardless of whether the intercurrent event occurs (treatment policy).	The percentage of participants by group who report each of the endpoint.

1.2. Study Design

Overview of Study Design and Key Features


Design Features	• **Type of study**: Self-contained. • **Experimental design**: Phase 3, randomized, open-label study with 2 parallel groups • **Study population**: Adults aged 50 years and above. • **Primary completion date**: Day 61 (1 month after the RSVPreF3 OA investigational vaccine dose in Control group). • **Duration of the study**: ~ 6 months for participants in Co-Ad group; ~ 7 months for participants in Control group. • **Control:** Active comparator, i.e., staggered administration of licensed COVID-19 mRNA vaccine and RSVPreF3 OA investigational vaccine. • **Blinding:** Open label. • **Data collection:** Standardized eCRF. Solicited events and unsolicited AEs will be collected using a participant Diary card (paper Diary card). • **Safety monitoring:** The study will be conducted with oversight by the project SRT.
Study intervention	**Co-Ad group**: Participants will receive a single dose of COVID-19 mRNA vaccine and a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1). **Control group**: Participants will receive a single dose of COVID-19 mRNA vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
Study intervention Assignment	Approximately 830 eligible participants will be randomly assigned (1:1) to the following 2 groups: Co-Ad group and Control group at Visit 1 (Day 1). The randomization algorithm will use a permutated block procedure, including age (50-59, 60-69 or ≥ 70 years) as stratification factor.
Primary Completion Achieved (PCA) Analysis	A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 2 (Day 31) for participant in co-ad group and to Visit 3 (Day 61) for participants in control group are available
End of Study Analysis	An end of study analysis will be performed when all data for at least secondary endpoints up to study conclusion (~ 6 months for participants in Co-Ad group; ~ 7 months for participants in Control group.) will be available for all participants.

2. STATISTICAL HYPOTHESES

Statistical hypotheses are associated to the confirmatory primary non-inferiority (NI) objectives, which will be tested to control overall Type I error. Global Type I error is controlled at 2.5% (1-sided). The study includes three confirmatory primary objectives. The NI margins associated to each objective are provided in Table 1.

Table 1 Study Objectives and Null Hypothesis

Objectives	Null hypothesis	Success criteria
Primary		
To demonstrate non-inferiority of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) for RSV-A neutralization titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5. • True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) in RSV-B neutralization titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5.	• The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5. • The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.
To demonstrate non-inferiority of humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to a COVID-19 mRNA vaccine administered alone.	• True Group GMT ratio between Control group (at Day 31) divided by Co-ad group (at Day 31) for SARS-CoV-2 neutralization titers 1-month after the COVID-19 mRNA vaccine dose is above 1.5.	• The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 31) versus Co-ad group (at Day 31) for SARS-CoV-2 neutralization titers 1-month after the COVID-19 mRNA vaccine dose is ≤1.5.

Abbreviations: Co-ad=co-administration group; CI=confidence interval, GMT=geometric mean titer, RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B; RSVPreF3-OA=respiratory syncytial virus prefusion protein 3 older adult investigational vaccine.

Co-ad group: RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine.

Control group: Administration of COVID-19 mRNA vaccine, followed by RSVPreF3 OA investigational vaccine with one month difference.

2.1. Multiplicity Adjustment

The three confirmatory primary non-inferiority (NI) objectives will be tested simultaneously to control overall Type I error. Global Type I error is controlled at 2.5% (1-sided).

3. ANALYSIS SETS

Analysis set	Description
Screened Set	All participants who were screened for eligibility.
Enrolled Set [1]	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure).
Exposed Set	All participants who received the study intervention. Analysis per group is based on the administered intervention.
RSV PPS [2]	All eligible participants: • Who received RSV vaccine as per-protocol in the control group and received all the study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for RSV neutralization titers • Who comply with the blood draw intervals for RSV samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post RSV vaccination • Who do not meet any of the criteria for elimination up to blood sample post RSV vaccination
COVID-19 mRNA PPS [2]	All eligible participants: • Who received a COVID-19 mRNA vaccine as per-protocol in the control group and received all the study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for SARS-CoV-2 neutralization titers • Who comply with the blood draw intervals for SARS-CoV-2 samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post COVID-19 mRNA vaccination • Who do not meet any of the criteria for elimination up to blood sample post COVID-19 mRNA vaccination

[1] Screen failures (who never passed screening) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrollment) are excluded from the Enrolled Set as they did not enter the study.

[2] Contribution of participants to PPS will be defined by timepoint.

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis. Details are provided below for the Enrolled Set, the Exposed Set (ES) and the Per Protocol Set (PPS).

3.1.1. Elimination from Enrolled Set

The following codes will be used for identifying participants to be eliminated from the Enrolled Set:

- Code 800 (Fraudulent data)
- Code 900 (Invalid informed consent)

3.1.2. Elimination from ES

The following codes will be used for identifying participants to be eliminated from the ES:

- Code 800 (Fraudulent data)
- Code 900 (Invalid informed consent)
- Code 1030 (Study intervention not administered at all)

3.1.3. Elimination from PPS

A participant will be excluded from the populations for analysis under the following conditions:

- For codes 800, 900, 1030 and 1050: participants will be eliminated for all visits.
- For codes 1040, 2010, 2040 and 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 1070, 1080, 1090: participants will be eliminated from a specific visit (at which the condition is met) onwards for the specific group/antigens in the control group and for both RSV PPS & mRNA COVID-19 PPS in the Co-ad group.
- For codes 2020, 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met for the specific group/antigens.
- For code 2080: participants in the control group will be eliminated from the specific visit at which the condition is met onwards for the RSV PPS.

Table 2 List of elimination codes

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
800	Fraudulent data	All	Enrolled Set, ES, RSV PPS, COVID-19 mRNA PPS
900	Invalid informed consent	All	Enrolled Set, ES, RSV PPS, COVID-19 mRNA PPS
1030	Study intervention not administered at all	All	ES, RSV PPS, COVID-19 mRNA PPS
1040	Administration of concomitant vaccine(s) forbidden in the protocol: • Use of any investigational or non-registered vaccine other than the study intervention during the period beginning 30 days before the dose of study intervention, or planned use during the study period.	All	RSV PPS, COVID-19 mRNA PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	• Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study intervention administration (1), 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. • Administration of any SARS-CoV-2 vaccine during the 3 months preceding the study COVID-19 mRNA vaccine administration • Previous vaccination with licensed or investigational RSV vaccine.		
1050	Randomization failure: participant not randomized in the correct stratum	Visit 1	RSV PPS, COVID-19 mRNA PPS
1070	Vaccine administration not according to protocol: • Participant was vaccinated with the correct vaccine but containing a lower volume. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular. • Side of administration wrong (only applicable for Co-ad group if both vaccines are given in the same arm) • Wrong reconstitution of administered vaccine	Visit 1 for Co-ad. Visit 1 & 2 for control group.	RSV PPS, COVID-19 mRNA PPS
1080	Vaccine administration after a temperature deviation Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Visit 1 for Co-ad. Visit 1 & 2 for control group.	RSV PPS, COVID-19 mRNA PPS
1090	Vaccine administration after expiration	Visit 1 for Co-ad. Visit 1 & 2 for control group.	RSV PPS, COVID-19 mRNA PPS
2010	Protocol deviation linked to inclusion/exclusion criteria	Visit 1 & 2 for Co-ad. Visit 1, 2 & 3 for control group.	RSV PPS, COVID-19 mRNA PPS
2020	Pre-dose results are missing	Visit 1 for Co-ad. Visit 1 & 2 for control group.	RSV PPS, COVID-19 mRNA PPS
2040	Administration of any medication forbidden by the protocol • Use of any investigational or non-registered product (drug or invasive medical device (2)) other than the study intervention during the period beginning 30 days before the dose of study intervention, or planned use during the study period. • Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the last blood sampling visit. • Up to 3 months prior to the study intervention administration:	Visit 1 & 2 for Co-ad. Visit 1, 2 & 3 for control group.	RSV PPS, COVID-19 mRNA PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	• For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed. • Administration of immunoglobulins and/or any blood products or plasma derivatives. • Up to 6 months prior to study intervention administration: • Long-acting immune modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.		
2050	Intercurrent medical condition: 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 or are confirmed to have an alteration of their initial immune status.	Visit 1 & 2 for Co-ad. Visit 1, 2 & 3 for control group.	RSV PPS, COVID-19 mRNA PPS
2080	Participants did not comply with vaccination schedule for the control group. • Number of days between COVID-19 mRNA vaccine and RSV vaccine is outside [30-42 days]	Visit 2 for control group	RSV PPS for control group
2090	Participants did not comply with blood sample schedule: For Co-ad and control group: • Number of days between vaccination (Visit 1) and blood sample (Visit 2) is outside [30-42] days. For control group: • Number of days between vaccination (Visit 2) and blood sample (Visit 3) is outside [30-42] days.	Visit 2, Visit 3	RSV PPS, COVID-19 mRNA PPS
2100	Immunological results not available post-vaccination	Visit 2, Visit 3	RSV PPS, COVID-19 mRNA PPS
2120	Obvious incoherence/abnormality or error in laboratory data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at laboratory.	Visit 1 & 2 for Co-ad. Visit 1, 2 & 3 for control group.	RSV PPS, COVID-19 mRNA PPS

(1) In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended a1d/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.

(2) 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'.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

- For the purpose of immunogenicity analyses, any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each time point will exclude participants with a missing or non-evaluable measurement.
- Titers/concentrations below the assay cut-off (LLOQ) will be replaced by half the assay cut-off (LLOQ/2) and titers/concentrations above the upper limit of quantification (ULOQ) will be replaced by the ULOQ to compute GMTs/GMCs, SRRs and MGIs. For the display of reverse cumulative curve, titers/concentrations below LLOQ will be replaced by half the assay cut-off (LLOQ/2) and titers/concentrations above ULOQ will not be replaced.
- Confidence intervals (CIs) will use 95% confidence levels unless otherwise specified (e.g., primary endpoints analysis, refer to Section 4.2.2). 95% CIs for GMT/GMC and MGI will be based on a back transformation of CI for the mean of $\log_{10}$-transformed values. Exact 95% CIs around proportions are derived using the method of Clopper and Pearson [Clopper, 1934]. 95% CI for group difference in proportion will be based on Miettinen and Nurminen confidence interval [Miettinen, 1985].
- Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.
- Analysis based on ES and PPS will be performed based on the actual stratum per data collected in the eCRF.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint(s) Analyses

The primary analysis set will be the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis.

4.2.1. Definition of endpoints

- RSV-A and RSV-B neutralizing titers measured at 1 month (at Day 61 for Control group, at Day 31 for Co-ad group) after RSVPreF3 OA investigational vaccine administration) expressed as GMT ratio with 95% CIs between Control group versus Co-ad group.
- SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at 1 month (at Day 31 for both groups) after COVID-19 mRNA vaccine administration expressed as GMT ratio with 95% CIs between Control group versus Co-ad group.

4.2.2. Main analytical approach

Considering the sampling timepoint at 1-month post-study intervention administration:

The least square point estimate and the 2-sided 95% CI for group GMT ratio between RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine (Co-Ad group) will be derived from an analysis of covariance (ANCOVA) model on log10 transformed titer for each neutralization assay. The model will include the treatment group, the age category (age at vaccination: 50-59, 60-69 or ≥70 years) as fixed effects, and the pre-dose log10-transformed titer as covariate.

The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers. Missing data will not be replaced.

Titers below the assay lower limit of quantification (LLOQ) will be replaced by half the assay cut-off, titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

Success criteria for non-inferiority:

The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

AND

The upper limit of the 2-sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

AND

The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for SARS-CoV-2 neutralization titer 1-month after the COVID-19 mRNA vaccine dose is ≤1.5.

The results will be presented in tables as well as graphs using forest plots.

Results for RSV-A & RSV-B will be reported using ED60.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Immunogenicity analysis

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

4.3.1.1. Definition of endpoints

- RSV-A and RSV-B neutralizing titers measured at 1 month (at Day 61 for Control group, at Day 31 for Co-ad group) after RSVPreF3 OA investigational vaccine administration) expressed as GMC ratio with 95% CIs between Control group versus Co-ad group.
- RSV-A and RSV-B neutralizing titers measured at pre-vaccination (at Day 1 for Co-ad group and at Day 31 for Control group) and at 1 month (at Day 31 for Co-ad group and at Day 61 for Control group) after RSVPreF3 OA investigational vaccine administration expressed as GMTs/GMCs with 95% CIs.
- Fold increase in RSV-A and RSV-B neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration expressed as MGIs with 95% CIs.
- RSV-A and RSV-B neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose administration expressed as percentage of participants having RSV-A and RSV-B neutralizing titers/concentrations ≥ cut-off with 95% CIs.
- Seroresponse rate in RSV-A and RSV-B, defined as a fold increase in neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration ≥4 expressed as SRR with 95%CIs.
- SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at pre-vaccination (at Day 1) and at 1 month (at Day 31) after COVID-19 mRNA vaccine administration expressed as GMTs with 95% CIs.
- Fold increase in SARS-CoV-2 Omicron XBB.1.5 neutralization titers from pre-vaccination to 1-Month post COVID-19 mRNA vaccine administration expressed as MGIs with 95% CIs.
- SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the COVID-19 mRNA vaccine dose administration expressed as percentage of participants having SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ cut-off with 95% CIs.

4.3.1.2. Main analytical approach

For each study group, each immunological assay and at each time point that blood samples are collected, the following analysis will be performed:

- Considering the sampling timepoint at 1-month post-study intervention administration, same analysis as for RSV-A/RSV_B primary endpoint (refer to Section 4.2.2) will be performed using IU/ml unit for computation of the GMC ratio.
- Percentage of participants with neutralizing titers/concentrations equal to or above pre-defined assay cut-offs and their 2-sided 95% CIs will be tabulated.
- Percentage of participants having a fold increase in RSV-A & RSV-B neutralizing titers/concentrations ≥4 and their 2-sided 95% CIs will be tabulated.
- Unadjusted GMTs/GMCs and their 95% CIs will be tabulated and displayed graphically.
- Unadjusted MGIs and their 95% CIs will be tabulated.
- Results for RSV-A & RSV-B will be reported using both ED60 and IU/ml units.
- Distribution of neutralizing titers/concentrations will be displayed using reverse cumulative curves.

4.4. Safety Analyses

The safety analyses will be based on the ES.

4.4.1. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after study intervention start date. All AE summaries will be based on study intervention emergent events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of study intervention emergent or not. All AE and SAE summaries will be grouped by SOC, HLT and PT and summarized by study intervention group at time of onset of the AE, unless otherwise specified.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activity (MedDRA dictionary). The verbatim reports of unsolicited AEs, including SAE and AESI, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

For the summaries of AE and SAE, participants who experience the same AE/SAE (in terms of the MedDRA SOC, HLT and PT) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

A study intervention-related AE/SAE is defined as an AE/SAE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study intervention as 'Yes' or missing.

The analyses of unsolicited AEs will include SAEs and AESIs (unless otherwise specified).

The following analysis will be performed:

- Compliance in completing solicited events information will be tabulated after each dose and overall.
- The number and percentage of participants with at least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE (solicited and unsolicited) during the 4-day or 30-day follow-up period after vaccination will be tabulated with exact 95% CI for each group, after each dose and overall.
- The same computations will be done for Grade 3 AEs, for Grade 3 non-serious AEs and for AEs resulting in a medically attended visit.

  Those analyses will present all solicited and unsolicited AEs, including SAEs and AESIs (unless otherwise specified).
- The number and percentage of participants with at least one administration site event (solicited only), with at least one systemic event (solicited only) and with any solicited event during the 4-day follow-up period after vaccination will be tabulated with exact 95% CI for each group, after each dose and overall.
- The same computations will be done for Grade 3 AEs and for AEs resulting in a medically attended visit.
- The number and percentage of participants reporting each individual solicited administration site or systemic event (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period after vaccination will be tabulated with exact 95% CI for each group, after each dose and overall.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period after vaccination will be tabulated for each group, after each dose and overall.
- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and Grade 3) during the 4-day follow-up period after vaccination will be represented graphically for each group after each dose and overall.
- The duration in days of each individual solicited events will be tabulated using descriptive statistics (mean, min, Q1, median, Q3, maximum).
- The number of days with Grade 3 solicited events will be tabulated for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum).

- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT), after each dose and overall. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- The number and percentage of participants with any non-serious unsolicited AEs during the 30-day follow-up period with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT), after each dose and overall. Similar tabulation will be done for Grade 3 non-serious unsolicited AEs, for any causally related non-serious unsolicited AEs, for Grade 3 causally related non-serious unsolicited AEs and for non-serious unsolicited AEs resulting in a medically attended visit.
- The number and percentage of participants with any unsolicited AEs reported within 30 minutes following vaccination with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT), after each dose and overall. Similar tabulation will be done for Grade 3 unsolicited AEs reported within 30 minutes following vaccination.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PT from vaccination up to study end (i.e., 6 months after last vaccination) will be tabulated with exact 95% CI.
- The same tabulation will be presented for causally related SAE, fatal SAE, pIMD and causally related pIMD.
- All SAEs/AESIs up to study end (i.e., 6 months after last vaccination) will also be described in detail in a tabular listing.
- AEs/SAEs leading to study discontinuation from vaccination up to study end will be tabulated.
- For web posting purposes, the number of occurrences and the number and percentage of participants with non-serious AEs (solicited and unsolicited combined) during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) will be produced by SOC and PT.
- In case of pregnancies, these will be described in detail.

For analysis of SAEs/AESIs within 6 months, the reporting period will start at vaccination and will end at Day 183 after each dose, computed as 6 x 30.5 days = 183 days.

Refer to Section 6.1.4 and Section 6.1.5 for the analysis of concomitant medications and concomitant vaccination.

4.4.1.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses:

- Atrial Fibrillation (AF)
- potential Immune Mediated Disease (pIMD)

AF AESIs will be identified through the MedDRA preferred term of interest atrial fibrillation (10003658). Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF. Additional analysis might be performed on those additional data collected for AF AESIs.

pIMDs will be identified using a lookup table containing the list of MedDRA preferred term.

4.5. Other Analyses

4.5.1. Subgroup analyses

4.5.1.1. Immunogenicity analysis

Subgroup analyses of the secondary immunogenicity endpoints will be made to assess consistency of the intervention effect across the following subgroups:

- Age group: 50-59 YOA, 60-69 YOA, ≥ 60 YOA, ≥ 70 YOA, ≥ 80 YOA

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to first analysis.

4.5.1.2. Safety analysis

Subgroup analyses of the secondary safety endpoints will be made to assess consistency of the safety profile across the following subgroups:

- Age group: 50-59 YOA, 60-69 YOA, ≥ 60 YOA, ≥ 70 YOA, ≥ 80 YOA

Specifically, the following safety analysis will be generated:

- The number and percentage of participants reporting each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period (i.e., the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.
- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by MedDRA Primary SOC, HLT and PTs

- For clinicaltrials.gov and EudraCT posting purposes, percentage of participants of combined solicited and unsolicited non-serious adverse events during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) will be produced by System Organ Class and preferred terms and according to occurrence of each event.

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to first analysis.

4.6. Interim Analyses

No interim analysis will be performed.

4.6.1. Sequence of analyses

The analyses will be performed stepwise:

- A first analysis will be performed on all immunogenicity, reactogenicity and safety data as clean as possible, when data are available for primary and secondary endpoints up to and including Visit 3 (Day 61) for all participants. This analysis will be considered as final for those endpoints.
- An end of study (EoS) analysis will be performed when all data up to the contact 6 months post-last dose will be available for all participants.

  In the event of a delay in data availability for the first analysis, the first analysis and the end of study (EoS) analysis may be combined and performed concurrently.

4.7. Changes to Protocol Defined Analyses

In the protocol amendment 4 section 9.4.1: the possibility of performing a combined first and end of study (EoS) analysis if the data for the first analysis are not immediately available

5. SAMPLE SIZE DETERMINATION

Table 3 shows that the probability (global power) to reach the non-inferiority criterion with 722 evaluable participants (361 in Co-Ad and 361 in Control group) is at least 90.1%, with a 1-sided alpha = 0.025.

Table 3 Power to demonstrate non-inferiority of the Co-Ad group compared to the Control group in terms of GMT with 361 evaluable participants per group.

Endpoint	Standard deviation of log10 concentration	Reference ratio	Non inferiority margin	Type II error	Power
RSVPreF3 OA investigational vaccine Non-inferiority* (1-sided test with alpha = 2.5%)					
GMT RSV-A neutralization titers	0.45	1.05	1.5	0.4%	99.6%
GMT RSV-B neutralization titers	0.45	1.05	1.5	0.4%	99.6%
COVID-19 mRNA vaccine Non-inferiority* (1-sided test with alpha=2.5%)					
GMT SARS-CoV-2 neutralization titer	0.63	1.05	1.5	9.1%	90.9%
Global Power and Global Type II error				9.9%	90.1%

GMT: geometric mean titer

Non-inferiority limit = 0.176 (=$\log_{10}$[1.5]).

Reference Ratio = 0.0212 (=$\log_{10}$[1.05])

Pass 2022 (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).

The primary objective analysis will be performed on the PPS. Assuming about 13% non-evaluable rate among enrolled participants up to 2-month post-vaccination (participants dropped-out or excluded from the PPS), a total of 830 participants (415 per group) will have to be vaccinated in order to reach 361 participants evaluable for the primary objective.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorized as on study intervention or in follow up.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

Those analysis will be based on the Screened set, Enrolled set, ES.

6.1.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics (age at vaccination in years, sex, race, ethnicity, country) will be summarized by group using descriptive statistics, as described in Section 4.1.1. This analysis will be based on all analysis sets.

The following age categories will be considered in the analysis: 50-59 YOA, 60-69 YOA, ≥ 60 YOA, ≥ 70 YOA, ≥ 80 YOA. In addition, for web posting purposes: 18-64 YOA, 65-84 YOA and ≥85 YOA.

If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version should be produced.

Past medical conditions and current medical conditions as of screening will be summarized respectively and grouped by SOC, HLT and PT. This analysis will be based on ES.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the analysis set will also be summarized.

- Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).]

A summary of important protocol deviations leading to exclusions from any analysis set will be provided by group, based on the Screened Set.

The number of participants screened for the study as well as the number of participants excluded from the Enrolled set, ES and the PPS analyses will be tabulated. These will be based on the Screened set, Enrolled Set and the ES, respectively.

6.1.4. Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically) during the 4-day and the 30-day follow-up period after vaccination will be tabulated with exact 95% CI per group, after each vaccine dose and overall. The analysis will be performed on ES.

See Section 6.3.5 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e., concomitant.

6.1.5. Concomitant Vaccinations

The number and percentage of participants and doses with concomitant vaccination during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be tabulated with exact 95% CI per study group, after each vaccine dose and overall. The analysis will be performed on ES.

See Section 6.3.5 for handling of partial dates for vaccinations, in the case where it is not possible to define a vaccination as prior or concomitant, the vaccination will be classified by the worst case, i.e., concomitant.

6.1.6. Study Intervention Compliance

Exposure to study intervention will be presented for the ES. The number and percentage of participants who received the study intervention will be tabulated by per study intervention group and overall.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

Not applicable.

6.3. Appendix 3 Data Derivations Rule

6.3.1. Attributing events to vaccine doses

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the event will not be attributed to the study vaccination.

6.3.2. Study Day and Reference Dates

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

6.3.3. Assessment Window

For data summaries by visit, the nominal visit description will be used.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Immunogenicity	RSV-A & RSV-B Nab and SARs-COV-2 Nab (Co-ad) SARs-COV-2 Nab (control)	Day 1	Day 1	Day 1	VISIT 1
Immunogenicity	RSV-A & RSV-B Nab and SARs-COV-2 Nab (Co-ad & Control)	Day 31	Day 31	Day 42	VISIT 2
Immunogenicity	RSV-A & RSV-B Nab (Control)	Day 61	Day 61	Day 84	VISIT 3

6.3.4. Multiple measurements at One Analysis Time Point

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.3.5. Handling of missing data

6.3.5.1. Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).
The following standard rules will be applied:

A missing day will be replaced by 15
A missing day and month will be replaced by June 30th.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:

If month and year of start date = month and year of study intervention start date, then

If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
Else, the flag indicating if the event occurred before or after vaccination will be used to complete the date. If ‘after vaccination’ is selected, the imputed start date will match the vaccine dose given during that month. If ‘before vaccination’ is selected, the imputed date will be one day before the last vaccine dose given during that month.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:

If year of start date = year of study intervention start date, then

If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
Else, the flag indicating if the event occurred before or after vaccination will be used to complete the date. If ‘after vaccination’ is selected, the imputed start date will match the vaccine dose given during that year. If ‘before vaccination’ is selected, the imputed date will be one day before the last vaccine dose given during that year.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year) or the study conclusion date whichever comes first.</td></tr>
<tr><td>Missing end day and month</td><td>The imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	*If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.* *Else if study intervention start date is not missing:* • *If month and year of start date = month and year of study intervention start date, then* • *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.* • *Else, the flag indicating if the event occurred before or after vaccination will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that year.* *Else set start date = 1st of month.*
	Missing start day and month	*If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.* *Else if study intervention start date is not missing:* • *If year of start date = year of study intervention start date, then* • *If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.* • *Else, the flag indicating if the event occurred before or after vaccination will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that year.* *Else set start date = January 1.*
	Missing end day	*A '28/29/30/31' will be used for the day (dependent on the month and year) or the study conclusion date whichever comes first.*
	Missing end day and month	*A '31' will be used for the day and 'Dec' will be used for the month or the study conclusion date whichever comes first.*
	Completely missing start/end date	*No imputation*

6.3.5.2. Laboratory data

Any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each timepoint will exclude participants with a missing or non-evaluable measurement. This is applicable to the standard way of computing geometric mean titers/concentration (GMTs/GMCs)

Computation of GMTs/GMCs from the mixed effects model inherently accounts for the missingness, under the assumption that the missing data are missing at random (MAR). Subject having missing pre-vaccination titer/concentration will be excluded from ANCOVA models (refer Section 4.2.2)

6.3.5.3. Daily recording of solicited events

The following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.

The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

6.3.5.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

6.3.6. Data derivation

6.3.6.1. Age at vaccination in years and age group

Age will be calculated as the number of years between the year of birth and the year of first vaccination. The age group will be derived based on derived age.

6.3.6.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

6.3.6.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is >ULOQ	ULOQ
All other cases	missing

6.3.6.4. Geometric mean titers/concentrations (GMTs/GMCs)

GMT/GMC calculations are performed by taking the inverse logarithm of the mean of the log titer/concentration transformations. Non quantifiable neutralizing titers/concentrations will be converted as described in Section 6.3.6.3 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.3.6.5. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

6.3.6.6. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

For solicited administration site and systemic events:

- The duration of a solicited AE with at least one day Grade > 0 is defined as End date(CEENDY) – Start date(CESTDY) + 1, with Start date defined as the first day with the symptom and End date defined as the last day with the symptom in or beyond the solicited period.

- A missing start date will be imputed with the vaccination date.
- For paper diaries, if an ongoing symptom has a missing end date, the end date will be considered equal to vaccination date + 29 days. Partial end dates will be imputed according to Section 6.3.5.1
- The number of days with grade 3 solicited symptom will be defined considering each day with a known grading=3 (for paper CRF, if the max intensity during the ongoing period is 3, each day of the ongoing period will be counted as grade 3).

6.3.6.7. Counting rules for combining solicited and unsolicited adverse events

Unsolicited adverse events with missing administration site flag will be considered systemic.

Solicited events will be coded by MedDRA as per the following codes:

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia

Note that these codes might be adapted depending on the current version of MedDRA at the time of analysis.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

6.3.6.8. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

The intensity of administration site redness/swelling and fever will be scored as follows:

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

6.3.7. Display of decimals

6.3.7.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.3.7.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (age) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

6.3.7.3. Serological summary statistics

For each assay, GMTs/GMCs and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-vaccination.

GMT/GMC group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

7. REFERENCES

Clopper C.J., Pearson E., The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26: 404-13.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985;4,213-226.