Statistical Analysis Plan Amendment 3

Study ID: 219238

Official Title of Study:A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥60 years of age.

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TITLE PAGE

Protocol Title: A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥60 years of age.

Study Number: 219238

Compound Number: GSK3844766A

Abbreviated Title: RSV OA=ADJ-018

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clintrials.gov	*Not Available*
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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
AIR	At-Increased-Risk
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CMI	Cell-Mediated Immunity
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
eCRF	electronic Case Report Form
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HA	Healthy Adults
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean Geometric Increase
NI	Non-inferiority
OA	Older Adults
PCA	Primary Completion Analysis
pIMD	Potential Immune-Mediated Disease
PPS	Per-Protocol Set
RR	Relative Risk
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRR	Seroresponse rate

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	19 October 2022	Final: 26 July 2022	Not Applicable	Original version
SAP Amendment 1	09 May 2023	Final: 26 July 2022	Section 4.3.2.1: Change to safety reporting for participant belonging to OA stratum who received placebo: SAEs and AESIs reported (if any) will be described. Section 4.3.2.1: Addition of AF as AESIs for tabular listing. Section 4.3.2.2.2 & Section 4.3.2.3: Change from 65-69 YOA in 60-69 YOA in all age category definition Section 4.3.3.3: Add section for additional considerations for analysis of AF Section 4.4.1: CCI [redacted]. Section 4.4.1.2: Lower threshold to 3 for subgroup categories based on uCCI. Section 6.1.1: Summary of participant disposition will be additionally performed	Section 4.3.2.1: Safety narrative will only be generated in participant belonging to OA stratum who received placebo, if SAEs and AESIs are reported. Section 4.3.2.1: Addition following project update to consider atrial fibrillation (AF) as Adverse Events of Special interest (AESIs) Section 4.3.2.2.2 & Section 4.3.2.3: Correction for age category Section 4.3.3.3: Supportive information for analysis of AF Section 4.4.1: Additional exploratory analysis Section 4.4.1.2: Number of

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			on Screened set and Enrolled set. Section 6.1.2: Demography and baseline characteristics will be additionally performed on Screened set. Section 6.1.3: Change from Enrolled Set to Screened Set as analysis set for the summary of important protocol deviations leading to exclusions from any analysis set. Across section: Change from “neutralization antibody titer” to “neutralization titer”.	participants too small (less than 20%) within high-risk subgroup with a threshold of 5 Section 6.1.1: Addition of analysis for participant disposition. Section 6.1.2: Addition of analysis for demography and baseline characteristics. Section 6.1.3: Change in analysis set for protocol deviation analysis. Across section: Correction in wording for neutralization assay.
SAP Amendment 2	15 May 2023	Final: 26 July 2022	Section 3.1.3: Addition of elimination code 1060 “Randomization code was broken”.	Section 3.1.3: Elimination code was added to eliminate participant whose randomization was broken from PPS
SAP Amendment 3	28 Feb 2024	Final: Amendment 1: 25 May 2023	Section 3.1.3: Change visit specification for elim code 1060.	Section 3.1.3: Participants having elim code 1060 will be eliminated

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.3.2.1: Change in tabulation of solicited event duration and number of days with Grade 3 solicited events. Addition of specific analysis for Demyelinating disorder Add sentences to clarify 6 months = 183 days. Section 6.2.3.9: Addition of the definition of duration of solicited AE.	from a specific visit (at which the condition is met) onwards. Section 4.3.2.1 & Section 6.2.3.9: Change following project update for the definition of duration of solicited symptoms. Addition of specific analysis for Demyelinating disorder following project update Add clarification for the number of days considered in 6 Months safety follow-up.

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses for Study RSV OA=ADJ-018 (219238).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints and estimands
Primary*	
• To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-A neutralization titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline.
• To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralization titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline.
• To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-A neutralization titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline.
• To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralization titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline.
Secondary - Safety	
• To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.	• Percentage of participants reporting each solicited administration site event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Percentage of participants reporting each solicited systemic event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days).

Objectives	Endpoints and estimands
	• Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Percentage of participants reporting any SAEs and pIMDs after study intervention administration (Day 1) up to Month 6. • Percentage of participants reporting SAEs and pIMDs related to study intervention administration after study intervention administration (Day 1) up to study end (Month 12). • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 12).
Secondary - Immunogenicity	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration.	• RSV-A and RSV-B neutralization titers expressed as GMT, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration.
• To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration.	• CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration, in a subset of participants.
Tertiary *(Note that tertiary objectives, endpoints, and estimands are optional and might be assessed only if needed; therefore, not all testing might be performed and reported)*	
CCI [redacted]	

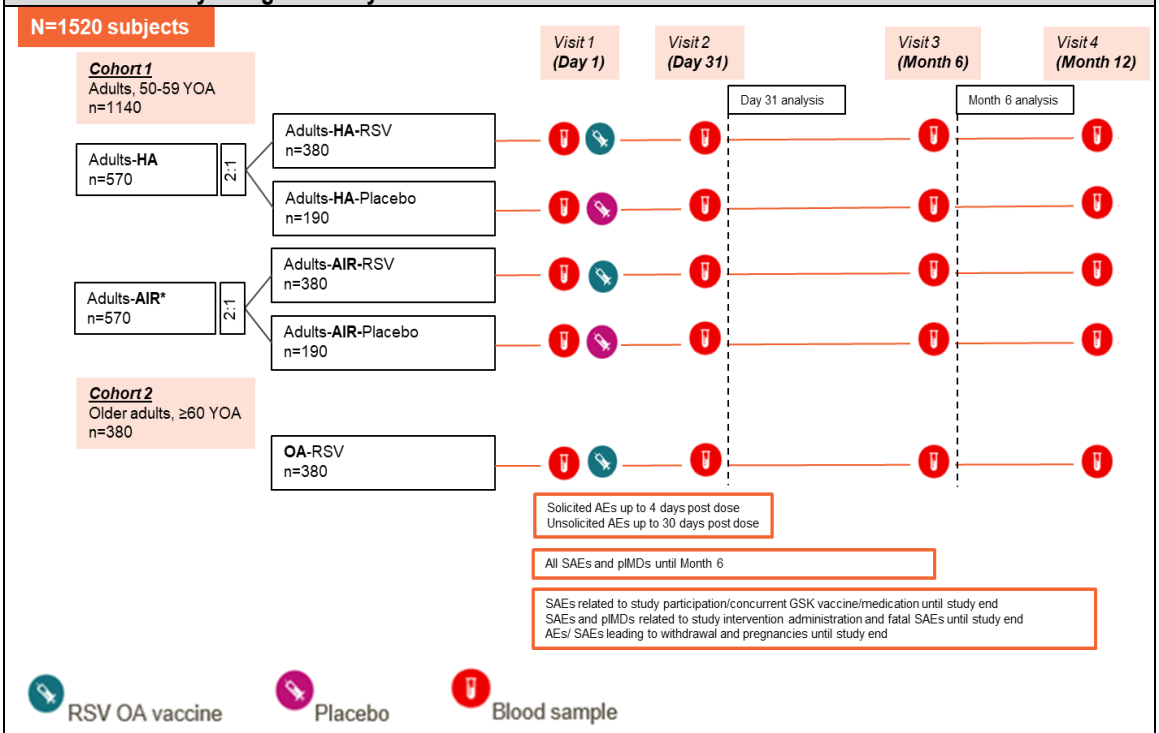
AE=Adverse event; AIR=At increased risk; CD=Cluster of differentiation; CD40L=CD40 ligand; CMI=Cell-mediated immunity; GMT=Geometric mean titer; HA=Healthy adults; IFN=Interferon; IL=Interleukin; LRTD=Lower respiratory tract disease; NI=Non-inferiority; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; SRR=Seroresponse rate; TNF=Tumor necrosis factor; YOA=Years of Age.

Primary estimands

The primary scientific question of the study is to demonstrate the non-inferiority of the immune response of RSVPreF3 OA investigational vaccine in healthy adults 50-59 years of age (YOA) and adults 50-59 years at increased risk of RSV-lower respiratory tract disease (LRTD), versus adults ≥60 YOA, in terms of RSV-A and RSV-B neutralizing titer (ED60) group GMT ratios and SRR difference at 1 month after vaccination in eligible participants who complied with the study requirements as defined per protocol (refer to Section 3 for the definition of the PPS used for the primary analysis and to Section 4.2 for the statistical methods).

1.2. Study Design

Overview of Study Design and Key Features



AE=Adverse event; AIR=At increased risk; GSK=GlaxoSmithKline Biologicals SA; HA=Healthy adults; n=Number; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

* Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, and chronic liver and renal diseases

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.

Overview of Study Design and Key Features	
Design Features	Phase 3 study to demonstrate the non-inferiority of the immune response of RSVPreF3 OA investigational vaccine in adults 50-59 years of age (YOA), including those who are at increased risk of RSV-lower respiratory tract disease (LRTD), versus adults ≥60 YOA. Blinding: observer-blind for Cohort 1, and open-label for Cohort 2. The study will be conducted in an observer-blind manner for Cohort 1 from study start-up to Day 31 analysis, beyond which the study will be considered single-blind (see Section 4.7.1 for details).
Study intervention	Participants will receive a single dose of study intervention (either RSVPreF3 OA investigational vaccine or placebo) at Visit 1 (Day 1).
Study cohorts, groups	Cohort 1 (adults 50-59 YOA), with 2 sub-cohorts (Adults-HA and Adults-AIR) and 4 parallel groups: • Adults-HA-RSV Group • Adults-HA-Placebo Group • Adults-AIR-RSV Group • Adults-AIR-Placebo Group Cohort 2 (adults ≥60 YOA) with a single group (OA-RSV Group)
Study intervention Assignment	• Participants in Cohort 1, Adults-HA Sub-cohort will be randomly assigned to the Adults-HA-RSV Group and Adults-HA-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively. • Participants in Cohort 1, Adults-AIR Sub-cohort will be randomly assigned to the Adults-AIR-RSV Group and Adults-AIR-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively. • All participants in Cohort 2 (OA-RSV Group) will be assigned to receive the RSVPreF3 OA investigational vaccine. The randomization algorithm will use a stratification by healthy/at increased risk status and CMI subset (participant included in the CMI subset or not) and a minimization procedure accounting for the study and center within each stratum. Minimization factors will have equal weight in the minimization algorithm.
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) are available for all participants.
Month 6 Analysis	A second analysis will be performed on all immunogenicity and safety data available and as clean as possible, when data for at least secondary endpoints up to Visit 3 (Month 6) are available for all participants.
End-of-study Analysis	An end of study analysis will be performed when all data for at least secondary endpoints up to study conclusion (Visit 4, Month 12) will be available for all participants.

2. STATISTICAL HYPOTHESES

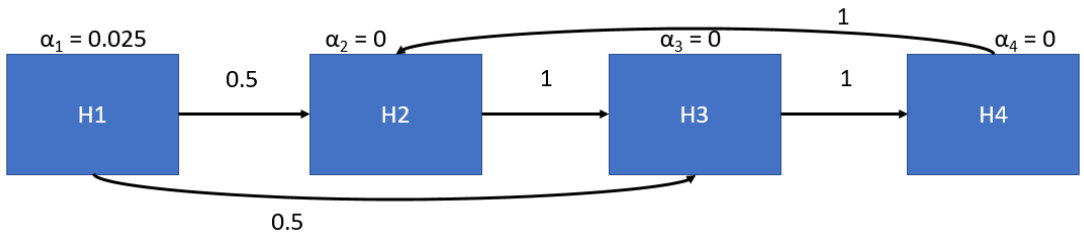
Statistical hypotheses are associated to the confirmatory primary NI objectives, which will be tested according to the graphical procedure detailed in Section 2.1. Global type I error is controlled at 2.5% (1-sided).

Table 1 Study objectives and null hypothesis

Objectives	Null hypothesis
Primary	
a. To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 1 (H1):** The anti-RSV-A GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
b. To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 2 (H2):** The anti-RSV-B GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
c. To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 3 (H3):** The anti-RSV-A GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
d. To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 4 (H4):** The anti-RSV-B GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

2.1. Multiplicity Adjustment

The following graphical testing procedure will be applied to control the global type I error at 2.5% (1-sided) [Bretz, 2009].



Refer to Table 1 where H1/H2/H3/H4 labels are assigned.

The initial allocation of α among the null hypotheses is (0.025, 0, 0, 0), while the propagation rules are specified by the transition matrix:

$$\begin{pmatrix} 0 & 0.5 & 0.5 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \end{pmatrix}$$

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened Set	All participants who were screened for eligibility.	Study Population
Enrolled Set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrolment) are excluded from the Enrolled Set as they did not enter the study.	Study Population
Exposed Set	All participants who received the study intervention. Analysis per group is based on the administered intervention.	Study Population, Safety
Per-Protocol Set*	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on the administered intervention.	Immunogenicity

* 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)
- Code 1100 (OA-RSV Group administered with placebo)

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, 1050, 1070, 1080, 1090, 1100 and 2010: participants will be eliminated for all visits.
- For codes 1040, 1060, 2040 and 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2020, 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

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, PPS
900	Invalid informed consent	All	Enrolled Set, ES, PPS
1030	Study intervention not administered at all	All	ES, 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. • 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, with the exception of inactivated and subunit influenza vaccines or COVID-19 vaccines (fully licensed or with EUA) which can be administered up to 14 days before or from 14 days after the study intervention administration. * • Previous vaccination with an RSV vaccine, including investigational RSV vaccines.	All	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
1050	Randomization failure: participant not randomized in the correct stratum	Visit 1	PPS
1060	Randomization code was broken	All	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 • Wrong reconstitution of administered vaccine	Visit 1	PPS
1080	Vaccine administration after a temperature deviation Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Visit 1	PPS
1090	Vaccine administration after expiration	Visit 1	PPS
1100	Other deviations related to wrong study treatment/administration/dose: OA-RSV Group = Administration of placebo	Visit 1	ES, PPS
2010	Protocol deviation linked to inclusion/exclusion criteria	All	PPS
2020	All Pre-dose results are missing	Visit 1	PPS
2040	Administration of any medication forbidden by the protocol • Use of any investigational or non-registered product (drug or medical device) 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 administration of long-acting immune modifying treatments or planned administration at any time up to the end of the study. – Up to 3 months prior to the study intervention administration: o For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed. o 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.	All	PPS
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.	All	PPS
2090	Participants did not comply with blood sample schedule*:	Visit 2, Visit 3, Visit 4	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Applicable for analysis set/endpoint
	• Number of days between vaccination (Visit 1) and blood sample (Visit 2) is outside [30-42] days. • Number of days between vaccination (Visit 1) and blood sample (Visit 3) is outside [180-210] days. • Number of days between vaccination (Visit 1) and blood sample (Visit 4) is outside [350-380] days.		
2100	Immunological results not available post-vaccination	Visit 2, Visit 3, Visit 4	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.	All	PPS

* 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.

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.
- The mean geometric increase (MGI) is defined as the geometric mean of the within-participant ratios of the post-vaccination titer over pre-vaccination (Visit 1, Day 1).
- Titers below the assay cut-off (LLOQ) will be replaced by half the assay cut-off (LLOQ/2) and titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ to compute GMTs, SRRs and MGIs. For the display of reverse cumulative curve, titers below LLOQ and above ULOQ won't 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 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.

- For the purpose of displays based on the ES, in the exceptional case of a participant belonging to the OA stratum and receiving placebo (e.g., due to wrong stratification), the participant will be excluded from ES summaries.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, i.e., the assessment at Visit 1 (Day 1).

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

4.2.1. Definition of endpoints

RSV-A and RSV-B neutralizing group GMT ratios at 1 month after the RSVPreF3 OA investigational vaccine administration will be computed for OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group.

RSV-A and RSV-B neutralizing group SRR differences at 1 month after the RSVPreF3 OA investigational vaccine administration will be computed for OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group.

4.2.2. Main analytical approach

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.

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

- The 2-sided 95% and 97.5% CIs for group GMT ratios (OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group) will be derived from an ANCOVA model on $\log_{10}$-transformed titers for each neutralization assay. The model will include the group and the baseline $\log_{10}$-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.
- The SRR is defined as the proportion of participants having a fold increase in neutralizing titers (1-month post-study intervention administration over pre-vaccination) ≥4. The 2-sided 95% and 97.5% CIs for group SRR difference (OA-RSV minus Adults-AIR-RSV group and OA-RSV minus Adults-HA-RSV group) will be derived using the method of Miettinen and Nurminen [Miettinen, 1985].

Success criteria for NI:

NI for each primary objective will be claimed if the upper limit of the 2-sided CI for the GMT ratio will be ≤1.5 and the upper limit of the 2-sided CI for the SRR difference will be ≤ 0.10, according to the significance level provided by the graphical testing procedure detailed in Section 2.1.The RSV-A and RSV-B neutralizing titer's unit used for computation of the GMT ratio and SRR difference will be ED60. Refer to Section 2 for the definition of null and alternative hypotheses associated to each primary NI objective.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of endpoints

Refer to Section 1.1 for the definition of secondary safety and immunogenicity (humoral and CMI response) endpoints.

4.3.2. Main analytical approach

4.3.2.1. Safety analysis

The safety analysis will be performed per study group, on the ES, as follows:

- 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. 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 (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. The same computations will be done for Grade 3 AEs and for AEs resulting in a medically attended visit.

- Compliance in completing solicited events information will be tabulated.

- 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 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.

- 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.
- 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 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). 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 analyses of unsolicited AEs will include SAEs, AESIs (including pIMDs and AF), unless otherwise specified.
- 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). 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). Similar tabulation will be done for Grade 3 unsolicited AEs reported within 30 minutes following vaccination.
- 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.
- 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 Month 6 will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration, from vaccination up to Month 6 and study end (Month 12) will be tabulated with exact 95% CI.
- The number and percentage of participants with any fatal SAE, from vaccination up to Month 6 and study end (Month 12) will be tabulated with exact 95% CI.

- The number and percentage of participants with at least one report of pIMD classified by the MedDRA Primary SOC, HLT and PT from vaccination up to Month 6 will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of pIMD classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration, from vaccination up to Month 6 and study end (Month 12) will be tabulated with exact 95% CI.
- The number and percentage of participants with specific Demyelinating disorder with onset within 30 days of vaccination will be tabulated with exact 95% CI.
- The number and percentage of participants with specific Serious Demyelinating disorder from vaccination up to Month 6 and study end (Month 12) will be tabulated with exact 95% CI.
- All SAEs/AESIs (including pIMDs and AF) up to study end (Month 12) 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.
- In case participants belonging to the OA stratum receive placebo (i.e., participants eliminated from the ES following code 1100, refer to Section 3.1.2), SAEs and AESIs (including pIMDs and AF) reported (if any) will be described.
- AF AESIs will be tabulated within the summary of AEs or SAEs according to their classification.

For analysis of SAEs/AESIs (including pIMD and AF) within 6 months after vaccination, 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 6.1.5 and Section 6.1.6 for the analysis of concomitant medications and concomitant vaccination.

4.3.2.2. Immunogenicity analysis: humoral immune response

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.

4.3.2.2.1. Between groups assessment

Considering the sampling timepoint at 1-month post-study intervention administration, same analysis as for primary endpoint (refer to Section 4.2.2) will be performed using IU/ml unit for computation of the GMT ratio and SRR difference.

Considering the sampling timepoint at 6-month and 12-month post-study intervention administration, the following analysis will be performed:

- The 2-sided 95% CIs for group GMT ratios (OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group) will be derived from an ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the group and the baseline log_{10}-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.
- The 2-sided 95% CIs for group SRR difference (OA-RSV minus Adults-AIR-RSV group and OA-RSV minus Adults-HA-RSV group)
- Results will be reported using both ED60 and IU/ml units.

All between groups analyses of secondary endpoints presented in this section will be descriptive with the aim to characterize the difference in immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

4.3.2.2.2. Within groups assessment

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

a. Percentage of participants with neutralizing titers equal to or above pre-defined assay cut-offs and their 2-sided 95% CIs will be tabulated.

b. Percentage of participants having a fold increase in neutralizing titers ≥4 and their 2-sided 95% CIs will be tabulated.

c. Unadjusted GMTs and their 95% CIs will be tabulated and displayed graphically.

d. Furthermore, to account for the multiples timepoints at which the blood samples are collected, a mixed effects model (see Section 4.3.3.1) will be fitted, from which the adjusted GMTs and their 95% CIs will be computed and tabulated.

e. The kinetics of unadjusted GMTs will be plotted as a function of time for participants with results available at all timepoints.

f. Unadjusted MGIs and their 95% CIs will be tabulated and displayed graphically.

g. Distribution of neutralizing titers will be displayed using reverse cumulative curves.

h. Results will be reported using both ED60 and IU/ml units.

The above mentioned descriptive within group immunogenicity analysis will also be generated by age at vaccination (50-59 YOA, 60-69 YOA, 70-79 YOA and ≥80 YOA years) with the exception of analysis described in point d, e and g. No graphical display will be produced.

4.3.2.3. Immunogenicity analysis: CMI response

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

At each time point blood samples are collected, the following parameters will be summarized by group using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) in the CMI subset:

- Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by intracellular cytokine staining (ICS) using Peripheral Blood Mononuclear Cells (PBMCs).
- The kinetics of the frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by ICS, will be plotted as a function of time for participants with results available at all timepoints.
- Fold increase of the frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by ICS at the post-vaccination time point over pre-vaccination (Visit 1, Day 1). The percentage of subjects with at least a 4-fold increase, post-vaccination as compared to pre-vaccination will be tabulated by timepoint.
- The frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN- γ, IL-13, IL-17, measured by ICS, will be displayed graphically using boxplots (min, Q1, median, Q3, max)

The above mentioned descriptive within group immunogenicity analysis will also be generated by age at vaccination (50-59 YOA, 60-69 YOA, 70-79 YOA and ≥80 YOA years) at the exception of the graphical displays

4.3.3. Additional considerations

4.3.3.1. Mixed-effects model

For the GMTs calculation based on the mixed effects model mentioned in Section 4.3.2.2, repeated measures analysis of covariance (ANCOVA) model will be fitted including study group (OA-RSV, Adults-AIR-RSV, Adults-AIR-Placebo, Adults-HA-RSV, Adults-HA-Placebo) and post-vaccination visit (Day 31, Months 6, 12), as fixed effects, pre-vaccination log10-transformed titers as a covariate and the response variable is the post-vaccination log10-transformed titers. The PROC MIXED procedure in SAS® will be used to carry out the ANCOVA.

The following SAS codes will be used:

```
     PROC MIXED DATA=SERO method=reml empirical;
CLASS subjid group visit ;
MODEL post-vac=pre-vacc group visit visit*group/ noint s cl;
REPEATED visit/type=un subject=subjid;
LSMEANS visit*group/ E cl;
     ODS OUTPUT LSMEANS=LS;
     RUN;
```

The above SAS codes may be adapted in case of convergence issues.

4.3.3.2. Cell-mediated immune response

The RSVPreF3-specific CD4+/ CD8+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geometric mean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+/ CD8+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+/ CD8+ T cells expressing at least 2 activation markers including at least one cytokine [$Freq^{2+}$] will be computed as follows:

$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

and

$$Freq^{2+}_{Specific} = Freq^{2+}_{Induction} - Freq^{2+}_{Background}$$

where

$n^{2+}_{Background}$= number of CD4+ T cells expressing at least 2 activation markers including at least one cytokine after stimulation with medium only (background)

$n^{2+}_{Induction}$ = number of CD4+ T cells expressing at least 2 activation markers including at least one cytokine after stimulation with a pool of peptides covering RSVPreF3 (induction)

$N^{CD4}_{Back/Ind}$ = Total number of CD4+ T cells involved in the assay (background or induction)

For the computation of the fold increase (post- over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, the results below the lower limit of quantification (LLOQ) of the assay will be replaced by the value of the LLOQ.

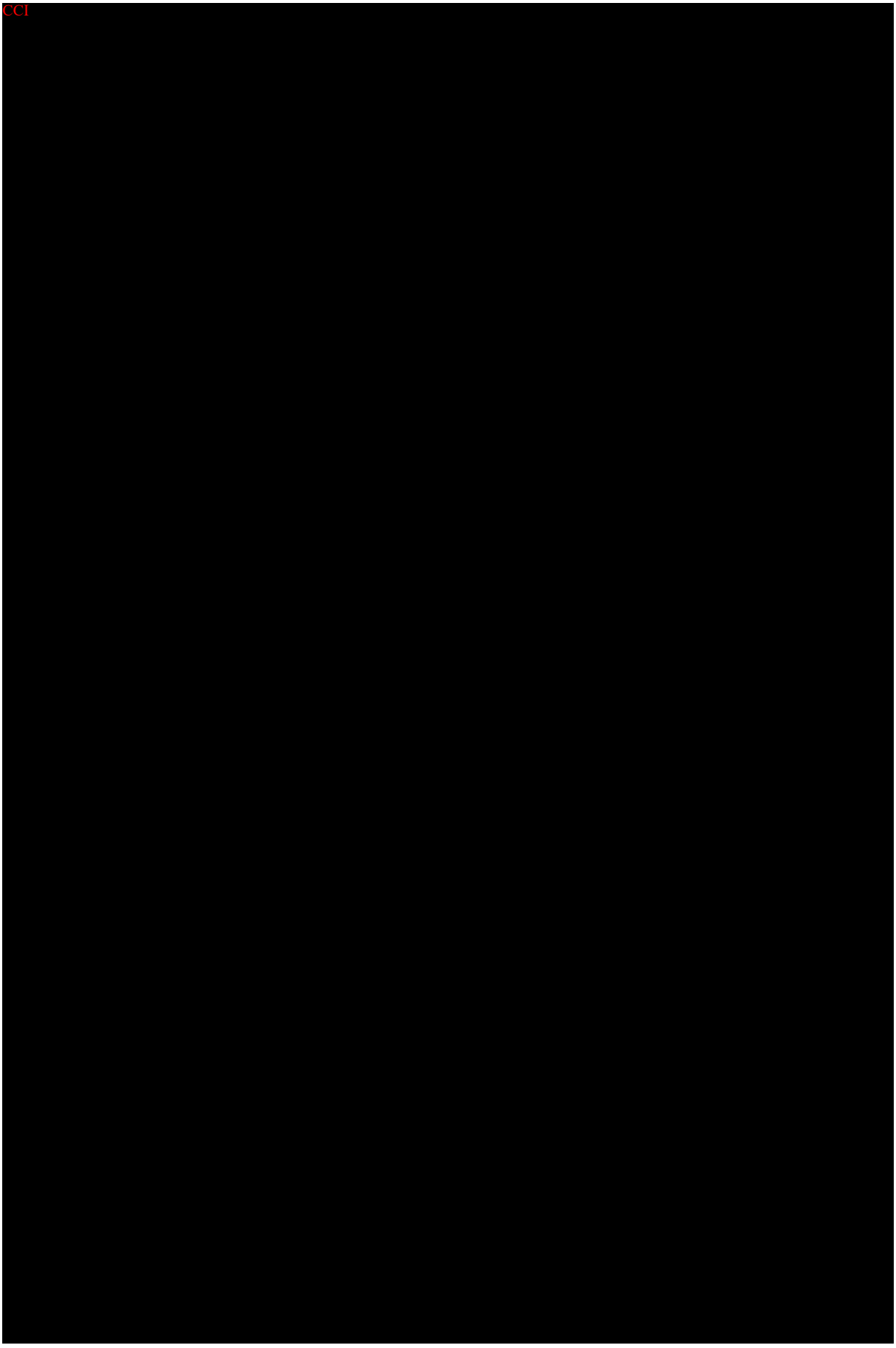
4.3.3.3. Atrial Fibrillation (AF) AESIs

Potential 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.

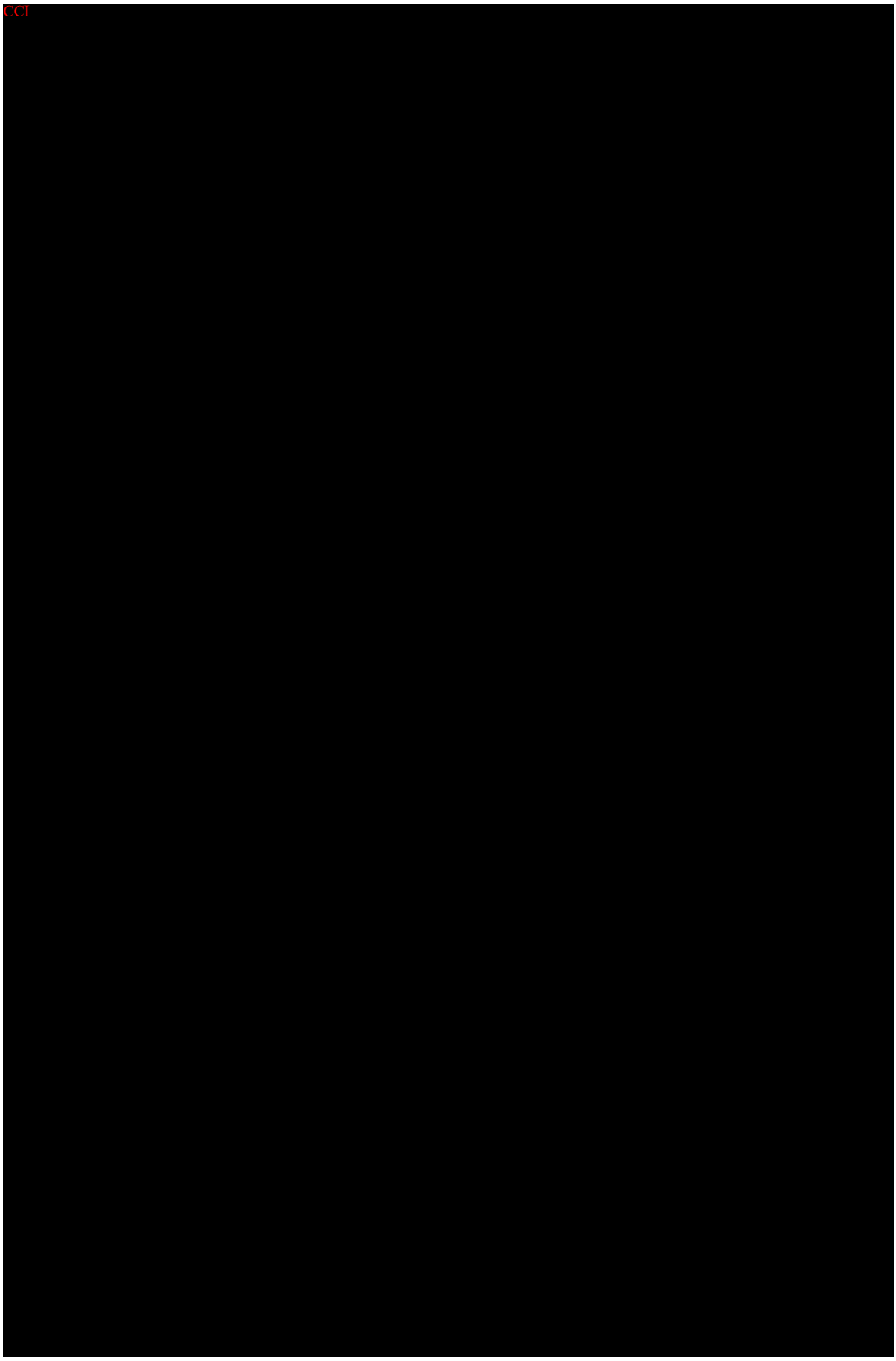
AF AESIs will be described in a tabular summary including the characteristics of the AE (seriousness, causality, maximum intensity), time to onset and outcome.

CCI

CCI



CCI



CCI

4.5. Other Safety Analyses

Not Applicable.

4.6. Other Analyses

Not Applicable.

4.7. Interim Analyses

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

4.7.1. Sequence of analyses

The analyses will be performed stepwise:

- **Day 31 (PCA)**: 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) are available for all participants. This analysis will be considered as final for those endpoints*.
- **Month 6**: A second analysis will be performed on all immunogenicity and safety data available and as clean as possible, when data for at least secondary endpoints up to Visit 3 (Month 6) are available for all participants. This analysis will be considered as final for those endpoints*.
- An **end of study** analysis will be performed when all data for at least secondary endpoints up to study conclusion (Visit 4, Month 12) will be available for all participants.

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

  * Each analysis can be considered as final, as it is based on data that is as clean as possible. However, the consecutive analysis of the same time point might slightly differ at the next analysis e.g., when Month 6 data are re-analyzed at the time of Month 12 analysis. If major changes are identified, they will be described in the clinical study report.

4.7.2. Statistical considerations for interim analysis

No statistical adjustment for interim analysis is required.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 26-JUL-2022).

5. SAMPLE SIZE DETERMINATION

The target sample size for the study is approximately 1520 participants: 380 participants each in the Adults-HA-RSV Group and Adults-AIR-RSV Group, 190 participants each in the Adults-HA-Placebo Group and Adults-AIR-Placebo Group and 380 participants in the OA-RSV Group.

The sample size in the groups receiving the investigational vaccine is driven by the statistical power to prove the primary NI objectives.

Assuming 342 evaluable participants in each group receiving the investigational vaccine, the power to demonstrate the primary NI objectives following the graphical testing procedure in Section 2.1 is presented in Table 4. Power was estimated by 10 000 simulations, using SAS 9.4:

- Individual RSV-A and RSV-B neutralizing titers at baseline and at 1-month post-study intervention administration were modeled by a multivariate log-normal distribution, means and variance-covariance matrix based on historical data from other RSV OA vaccine clinical trials. The Adults-AIR-RSV Group was assumed to have the same multivariate log-normal distribution of the OA-RSV Group (i.e., same means and variance-covariance matrix), while the Adults-HA-RSV Group was assumed to have a 1.25-fold higher mean at 1-month post-study intervention administration for both neutralizing antibodies.
- Raw p-values were obtained from shifted 1-sided t-tests (for group GMT ratios) and using the method of Miettinen and Nurminen (for group SRR difference). The p-value associated to each NI objective is the maximum between the p-values from the GMT ratio and from the SRR difference (co-primary endpoints).

- P-values associated to each NI objective were compared with the corresponding alpha, as propagated by the graphical testing procedure, to identify which NI objectives were successfully demonstrated at each simulation.

Table 4 Power of primary NI objectives

Objective	Power
NI in the Adults-HA-RSV Group for the RSV-A strain	>99%
NI in the Adults-HA-RSV Group for the RSV-B strain	>99%
NI in the Adults-AIR-RSV Group for the RSV-A strain	93.6%
NI in the Adults-AIR-RSV Group for the RSV-B strain	82.8%
All	82.7%

All=power to demonstrate all primary NI objectives simultaneously; AIR=At increased risk; HA=Healthy adults; NI=Non-inferiority; RSV=Respiratory syncytial virus.

A 10% attrition rate is accounted from enrolled to evaluable participants. Participants who withdraw from the study will not be replaced.

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. This 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, vital signs, Body Mass Index (BMI) and smoking status) 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, 70-79 YOA and ≥80 YOA. In addition, for web posting purposes: 18-64 YOA, 65-84 YOA and ≥85 YOA.

CCI [redacted].

6.1.3. Protocol Deviations

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 unblinding (at the Day 31 Analysis) and 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 and all deviations leading to exclusions from analysis sets are captured.
- This dataset will be the basis for the summaries of important protocol deviations.

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. Participant exposure

The number and percentage of participants who received the study intervention will be tabulated by group for the ES.

6.1.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary.

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 study group.

6.1.6. 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.

6.1.7. Additional Analyses due to the COVID-19 Pandemic

Would COVID-19 still be classified as pandemic in one of the study countries, the following analyses will be performed:

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The overall incidence of COVID-19 AEs (during the 30-day follow-up period), COVID-19 SAEs and COVID-19 AEs leading to study withdrawal (from vaccination up to study end) will be summarized. The incidence of these events will be obtained from standard AE and SAE summaries (i.e., by SOC and PT).

COVID-19 assessments (confirmed, probable and suspected diagnosis) for participants with COVID-19 AEs will be summarized.

The number and percentage of participants with previous or concomitant COVID-19 vaccination, before and during the study (during the 30-day follow-up period after vaccination), will be tabulated with exact 95% CI.

6.2. Appendix 2 Data Derivations Rule

6.2.1. 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.

6.2.2. Handling of missing data

6.2.2.1. Dates

When partially completed dates (i.e., dates missing a day and/or month) are used in calculations, 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.

The following exceptions apply:

- Adverse events start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month.
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) 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 vaccine dose given during that month.
- Adverse events start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) 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.
- Adverse event end dates with missing day: the imputed end date will be the last day of the month or the study conclusion date whichever comes first.

- Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.
- All incomplete concomitant medication/vaccination start/end dates will follow the rules above.

6.2.2.2. 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/concentrations (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 will be excluded from ANCOVA and mixed effects models (refer Section 4.3.3.1)

6.2.2.3. Daily recording of solicited events

For studies using paper diaries which have questions in the CRF indicating the presence or absence 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

6.2.2.4. Unsolicited adverse events

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

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the Adverse Events (AE) domain, but they do not contribute to the summaries of unsolicited adverse events.

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.

6.2.3. Data derivation

6.2.3.1. Age at vaccination in years and age category

Age at vaccination in years and age categories are based on the information provided in the eCRF and available in DM.AGE.

6.2.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.2.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.2.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

6.2.3.5. 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

6.2.3.6. 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

6.2.3.7. Geometric mean titers (GMTs) and concentrations (GMCs)

GMT or GMC calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable neutralizing titres or concentrations will be converted as described in Section 6.2.3.6 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.3.8. 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).

6.2.3.9. 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 6.2.2.1.
- 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).

6.2.3.10. 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.

6.2.3.11. 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)

6.2.4. Display of decimals

6.2.4.1. Percentages

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

6.2.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-dose body temperature) 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.

The maxima and minima of transformed height/weight variables will be displayed without decimals.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.2.4.3. Serological summary statistics

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

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

The mean, median, standard deviation, and quartile values for frequency of RSVPreF3 specific-CD4+ and CD8+ T cells and for the fold increase (post over pre-vaccination) will be presented with one decimal. The minimum and maximum values will be presented with no decimal.

7. REFERENCES

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