Statistical Analysis Plan Amendment 4

Study ID: 222253

Official Title of Study: A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.

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TITLE PAGE

Protocol Title:	A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.
Study Number:	222253
Compound Number:	GSK3844766A
Abbreviated Title:	RSV OA=ADJ-025
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
AIR	At Increased Risk
CCI [redacted]	
BMI	Body Mass Index
CI	Confidence Interval
CCI [redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
eCRF	electronic Case Report Form
ED60	Estimated dilution 60
EOS	End of study
ES	Exposed Set
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HLT	High Level Term
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

PT	Preferred Term
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
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	12 February 2024	Final: 18 December 2023	Not Applicable	Original version
SAP Amendment 1	19 July 2024	Amendment 1: 03 May 2024	Updates to align with changes according to protocol amendment: addition of Cohort 3 (addition of Part A or Part B where appropriate, update of Section 4.7.1 and Section 5). Section 4.3.2.1 and 6.3.3.9 (previously 6.2.3.9): Change in tabulation of solicited event duration and number of days with Grade 3 solicited events. Removal of tables for demyelinating disorder AEs. New Section 6.2 following SAP template update. Section 6.3.2.3 (previously	The study population has been extended to include a cohort of AIR participants 18-49 YOA to better characterize the safety profile of the RSVPreF3 OA investigational vaccine in this population. Section 4.3.2.1 and 6.3.3.9 (previously 6.2.3.9): Change following project update for the definition of duration of solicited symptoms. Demyelinating disorder AEs will be part of overall AE tables showing different SMQs.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			6.2.2.3): Update on daily recording of solicited events using eDiary.	New Section 6.2 : Definition and analysis of eDiary compliance Section 6.3.2.3 (previously 6.2.2.3): Update following finalization of eDiary and eCRF completion guidelines.
SAP Amendment 2	12 September 2024	Amendment 1: 03 May 2024	Changes for duration analyses (Section 4.3.2.1, 6.3.3.9), Endpoint level compliance (Section 6.2.2) and missing data for solicited events (Section 6.3.2.3)	To account for missing eDiary data as of day 5 onwards, due to non-activation of the eDiary alerts for participants from day 5 onwards in the vendor system. The alerts were re-installed as of 8August2024 onwards.
SAP Amendment 3	04 October 2024	Amendment 1: 03 May 2024	Changes for solicited events analysis (Section 4.3.2.1) and Endpoint level compliance (Section 6.2.2)	To align the solicited events analysis following a request from CBER on study RSV OA=ADJ-017.
SAP Amendment 4	15 Jan 2025	Amendment 1: 03 May 2024	Changes for duration of events (Section 6.3.3.9) and	To include additional analyses on duration of

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Endpoint level compliance (Section 6.2.2)	solicited adverse events and eDiary compliance to account for missing eDiary data as of day 5 onwards, due to non-activation of the eDiary alerts for participants from day 5 onwards in the vendor system.

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses to be included in the CSR for Study RSV OA=ADJ-025 (222253). Details of the planned interim analyses, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Objectives and Endpoints

Objective	Endpoint
Primary* (Part A)	
• To demonstrate the NI** of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AIR) at 1 month (Day 31) after study intervention administration*** • Seroresponse in RSV-A neutralizing titers from Day 1 to Day 31***.
• To demonstrate the NI** of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AIR) at 1 month (Day 31) after study intervention administration*** • Seroresponse in RSV-B neutralizing titers from Day 1 to Day 31***.
Secondary Safety (Part A and Part B)	
• To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.	• Occurrence of each solicited administration site event with onset within 4 days after dosing (i.e., the day of study intervention administration and 3 subsequent days). • Occurrence of 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). • Occurrence of unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Occurrence of all SAEs (including fatal and related SAEs) and AESIs after study intervention administration (Day 1) up to study end (Month 6).
Secondary Immunogenicity (Part A)	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 6 months after study vaccination for both populations.	• RSV-A and RSV-B neutralizing titers, at pre-study intervention administration and 1 month and 6 months after study intervention administration.
Tertiary Immunogenicity (Part A)	
CCI [redacted]	

AE=Adverse event; AESI=Adverse event of special interest; AIR=At increased risk; CCI [redacted]; GMT=Geometric mean titer; NI=Non-inferiority; OA=Older adults; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

* Refer to Section 4.2.2 for the testing sequence of primary objectives.

** NI criteria are defined in Section 4.2.2.

*** Co-primary endpoints. Refer to Section 2 for statistical hypotheses.

Primary estimands (for Part A)

The primary question of interest is to evaluate the NI of the humoral immune response after RSVPreF3 OA investigational study intervention in RSV-A-AIR group (18-49 YOA), vaccinated as per protocol when compared to RSV-OA (≥60 YOA) group.

Table 2 Primary estimands (Part A)

Attributes					Summary measure
Treatment	Population	Endpoint (variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine at Day 1.	Non-immunocompromised adults at increased risk for RSV disease with 18-49 YOA. OA with ≥60 YOA.	• RSV-A neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-A neutralizing titers (expressed in ED60) from Day 1 to Day 31. • RSV-B neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-B neutralizing titers (expressed in ED60) from Day 1 to Day 31.	Taking prohibited medication /vaccine or intercurrent medical condition prior to Day 31.	Data collected after ICEs will be excluded from the analysis at Day 31 (Hypothetical strategy). Rationale: To evaluate the immunogenicity parameters in the absence of ICE.	Ratio of GMTs with 95% CI and difference in seroresponse rate (SRR) with 95% CI for RSV-A and RSV-B neutralizing titers (ED60) at Day 31 between the RSV-OA group (≥60 YOA) and the RSV-A-AIR group (18-49 YOA).

SRR is defined as the proportion of participants having a fold increase in neutralizing titers (1-month post-study intervention administration over pre-study intervention administration) ≥4.

AIR=At increased risk; CI=Confidence interval; ED60= Estimated dilution 60; GMT=Geometric mean titer; OA=Older adults; YOA=Years of age

Rationale for estimand: The primary estimands address the objective of demonstrating the NI of the humoral immune response in non-immunocompromised adults aged 18-49 YOA AIR for RSV disease, when compared to older adults aged ≥ 60 YOA after administration of a single dose of RSVPreF3 OA investigational vaccine. This is done by estimating the true effect of the vaccine without any confounding of other medications/vaccinations/medical condition(s) on the target population since the impact of developing medical condition(s) forbidden by protocol and use of forbidden medications and vaccinations is anticipated to modify the vaccine effect.

Secondary estimands (for Part A and Part B)

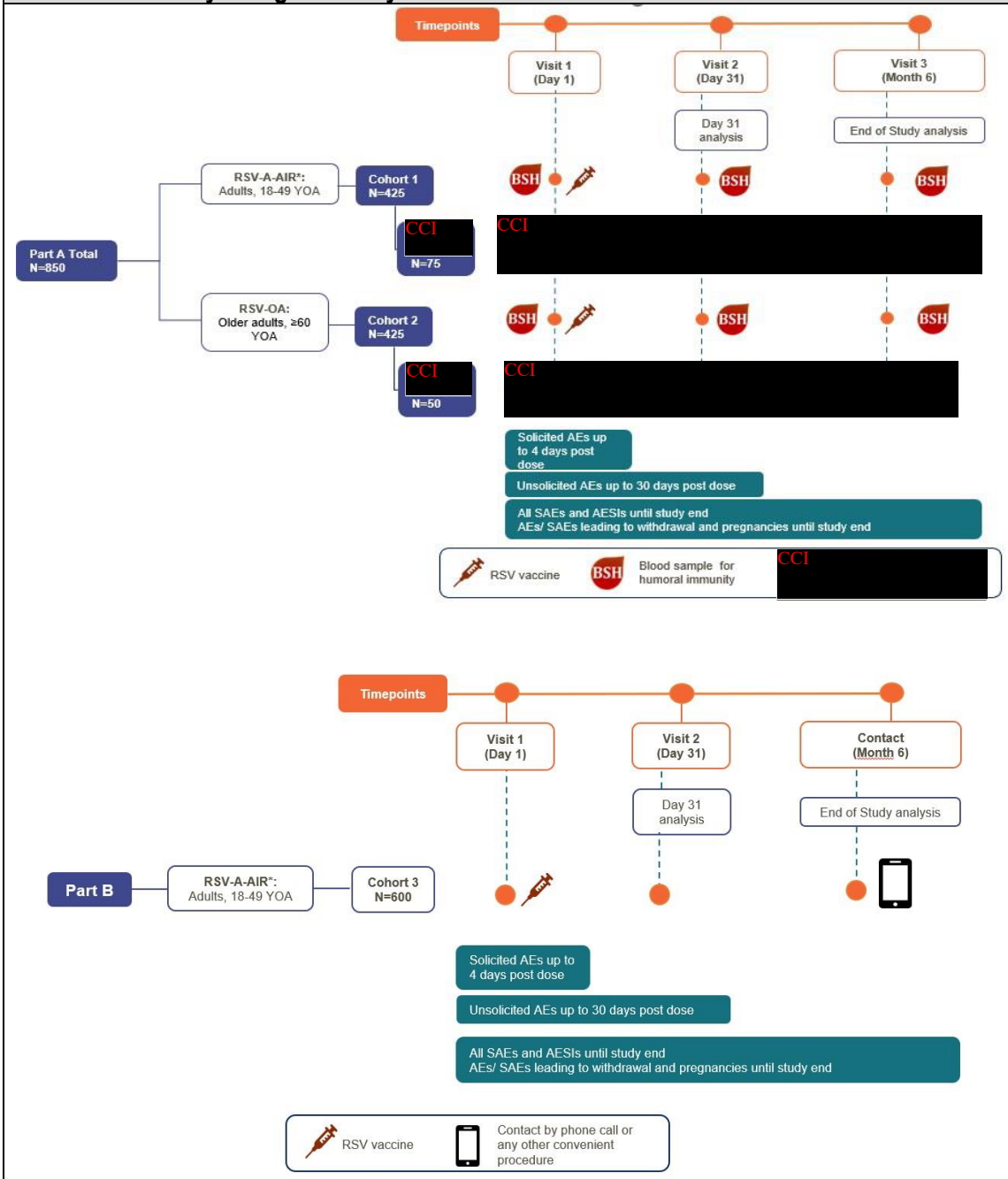
Table 3 Secondary estimands for safety (Part A and Part B)

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine at Day 1.	Non-immunocompromised adults at increased risk for RSV disease with 18-49 YOA. OA with ≥60 YOA.	• 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 (including fatal and related SAEs) and AESIs after study intervention administration (Day 1) up to study end (Month 6).	Taking prohibited medication /vaccine or intercurrent medical condition during respective duration.	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 endpoints.

AE=Adverse event; AESI=Adverse event of special interest; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

1.2. Study Design

Overview of Study Design and Key Features



A= Adults; AE=Adverse event; AESI=Adverse events of special interest; AIR=At increased risk; CCI [redacted]; N=Number of participants; 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, chronic liver and renal diseases, and neurologic or neuromuscular conditions

Overview of Study Design and Key Features

Interval	Planned visit interval	Allowed interval range
Visit 1→Visit 2	30 days	30-42 days
Visit 1→Visit 3 (Part A)	180 days	180-210 days
Visit 1→ Contact (Month 6) (Part B)	180 days	180-210 days

If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.
Interval is computed as the difference between 2 dates.

Design Features	Phase 3b, open-label, uncontrolled (as there is no comparative intervention), non-randomized study. The study will be conducted in 2 Parts – Part A and Part B. Part A will include 2 parallel cohorts (Cohort 1 and Cohort 2) and Part B will include 1 cohort (Cohort 3). Duration of the study: Approximately 6 months for all participants.
Study intervention	Participants will receive 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
Study intervention Assignment	Participants will be enrolled into ***3*** different cohorts. <u>Part A:</u> Cohort 1: Participants 18-49 YOA at increased risk for RSV disease will be enrolled into Cohort 1 in 3 disease categories (cardiopulmonary conditions, diabetes mellitus and other disease categories), with approximately 25% of participants with cardiopulmonary conditions and approximately 25% of participants with diabetes mellitus. The remaining approximately 50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease. Cohort 2: Participants ≥60 YOA will be enrolled into Cohort 2 in 2 age categories (60-69 YOA and ≥ 70 YOA), with approximately 40% of participants 60-69 YOA and approximately 30% of participants ≥ 70 YOA. The remaining 30% can be distributed freely across the 2 age categories. <u>Part B:</u> Cohort 3: Participants 18-49 YOA at increased risk for RSV disease will be enrolled into Cohort 3 in 3 disease categories (cardiopulmonary conditions, diabetes mellitus and other disease categories), with approximately 25% of participants with cardiopulmonary conditions and approximately 25% of participants with diabetes mellitus. The remaining approximately 50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease. In addition, enrolment rules will be applied to ensure adequate representation by sex category within all 3 Cohorts, with approximately 35% of male participants per cohort and approximately 35% of female participants per cohort. The remaining 30% can be distributed freely across the 2 categories. Participants contributing to the CCI [redacted] (only Part A) will be recruited from a selected number of countries and selected number of clinical sites. In the selected sites, the investigator will allocate if possible, at Visit 1, the first participants in each group to the CCI [redacted] until the allocated target is reached.
Day 31 Analysis (Part A)	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 in Part A. This analysis will be considered as final for the primary endpoints
Month 6 Analysis (Part A)	An optional and separate analysis may be performed when safety data up to Month 6 are available for all participants in Part A, if required.

Overview of Study Design and Key Features	
Day 31 Analysis (Part B)	An optional and separate analysis may be performed when safety data up to Visit 2 (Day 31) are available for all participants in Part B, if required. This analysis may be combined with Month 6 analysis for Part A.
Month 6 Analysis (Part A)	An optional and separate analysis may be performed when immunogenicity data up to study conclusion (Visit 3, Month 6) are available for all participants in Part A, if required.
End-of-study Analysis	An end of study analysis will be performed when all data for secondary endpoints up to study conclusion (Visit 3/Contact, Month 6) 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 hierarchical testing procedure described in Section 2.1. Global type I error is controlled at 2.5% (1-sided).

Table 4 Study objectives and null hypothesis

Objectives	Null hypothesis
Primary (Part A)	
• To demonstrate the NI of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease 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 RSV-OA (≥60 YOA) over RSV-A-AIR (18-49 YOA) is >1.5 or the SRR difference (RSV-OA [≥60 YOA] minus RSV-A-AIR [18-49 YOA]) 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%.
• To demonstrate the NI of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease 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 RSV-OA (≥60 YOA) over RSV-A-AIR (18-49 YOA) is >1.5 or the SRR difference (RSV-OA [≥60 YO]) minus RSV-A-AIR [18-49 YOA]) 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%.

A=Adults; AIR=At increased risk; GMT=Geometric mean titer; H1=Null hypothesis 1; H2=Null hypothesis 2; NI=Non-inferiority; OA=Older adults; RSV=Respiratory syncytial virus; SRR=Seroresponse rate; YOA=Years of age.

2.1. Multiplicity Adjustment

In order to control the global type I error at 2.5% (1-sided), the primary objectives will be assessed using a hierarchical testing. NI will be first tested for RSV-A strain and, only if NI has been demonstrated, will the NI be tested for RSV-B strain.

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 allocated a treatment number or received study intervention or underwent a post screening study procedure). Note: screening failures (who never passed screening) and participants screened (met eligibility) but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Exposed Set (ES)	All participants who received the study intervention. Analysis per group is based on age and medical condition (adults 18-49 YOA at increased risk for RSV disease versus older adults ≥60 YOA).	Study population, Reactogenicity, Safety
Per-Protocol Set (PPS)*	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on age and medical condition (adults 18-49 YOA at increased risk for RSV disease versus older adults ≥60 YOA).	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)

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

Table 5 List of elimination codes

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All	Enrolled Set, ES, PPS
900	Invalid informed consent	All	All	Enrolled Set, ES, PPS
1030	Study intervention not administered at all	Visit 1	All	ES, PPS
1040	Administration of concomitant vaccine(s) forbidden in the protocol (as defined in Section 5.2.2 of protocol)	All	From the specific visit the condition is met	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	All	PPS
1080	• Vaccine administration after a temperature deviation • Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Visit 1	All	PPS
1090	Vaccine administration after expiration	Visit 1	All	PPS
2010	Protocol deviation linked to inclusion/exclusion criteria	All	All	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
2020	All Pre-dose results are missing	Visit 1	At the specific visit the condition is met	PPS
2040	Administration of any medication forbidden by the protocol (as defined in Section 5.2.2 of protocol)	All	From the specific visit the condition is met.	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	From the specific visit the condition is met.	PPS
2090	Participants did not comply with blood sample schedule: • 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.	Visit 2, Visit 3	At the specific visit the condition is met	PPS
2100	Immunological results not available post-vaccination	Visit 2, Visit 3	At the specific visit the condition is met	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	At the specific visit the condition is met	PPS

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 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 level. 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.
- Seroresponse rate (SRR) is defined as the proportion of participants having a fold increase in neutralizing titers (post-study intervention administration over pre-study intervention administration) ≥4.
- 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).

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 Endpoints Analyses (Part A)

4.2.1. Definition of endpoints/estimands

Refer to Section 1.1 for the definition of primary immunogenicity (humoral response) endpoints/estimands.

4.2.2. Main analytical approach

Primary estimand analysis will be performed on the Per-Protocol Set (PPS) for participants in Part A. 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.

RSV-A and RSV-B neutralizing group GMT ratio at 1 month after the RSVPreF3 OA vaccine administration will be computed for RSV-OA (≥60 YOA) cohort over RSV-A-AIR (18-49 YOA) cohort, with 95% CI, using an CCI [redacted] on log10-transformed titers for each neutralization assay. The model will include the group (RSV-OA (≥60 YOA) and RSV-A-AIR (18-49 YOA)) and the baseline log10-transformed titer as covariate.

RSV-A and RSV-B neutralizing group SRR differences at 1 month after the RSVPreF3 OA vaccine administration will be computed for RSV-OA (≥60 YOA) cohort minus RSV-A-AIR (18-49 YOA) cohort, with 95% CI. The 95% CI will be derived using the method of CCI [redacted]

Missing data will not be imputed.

Success criteria for NI:

- In order to control the global type I error at 2.5% (1-sided), the primary objectives will be assessed using a hierarchical testing. NI will be first tested for RSV-A strain and, only if NI has been demonstrated, will the NI be tested for RSV-B strain.
- NI for RSV-A strain will be claimed to be successful if the upper limit of the 95% CI for the RSV-A neutralizing group GMT ratio will be ≤1.5 and the upper limit of 95% CI for the RSV-A neutralizing group SRR difference will be ≤10%.
- NI for RSV-B strain will be claimed to be successful if NI has been demonstrated for RSV-A strain and if the upper limit of the 95% CI for the RSV-B neutralizing group GMT ratio will be ≤1.5 and the upper limit of 95% CI for the RSV-B neutralizing group SRR difference will be ≤10%.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoints/estimands

Refer to Section 1.1 for the definition of secondary safety and immunogenicity (humoral and CCI [redacted]) endpoints/estimands.

4.3.2. Main analytical approach

4.3.2.1. Safety analysis

The estimand analysis for safety will be performed on the ES for participants in Part A and Part B. For the analysis of solicited events, the daily assessment from the investigator (either to correct the participant entry or to replace a missing participant entry) will take precedence over the participant's entry only when the investigator assessment is done up to 36 hours after 23h59 of the specified day.

Descriptive analysis by group will be summarized as follows:

- The safety follow-up time will be tabulated using descriptive statistics (mean, median, minimum, maximum), including the percentage of participants with at least 6 months safety follow-up post-vaccination.
- 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 and the 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 (i.e., the day of study intervention administration and 3 subsequent days) 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 (See Section 6.2.2).
- 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. If the proportion of participants who completed the eDiary entries from Day 1 through Day 4 is below 90%, the outputs will also be tabulated for these participants only (see Section 6.2.2).
- 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 event will be tabulated using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same computations will be done for the number of days with Grade 3 solicited events. The duration will be calculated for both definitions in Section 6.3.3.9 and the outputs will be tabulated for all participants and for the participants from Cohort 3 enrolled as of 8August24, as from then the eDiary alerts for participants from Day 5 onwards were activated in the vendor system.
- 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 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 and AESIs (i.e. pIMDs and AF).

- The number and percentage of participants with any non-serious 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 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 SOC, HLT and 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 study end (6 months after study intervention administration) 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 study end (6 months after study intervention administration) will be tabulated with exact 95% CI.
- The number and percentage of participants with any fatal SAE, from vaccination up to study end (6 months after study intervention administration) 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 study end (6 months after study intervention administration) 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 study end (6 months after study intervention administration) will be tabulated with exact 95% CI.
- All SAEs, pIMDs and AFs from vaccination up to study end (6 months after study intervention administration) will also be described in detail in a tabular listing.
- AEs/SAEs leading to study discontinuation from vaccination up to study end (6 months after study intervention administration) 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 will be produced by SOC and PT.
- In case of pregnancies, these will be described in detail in a tabular listing.
- AF AESIs will be tabulated within the summary of AEs or SAEs according to their classification.

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 estimand analysis for immunogenicity will be performed on the PPS for participants in Part A. 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 CCI unit for computation of the GMT ratio and SRR difference.

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

- The 95% CIs for group GMT ratios (RSV-OA (≥60 YOA) cohort over RSV-A-AIR (18-49 YOA) cohort) 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 95% CIs for group SRR difference (RSV-OA (≥60 YOA) cohort minus RSV-A-AIR (18-49 YOA) cohort)
- Results will be reported using both ED60 and CCI 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 timepoint with blood sample collection for humoral immune response and for RSV-A/B neutralizing titers, the following analysis will be performed by group:

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. SRR and 95% CI will be tabulated.

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

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

e. MGIs and their 95% CIs will be tabulated.

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

g. Results will be reported using both ED60 and CCI [redacted] units.

4.3.3. Additional considerations

4.3.3.1. Atrial Fibrillation (AF) AESIs

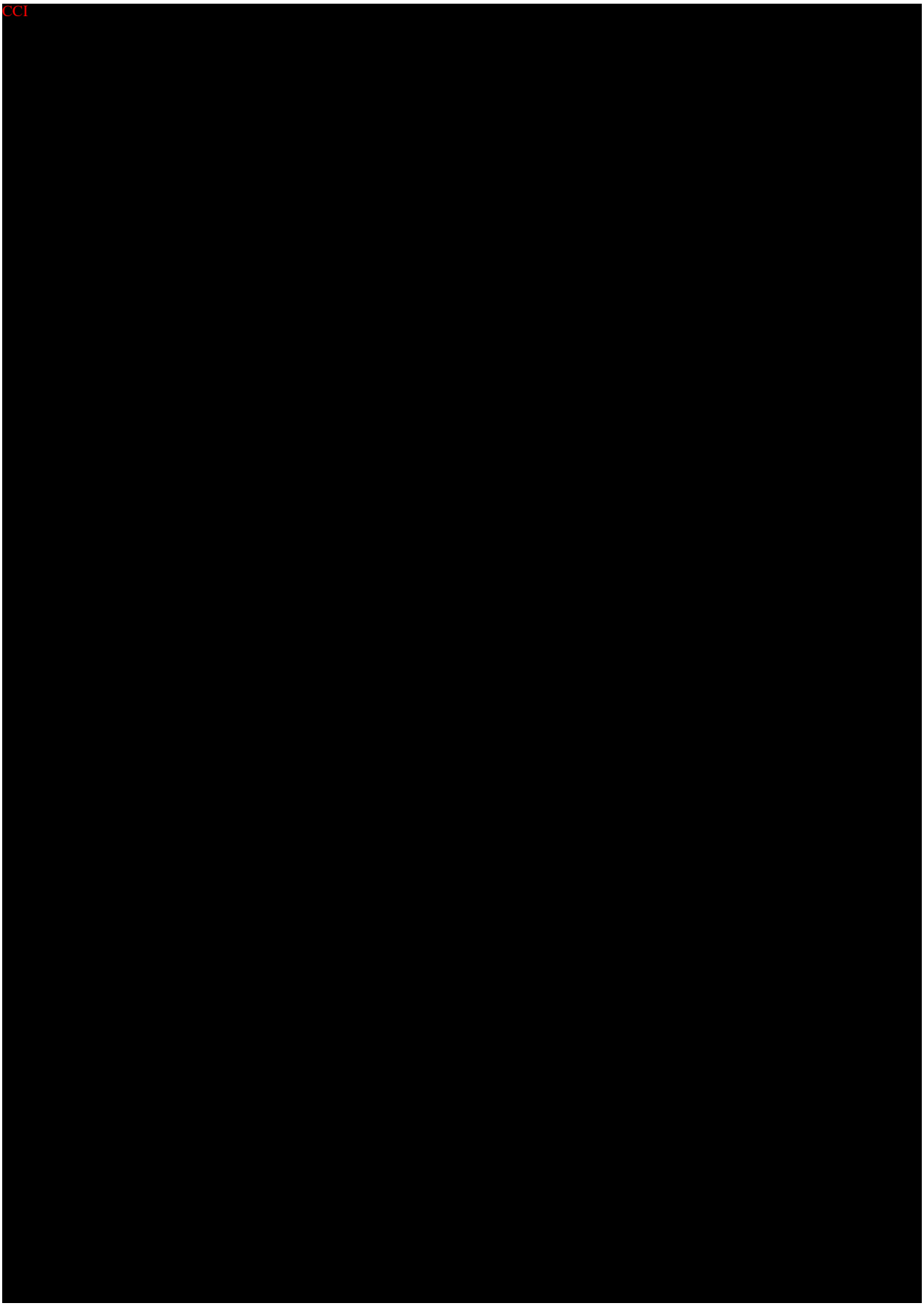
Potential AF AESIs will be identified through the MedDRA preferred term of interest atrial fibrillation (10003658). Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF. Additional analysis might be performed on those additional data collected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

4.4. Tertiary Endpoint Analyses

CCI [redacted]

CCI



CCI [redacted]

4.5. Other Safety Analyses

Not applicable.

4.6. Other Analyses

4.6.1. Subgroup analyses

4.6.1.1. Immunogenicity analysis by age at vaccination

As exploratory analysis, the descriptive within group immunogenicity analysis (humoral results) points a, b, c, e (except the graphical displays) and g described in Section 4.3.2.2.2 will also be generated by age at vaccination: 18-49 YOA, 60-69 YOA and ≥70 YOA.

CCI [redacted]

4.7. Interim Analyses

4.7.1. Sequence of analysis

The analyses will be performed stepwise:

- **Day 31 (Part A):** 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 in Part A. This analysis will be considered as final for the primary endpoints.
- **Month 6 (Part A):** If required, a safety analysis can be performed when safety data up to Month 6 are available and as clean as possible, for all participants in Part A.
- **Day 31 (Part B):** If required, a safety analysis can be performed when safety data up to Visit 2 (Day 31) are available and as clean as possible, for all participants in Part B. This analysis may be combined with Month 6 safety analysis for Part A.
- **Month 6 (Part A):** If required an immunogenicity analysis can be performed when all data for secondary endpoints up to study conclusion (Visit 3, Month 6) are available and as clean as possible, for all participants in Part A.

- An **EOS** analysis will be performed when all immunogenicity and safety data up to study conclusion (Visit 3/Contact, Month 6) will be available for all participants in Part A and Part B.
- If the data of different analyses become available around the same timepoint, these analyses can be combined into one analysis.

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: 18 Dec 2023).

5. SAMPLE SIZE DETERMINATION

The target sample size for the study is approximately 850 participants: 425 participants in Cohort 1 (RSV-A-AIR [18-49 YOA group]) and 425 participants in Cohort 2 (RSV-OA [≥60 YOA group]), to obtain at least 722 evaluable participants (361 participants in the RSV-A-AIR [18-49 YOA] cohort and 361 participants in the RSV-OA [≥60 YOA] cohort) for the evaluation of the primary objectives, assuming that approximately 15% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

The power to demonstrate the primary NI objectives following the hierarchical testing procedure described in Section 2.1 is presented in Table 6.

Table 6 Power for primary objectives of non-inferiority of the humoral immune response after RSVPreF3 OA vaccine between the RSV-A-AIR (18-49 YOA) Cohort 1 to RSV-OA (≥60 YOA) Cohort 2 for 361 evaluable participants per group

Objective	Standard deviation (SD) of log10 titers / SRR (%)	Non-inferiority margin	Type II Error	Power[1]
NI for RSV-A strain				
GMT RSV-A	SD=0.45	1.5	0.05	99.95%
SRR RSV-A	SRR=81.6%[2]	10%	6.92	93.08%
Global power for RSV-A strain				**93%**
NI for RSV-B strain				
GMT RSV-B	SD=0.45	1.5	0.05	99.95%
SRR RSV-B	SRR=78.7%[2]	10%	9.56	90.44%
If non-inferiority is demonstrated for RSV-A, global power for RSV-B strain				**90%**

NI=Non-inferiority; SRR=Seroresponse rate; GMT=Geometric mean titer; RSV=Respiratory syncytial virus

[1]Pass 2019 1-sided alpha=2.5% for each endpoint (GMT ratio and SRR difference), two-Sample T-Tests for Non-Inferiority assuming equal variance for group GMT ratios and Miettinen and Nurminen for Non-Inferiority tests for group SRR difference, Non-inferiority limit=0.176 (=log10(1.5)) for group GMT ratios

[2]Reference from RSV OA=ADJ-006

For the evaluation of reactogenicity and safety, the sample size of 1025 participants in combined Cohorts 1 and 3 (RSV-A-AIR group) has 64% and 87% probability of observing at least one vaccinated participant with AE if the true AE incidence rate is 0.1% and 0.2% respectively. This probability increases to at least 95% for true AE incidence rates ≥0.3%.

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. This analysis will be based on the ES, PPS and on the CCI subset of the ES and PPS for all the parameters except vital signs. The vital signs will be summarized based on the ES. If the summary of demographic characteristics for public disclosure meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version will be produced.

The following age categories will be considered in the analysis: 18-49 YOA, 60-69 YOA, ≥70 YOA and ≥80 YOA. In addition, for web posting purposes: 18-64 YOA, 65-84 YOA and ≥85 YOA.

The number and percentages of participants with medical history classified by the MedDRA Primary SOC, HLT and PTs will be tabulated by group for the ES. The same tabulation will be done for the ongoing baseline chronic diseases of interest.

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 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 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. Prior and 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 for the ES.

6.1.6. Concomitant Vaccinations

The number and percentage of participants and doses with concomitant vaccination during the 30-day follow-up period will be tabulated with exact 95% CI per study group for the ES.

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

6.2.1. Study Level compliance

An eDiary will be used in this study to capture solicited administration site or systemic events. All solicited events that occur during the four days following administration of the dose of the study intervention (Day 1 to Day 4) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this time frame. Daily eDiary compliance will be checked by the investigator or delegate on the eDiary portal. In case of non-compliance, the investigator should contact the participant within 36 hours to remind the importance of daily entries. After review and verbal discussion of the eDiary entries with the participant, if there are clear eDiary errors/omissions the investigator will complete his/her own assessment within 36 hours in the relevant sections of the eCRF.

During the enrolment period a review of the eDiary compliance during the 4-day follow-up period will be conducted by the central monitoring team for follow-up with the sites if needed.

eCOA compliance for *each day* of the 4-day follow-up period is defined as:

$$\frac{Number\ of\ participants\ with\ the\ eDiary\ completed\ for\ the\ corresponding\ day}{Expected\ number\ of\ participants\ with\ the\ eDiary\ completed\ for\ the\ corresponding\ day}$$

eCOA compliance for the overall 4-day follow-up period is defined as:

$$\frac{Number\ of\ participants\ with\ the\ eDiary\ completed}{Expected\ number\ of\ participants\ with\ the\ eDiary\ completed}$$

The above eCOA compliance will be calculated using the participant entries, with Quality Tolerance Limits (QTLs) defined as: 90% (action limit), 75% (critical limit)

6.2.2. Endpoint Level Compliance

In terms of compliance for each of Days 1-4, the number/percentage of completed eDiaries will be summarized by group and by day, using a frequency table. For each day, the numerator will be the number of participants who completed the eDiary on the specific day and the denominator will be the number of expected completed eDiaries on the specific day (i.e., the number of participants). An overall compliance for Day 1 to Day 4 will also be summarized. The numerator will be the sum of each numerator and the denominator will be the sum of each denominator from the daily compliance. In addition,

the compliance on the 4 consecutive days (Day 1 to Day 4) will be summarized. The numerator will be the number of participants who completed the 4 eDiaries for Day 1 to Day 4. The denominator will be the number of participants. If this compliance on the 4 consecutive days is less than 90%, a sensitivity analysis which includes only participants who completed the 4 eDiaries for Day 1 to Day 4 will be performed for the analysis of incidence of solicited administration site and systemic events within the 4-day follow-up period after vaccination.

For compliance of each day from Day 1 onwards, the number/percentage of completed eDiaries will be summarized by group and by symptom, using a frequency table. The denominator for each symptom will be the number of expected completed diaries (i.e., the number of symptom days from Day 1 onwards) and the numerator will be the number of symptom diaries completed for these expected symptom days. This will be summarized for all participants and for the participants from Cohort 3 enrolled as of 8August24, as from then the eDiary alerts for participants from Day 5 onwards were activated in the vendor system.

For compliance of each day from Day 5 onwards, the number/percentage of completed eDiaries will be summarized by group and by symptom, using a frequency table. The denominator for each symptom will be the number of expected completed diaries (i.e., the number of symptom days from Day 5 onwards) and the numerator will be the number of symptom diaries completed for these expected symptom days. This will be summarized for all participants and for the participants from Cohort 3 enrolled as of 8August24, as from then the eDiary alerts for participants from Day 5 onwards were activated in the vendor system.

For the above summaries, the daily assessment from the investigator (either to correct the participant entry or to replace a missing participant entry) will take precedence over the participant's entry only when the investigator assessment is done up to 36 hours after 23h59 of the specified day.

The number/percentage of daily assessments from the investigator/delegate within 36 hours will be summarized by group and by symptom using a frequency table. The denominator for each symptom will be the number of entries (by either the participant or investigator within 36 hours).

The reasons for investigator/delegate assessment will also be summarized by group and by symptom using a frequency table.

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. Handling of missing data

6.3.2.1. 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.

6.3.2.2. 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).

6.3.2.3. Daily recording of solicited events

For the analysis of solicited events, the daily assessment from the investigator (either to correct the participant entry or to replace a missing participant entry) will take precedence over the participant's entry only when the investigator assessment is done up to 36 hours after 23h59 of the specified day.

In case of missing/incomplete dates or times of either participant entries or investigator assessments, rules have been put in place to decide whether or not to use the investigator assessment. These derivation rules will be part of the ADaM specifications.

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
Grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

6.3.2.4. 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.

6.3.3. Data derivation

6.3.3.1. Age at vaccination in years and age category

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

6.3.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

6.3.3.3. 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

6.3.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

6.3.3.5. 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

6.3.3.6. 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

6.3.3.7. 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 6.3.3.6 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.3.3.8. 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).

6.3.3.9. 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 – Start date + 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, considering the investigator assessment within 36h and the intensity of the symptom.
- A missing start date will be imputed with the vaccination date.
- The number of days with grade 3 solicited symptom will be defined considering each day with a known grading=3, irrespective of whether the days are consecutive.

To account for missing eDiary data as of day 5 onwards (due to non-activation of the eDiary alerts for participants from day 5 onwards in the vendor system), a sensitivity analysis will be performed using the below definition of duration:

- The duration of a solicited AE with at least one day Grade > 0 is defined as End date– Start date + 1, with Start date defined as the first day with the symptom and End date defined as the day before the first occurrence of the symptom (in or beyond the solicited period) equals ‘N’ with no days having occurrence ‘Y’ afterwards.
- A missing start date will be imputed with the vaccination date.
- If a solicited event is still not reported as ‘N’ at day 30, the end date will be considered equal to vaccination date + 29 days.

6.3.3.10. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. 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 (Erythema)	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.

6.3.3.11. 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)

6.3.4. Display of decimals

6.3.4.1. Percentages

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

6.3.4.2. 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.

6.3.4.3. 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.

CCI

7. REFERENCES

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