Statistical Analysis Plan Amendment 1

Study ID: 221265

Official Title of Study: A Phase 3, randomized, placebo-controlled, observer-blind study in India to evaluate immune response, reactogenicity and safety of a single intramuscular dose of RSVPreF3 OA investigational vaccine when administered to older adults ≥60 years of age and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.

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TITLE PAGE

Protocol Title:	A Phase 3, randomized, placebo-controlled, observer-blind study in India to evaluate immune response, reactogenicity and safety of a single intramuscular dose of RSVPreF3 OA investigational vaccine when administered to older adults ≥60 years of age and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.
Study Number:	221265
Compound Number:	GSK3844766A
Abbreviated Title:	RSV OA=ADJ-024

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
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
DCF	Data Change Form
eCRF	electronic Case Report Form
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
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	05 August 2024	Protocol amendment 1 19 April 2024 (v1.0)	Not Applicable	Original version
SAP amendment 1	02 Dec 2024	Protocol amendment 1 19 April 2024 (v1.0)	Changes for solicited events analysis (Section 4.3.2.1) and End point level compliance (Section 6.2.2) Changes for duration analysis (Section 6.3.3.9) and missing data for solicited events (Section 6.3.2.3) Added Section 6.3.2.2 on handling of missing laboratory data.	To align with the latest updates in the RSV OA project.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for RSV OA=ADJ-024 (221265).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
To evaluate the humoral immune response following administration of a single dose of the RSVPreF3 OA investigational vaccine.	• RSV-A and RSV-B neutralizing titers pre-study intervention administration and at 1 month after study intervention administration.
Secondary	
To evaluate the safety and reactogenicity following administration of a single dose of the RSVPreF3 OA investigational vaccine.	• Occurrence of 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). • 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 after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (Month 6).

Primary estimand (immunogenicity)

The primary clinical question of interest is to evaluate humoral immunogenicity of a single dose of RSVPreF3 OA investigational vaccine administered in older adults ≥60 YOA, and in adults aged 50-59 YOA at increased risk of RSV-LRTD in the Indian population, when participants are vaccinated as per study protocol.

The primary estimand is described by the following attributes:

- **Population:** Indian OA ≥60 YOA and adults aged 50-59 YOA at increased risk of RSV-LRTD at the time of study intervention administration.
- **Endpoint (variable):** RSV-A and RSV-B neutralizing titers (expressed in ED60) measured at baseline (Day 1) and 1 month (Day 31) after the study intervention administration, fold increase in RSV-A and RSV-B neutralizing titers from Day 1 to Day 31, seroresponse in RSV-A and RSV-B neutralizing titers from Day 1 to Day 31.
- **Treatment condition:** RSVPreF3 OA investigational vaccine or Placebo at Day 1.

- **Intercurrent Events (ICEs) and strategies:** A hypothetical strategy will be used to manage the intercurrent events. Data collected after ICEs will be excluded from the analysis.

  The following intercurrent events will lead to data exclusion from the assessment of immunogenicity:

  - Medical condition forbidden by the protocol.
  - Vaccine and/or medication forbidden by the protocol.

- **Population level summary:** GMT with 95% CI at Day 1 (baseline) and at Day 31, MGI with 95% CI at Day 31, and SRR with 95% CI at Day 31 will be summarized separately for RSV-A/B antigen and by treatment group.

  MGI is defined as the geometric mean of the within-participant ratios of post-vaccination titers over pre-vaccination titers.

  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.

Rationale for estimand: The above estimand addresses the objective of evaluating humoral immunogenicity in Indian OA ≥ 60 YOA and adults aged 50-59 YOA at increased risk of RSV-LRTD after administration of a single dose of RSVPreF3 OA investigational vaccine without confounding of other medications/vaccinations/medical condition on the target population since the impact of developing medical condition forbidden by protocol and use of forbidden medications and vaccinations is anticipated to modify the vaccine effect.

Secondary estimand (safety)

The primary question of interest is to evaluate the reactogenicity and safety of RSVPreF3 OA investigational vaccine in adults aged 50-59 YOA at increased risk of RSV-LRTD and ≥ 60 YOA.

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine or Placebo at Day 1.	Indian adults aged 50-59 YOA at increased risk of RSV-LRTD and ≥ 60 YOA at the time of study intervention administration.	• 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.	Taking prohibited medication /vaccine or forbidden 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 treatment group who report each of the endpoints.

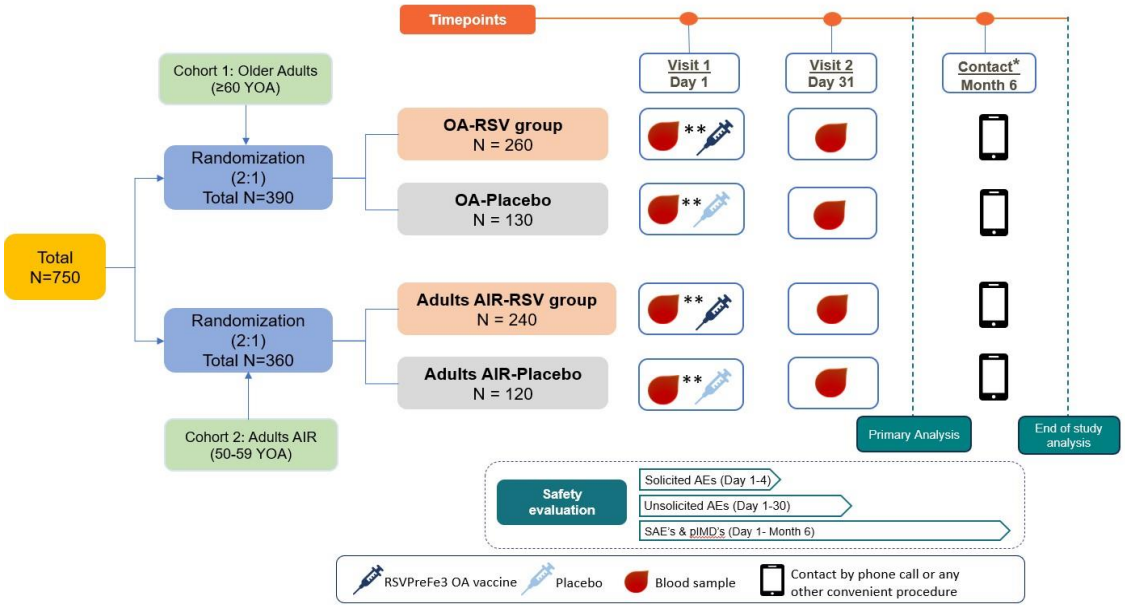
Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events		
			Description	Handling strategy	
		• Occurrence of unsolicited AEs within 30 days after study intervention administration. • Occurrence of SAEs after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (Month 6).			

AE, Adverse event; pIMD, Potential immune-mediated Disease; SAE, Serious adverse event.

The estimand for reactogenicity and safety aim at evaluating incidence in the randomized and vaccinated adults aged 50-59 YOA at increased risk of RSV-LRTD and ≥ 60 YOA.

1.2. Study Design

Overview of Study Design and Key Features



N: Number of participants; OA: Older adults; AEs: Adverse events; SAEs: Serious adverse events; pIMDs: potential immune-meditated diseases; YOA: Years of age.
AIR: At increased risk-Participants with underlying medical conditions such as chronic pulmonary and cardiovascular disease, diabetes mellitus types 1 and 2, chronic liver and renal diseases.
* Contact by telephone call or any other convenient procedure for the safety follow-up will take place 6 months after study intervention administration.
**Blood sample at Visit 1 (Day 1) should be collected prior to study intervention administration.

Overview of Study Design and Key Features

Table 1 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1 (Day 1)→ Visit 2 (Day 31)	30 days	30-42 days
Visit 1 (Day 1)→ Contact (6 months post-study intervention administration)	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 3, randomized, multicenter, placebo-controlled, observer-blind study in India. Duration of study: The total duration of the study, per participant, will be approximately 6 months.
Study intervention	Participants will receive 1 dose of RSVPreF3 OA investigational vaccine or Placebo at Visit 1 (Day 1).
Study intervention Assignment	Approximately 750 eligible participants aged ≥60 YOA and 50-59 YOA at increased risk of RSV-LRTD will be enrolled in 2 cohorts, as follows: Cohort 1 (Older adults): Approximately 390 eligible participants aged ≥ 60 YOA will be enrolled and randomly assigned (2:1) to 2 study groups, as follows: • OA-RSV group: participants will receive a single dose of the RSVPreF3 OA investigational vaccine on Visit 1 (Day 1). • OA-Placebo group: participants will receive a single dose of placebo (saline) on Visit 1 (Day 1). Cohort 2 (Adults-AIR): Approximately 360 eligible participants aged 50-59 YOA at increased risk of RSV-LRTD will be enrolled and randomly assigned (2:1) to 2 study groups, as follows: • Adults-AIR-RSV group: participants will receive a single dose of the RSVPreF3 OA investigational vaccine on Visit 1 (Day 1). • Adults-AIR-Placebo group: participants will receive a single dose of placebo (saline) on Visit 1 (Day 1). Cohorts and age categories for Cohort 1 will be considered as stratification factors. Enrollment rules will be applied for the proportion of participants enrolled within disease categories (Cohort 2) and within each age category of 60-69, 70-79 and ≥ 80 YOA (Cohort 1). Refer to Section 4.1.1 of the protocol.

Overview of Study Design and Key Features	
Day 31, Primary Completion 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. This analysis will be considered as final for those endpoints.
Month 6, End of Study (EoS) Analysis	An EoS analysis will be performed when data for the secondary endpoints up to study end/Month 6 Contact are available for all participants. This analysis will be considered as final for those endpoints.

2. STATISTICAL HYPOTHESES

The primary objective, as outlined in Section 1.1, will be addressed using an estimation approach with no hypothesis testing.

2.1. Multiplicity Adjustment

Not applicable as analyses in this study are descriptive.

3. ANALYSIS SETS

Table 2 Analysis set

Analysis set	Description
Screened Set	All participants who were screened for eligibility.
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 enrollment) are excluded from the Enrolled Set as they did not enter the study.
ES	All participants who received the study intervention. Analysis per group is based on the administered intervention.
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 the administered intervention.

* 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, 1050, 1060, 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, 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

Table 3 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
1050	Randomization failure: participant not randomized in the correct stratum	Visit 1	All	PPS
1060	Randomization code was broken	All	All	PPS
1070	Vaccine administration not according to protocol: • Participant was vaccinated with the correct vaccine but containing a lower volume.	Visit 1	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
	• 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			
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
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: • Blood sample planned at visit 1 is taken after vaccine administration. • Number of days between vaccination (Visit 1) and blood sample (Visit 2) is outside [30-42] days.	Visit 2	At the specific visit the condition is met	PPS
2100	Immunological results not available post-vaccination	Visit 2	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 (1-month 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 1-month post-vaccination titer (Visit 2, Day 31) over pre-vaccination (Visit 1, Day 1).
- In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the correct stratum for the ES.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value. In this study, the pre-dose assessment corresponds to 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

4.2.1. Definition of endpoints/estimands

Refer to Section 1.1 for the definition of primary immunogenicity endpoints/estimands.

4.2.2. Main analytical approach

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

For each timepoint with blood sample collection for humoral immune response and for each assay in ED60 (RSV-A/B neutralization), the following analysis will be performed by group:

- Percentage of participants with neutralizing titers equal to or above the technical assay cut-off and their exact 95% CI will be tabulated.
- GMTs and their 95% CI will be tabulated and represented graphically. GMTs will be computed by taking the anti-logarithm of the arithmetic mean of the log_{10}-transformed titers.
- Distribution of neutralizing titers will be displayed using reverse cumulative curves.
- MGIs will be tabulated with 95% CI. CIs for MGI will be based on a back transformation of CI for the mean of the difference between log_{10}-transferred values, assuming that log-transformed values are normally distributed with unknown variance.
- SRR and 95% CI will be tabulated.
- Any missing data will not be imputed.

4.2.3. Sensitivity analyses

No sensitivity analysis planned.

4.2.4. Additional analyses

Analyses described in Section 4.2.2 will also be performed using IU/ml unit.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoints/estimands

Refer to Section 1.1 for the definition of secondary reactogenicity and safety endpoints/estimands.

4.3.2. Main analytical approach

4.3.2.1. Safety analysis

The estimand analysis for reactogenicity and safety will be performed on the ES. 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 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.

4.3.3. 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/Exploratory Endpoint(s) Analyses

Not applicable.

4.5. Other Safety Analyses

Not applicable.

4.6. Other Analyses

Not applicable.

4.7. Interim Analyses

4.7.1. Sequence of analyses

The following analysis will be performed stepwise:

- **Day 31, Primary Completion 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. This analysis will be considered as final for those endpoints.

  Refer to Section 6.4 of protocol for details on the blinding strategy.

- **Month 6, EoS**: An EoS analysis will be performed when data for the secondary endpoints up to study end/Month 6 Contact are available for all participants. This analysis will be considered as final for those endpoints.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 19 April 2024).

5. SAMPLE SIZE DETERMINATION

The target sample size for the study is to enrol approximately 750 participants: i.e., approximately 390 participants in Cohort 1 (≥ 60 years of age, OA) and approximately 360 participants in Cohort 2 (50-59 years of age, AIR). Participants will be randomized in a 2:1 ratio within each cohort. Assuming approximately 15% attrition rate, approximately 220 participants in OA-RSV group, 110 participants in OA-Placebo group, 200 participants in Adults-AIR-RSV group and 100 participants in Adults-AIR-Placebo group are expected to be evaluable for the primary objective.

5.1. Evaluation of humoral response at Day 31 (primary objective)

5.1.1. Mean Geometric Increase (MGI, Day 31 over Day 1) in RSV-A and RSV-B neutralizing titers (ED60)

Table 4 presents the power to show that the LL of the 95% CI for MGI at one month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and MGI, in the OA-RSV group and in the Adults-AIR-RSV group. MGI is defined as the geometric mean of the within-participant ratios of post-vaccination titers (at Day 31) over pre-vaccination titers.

In the pivotal efficacy study RSV OA=ADJ-006, an MGI of 10.2 (95% CI, 9.5-11.0) and 8.6 (95% CI, 8.0-9.2) was observed at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 220 evaluable participants in RSV OA vaccination group, the study has at least 99% power to show that the LL of 95% CI for MGI is greater than or equal to 5-fold increase if the true MGI is at least 8-fold.

In the study RSV OA=ADJ-018, an MGI of 11.63 (95% CI, 10.52-12.86) and 9.05 (95% CI, 8.23-9.94) was observed in Adults-AIR-RSV group at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 200 evaluable participants in Adults-AIR-RSV vaccination group, the study has at least 99% power to show that the LL of 95% CI for MGI is greater than or equal to 5-fold increase if the true MGI is at least 8-fold.

Table 4 Power that the LL of the 95% CI for MGI in RSV-A/B neutralizing titers (ED60) at 1 month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and MGI.

Summary measure	Number of evaluable participants	Threshold	True MGI (Day 31 over Day 1)	Power (%)
MGI (fold increase of post vaccination Day 31 titers over pre-vaccination titer)	220 (OA-RSV group)	LL of 95% CI for MGI ≥4	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥5	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥6	8-fold	97.5
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥7	8-fold	44.5
			9-fold	92.9
			10-fold	99.8
	200 (Adults-AIR-RSV group)	LL of 95% CI for MGI ≥4	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥5	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥6	8-fold	99.0
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥7	8-fold	51.2
			9-fold	96.3
			10-fold	>99.9

Power computed using PASS 2019 software, Paired T-Tests for Superiority by a Margin, 1-sided alpha=2.5%; assuming a SD of 0.47 in OA RSV group and 0.41 in Adults-AIR-RSV group.

As reference, a SD of 0.47 and 0.45 for RSV-A and RSV-B antigen respectively was observed in the pivotal efficacy RSV OA=ADJ -006 study in terms of MGI in RSV A/B neutralizing titers at Day 31 compared to baseline. A MGI of 10.2 and 8.6 for RSV-A and RSV-B respectively was observed in the same study. A SD of 0.41 and 0.39 for RSV-A and RSV-B antigen respectively was observed in RSV OA=ADJ -018 study in terms of MGI in RSV A/B neutralizing titers at Day 31 compared to baseline. MGI of 11.63 and 9.05 for RSV-A and RSV-B respectively was observed in the same study in the Adults-AIR-RSV group.

5.1.2. Seroresponse rate (SRR) in RSV-A and RSV-B neutralizing titers (ED60) from Day 1 to Day 31

Table 5 presents the power to show that the Lower Limit (LL) of the 95% CI for SRR at one month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and SRR, in the OA-RSV group and in the Adults-AIR-RSV group. 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.

In RSV OA=ADJ-006, the pivotal efficacy study, a SRR of 81.6% (95% CI, 78.9-84.2) and 78.7% (95% CI, 75.8-81.4) was observed at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 220 evaluable participants in RSV OA vaccination group, the study has at least 99% power to show that the LL of 95% CI for SRR is above 60% if the true SRR is at least 75%.

In RSV OA=ADJ-018, a SRR of 86.9% (95% CI, 82.8-90.3) and 81.6% (95% CI, 77.1-85.6) was observed in Adults-AIR-RSV group at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 200 evaluable participants in Adults-AIR-RSV vaccination group, the study has at least 99% power to show that the LL of 95% CI for SRR is above 60% if the true SRR is at least 75%.

Table 5 Power that the LL of the 95% CI for SRR in RSV-A/B neutralizing titers (ED60) at 1 month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and SRR.

Summary measure	Number of evaluable participants	Threshold	True SRR (%)	Power (%)
SRR in RSV A / RSV-B neutralizing titers at Day 31 over pre-vaccination	220 (OA-RSV group)	LL of 95% CI for SRR ≥60%	75	99.7
			80	>99.9
			85	>99.9
		LL of 95% CI for SRR ≥65%	75	87.8
			80	99.9
			85	>99.9
		LL of 95% CI for SRR ≥67%	75	71.0
			80	99.1
			85	>99.9
		LL of 95% CI for SRR ≥70%	75	35.3
			80	92.2
			85	>99.9
		LL of 95% CI for SRR ≥72%	80	77.8
			85	99.7
		LL of 95% CI for SRR ≥75%	80	40.6
			85	96.0
	200 (Adults-AIR-RSV group)	LL of 95% CI for SRR ≥60%	75	99.6
			80	>99.9
			85	>99.9
		LL of 95% CI for SRR ≥65%	75	85.5
			80	99.8
			85	>99.9
		LL of 95% CI for SRR ≥67%	75	66.3
			80	98.4

Summary measure	Number of evaluable participants	Threshold	True SRR (%)	Power (%)
			85	>99.9
		LL of 95% CI for SRR ≥70%	75	34.6
			80	90.6
			85	99.9
		LL of 95% CI for SRR ≥72%	80	73.6
			85	99.5
		LL of 95% CI for SRR ≥75%	80	33.5
			85	92.8

Power computed using PASS 2019 software, Non-Inferiority Test for one proportion, 1-sided alpha=2.5%;
A SRR of 81.6% and 78.7% for RSV A and RSV B neutralizing titers was observed in RSV OA=ADJ-006 (212494) study. A SRR of 86.9% and 81.6% for RSV A and RSV B neutralizing titers was observed in RSV OA=ADJ-018 (219238) study in the Adults-AIR-RSV group.

5.2. Evaluation of reactogenicity and safety

Table 6 presents the probabilities to observe at least one participant with AE by group, for a range of true AE incidence rates.

The sample size of 260 participants in the OA-RSV group and 240 participants in the Adults-AIR-RSV group have, respectively, 72.8% and 70% probabilities of observing at least one vaccinated participant with the AE if the true AE incidence rate is 0.5%. This probability increases to at least 92.7% and 91% respectively for true incidence rates ≥1%.

Table 6 Probability (%) to observe at least one AE for a range of incidence rates.

AE incidence rate (%)	Probability§ (%) to observe at least one vaccinated participant with AE in OA-RSV group (N=260)	Probability§ (%) to observe at least one participant with AE in OA-Placebo group (N=130)	Probability§ (%) to observe at least one vaccinated participant with AE in Adults-AIR-RSV group (N=240)	Probability§ (%) to observe at least one participant with AE in Adults-AIR-Placebo group (N=120)
0.3	54.2	32.3	51.4	30.3
0.4	64.7	40.6	61.8	38.2
0.5	72.8	47.9	70.0	45.2
0.6	79.1	54.3	76.4	51.4
0.7	83.9	59.9	81.5	57.0
0.8	87.6	64.8	85.5	61.9
0.9	90.5	69.1	88.6	66.2
1.0	92.7	72.9	91.0	70.1
2.0	99.5	92.8	99.2	91.1
3.0	100	98.1	99.9	97.4

§Binomial distribution, N=Number of enrolled participants.

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 and Exposed Set.

6.1.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics (age at study entry, sex, race, ethnicity, vital signs, Body Mass Index (BMI), comorbidities and smoking status) will be summarized by group using descriptive statistics, as described in Section 4.1.1. This analysis will be based on the ES, 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 number and percentages of participants with medical history and pre-existing comorbidities classified by the MedDRA Primary SOC, HLT and PTs will be tabulated by group for the ES.

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 and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized 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 interview the participant within a 24-to-36-hour recall period to check on the reasons for non-compliance as well as to retrieve clinical information requested in the eDiary. In case of obvious error in the clinical data reported by the participant in the eDiary, the investigator should contact the participant within a 24-to-36-hour recall period to retrieve correct clinical information requested in the eDiary. Missing eDiary and wrong eDiary data submitted by the participant can be corrected in the EDC system, using the eDiary related eCRFs. Administrative changes (Meta Data) will be managed via Data Change Form (DCF).

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 eDairies 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.

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 dose

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 intervention' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study intervention' 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 study intervention' is selected, the imputed start date will match the vaccine dose given during that month. If 'before study intervention' 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 study intervention' is selected, the imputed start date will match the vaccine dose given during that year. If 'before study intervention' 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. Therefore, there might be some discrepancies between the age computed and the age categories (60-69 YOA, 70-79 YOA and ≥80 YOA) used in the GSK Randomization and Trial Supply Management (RTSM) system for participants in Cohort 1.

For the analysis, the age categories for participants in Cohort 1 will be determined according to the information entered in the RTSM system.

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.

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 eCRF 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.

6.3.5. Trademarks

In this document, vaccine is referred as RSVPreF3 OA vaccine. Trademark name is AREXVY.

Trademarks of the GlaxoSmithKline Group of Companies
AREXVY

7. REFERENCES

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