Statistical Analysis Plan Amendment 1

Study ID: 219815

Official Title of Study: A Phase 3, randomized, controlled, partially blind, immunobridging study to evaluate immunogenicity, reactogenicity, safety and the occurrence of RSV associated respiratory tract illness after administration of a single dose of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and older.

NCT number: NCT06551181

Date of Document: 06 Aug 2025

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase 3, randomized, controlled, partially blind, immuno-bridging study to evaluate immunogenicity, reactogenicity, safety and the occurrence of RSV associated respiratory tract illness after administration of a single dose of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and older.
Study Number:	219815
Compound Number:	GSK3844766A
Abbreviated Title:	RSV OA=ADJ-021

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	26 July 2024	Protocol Amendment 1 dated 15 February 2024	Not Applicable	Original version
SAP amendment 1	06 Aug 2025	Protocol Amendment 1 dated 15 February 2024	Define RSV positive for ARI confirmation, add Korea subgroup analysis, etc.	Based on updated information from Lab, Korea local requirement etc.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the clinical study report (CSR) for Study 219815 (RSV OA=ADJ-021). Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints and estimands
Co-primary Immunogenicity	
To demonstrate the non-inferiority (NI) of humoral immune response in Chinese older adults (OA) enrolled in the RSV OA group (China) compared to OA enrolled in the RSV OA group (Overseas), for the RSV-A strain after the RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titres expressed as group GMT ratio (RSV OA group [Overseas] / RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-A neutralization titres expressed as group seroresponse rate (SRR) difference (RSV OA group [Overseas] - RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration.
To demonstrate the NI of humoral immune response in Chinese OA enrolled in the RSV OA group (China), compared to OA enrolled in the RSV OA group (Overseas), for the RSV-B strain after the RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titres expressed as group GMT ratio (RSV OA group [Overseas] / RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralization titres expressed as group SRR difference (RSV OA group [Overseas] - RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration.
Secondary Immunogenicity (descriptive)	
To evaluate the humoral immune response in Chinese OA enrolled in the RSV OA group (China) compared to OA enrolled in the RSV OA group (Overseas), up to 6 months post vaccination.	• RSV-A and RSV-B neutralization titres expressed as GMT, at baseline, 1 month and 6 months after the RSVPreF3 OA investigational vaccine administration. • RSV-A and RSV-B neutralization titers expressed as SRR, 1 month and 6 months after the RSVPreF3 OA investigational vaccine administration.
To evaluate the humoral immune response in Chinese OA enrolled in the RSV OA group (China) compared to historical data generated in the immunogenicity subset of the global efficacy study RSV OA=ADJ-006.	• RSV-A and RSV-B neutralization titres expressed as group GMT ratio (RSV OA=ADJ-006 / RSV OA Vaccine group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-A and RSV-B neutralization titres expressed as group SRR difference (RSV OA=ADJ-006 - RSV OA Vaccine group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration.
Secondary ARI surveillance (Study participants in China only)	
To describe the RSV-confirmed ARI and RSV confirmed LRTD in RSV OA Vaccine group (China) and Placebo group (China).	Occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI and LRTD, according to the case definition. In study participants in China with RT-PCR-confirmed RSV A and/or B associated ARI and LRTD cases: • Duration of episodes. • Reported symptoms/signs. • ARI/LRTD severity. • Frailty status.

Objectives	Endpoints and estimands
Secondary Safety	
To evaluate the safety and reactogenicity following the administration of the investigational RSVPreF3 OA vaccine.	For RSV OA group (China) and Placebo group (China): • Percentage of participants reporting each solicited administration site event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 subsequent days). • Percentage of participants reporting each solicited systemic event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to 6 months after study intervention. • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to 6 months after study intervention. • Percentage of participants reporting SAEs related to study intervention after study intervention administration (Day 1) up to study end. • Percentage of participants reporting pIMDs related to study intervention after study intervention administration (Day 1) up to study end. • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end. For RSV OA group (Overseas): • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting SAEs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting pIMDs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 6).

PRIMARY ESTIMAND

The primary clinical question of interest is: to evaluate the non-inferiority (NI) of the humoral immune response after RSVPreF3 OA investigational study intervention in Chinese older adult with ≥60 YOA compared to RSV-OA overseas group, when vaccinated as per protocol.

The primary immunogenicity estimand is described in Table 1:

Table 1 Study estimand - primary objective

Attributes					
Treatment	Population	Endpoint (variable)	Intercurrent events (ICEs)		Population level summary
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine at Day 1.	Chinese and Oversea OA with ≥60 YOA	• RSV-A neutralizing titers at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-A seroresponse at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralizing titers at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-B seroresponse at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration.	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 at 1 month (Day 31) after RSVPreF3 OA investigational vaccine between the RSV-OA overseas group and RSV-OA China group.

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

CI=Confidence interval; GMT=Geometric mean titer; OA=Older adults; YOA=Years of age

Rationale for the primary estimand:

The primary estimand address the objective of demonstrating the NI of humoral immune response in RSV OA Chinese participants with ≥60 YOA compared to RSV-OA overseas group, for the RSV-A and RSV-B strains, 1 month after RSVPreF3 OA investigational vaccine administration. This is done by estimating the treatment 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.

ESTIMAND FOR SECONDARY IMMUNOGENICTY

The clinical question of interest is:

- to evaluate the humoral immune response after RSVPreF3 OA investigational vaccine administration in Chinese older adult with ≥60 YOA compared to RSV-OA overseas group, when vaccinated as per protocol, up to 6 months post-vaccination.
- to evaluate the humoral immune response after RSVPreF3 OA investigational vaccine administration in Chinese older adult with ≥60 YOA compared to RSV-OA immunogenicity subset of global efficacy study RSV OA=ADJ-006, when vaccinated as per protocol.

The estimand for secondary immunogenicity objectives are described in Table 2:

Table 2 Study estimand - secondary immunogenicity objective

Attributes					
Treatment	**Population**	**Endpoint (variable)**	**Intercurrent events (ICEs)**		**Population level summary**
			Description	**Handling strategy**	
RSVPreF3 OA investigational vaccine at Day 1.	Chinese and Oversea OA with ≥60 YOA	• RSV-A neutralizing titers at baseline, 1 month (Day 31) and 6 months after the RSVPreF3 OA investigational vaccine administration. • RSV-A seroresponse at 1 month (Day 31) and 6 months after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralizing titers at baseline, 1 month (Day 31) and 6 months after the RSVPreF3 OA investigational vaccine administration. • RSV-B seroresponse at 1 month (Day 31) and 6 months after the RSVPreF3 OA investigational vaccine administration.	Taking prohibited medication /vaccine or intercurrent medical condition prior to analysis timepoint.	Data collected after ICEs will be excluded from the analysis (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE.	GMTs with 95% CI for RSV-A and RSV-B neutralizing titers at baseline, 1 month (Day 31) and 6 month after RSVPreF3 OA investigational vaccine administration Seroresponse rate (SRR) with 95% CI for RSV-A and RSV-B neutralizing titers at 1 month (Day 31) and 6 months after RSVPreF3 OA investigational vaccine administration
RSVPreF3 OA investigational vaccine at Day 1.	Chinese OA with ≥60 YOA, Oversea OA with ≥60 YOA (from RSV OA immunogenicity subset of the global efficacy study RSV OA=ADJ-006)	• RSV-A neutralizing titers at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-A seroresponse at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-B neutralizing titers at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration. • RSV-B seroresponse at 1 month (Day 31) after the RSVPreF3 OA investigational vaccine administration.	Taking prohibited medication /vaccine or intercurrent medical condition prior to Day 31.	Data collected after ICEs will be excluded from the analysis (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE.	Ratio of GMTs with 95% CI and difference in seroresponse rate (SRR) with 95% CI for RSV-A and RSV-B neutralizing titers at 1 month (Day 31) after RSVPreF3 OA investigational vaccine between RSV OA=ADJ-006 and RSV-OA China group.

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

CI=Confidence interval; GMT=Geometric mean titer; OA=Older adults; YOA=Years of age

Rationale for the estimands for secondary immunogenicity:

The estimands for secondary immunogenicity address the objective of evaluating the humoral immune response after RSVPreF3 OA investigational vaccine administration in Chinese older adult with ≥60 YOA and in RSV OA overseas participants or in the immunogenicity subset of the global efficacy study RSV OA=ADJ-006, for the RSV-A and RSV-B strains. This is done by estimating the treatment 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.

ESTIMAND FOR SECONDARY ARI SURVEILLANCE

The clinical question of interest is to describe the RSV-confirmed ARI and RSV confirmed LRTD in RSV OA Vaccine group (China) and Placebo group (China).

The estimand for secondary ARI surveillance is described in Table 3:

Table 3 Study estimand - secondary ARI surveillance objective

Attributes					
Treatment	**Population**	**Endpoint (Variable)**	**Intercurrent events (ICEs)**		**Population level summary**
			Description	**Handling strategy**	
RSVPreF3 OA investigational vaccine at Day 1.	China older adult with ≥60 YOA	Occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI and LRTD, according to the case definition. In study participants in China with RT-PCR-confirmed RSV A and/or B associated ARI and LRTD cases: • Duration of episodes. • Reported symptoms/signs. • ARI/LRTD severity. • Frailty status.	Taking prohibited medication /vaccine or intercurrent medical condition during study duration.	All the data collected for the variable of interest are used regardless of whether the intercurrent event occurs (treatment policy strategy).	The percentage of participants by group who report each of the endpoints except duration of episodes. Group mean of duration of episodes

RSV=Respiratory syncytial virus; YOA=Years of age.

The estimands for secondary ARI surveillance is to characterize the RSV-confirmed ARI and LRTD cases in Chinese older adult.

ESTIMANDS FOR SAFETY

The clinical question of interest is to evaluate the safety and reactogenicity after RSVPreF3 OA investigational vaccine administration in vaccinated Chinese older adults.

The estimands for safety evaluation are described in Table 4:

Table 4 Study estimand - secondary safety objective

Attributes					
Treatment	**Population**	**Endpoint (Variable)**	**Intercurrent events (ICEs)**		**Population level summary**
			Description	**Handling strategy**	
RSVPreF3 OA investigational vaccine at Day 1.	Chinese and overseas OA with ≥60 YOA	For RSV OA group (China) and Placebo group (China): • Occurrence of each solicited administration site event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 subsequent days). • Occurrence of each solicited systemic event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 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 SAEs after study intervention administration (Day 1) up to 6 months after study intervention. • Occurrence of pIMDs after study intervention administration (Day 1) up to 6 months after study intervention. • Occurrence of SAEs related to study intervention after study intervention administration (Day 1) up to study end. • Occurrence of pIMDs related to study intervention after study intervention administration (Day 1) up to study end. • Occurrence of any fatal SAEs after study intervention administration (Day 1) up to study end.	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 strategy).	The percentage of participants by group who report each of the endpoints.

Attributes					
Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		Population level summary
			Description	Handling strategy	
		For RSV OA group (Overseas): • 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). • Occurrence of SAEs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of pIMDs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of any fatal SAEs after study intervention administration (Day 1) up to study end (Month 6).			

AE=Adverse event; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

The estimand for safety and reactogenicity aim at evaluating incidence in the randomized and vaccinated Chinese older adult.

1.2. Study Design

Overview of Study Design and Key Features

Figure 1 Study design overview

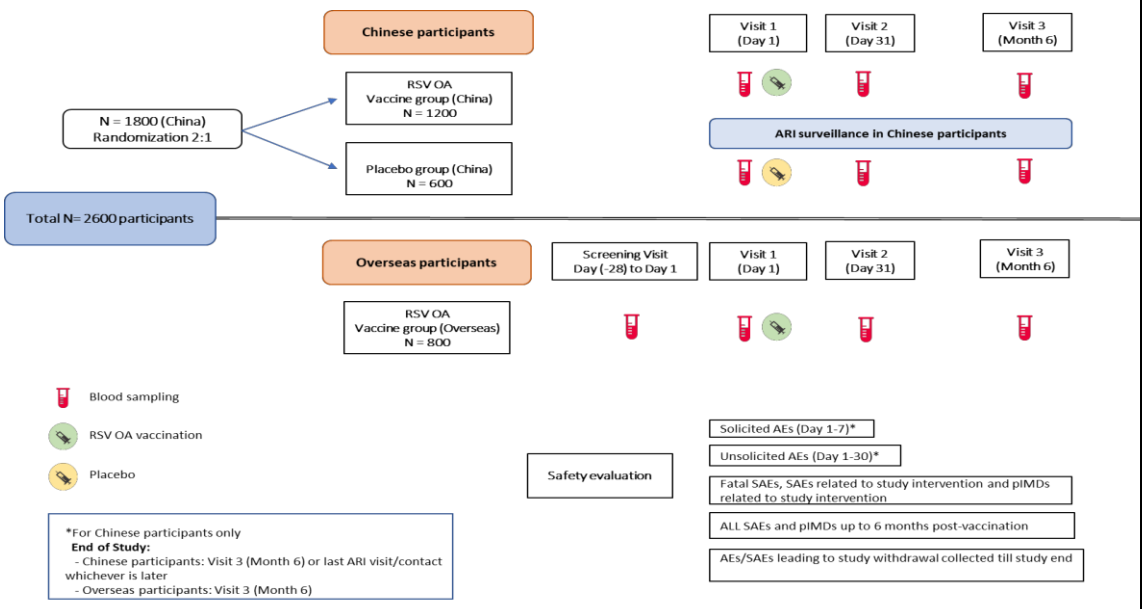
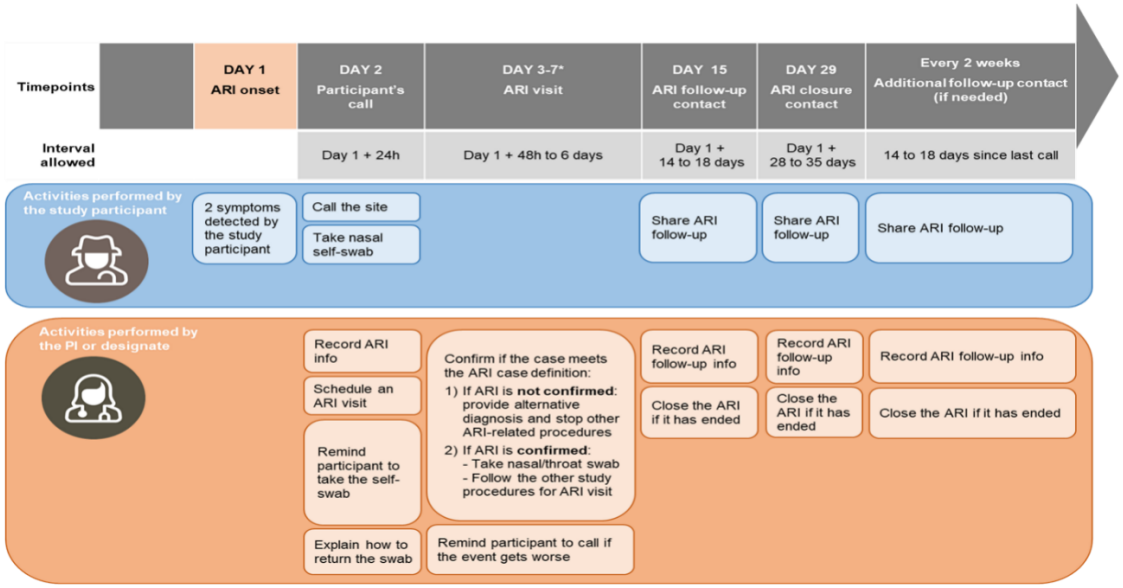


Figure 2 ARI capture and follow-up



Design Features	Phase 3, randomized, controlled, partial blind study with 3 parallel treatment groups. The total duration of the study per participant will be approximately 7 months.
Study intervention	Study participants in China will be randomly assigned (2:1) to receive 1 single dose of investigational RSVPreF3 OA vaccine or Placebo on Visit 1 (Day 1).

Overview of Study Design and Key Features	
	The participants in overseas country will receive 1 single dose of investigational RSVPreF3 OA vaccine on Visit 1 (Day 1).
Study intervention Assignment	The study will aim to enroll approximately 2600 participants, i.e., 1800 participants in China [2:1 randomization allocation between RSV OA group (China) and Placebo group (China)], 800 participants in RSV OA group (Overseas).
Day 31 (PCA) analysis	The first analysis will be performed when immunogenicity and reactogenicity data up to Visit 2 (Day 31) are available. This analysis will be considered as final for those data. Safety data up to database lock point will also be included into the analysis.
Month 6 Safety Analysis	An optional analysis may be conducted when safety data up to Month 6 are available.
End of Study Analysis	The final analysis will be performed when all data for the secondary endpoints of descriptive immunogenicity at Month 6, ARI surveillance and safety up to study conclusion are available.

2. STATISTICAL HYPOTHESES

Statistical hypotheses provided in Table 5 are associated to the confirmatory co-primary NI objectives.

Table 5 Study null hypothesis

Null hypothesis	Description
H1	The GMT ratio for RSV-A neutralization titers (RSV OA group [Overseas] / RSV OA group [China]) is > 1.5 at 1 month post RSVPreF3 OA vaccine administration.
H2	The SRR difference for RSV-A neutralization titers (RSV OA group [Overseas] - RSV OA group [China]) is > 10% at 1 month post RSVPreF3 OA vaccine administration.
H3	The GMT ratio for RSV-B neutralization titers (RSV OA group [Overseas] / RSV OA group [China]) is > 1.5 at 1 month post RSVPreF3 OA vaccine administration.
H4	The SRR difference for RSV-B neutralization titers (RSV OA group [Overseas] - RSV OA group [China]) is > 10% at 1 month post RSVPreF3 OA vaccine administration.

GMT=Geometric mean titer; OA=Older adults; RSV=Respiratory syncytial virus; SRR=Seroresponse rate.

2.1. Multiplicity Adjustment

Each hypothesis will be tested at 2.5% (1-sided), no multiplicity adjustment is needed.

3. ANALYSIS SETS

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 enrolment) are excluded from the Enrolled Set as they did not enter the study.
Exposed Set (ES)	All participants who received the study intervention. Analysis per group is based on the administered intervention.
Per-Protocol Set* (PPS)	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, 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 Per-Protocol Set will be defined by timepoint.

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes in Table 6 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 Exposed Set

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 Per-Protocol Set

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

- For codes 800, 900, 1030, 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 6 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
1060	Randomization code was broken (Chinese participants only)	All	All	PPS
1070	Vaccine administration not according to protocol: • Participant was vaccinated with the correct vaccine but containing a lower volume • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular • Wrong reconstitution of administered vaccine	Visit 1	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
2020	All Pre-dose results are missing	Visit 1	At the specific visit the condition is met	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
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. Treatment group names

For simplification the treatment group names RSV OA Overseas, RSV OA China, Placebo China will be used in the subsequent SAP sections and data displays:

Treatment group names in the protocol	Treatment group names in SAP & data displays
RSV OA group (Overseas)	RSV OA (Overseas)
RSV OA group (China)	RSV OA (China)
Placebo group (China)	Placebo (China)
The immunogenicity subset of the global efficacy study RSV OA=ADJ-006	RSV OA Overseas (006 study)

4.1.2. General Methodology

- Unless otherwise specified, data summaries will be presented by treatment groups when applicable, in the order of RSV OA Overseas, RSV OA China, Placebo China.
- Data summaries with both RSV OA Overseas (006 study) and RSV OA China groups will be presented in the order of RSV OA Overseas (006 study) and RSV OA China.
- 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.
- Confidence intervals (CIs) will use 95% confidence level. Exact 95% CIs around proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

4.1.3. General Methodology for Immunogenicity

- 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 and treatment differences. For the display of reverse cumulative curve, titers below LLOQ and above ULOQ won't be replaced. 95% CIs for GMT and MGI will be based on a back transformation of CI for the mean of $\log_{10}$-transformed values. 95% CI for group difference in proportion will be based on Miettinen and Nurminen confidence interval [Miettinen, 1985].
- Seroresponse rate (SRR) is defined as the proportion of participants having a fold increase in neutralizing titers ≥4 (post-study intervention administration over pre-study intervention administration).
- 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).

4.1.4. 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

4.2.1. Definition of endpoint/estimands

Refer to Section 1.1 for the definition of primary estimand for immunogenicity (humoral response).

4.2.2. Main analytical approach

Primary estimand analysis will be performed on the Per-Protocol Set (PPS).

RSV-A and RSV-B neutralizing group GMT ratio at 1 month after the RSVPreF3 OA vaccine administration will be computed for RSV OA Overseas group over RSV OA China group with 95% CI, using an ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the treatment group (RSV OA Overseas and RSV OA China) and the baseline log_{10}-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 Overseas group minus RSV OA China group, with 95% CI. The 95% CI will be derived using the method of Miettinen and Nurminen.

The primary analysis result will be reported using the ED60 (Estimated Dilution 60) unit.

Missing data will not be imputed.

NI for co-primary objectives will be claimed to be successful if the upper limit of the 2-sided 95% CI for the GMT ratio will be ≤1.5 and the upper limit of the 2-sided 95% CI for the SRR difference will be ≤ 10% for both RSV-A and B.

4.2.3. Additional estimand/analysis

An additional analysis will be conducted analogously using the IU/ml unit.

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. Secondary Endpoints Analyses

Refer to Section 1.1 for the definition of the estimands for secondary endpoints.

4.3.1. Secondary Immunogenicity

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.

4.3.1.1. Humoral immune response in RSV OA (Overseas) group and RSV OA (China) group

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

4.3.1.1.1. 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, using both ED60 and IU/ml unit.

- Percentage of participants with neutralizing titers equal to or above pre-defined assay cut-offs and their 2-sided 95% CIs will be tabulated.
- SRR and 95% CI will be tabulated.
- Unadjusted GMTs and their 95% CIs will be tabulated and displayed graphically.
- The kinetics of unadjusted GMTs will be plotted as a function of time for participants with results available at all timepoints.
- MGIs and their 95% CIs will be tabulated.
- Distribution of neutralizing titers will be displayed using reverse cumulative curves.

4.3.1.1.2. Between groups assessment

The following will be reported for RSV-A/B neutralizing titers:

- The 95% CIs for group GMT ratios and group SRR difference between RSV OA Overseas and RSV OA China at baseline, using both ED60 and IU/ml unit, by the ANCOVA model on $\log_{10}$-transformed titers for each neutralization assay.
- The 95% CIs for group GMT ratios and group SRR difference between RSV OA Overseas and RSV OA China at 6-month after study intervention administration, using both ED60 and IU/ml unit, with the analysis model analogous to the primary analysis.

4.3.1.1.3. Subgroup analysis

The following subgroup analyses will be performed by age categories (60-69, 70-79, ≥ 80 YOA) for RSV-A/B neutralizing titers:

- The 95% CIs for group GMT ratios and group SRR difference between RSV OA Overseas and RSV OA China at baseline, 1-month and 6-month after study intervention administration, using both ED60 and IU/ml unit.
- Unadjusted GMTs and their 95% CIs by group.
- SRR and 95% CI by group.
- MGIs and their 95% CIs by group.

4.3.1.2. Humoral immune response in the immunogenicity subset of RSV OA=ADJ-006 and RSV OA China group

The analysis will be performed on the PPS in the RSV OA China group and the PPS for immunogenicity in the immunogenicity subset of the global study RSV OA=ADJ-006.

The following will be reported for RSV-A/B neutralizing titers using both ED60 and IU/ml unit, with the analysis models/methods analogous to the primary analysis:

- The 95% CIs for group GMT ratios and group SRR difference between RSV OA=ADJ-006 and RSV OA China at 1-month after study intervention administration.

4.3.2. Secondary ARI surveillance (Chinese participants only)

ARI surveillance data are collected from Chinese participants only.

The analysis will be performed on the Exposed Set.

RT-PCR-confirmed RSV A and/or B-associated ARI and LRTD are the cases according to the case definition which have at least 1 sample is tested positive for RSV A and/or B by RT-PCR or equivalent as per the RT-PCR result from nasal/throat swab specimen by site staff or from self-swab taken by the participant.

RSV-confirmed ARI cases and RSV-confirmed LRTD cases will be characterized separately. RSV-confirmed LRTD cases are the LRTD and/or severe LRTD cases evaluated by the adjudication process and confirmed by the results of the RSV RT-PCR.

A case will be considered as RSV positive if the quantitative RT-PCT result is ≥ 726 copies/ml for RSV-A and/or ≥ 704 copies/ml for RSV-B.

The following summaries will be provided by group using the descriptive statistics based on the RSV-confirmed cases:

- The number and percentage of participants who reported 1 or more RSV-confirmed ARI/LRTD cases, RSV-confirmed severe LRTD as per the definitions provided in protocol table 8, during the entire study period (Day 1 up to study end), and those start on or after Day 15 post vaccination up to study end.
- Duration in days of episodes for RSV-confirmed ARI/LRTD cases from Day 15 up to study end, defined as (ARI end date – ARI onset date +1).
- The number and percentage of each of the symptoms/signs associated to RSV-confirmed ARI/LRTD cases from Day 15 up to study end
- The number and percentages of participants with RSV-confirmed ARI/LRTD cases from Day 15 up to study end by intensity (mild, moderate, severe as per protocol table 10)
- The number and percentages of participants with RSV-confirmed ARI/LRTD cases from Day 15 up to study end by frailty status (frail, pre-frail, fit).

Complications and hospitalizations will be summarized by group as:

- The number and percentages of participants with any respiratory and/or non-respiratory complications, for any complications and those related to any RSV confirmed ARI/LRTD episode from Day 15 up to study end.
- The number and percentages of participants with hospitalization related to the RSV confirmed episode from Day 15 up to study end due to respiratory and /or non-respiratory complications.

4.3.3. Secondary Safety

The analyses will be based on the Exposed Set.

The safety follow-up time will be tabulated by group using descriptive statistics (mean, median, minimum, maximum).

4.3.3.1. Solicited events (Chinese participants only)

- For solicited events during the 7-day follow-up period (i.e., the day of study intervention administration and 6 subsequent days) after vaccination, the following summaries will be provided by group: Compliance in completing solicited events information will be tabulated:
    - Number and percentage of participants with solicited events occurrence status data will be tabulated with exact 95% CI.
- Number and percentage of participants reporting below each individual event will be tabulated with exact 95% CI, for any grade, grade 3 and resulting in medically attended visit:
    - any solicited administration site event
    - any solicited systemic event
    - any solicited event
    - each individual administration site event
    - each individual systemic event
- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and grade 3) will be represented graphically.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period after vaccination will be tabulated as per GSK grading scale and China grading scale.
- The duration in days of each individual solicited events 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.

4.3.3.2. Unsolicited adverse events (Chinese participants only)

The verbatim reports of unsolicited AEs, including SAE and AESI (i.e. pIMDs and AF), will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The unsolicited AEs will be reported using MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT), unless otherwise specified.

The unsolicited AEs during the 30-day follow-up period (i.e., the day of study intervention administration and 29 subsequent days) after the study intervention, including SAEs and AESIs (i.e. pIMDs and AF), will be summarized by group as:

- Number and percentage of participants reporting each below type event with exact 95% CI, for all events and for non-serious events:
  - unsolicited AEs
  - grade 3 unsolicited AEs
  - causally related unsolicited AEs
  - grade 3 causally related unsolicited AEs
  - unsolicited AEs resulting in a medically attended visit
- Number and percentage of participants reporting each below type event will summarized with exact 95% CI:
  - unsolicited AEs reported within 30 minutes following vaccination
  - grade 3 unsolicited AEs reported within 30 minutes following vaccination

4.3.3.3. Pooling analysis of solicited and unsolicited AEs (Chinese participants only)

Solicited events and unsolicited events, including SAE and AESI (i.e. pIMDs and AF), will be pooled and summarized by group as:

- Number and percentage of participants reporting each below type event with exact 95% CI, for events during the 7-day and for events during the 30-day follow-up period after the study intervention, and for any grade, grade 3, grade 3 non-serious AE, and AEs resulting in a medically attended visit:
  - any solicited administration site event
  - any solicited systemic event
  - any AE
- For web posting purposes, the number of occurrences and the number and percentage of participants with non-serious AEs (solicited and unsolicited combined, also including pIMD) during the 30-day follow-up period will be produced by SOC and PT.

4.3.3.4. SAEs, pIMDs and AEs leading to withdrawal from study

The following summarized will be provided by group:

- Number and percentage of participants reporting each below type event up to study end, with exact 95% CI:
  - any SAE (for overseas participants only)
  - any pIMD (for overseas participants only)
  - any SAE related to study intervention administration
  - any pIMD related to study intervention administration
  - any fatal SAE
- Number and percentage of participants reporting each below type event up to 6 months after vaccination, i.e. during Day 1-183, by the MedDRA Primary SOC, HLT and PT, with exact 95% CI:
  - SAE
  - pIMD
  - SAE related to study intervention administration
  - pIMD related to study intervention administration
  - fatal SAE
- All SAEs, pIMDs and AEs leading to withdrawal from study will also be described in detail in tabular listings.

4.3.3.5. Other adverse events

- For Chinese participants only:
  - Atrial Fibrillation (AF) AESIs will be described in a tabular listing including the characteristics of the AE (causality, maximum intensity), day to onset and outcome.
  - AF AESIs will be tabulated within the summary of AEs or SAEs according to their classification.

4.4. Tertiary/Exploratory Analyses

Not Applicable.

4.5. Other Safety Analyses

Not applicable.

4.6. Other Analyses

As per the local requirement, descriptive immunogenicity analysis will be performed for participants from Republic of Korea. Details refer to Humoral immune response in terms of RSV-A and RSV-B neutralizing antibody titres expressed as GMT and SRR will be calculated at baseline (GMT only), 1 month and 6 months after the RSVPreF3 OA investigational vaccine administration. The comparison between humoral antibody response at 1-month post-vaccination and historical antibody response collected from Korean participants in RSV OA=ADJ-006 study will be conducted descriptively.

4.7. Interim Analyses

4.7.1. Sequence of analyses

The analyses will be performed stepwise:

- **Day 31 (PCA) analysis**: The first analysis will be performed when immunogenicity and reactogenicity data up to Visit 2 (Day 31) are available. This analysis will be considered as final for those data. Safety data up to database lock point will also be included into the analysis. The analysis will be performed by study statistician who will be unblinded to the details of the treatment assignments at the time of the Day 31 analysis.
- **Month 6 Safety Analysis**: An optional analysis may be conducted when safety data up to Month 6 are available.
- **End of Study Analysis**: The final analysis will be performed when all data for the secondary endpoints of descriptive immunogenicity at Month 6, ARI surveillance and safety up to study conclusion are available.

4.8. Changes to Protocol Defined Analyses

A blinded safety analysis was conducted using data of 11Mar2025 to support the CDE consultation of RSV OA=ADJ-028 study.

There were no other changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 15 Feb 2024).

5. SAMPLE SIZE DETERMINATION

The target sample size for the study is approximately 2600 participants: i.e. 1800 participants in China [2:1 randomization allocation between RSV OA group (China) and Placebo group (China)], 800 participants in RSV OA group (Overseas).

The sample size in the groups receiving the investigational vaccine is driven by need to meet local regulatory requirements and the statistical power to prove the primary NI objectives.

Based on a sensitivity analysis for the study power (Table 7), the sample size is able to provide ≥ 90% power to demonstrate the primary NI objectives in RSV OA group (China) compared to the RSV OA group (Overseas) for all the scenarios presented, assuming an attrition rate of 10%:

- The Power of the NI testing for the GMT is calculated by SAS 9.4 using the two-sample t-test for non-inferiority assuming equal variance.
- The Power of the NI testing for the SRR is calculated by SAS 9.4 using the non-inferiority tests for the difference between two proportions applying the method of Miettinen and Nurminen.

Table 7 Sensitivity analysis for the power of co-primary NI testing

	Statistical Assumptions				Individual Powers				Overall Power
Hypothesis	**H1**	**H2**	**H3**	**H4**	**H1**	**H2**	**H3**	**H4**	
Endpoint	**GMR***	**SRR****	**GMR***	**SRR****	**GMR**	**SRR**	**GMR**	**SRR**	
Scenario 1	1.06	80.3%, 82.3%	1.10	76.7%, 73.4%	100%	100%	100%	90.5%	90.5%
Scenario 2	1.11	80.3%, 83.2%	1.14	76.7%, 75.0%	100%	100%	100%	98.2%	98.2%
Scenario 3	1.17	80.3%, 84.5%	1.18	76.7%, 77.0%	99.9%	100%	99.8%	99.9%	99.6%
Scenario 4	1.17	81.7%, 83.2%	1.19	77.4%, 75.0%	99.9%	100%	99.6%	96.5%	96.0%

H1, H2, H3, H4 = Null hypothesis 1, 2, 3 and 4 respectively.

* GMR is the geometric mean titer ratio of RSV OA group (Overseas) / RSV OA group (China). Its individual level standard deviation of log10 titers for RSV neutralization is assumed as 0.45.

** The values are the assumed seroresponse rate in the RSV OA group (Overseas) and RSV OA group (China), respectively.

SRR = Seroresponse rate.

The assumptions are based on the data from RSV OA=ADJ-004 study.

Participants who withdraw from the study will not be replaced.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Exposed Set. A summary of the number of participants in each analysis set will be provided.

6.1.1. Participant Disposition

A summary of the number and percentage of participants screened, screen failures, those who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for screen failure and 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

Below demographic will be summarized descriptively by group on the Exposed Set and Per-Protocol Set:

- Age at vaccination
  - age will be presented in years.
  - summarized as continuous and categorical (60-69, 70-79, ≥ 80 YOA)
- Sex
- Ethnicity
- Race
- Country
- Body Mass Index (BMI), which is auto-calculated by the eDC system.

Subgroup analyses will be performed by age categories (60-69, 70-79, ≥ 80 YOA) for the characteristics.

Below baseline characteristics will be summarized descriptively by group on the Exposed Set:

- Vital signs: height, weight, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate
- Smoking status
- Frailty status determined using the Gait speed test

The number and percentages of participants with medical history (including baseline comorbidities) classified by the MedDRA Primary SOC, HLT and PTs will be tabulated by group for the Exposed Set.

The number and percentages of participants with each comorbidity category will be summarized by group for the Exposed Set.

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

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

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

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

A summary of important protocol deviations will be provided by group based on the Screened Set and Enrolled Set.

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

6.1.4. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary.

The number and percentage of participants starting any concomitant medication (any medication, any antipyretic, any antipyretic taken prophylactically and any antibiotic) during the 7-day and the 30-day follow-up period after the study intervention will be tabulated per study group with exact 95% CI for the Exposed Set.

6.1.5. Concomitant Vaccinations

The number and percentage of participants starting any concomitant vaccination during the 30-day follow-up period after the study intervention will be tabulated per study group with exact 95% CI for the Exposed Set.

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

Not applicable.

6.3. Appendix 3 Data Derivations Rule

6.3.1. Attributing events to vaccine doses

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the eCRF using the contents of the flag indicating if the event occurred before or after study dose. If ‘after study 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 Partial 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 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 study intervention 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.

Incomplete ARI onset/end dates will follow the rules analogous to above.

Incomplete concomitant medication/vaccination start/end dates will follow the rules analogous to above with CM.CMENRTPT status "BEFORE" or "ONGOING" status considered.

6.3.3. Onset day

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

6.3.4. Reporting period of adverse events

Safety data	Collected from	Reporting period for analysis
Solicited events	Chinese participants	Within 7 days following the vaccination, i.e. Day 1-7
Unsolicited solicited events	Chinese participants	Within 30 days following the vaccination, i.e. Day 1-30
SAEs, pIMDs	Chinese participants	6 months after vaccination, i.e. Day 1-183
	Overseas participants	• Up to study end (Month 6) • 6 months after vaccination, i.e. Day 1-183
SAEs related to study intervention, pIMDs related to study intervention, fatal SAEs, AE/SAE leading to withdrawal from study	Chinese participants	• Up to study end (Month 6 or last ARI visit, whichever is later) • 6 months after vaccination, i.e. Day 1-183
	Overseas participants	• Up to study end (Month 6) • 6 months after vaccination, i.e. Day 1-183

Atrial fibrillation (AF) reported as AE or SAE would follow the reporting period of unsolicited AE or SAE, respectively.

6.3.5. Solicited events

6.3.5.1. Daily recording of solicited events

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

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

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

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

6.3.5.2. Duration of events

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

For solicited administration site and systemic events:

- The duration of a solicited AE with at least one day Grade > 0 is defined as End date(CEENDY) – Start date(CESTDY) + 1, with Start date defined as the first day with the symptom and End date defined as the last day with the symptom in or beyond the solicited period.
- A missing start date will be imputed with the vaccination date.
- For paper diaries, if an ongoing symptom has a missing end date, the end date will be considered equal to vaccination date + 29 days.
- 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 (if only the max intensity during the ongoing period is recorded and the value is 3, each day of the ongoing period will be counted as grade 3).

6.3.5.3. 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.

6.3.5.4. Intensity grading for solicited events

Unless otherwise specified, the intensity for solicited events are as per GSK grading scale.

The intensity of administration site erythema/swelling, and fever will be scored as per GSK grading scale and China grading scale as follows:

GSK Grading Scale		
Intensity grade	**Erythema/Swelling**	**Fever (by any measurement)**
0	≤20 mm	< 38.0°C
1	>20 - ≤50 mm	≥38.0°C – ≤38.5°C
2	>50 - ≤100 mm	>38.5°C – ≤39.0°C
3	>100 mm	>39.0°C
China Grading Scale *		
Intensity grade	**Erythema/Swelling**	**Fever (by axillary measurement)**
0	< 25 mm	<37.3°C
1	25 - <50 mm	37.3°C - <38.0°C
2	50 - <100 mm	38.0°C - <38.5°C
3	≥100 mm	≥38.5°C
4	Abscess, exfoliative dermatitis, and dermis or deep tissue necrosis **	>=39.5 and persistent for more than 3 days

* According to the Chinese guidelines [Grading Criteria for Adverse Events in Clinical Trials of Preventive Vaccines (draft version) issued by NMPA in 2025].

** It will not be derived in the analysis given the solicited events eCRF data are based on GSK grading scale.

6.3.6. Unsolicited adverse events

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

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

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

6.3.7. Pooling of solicited and unsolicited adverse events

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

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

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Redness (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.

6.3.8. Data derivation

6.3.8.1. Age at vaccination

Age will be calculated from date of birth and the date of study intervention, and rounded down to integers, i.e. age at vaccination =FLOOR[(date of study intervention- date of birth+1)/365.25], where FLOOR is the SAS function to round down a decimal number to integer. Partial date will be imputed.

Given only year of birth is collected, if a derived age is equal to 59 and the participant has no any violation to the ≥60 YOA inclusion criterion (i.e. INC#1 in protocol 5.1), the derived age is considered as 60.

6.3.8.2. Temperature

Temperatures will be presented in degrees Celsius (°C). For China grading temperatures reported in oral measurement will be converted as follows:

Axillary temperature (°C) = oral temperature - 0.2 (°C)

6.3.8.3. Frailty status

The frailty status at baseline will be classified to frail, pre-frail and fit as per the Gait speed test:

Frailty Status	Definition
Frail	Participants with a walking speed <0.4m/s or who were not able to perform the test*
Pre-Frail	Participants with a walking speed between 0.4-0.99 m/s
Fit	Participants with a walking speed ≥1 m/s

* Participants who were not able to perform the test for the following reasons in the eCRF: Tried but unable, Could not walk unassisted, Not attempted – study staff or participant felt unsafe, participants unable to understand the instructions

6.3.8.4. 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 in SDTM	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

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

GMT calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable neutralizing titres will be converted as described in Section 6.3.8.4 for the purpose of GMT calculation. Cut-off values are defined by the laboratory before the analysis.

6.3.9. Display of decimals

6.3.9.1. Percentages

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

6.3.9.2. 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 with 0 and 1 decimal respectively.

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

6.3.9.3. 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.

6.3.10. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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