Statistical Analysis Plan

Official Title of Study: A phase 3, randomized, double blind, multi country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above

Study ID: 217131

Approval Date of Document: 15-NOV-2021

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above
Study Number:	217131 (RSV OA=ADJ-009)
Compound Number:	GSK3844766A
Abbreviated Title:	A study of 3 lots of an investigational vaccine against respiratory syncytial virus (RSV) in adults aged 60 years and above.

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) IND 18540 RSV PreF3 Older Adult

Registry	**ID**
Clintrials.gov	Not Available

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
UL	Upper Limit of the confidence interval

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	23 SEP 2021	10 May 2021	Not Applicable	Original version
SAP amendment 1	15 Nov 2021	10 May 2021	Addition of sensitivity analysis	Amendment 1: FDA request

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses for Study RSV OA=ADJ-009 (217131).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the lot-to-lot consistency of 3 lots of the RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine in terms of immunogenicity.	• RSVPreF3-specific immunoglobin (Ig)G antibody concentrations expressed as group geometric mean concentration (GMC) ratio at 30 days post-vaccination (Day 31).
Secondary	
• To evaluate the humoral immune response of the 3 lots of the RSVPreF3 OA investigational vaccine.	• RSVPreF3-specific IgG antibody concentrations expressed as mean geometric increase (MGI) at 30 days post-vaccination (Day 31).
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine.	• Percentage of participants reporting each solicited event with onset within 4 days after study intervention administration (i.e. the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited adverse events (AE) within 30 days after study intervention administration (i.e. the day of vaccination and 29 subsequent days). • Percentage of participants reporting serious AEs after study intervention administration (Day 1) up to study end (6 months after vaccination). • Percentage of participants reporting potential immune-mediated diseases after study intervention administration (Day 1) up to study end (6 months after vaccination).
Tertiary	
CCI [redacted]	

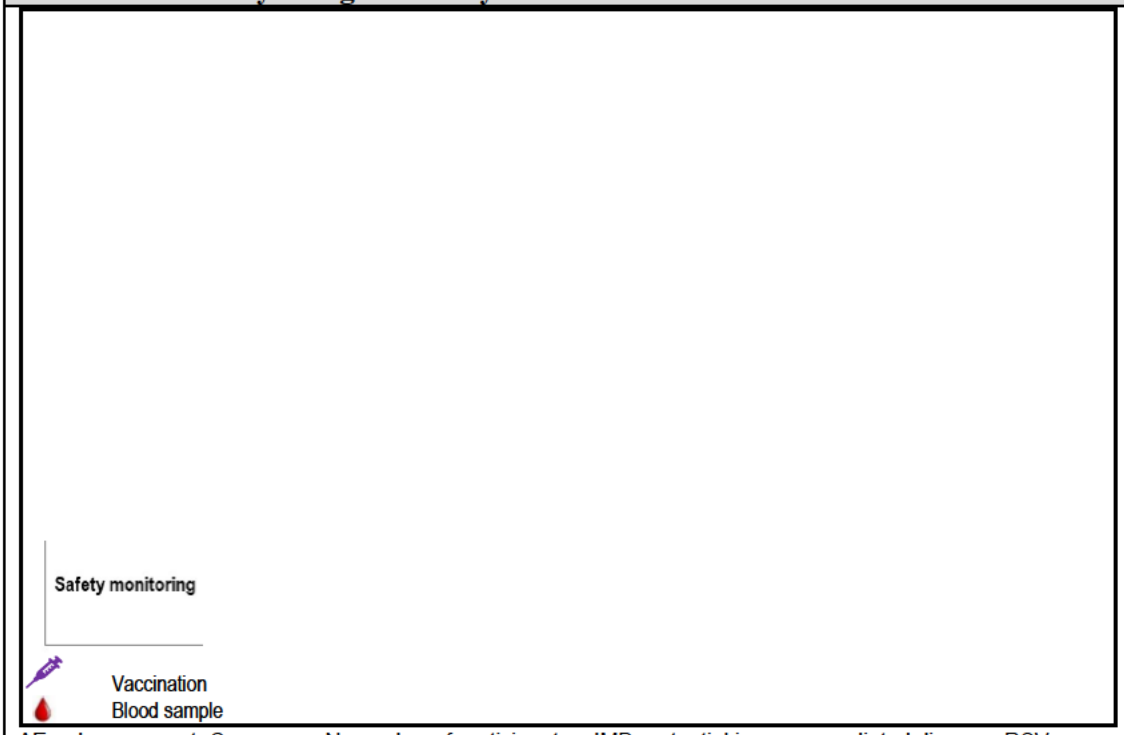
RSV: respiratory syncytial virus.

Primary estimand

The primary scientific question is to show equivalence of 3 lots of the RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine in terms of immunogenicity 1 month after vaccination in eligible participants who complied with the study requirements as defined per protocol (refer to section 3 for the definition of the per protocol set used for the primary analysis and to section 4.2 for the statistical methods).

1.2. Study Design

Overview of Study Design and Key Features



AE: adverse event; Grp: group; N: number of participants; pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
BS: blood samples. Blood samples will be collected from all participants at Visit 1 and Visit 2 to assess humoral immune response.
Note: All SAEs related to study participation or a GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study (prior to study vaccination) up to study end.

Design Features	The current study is designed as a phase 3, double-blind study to assess lot-to-lot consistency in terms of immunogenicity and evaluate safety and reactogenicity of the 3 RSVPreF3 OA investigational vaccine lots in adults ≥ 60 YOA. There are 3 parallel investigational groups (RSVPreF3_Grp1, RSVPreF3_Grp2, RSVPreF3_Grp3)
Study intervention	Participants will receive 1 dose of the RSVPreF3 OA investigational vaccine at Day 1.
Study intervention Assignment	Approximately 750 eligible participants will be randomly assigned to 3 study groups in a 1:1:1 ratio (approximately 250 participants in each group)
Interim Analysis	There is no interim analysis planned for this study
Final analysis	A final analysis will be conducted once all the immunogenicity data are available for the primary endpoint. This final analysis will include immunogenicity and safety data up to Visit 2 (Day 31).
End-of-study analysis	An end-of-study analysis with all data including the data obtained until 6 months post-vaccination will be performed

2. STATISTICAL HYPOTHESES

The study includes 1 confirmatory primary objective.

To demonstrate the lot to lot consistency of 3 lots of the RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine in terms of immunogenicity.

Null hypothesis vs. Alternative hypothesis:

At least 2 of the 3 vaccine lots differ by more than 1.5-fold with respect to their GMCs ratio

$$H_0: |\mu A/\mu B| > 1.5$$

vs. Clinical equivalence (consistency) between each pair of the 3 lots with respect to their GMCs ratio

$$H_a: |\mu A/ \mu B| \leq 1.5$$

where μA and μB representing geometric mean of IgG specific antibody concentration at day 31 (30 days post vaccination) after the RSVPreF3 OA investigational vaccine dose in vaccines lots A and B respectively and 1.5, the equivalence margin.

The null hypothesis will be rejected if the 2-sided 95% confidence interval (CI) of the GMC ratios between each pair of the 3 lots is within the pre-defined clinical limit of [0.67, 1.5].

2.1. Multiplicity Adjustment

A 1-sided alpha of 2.5% will be used for the 3 equivalence tests.

No adjustment of Type 1 error is needed because all the Lot to Lot consistency criteria must be met simultaneously.

3. ANALYSIS SETS

Definition of population to be analysed:

Analysis Set	Definition / Criteria
Enrolled set	Participants who agreed to participate in a clinical study after completion of the informed consent process*.
Exposed set (ES)	All participants who received the study intervention. The analysis per group will be performed according to the administered study 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. The analysis per group will be performed according to the administered study intervention.

*All participants enrolled and included in the database will be part of the Enrolled Set.
** 30-42 days between Visit 1 and Visit 2.

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 exposed and per protocol sets.

3.1.1. Elimination from Exposed set

The following codes will be used for identifying participants to be eliminated from the Exposed set (see, Table 1):

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

3.1.2. Elimination from Per Protocol set (PPS)

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

- For codes 800, 900, 1030, 1050 and 2020: participants will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2010, 2040 and 2050: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

Table 1 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	ES and PPS for analysis of immunogenicity
900	Invalid informed consent	All	All	ES and PPS for analysis of immunogenicity
1030	Study intervention not administered at all	All	All	ES and PPS for analysis of immunogenicity
1040	Administration of concomitant vaccine(s) forbidden in the protocol Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before study intervention administration and ending 30 days after study intervention administration, or planned use during the study period. Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the study intervention administration and ending 30 days after the study intervention administration. Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.	Visit 1,2 and contact 6 months post-vaccination	From the specific visit the condition is met	PPS for analysis of immunogenicity
1050	Randomization failure: Subject not randomized in the correct group (To be attributed by Statistician only; Check SBIR, replacement, vaccine administration)	Visit 1	All	PPS for analysis of immunogenicity
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	Vaccination visit 1	From the specific visit (1) the condition is met	PPS for analysis of immunogenicity

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
1080	Vaccine temperature deviation Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visit 1	From the specific visit (1) the condition is met	PPS for analysis of immunogenicity
1090	Expired vaccine administered	Vaccination visit 1	From the specific visit (1) the condition is met	PPS for analysis of immunogenicity
2010	Protocol violation linked to inclusion/exclusion criteria All inclusion/exclusion criteria defined in the protocol to be checked.	Visit 1,2 and contact 6 months post-vaccination	From the specific visit (1,2) or contact (6 month) the condition is met.	PPS for analysis of immunogenicity
2020	All Pre-dose results are missing	Visit 1	All	PPS for analysis of immunogenicity
2040	Administration of any medication forbidden by the protocol Use of any investigational or non-registered drug, or medical device other than the study interventions during the period beginning 30 days before the dose of study vaccines and ending 30 days after the study intervention administration, or planned use during the study period. Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab). Administration of immunoglobulins and/or any blood products or plasma derivatives planned administration during the study period. Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.	Visit 1,2 and contact 6 months post-vaccination	From the specific visit (1,2) or contact (6 months) the condition is met	PPS for analysis of immunogenicity
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 (intercurrent medical condition) or are confirmed to have an alteration of their initial immune status.	Visit 1,2 and contact 6 months post-vaccination	From the specific visit (1,2) or contact (6 months) the condition is met	PPS for analysis of immunogenicity

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
2090	Participants did not comply with blood sample schedule: Number of days between vaccination (visit1) and blood sample (visit2) is outside [30-42] days	Visit 2	At the specific visit (2) the condition is met	PPS for analysis of immunogenicity
2100	Serological results not available at the post dose time point	Visit 2	At the specific visit (2) the condition is met	PPS for analysis of immunogenicity
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 lab	Visit 2	At the specific visit (2) the condition is met	PPS for analysis of immunogenicity

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Confidence intervals will use 95% confidence levels.

The group GMC ratio will be based on a back transformation of group contrast in an ANCOVA model applied to the logarithm- transformed titers.

Primary analysis: The ANCOVA model will include the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) as fixed effects and the pre-dose log-10 titer as covariate.

Sensitivity analysis: The ANCOVA model will include the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) and the center as fixed effects and the pre-dose log-10 titer as covariate.

95% CI for GMC will be based on a back transformation of CI for the mean of log-transformation.

The equivalence will be shown if the 95% CIs of the geometric mean concentration (GMC) ratio of each lot over the each other lot is inside the acceptance limit 0.67-1.5 for the antibody concentration 30 days post vaccination (day 31).

95% CI for proportion will be based on exact [Clopper,1934] Pearson CI.

Summary results will be presented by group for immunogenicity and safety and by group and in total for demographic characteristics (pooling of the 3 groups).

4.1.2. Baseline Definition

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

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

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoints

4.2.1.1. Immunogenicity endpoint

The GMC ratios will be computed for each pair of RSVPreF3 OA investigational vaccine lots (RSVPreF3_Grp1 versus RSVPreF3_Grp2, RSVPreF3_Grp1 versus RSVPreF3_Grp3, RSVPreF3_Grp2 versus RSVPreF3_Grp3).

4.2.2. Main analytical approach

The primary analysis of lot-to-lot consistency will be performed on the PPS for immunogenicity.

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

The 3 RSVPreF3 OA investigational vaccine lots will be compared in terms of RSVPreF3 IgG-specific antibody concentrations at 1-month post-vaccination, with a 1-sided alpha of 2.5%.

The 2-sided 95% CI for group GMC ratio will be derived from an ANCOVA model* on $\log_{10}$ transformed titer.

* **Primary analysis**: The model will include the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) as fixed effects, and the pre-dose log10-transformed titer as covariate. **Sensitivity analysis:** The model will include the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) and center as fixed effects, and the pre-dose log10-transformed titer as covariate. Missing data will not be replaced. Titers below the assay cut-off will be replaced by half the assay cut-off, titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

Success criteria for equivalence:

- The 2-sided 95% CI on the group GMC ratio (RSV PreF3 OA lot divided by another RSVPreF3 OA lot) for RSV investigational vaccine inside [0.67; 1.5]

4.2.3. Sensitivity analyses

Not Applicable

4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of endpoints

4.3.1.1. Immunogenicity endpoints

A seronegative participant will be defined as a participant whose antibody concentration is below the cut-off value of the assay. A seropositive participant is a participant whose antibody concentration is greater than or equal to the cut-off value of the assay.

MGI (mean geometric increase): The geometric mean of the within participant ratios of the post-dose concentration over the pre-dose concentration.

4.3.2. Main analytical approach

4.3.2.1. Immunogenicity analysis

The primary analysis of secondary immunogenicity endpoints will be based on the PPS for analysis of humoral response. If, in any vaccine group, the percentage of vaccinated participants with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

For each group, at each time point that blood samples are collected (unless otherwise specified):

- Percentage of participants above pre-defined assay cut-off and their exact 95% CI will be tabulated.
- GMCs and their 95% CI will be tabulated and represented graphically.
- MGI will be tabulated with 95% CI.
- Antibody titer/concentration will be displayed using reverse cumulative curves.

The above mentioned descriptive within group immunogenicity analysis will also be generated by age at first vaccination (60-69, 70-79, ≥ 65, ≥ 70 and ≥ 80 years).

4.3.2.2. Safety analysis

The safety analysis will be performed on the ES as follows:

- The number and percentage of participants and doses with at least one administration site event AE (solicited and unsolicited), with at least one systemic AE (solicited and unsolicited) and with any AE during the 4-day and 30-day follow-up period will be tabulated with exact 95% CI after vaccination. 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.

These analyses will present all solicited and unsolicited AEs, including SAEs and pIMDs (unless otherwise specified).

The above analysis will also be performed for the solicited symptoms only during the 4-day follow-up period.

- The number and percentage of participants reporting each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period (i.e. the day of vaccination and 3 subsequent days) will be tabulated for each group after each dose and overall. The percentage of doses followed by each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period (i.e. the day of vaccination and 3 subsequent days) will be tabulated, with exact 95% CI.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period (i.e. the day of vaccination and 3 subsequent days) will be tabulated for each group after the study dose.
- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and Grade 3) will be represented graphically for each group after the study dose.
- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each individual solicited event using descriptive statistics (mean, minimum, Q1, median, Q3, maximum). The same computations will be done for 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 Medical Dictionary for Regulatory Activities (MedDRA) preferred term. 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 verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA. 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 Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after vaccination) will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of causally related SAE classified by the MedDRA Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after vaccination) will be tabulated with exact 95% CI.

- The same tabulation will be presented for fatal SAEs.
- All SAEs will also be described in detail in a tabular listing.
- All pIMD will also be described in detail in a tabular listing.
- All AEs/SAEs leading to study/intervention discontinuation from dose 1 up to study end will be tabulated.
- The percentage of participants with at least one report of pIMD classified by the MedDRA Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after vaccination) will be tabulated with exact 95% CI. The percentage of participants with at least one report of related pIMD classified by the MedDRA Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after vaccination) will be tabulated with exact 95% CI.
- The number and percentage of participants using concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after the study dose will be tabulated with exact 95% CI.
- Compliance in completing solicited events information will be tabulated after the study dose.
- Some of the key safety analysis will be generated by age group at first vaccination (60-69, 70-79, ≥ 65, ≥ 70 and ≥80 years) as mentioned below.

  The number and percentage of participants reporting each individual solicited administration site AE (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic AE (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period (i.e. the day of vaccination and 3 subsequent days) will be tabulated for each group after the study dose.

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

4.4. Tertiary Analyses

4.4.1. Definition of endpoint

CCI [redacted]

4.4.2. Main analytical approach

Not applicable

4.5. Interim Analyses

There are no interim analyses planned for this study.

4.5.1. Sequence of analyses

A final analysis will be conducted once all the immunogenicity data are available for the primary endpoint. This final analysis will include immunogenicity and safety data up to Visit 2 (Day 31). The individual data listings and participant treatment assignments will not be provided at this time.

An end-of-study analysis with all data including the data obtained until 6 months post-vaccination will be performed.

Note that the GSK central study team (Clinical Research and Development Lead, Statistician, Safety Representative, etc.) will be unblinded to the details of the study intervention lots at the time of final analysis in order to prepare the CSR of the final analysis.

4.5.2. Statistical considerations for interim analysis

Not applicable.

4.6. Changes to Protocol Defined Analyses

Not applicable.

5. SAMPLE SIZE DETERMINATION

The target enrolment will be 750 participants based on the assumptions described below:

Primary Objectives:

- **Endpoint:** RSVPreF3 IgG specific antibody concentration at 1-month post-vaccination (Day 31).
- **Group level summary:** Antibody geometric mean concentration (GMC) per group.
- **Reference for the sample size calculation:** A standard deviation (SD) of the log10-transformed concentrations of 0.45 is used as reference. It is the highest SD observed in the RSV OA=ADJ 002 (208851) study among all treatment groups and humoral assays.
- **Success criteria for consistency:** the 2 sided 95% confidence interval (CI) of the GMC ratios between each pair of the 3 lots is within the pre-defined clinical limit of [0.67, 1.5].
- **Null hypothesis:** At least 2 of the 3 vaccine lots differ by more than 1.5-fold (1 sided non-inferiority limit) with respect to their GMC.

- **Alternative hypothesis:** Clinical equivalence (consistency) between each pair of the 3 lots with respect to their GMCs.
- **Type I error:** a 1-sided alpha of 2.5% will be used for the 6 non inferiority tests, no adjustment of Type 1 error is needed because all the lot-to-lot consistency criteria have to be met simultaneously
- **Type II error:** Considering a Bonferroni correction for multiplicity, the global Type II error will be equal to 6 time the nominal Type II error calculated for one non inferiority test. The sample size is determined to reach a global power of at least 90%.

Table 2 shows that the probability (global power) to reach the lot-to-lot consistency criterion with 225 evaluable participants in each vaccine lot group is at least 91%, with a 1-sided alpha = 0.025.

Table 2 Power to demonstrate consistency between each pair of the 3 lots in terms of RSVPreF3 IgG GMCs with 225 evaluable participants per group

Vaccine component	Endpoints	Reference SD*	Clinically acceptable bounds for consistency	N per group	1-sided alpha	Power	Type II error
RSVPreF3 IgG-specific	GMC	0.45	[0.67, 1.5]	225	0.025	91%	9%

GMC: geometric mean concentration; Ig: immunoglobin; N = number of participants; SD: Standard Deviation (of the log_{10} transformed concentration)
Pass 2019 (Non-Inferiority test of 2 independent means). Power = 100-the Type II error (Beta). The Type II error (Beta) has been adjusted using Bonferroni's method (overall Type II error = sum of the individual Type II errors) since 6 non-inferiority tests are needed for lot-to-lot consistency (nominal Beta for each non-inferiority test is 1.5%).
* SD = 0.45 was selected based on the results from the RSV OA=ADJ-002 study. A conservative approach was used by selecting the highest value observed for SD across groups and humoral assays.

The primary objective analysis will be performed on the PPS. Assuming a 10% non-evaluable rate up to Day 31 (participants dropped-out or excluded from the PPS), a total of 750 participants (250 per group) will have to be enrolled in order to reach 225 participants evaluable for the primary objective.

Secondary Objectives: NA

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

The number of participants who withdraw from the study will be tabulated by group according to the reason for drop-out. This analysis will be based on the ES and the PPS.

6.1.2. Demographic and Baseline Characteristics

The median, mean, range and standard deviation of age (in years) at vaccination will be computed by group. The center distribution, distribution of participants in each age category (60-69, 70-79, ≥ 65, ≥ 70 and ≥80 years), geographical ancestry and sex composition will be presented. This analysis will be based on the ES and the PPS.

Medical history will be summarized respectively.

6.1.3. Protocol Deviations

The number of participants enrolled into the study as well as the number of participants excluded from per protocol set (PPS) analyses will be tabulated for the total population. This analysis, also broken down by study group, will be based on the ES.

The number of participants enrolled into the study as well as the number of participants excluded from per the ES will be tabulated for the total population. This will be based on all enrolled participants.

6.1.4. Subject exposure

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

6.1.5. Prior and Concomitant Medications

The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group after vaccine dose.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

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

The overall incidence of COVID-19 AEs and SAEs, COVID-19 AEs leading to study intervention discontinuation, COVID-19 AEs leading to study withdrawal, and severe COVID-19 AEs will be summarized. The incidence of these events at individual PT level can be obtained from the standard AE/SAE summaries.

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

The number and percentage of participants with concomitant vaccination (COVID-19) before and during the study will be tabulated with exact 95% CI.

6.2. Appendix 2 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

6.2.1. Attributing events to vaccine doses

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. The relative dose for the event will be the one administered on the start day of the event.

6.2.2. Handling of missing data

6.2.2.1. Dates

When partially completed dates (i.e. dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

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

The following exceptions apply:

When partially completed dates (i.e. with missing day or month) are used in calculations, the following rules will be applied:

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to

complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.

- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first 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 (30 or 31) 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 date will follow the rules above.

6.2.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

6.2.2.3. Daily recording of solicited events

6.2.2.3.1. Studies with paper diaries

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

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

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

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

6.2.3. Data derivation

6.2.3.1. Age at first dose in years

Age will be calculated as the number of years between the date of birth and the date of first vaccination.

In case of partial dates, the following 2 dates will be used as replacement dates:

- 15th of month, if the day is missing.
- 30th of June, if day and months are missing.

6.2.3.2. Age category at vaccination

As only the year of birth will be collected in the eCRF, there might be some discrepancies between the age computed using standard derivation rules and the age category used in SBIR for the minimization.

Therefore, for the analysis by age, the age categories will be determined according to the information entered in SBIR (add name of variable in SDTM), except for "≥65 YOA" category which will be obtained using the derived age because this category is not used in SBIR for minimization.

6.2.3.3. Temperature

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

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

6.2.3.4. 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	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	Value
"value" and value is > ULOQ	ULOQ
All other cases	missing

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

Geometric Mean Titer (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titer or concentration transformations. Non quantifiable antibody titers or concentrations will be converted as described in section 6.2.3.4 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.3.6. Onset day

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

6.2.3.7. 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 3 March 2018 and ends on 12 March 2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited event period.

6.2.3.8. Counting rules for combining solicited and unsolicited adverse events

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

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

Table 3 Solicited event and their corresponding lower level term code/decode

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

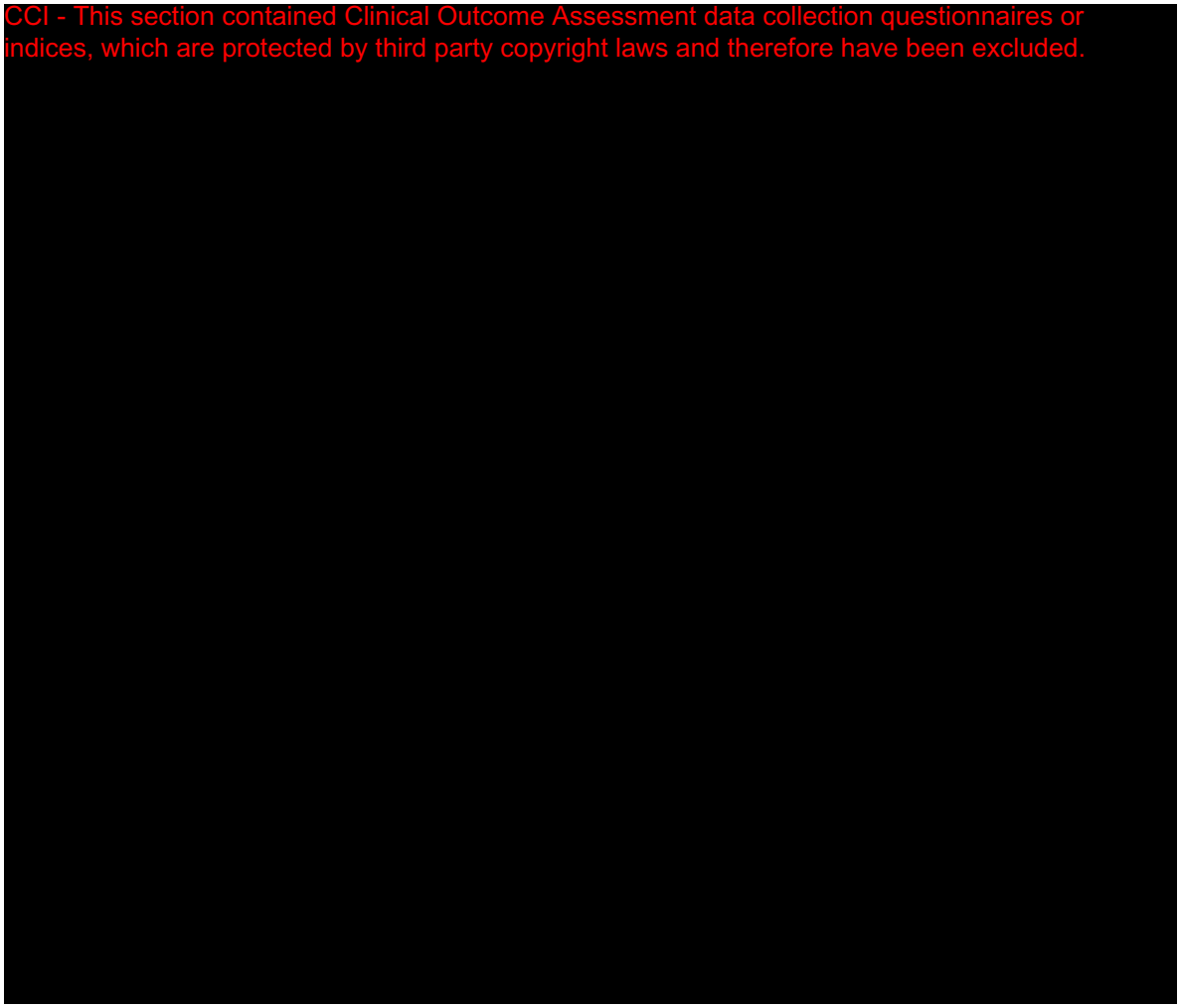
The latest available MedDRA version will be used for coding

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

6.2.3.9. 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.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



The maximum intensity of local injection site erythema/swelling and fever will be scored at GSK as follows:

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

6.2.3.10. Counting rules for occurrence of unsolicited adverse events

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

For analysis of unsolicited AEs, SAEs and pIMDs, all vaccinated participants will be considered. Participants who did not report an event will be considered as participants without the event.

When an unsolicited adverse event occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted. The selection of unsolicited AEs reported during the follow-up period will be done using the day of onset.

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

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

6.2.3.11. Counting rules for concomitant medications

For analysis of concomitant medications, all vaccinated participants will be considered. Participants who did not report a concomitant medication will be considered as participants without concomitant medication.

Medications will be coded using the GSKDRUG dictionary.

6.2.4. Display of decimals

6.2.4.1. Percentages

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

6.2.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (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 maximum and minimum of transformed body temperatures will be displayed with one decimal.

6.2.4.3. Serological summary statistics

For each assay, geometric mean titers (GMT) or concentrations (GMC) and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-dose.

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

7. REFERENCES

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