Statistical Analysis Plan Amendment 1

Study ID: 214489

Official Title of Study: A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU HD vaccine in adults aged 65 years and above

NCT number: NCT05559476

Date of Document: 20-Dec-2022

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU HD vaccine in adults aged 65 years and above.
Study Number:	214489
Compound Number:	GSK3844766A
Abbreviated Title:	A study on the immune response and safety elicited by a vaccine against respiratory syncytial virus (RSV) when given alone and together with a vaccine against influenza in adults aged 65 years and above (RSV OA=ADJ-008).

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

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

Registry	**ID**
Clintrials.gov	Not available

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	13 May 2022	8 March 2022	Not Applicable	Protocol Amendment 1
SAP amendment 1	20 Dec 2022	Amendment 2 Final: 16 December 2022	Addition of RSV-B as part of primary endpoint	Protocol Amendment 2

1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses for Study RSV OA=ADJ-008 (214489).

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary*	
• To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-A neutralization antibodies when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralization antibody titers expressed as group GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose.
• To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• HI antibody titers for each of the FLU vaccine strains expressed as group GMT ratio, 1 month after the FLU vaccine dose.
• To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-B neutralization antibodies when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-B neutralization antibody titers expressed as group GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose.
Secondary	
• To evaluate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone.	• HI seroconversion status for each of the FLU vaccine strains expressed as SCR, 1 month after the FLU vaccine dose.
• To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine or administered alone.	• RSV-A neutralization antibody titers expressed as MGI at 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing antibody titers expressed as MGI at 1 month after the RSVPreF3 OA investigational vaccine dose.
• To evaluate the humoral immune response to the FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine or administered alone.	• HI antibody titers for each of the FLU vaccine strains expressed as GMT, at Day 1 and Day 31. • HI seroconversion status for each of the FLU vaccine strains expressed as SCR, from Day 1 to Day 31. • HI seroprotection status for each of the FLU vaccine strains expressed as SPR, at Day 1 and Day 31. • HI antibody titers for each of the FLU vaccine strains expressed as MGI, 1 month after the FLU vaccine dose.
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and FLU vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited event with onset within 4 days after vaccine administration (i.e. the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited adverse events (pIMD, non-serious AE or serious AE) within 30 days after vaccine administration (i.e. the day of vaccination and 29 subsequent days).

Objectives	Endpoints
	• Percentage of participants reporting SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination). • Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination).
Tertiary	
CCI [redacted]	

FLU vaccine is referring to FLU HD quadrivalent; CCI [redacted] G; GMT: Geometric Mean Titer; CCI [redacted]; HI: Hemagglutinin Inhibition; pIMD: potential immune-mediated disease. AE: adverse event; SAE: serious adverse event.
SCR: Seroconversion rate: the percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥ 1:40 or a pre-dose titer ≥ 1:10 and at least a four-fold increase in post-dose titer.
SPR: Seroprotection rate: The percentage of vaccinees with a serum HI titer ≥ 1:40 that usually is accepted as indicating protection.
MGI: Mean Geometric Increase, the geometric mean of the within participant ratios of the post-dose titer over the pre-dose titer.
*Refer to Section 4.2.2 for the testing sequence of primary objectives.

Primary Estimand

The primary clinical question of interest is to show non-inferiority of the RSVPreF3 OA investigational vaccine and the FLU vaccine when co-administered versus separate administration 1 month apart 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 4.2.2 for the statistical method).

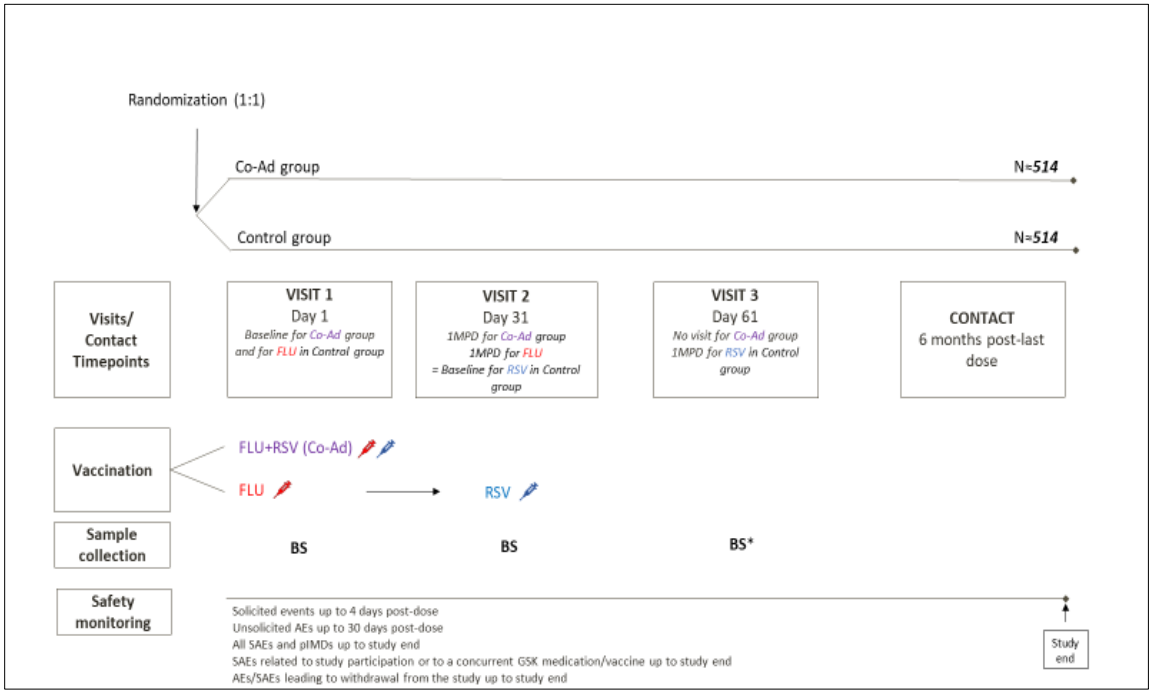
1.2. Study Design

The current study is designed to assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with a FLU vaccine, compared with administration of the vaccines separately. There are 2 parallel arms:

- **Co-Ad group:** Participants will receive a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU vaccine at Visit 1 (Day 1).
- **Control group**: Participants will receive a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).

All participants will be followed up for safety (in terms of SAEs and pIMDs) for 6 months after the last study vaccine administration.

Figure 1 Study design overview



1MPD = 1-month post-dose.
* Blood sample only from participants in Control group.
FLU = FLU HD quadrivalent; RSV = RSVPreF3 OA investigational vaccine; BS = Blood sample from all participants (except for blood sample at Visit 3 which is only applicable for Control group).
Note: Unsolicited AEs will be collected from first dose to 30 days post-dose. SAEs and pIMDs will be collected from first dose through the entire study period. SAEs related to study participation will be collected from the time of consent.

2. STATISTICAL HYPOTHESES

The study includes the following confirmatory primary objectives.

- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone in terms of RSV-A neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e. at Day 31[Visit 2] for the Co-Ad group and at Day 61[Visit 3] for the Control group).

  Null hypothesis vs. Alternative hypothesis:

  $$H_0: \mu_{\text{Control group}}/\mu_{\text{Co-Ad group}} > \log(1.5) \text{ vs. } H_a: \mu_{\text{Control group}}/\mu_{\text{Co-Ad group}} \leq \log(1.5)$$

  where μ represents the expected mean of log transformed RSV-A neutralization antibody titers at 1 month after the RSVPreF3 OA investigational vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% CI for the group GMT ratio (Control group divided by Co-Ad group) in RSV-A neutralization antibody titers 1 month after the RSVPreF3 OA investigational vaccine dose ≤ 1.5.

- To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU vaccine administered alone

in terms of HI GMT ratio for each of the FLU vaccine strains at 1 month after the FLU vaccine (i.e. at Day 31[Visit 2] for both groups).

Null hypothesis vs. Alternative hypothesis:

H_0: $\mu_{\text{Control group}}/\mu_{\text{Co-Ad group}} > \log(1.5)$ vs. H_a: $\mu_{\text{Control group}}/\mu_{\text{Co-Ad group}} \leq \log(1.5)$

where μ represents the expected mean of log transformed HI antibody titers at 1 month after the FLU vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% CI for the group GMT ratio (Control group divided by Co-Ad group) in HI antibody titers for each of the FLU vaccine strains 1 month after the FLU vaccine ≤ 1.5.

- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3 OA investigational vaccine administered alone in terms of RSV-B neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e. at Day 31[Visit 2] for the Co-Ad group and at Day 61[Visit 3] for the Control group).

  Null hypothesis vs. Alternative hypothesis:

  H_0: $\mu_{\text{Control group}}/\mu_{\text{Co-Ad group}} > \log(1.5)$ vs. H_a: $\mu_{\text{Control group}}/\ \mu_{\text{Co-Ad group}} \leq \log(1.5)$

  where μ represents the expected mean of log transformed RSV-B neutralization antibody titers at 1 month after the RSVPreF3 OA investigational vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% CI for the group GMT ratio (Control group divided by Co-Ad group) in RSV-B neutralization antibody titers 1 month after the RSVPreF3 OA investigational vaccine dose ≤ 1.5.

2.1. Multiplicity Adjustment

Using a nominal alpha of 2.5% for each of them will ensure the global type I error for the primary objectives is controlled below 2.5%.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria
Enrolled set*	Participants who agreed to participate in a clinical study after completion of the informed consent process.
Safety/Exposed set (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered.
Per-Protocol set (PPS)	All eligible participants who received **at least one study intervention** as per-protocol in the **control group and all study interventions in the Co-Ad group**, had immunogenicity results pre-post-dose for at least one antigen, complied with blood draw intervals (**refer to intervals mentioned below**) and contribution of participants to PPS at specific timepoint will be defined by timepoint, without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

*All participants enrolled and included in the database will be part of the enrolled set.
Intervals for the Co-Ad group: Visit1-Visit2=30-37 days
Intervals for the Control group: Visit1-Visit2=30-37 days, Visit2-Visit3=30-37 days

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis. Detail is provided below for each set.

3.1.1. Elimination from Exposed Set (ES)

Code 1030 (Study intervention not administered at all), 800 (Fraudulent data) and code 900 (invalid informed consent) will be used for identifying participants eliminated from ES (see Table 1).

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 1070, 1080, 1090: participants will be eliminated from a specific visit (at which the condition is met) onwards as applicable for the respective group/antigens.
- For codes 1040, 2010, 2040, 2050, 2080: participants will be eliminated from a specific visit (at which the condition is met) onwards.
- 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 vaccine other than the study interventions during the period beginning **30 days before the first study vaccine 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	Visit 1,2,3	From the specific visit 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
	before the first study intervention administration and ending 30 days after the last 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.			
1050	Randomisation 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 Incomplete vaccination course 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 Side of administration wrong (for Co-ad group if both vaccines are given in the same arm) Wrong reconstitution of administered vaccine	Vaccination visit(s) 1 or 1 and 2 as applicable	From the specific visit (1 or 2) the condition is met as applicable for the respective group/antigens.	PPS for analysis of immunogenicity
1080	Vaccine temperature deviation Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visit(s) 1 or 1 and 2 as applicable	From the specific visit (1 or 2) the condition is met as applicable for the respective group/antigens.	PPS for analysis of immunogenicity
1090	Expired vaccine administered	Vaccination visit(s) 1 or 1 and 2 as applicable	From the specific visit (1 or 2) the condition is met as applicable for the respective group/antigens.	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 1,2,3	From the specific visit (1,2 or 3) 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
2020	All Pre-dose results are missing: RSV-A and HI for the FLU vaccine strains	Co-Ad group: Visit 1 Control group: Visit 1 and Visit 2	All	PPS for analysis of immunogenicity
2040	Administration of any medication forbidden by the protocol Use of any investigational or non-registered product (drug or medical device) other than the study interventions during the period beginning **30 days before the first study vaccine 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 1,2,3	From the specific visit (1,2 or 3) 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 1,2,3	From the specific visit (1,2 or 3) the condition is met	PPS for analysis of immunogenicity
2080	Participants did not comply with vaccination schedule for the control group number of days between dose 1 and dose 2 is outside [30-37 days]	Visit 2	Visit 3 for the control group	PPS for analysis of immunogenicity
2090	Participants did not comply with blood sample schedule: Co-Ad group: Number of days between vaccination (visit1) and blood sample (visit2) is outside [30-37] days Control group: Number of days between vaccination (visit1) and blood sample (visit2) or (visit2) and blood sample (visit3) is outside [30-37] days	Visit 2, Visit 3 as applicable for the group	At the specific visit (2 or 3) the condition is met as applicable for the respective group	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
2100	Serological results not available at the post dose time point for all antigens tested at that particular time point.	Visit 2,3	At the specific visit (2 or 3) the condition is met as applicable for the respective group	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, Visit 3	At the specific visit (2 or 3) the condition is met as applicable for the respective group	PPS for analysis of immunogenicity

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

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

95% CI for group difference in proportion will be based on Miettinen and Nurminen confidence interval [Miettinen, 1985].

The group adjusted GMT 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 age category (age at vaccination: 65-69, 70-79 or ≥80 years) as fixed effects and the pre-dose log-10 titer as regressors.

Sensitivity Analysis: The ANCOVA model will include the treatment group and age category (age at vaccination: 65-69, 70-79 or ≥80 years) as fixed effects, center as the random effect and the pre-dose log-10 titer as regressors.

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

4.1.2. Definitions

- For the RSV antigens:

  A seronegative participant will be defined as a participant whose antibody titer/concentration is below the cut-off value of the assay. A seropositive participant is a participant whose antibody titer/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 titer over the pre-dose titer.

- For the FLU antigens:

  SCR (seroconversion rate): The percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥ 1:40 or a pre-dose titer ≥1:10 and at least a four-fold increase in post-dose titer.

  HI SPR (seroprotection rate): The percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.

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

4.2. Primary Endpoints Analyses

The primary analysis will be based on the PPS for analysis of immunogenicity. 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.

4.2.1. Between groups assessment

- The 2-sided 95% CI for the group GMT ratio in terms of RSV-A neutralizing antibody titers between RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be computed at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e. at Day 31 [Visit 2] for the Co-Ad group and at Day 61 [Visit 3] for the Control group).
- The 2-sided 95% CI for the group GMT ratio in terms of HI antibody titers for each of the FLU vaccine strains between RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be computed at 1 month after the FLU vaccine (i.e. at Day 31 [Visit 2] for both groups):
- The 2-sided 95% CI for the group GMT ratio in terms of RSV-B neutralizing antibody titers between RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be computed at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e. at Day 31 [Visit 2] for the Co-Ad group and at Day 61 [Visit 3] for the Control group).

The results will be presented in tables as well as graphs using forest plots.

4.2.2. Main analytical approach

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

***Primary Analysis**: The model will include the treatment group and age category (age at vaccination: 65-69, 70-79 or ≥80 years) 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 non-inferiority and testing sequence:

The following testing sequence will be used:

1st sequence:

- The upper limit of the 2-sided 95% CI of the GMT ratio (Control group divided by Co-Ad group) for RSV-A neutralization antibodies is ≤1.5.

AND

- The upper limit of the 2-sided 95% CI of the GMT ratio (Control group divided by Co-Ad group) for each of the FLU vaccine strains are ≤1.5.

2nd sequence:

- The upper limit of the 2-sided 95% CI of the GMT ratio (Control group divided by Co-Ad group) for RSV-B neutralization antibodies is ≤1.5.

Testing will progress in the 2nd sequence only if the 1st sequence is a success, so that no further adjustment of alpha is required.

4.2.3. Sensitivity analyses

As for the main analytical approach an ANCOVA model will be performed with the treatment group and age category (age at vaccination: 65-69, 70-79 or ≥80 years) as fixed effects, **center as random effect** and the pre-dose log10-transformed titer as covariate.

In case the model with random effect does not converge we proceed with center as a fixed effect.

4.3. Secondary Endpoints Analyses

4.3.1. Immunogenicity analysis

The primary analysis of secondary immunogenicity endpoints will be based on the PPS for analysis of immunogenicity. 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.

4.3.1.1. Between groups assessment

- The asymptotic standardized 95% CI for the difference in seroconversion rate (Control group minus Co-Ad group) will be computed at 1 month after the FLU vaccine (i.e. at Day 31 [Visit 2] for both groups).

  Reference criteria for evaluation of non-inferiority:

  The upper limit of the 2-sided 95% CI on the group difference (Control group minus Co-Ad group) in seroconversion rate is ≤10% for anti-HI antibodies.

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

4.3.1.2. Within groups assessment

For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified):

- Percentage of participants above pre-defined assay cut-off and their exact 95% CI will be tabulated.
- Percentage of participants above seroprotection/seroconversion rate for HI antibody titer and their exact 95% CI will be tabulated.
- CCI /GMTs and their 95% CI will be tabulated.
- 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 (65-69 YOA, 70-79 YOA, ≥ 70 YOA and ≥80 YOA years).

- Additionally, the CBER and CHMP criteria for HI SPR and SCR will be assessed as follows:

  CBER criteria to be evaluated:

  – The lower limit (LL) of the 95% CI for SCR should be ≥30% in participants ≥65 YOA.

  – The LL of the 95% CI for SPR should be ≥60% in participants ≥65 YOA.

  CHMP criteria to be evaluated:

  – At least one of the 3 following criteria should be met:

  – the point estimates of SPR >60%, SCR >30%, and MGI >2.0 for elderly > 60 years for each of the antigen strains.

These above defined analyses evaluating the CBER and CHMP criteria should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

4.3.2. 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 (i.e. the day of vaccination and 3 subsequent days) and 30-day (i.e. the day of vaccination and 29 subsequent days) follow-up period will be tabulated with exact 95% confidence interval (CI) after each dose and overall. 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 (i.e. the day of vaccination and 3 subsequent days) 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 each dose and overall.

- 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 each 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 of days with solicited events ongoing beyond 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) System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term. The above analysis by dose will also be performed.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PTs and reported after vaccine administration (Day 1) up to study end (6 months after last 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 Primary SOC, HLT and PTs and reported after vaccine administration (Day 1) up to study end (6 months after last 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 SOC, HLT and Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after last vaccination) will be tabulated with exact 95% CI.
- The percentage of participants with at least one report of related pIMD classified by the MedDRA SOC, HLT and Preferred Terms and reported after vaccine administration (Day 1) up to study end (6 months after last 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 each dose and overall will be tabulated with exact 95% CI.
- The number and percentage of participants using concomitant vaccination during the 30-day follow-up period after each dose and overall will be tabulated with exact 95% CI.
- Compliance in completing solicited events information will be tabulated after each dose and overall.

Some of the key safety analysis will be generated by age group at first vaccination (65-69 YOA, 70-79 YOA, ≥ 70 YOA and≥80 YOA 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 each dose and overall.

  The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e. the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by MedDRA Primary SOC, HLT and PTs

- 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

CCI

4.5. Safety Analyses

Safety analyses are described in Section 4.3.2.

4.5.1. COVID-19 Assessment and COVID-19 AEs

Based on the study requirement, related analysis or a listing will be produced for the study.

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.

4.6. Other Analyses

Not Applicable.

4.7. Interim Analyses

There are no interim analyses planned for this study.

4.7.1. Sequence of analyses

A final analysis will be conducted once all the immunogenicity data (as clean as possible) are available for primary and secondary endpoints. This final analysis will include immunogenicity and safety data up to Visit 2 (Co-Ad group) or Visit 3 (Control group). Participants who undergo Visit 2 or Visit 3 assessments out of the allowed visit interval (refer to Table 3 and Table 4 of the protocol) will be excluded from the final analysis. The study conclusion on the primary objectives will be drawn based on this final analysis.

An end-of-study (EoS) analysis with all data including the safety data obtained until 6 months post-last dose will be performed. At the EoS analysis all statistical outputs will be re-generated and will be reported in an integrated Clinical Study Report.

4.8. Changes to Protocol Defined Analyses

No changes from the protocol defined analyses.

5. SAMPLE SIZE DETERMINATION

The target enrolment will be 1028 participants (514 in the group receiving the RSVPreF3 OA investigational vaccine co-administered with the FLU vaccine (Co-Ad group) and 514 in the Control group where RSVPreF3 OA investigational vaccine and FLU vaccine are administered staggered) to obtain at least 924 evaluable participants (462 in the Co-Ad group and 462 in Control group) for the evaluation of the primary objectives, assuming that approximately 10% of the enrolled participants will not be evaluable.

Each objective will be evaluated with a nominal type I error of 2.5%.

Table 2 Overall power to demonstrate primary objectives: non-inferiority of the immunogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU vaccine as compared to when administered alone- assuming 462 participants are available in each group

Endpoint	Standard deviation of log10 concentration	Reference ratio	Non-inferiority margin	Type II error	Power
RSV-A Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-A neutralization antibody	**0.45**	**1.05**	**1.5**	**0.1%**	**99.9%**
FLU Non-inferiority* (1-sided test with alpha=2.5%)					
GMTs HI H1N1 strain	**0.6**	**1.05**	**1.5**	**2.5%**	**97.5%**
GMTs HI H3N2 strain	**0.6**	**1.05**	**1.5**	**2.5%**	**97.5%**
GMTs HI B/Yamagata	**0.6**	**1.05**	**1.5**	**2.5%**	**97.5%**
GMTs HI B/Victoria strain	**0.6**	**1.05**	**1.5**	**2.5%**	**97.5%**
RSV-B Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-B neutralization antibody	**0.45**	**1.05**	**1.5**	**0.1%**	**99.9%**
Global Type II error to show non-inferiority				**~10.0%**	
Global power					**~90.0%**

* Pass 2019 alpha = 2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean
For RSV: non-inferiority limit = 0.176 (=log10[1.5]).
For each Flu vaccine strain: non-inferiority limit = 0.176 (=log10[1.5]).
Reference Ratio= 0.0212 (=log10[1.05])

Considering a slight interference of 1.05 in true GMTs in both groups with a common population standard error of 0.45 for the RSV-A and RSV-B neutralization antibodies and 0.6 for each of the FLU strains in $\log_{10}$ transformed concentration, the study has at least 90.0% power to meet the primary objectives.

Nominal powers to evaluate secondary objective

The nominal power to evaluate the non-inferiority on seroconversion rate for each of the FLU strains is above 86%, depending on the plausible rates.

Table 3 Evaluation of non-inferiority in terms of HI antibody SCR when the FLU vaccine is co-administered with the RSVPreF3 OA investigational vaccine as compared to FLU when administered alone assuming 462 participants are available in each group for a range of plausible SCRs.

N evaluable participants per group	Threshold	Plausible rates in Control group**	Type II error	Nominal power
		FLU vaccine: Non-inferiority* in terms of SCR		
462	10%	70%	8.7%	91.3%
462	10%	50%	13.9%	86.1%
462	10%	35%	11.0%	89.0%
462	10%	25%	6.1%	93.9%

SCR: Seroconversion Rate.
*Pass 2019 alpha = 2.5%, for SCR – Non-inferiority: Proportions – Two independent Proportions – Non-Inferiority Tests for the Difference Between Two Proportions based on Miettinen and Nurminen method
** SCR observed in the Control group in Zoster-004 study range from 35.3% to 60.9%.

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 first vaccination will be computed by group. The center distribution, distribution of participants in each age category (65-69 YOA, 70-79 YOA, ≥70 YOA and ≥80 YOA) geographical ancestry and sex composition will be presented. This analysis will be based on the ES and the PPS.

The number and percentages of participants with medical history classified by the MedDRA Primary SOC, HLT and PTs will be tabulated by group for the ES.

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 co-administered vaccine and the control vaccine will be tabulated by group and by vaccine for the ES.

6.1.5. Concomitant Medications

The number and percentage of participants and doses 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 each vaccine dose and overall.

6.1.6. Concomitant Vaccinations

The number and percentage of participants and doses with concomitant vaccination during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group after each vaccine dose and overall.

6.1.7. Additional Analyses Due to the COVID-19 Pandemic

Depending on how the Covid-19 situation evolves, the SAP might be amended to reflect the analysis corresponding to Covid-19.

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

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

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. If ‘after study dose’ is selected, the relative dose for the event will be the one administered on the start day of the event. If ‘before study dose’ is selected, the relative dose for the event will be the dose prior to this one.

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 for all solicited events except fever:

- 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 None.
- 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.
- When the group of solicited events (administration site or systemic) occurred is missing (i.e. SDTM CE.CEOCCUR=''), all missing daily recordings will be considered as missing for 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

For fever, the summary tables will not include the row 'Any'. The missing daily records do not contribute to the number participants reporting fever by half degree (°C): >=38; >38.5, >39, >39.5 and >40.

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] × 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 all the assays available for the study, 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

Note: The Reverse Cumulative Distribution curves (RCC) generated will not use the ULOQ values but the exact value if the exact value is greater than ULOQ.

CCI

[redacted]

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 last 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

For the duration of solicited AEs within the 4-day period:

- The duration of the event will be calculated as the sum of the individual days with the event reported as Grade 1 or higher or reported as missing during the solicited event period (see Section 6.2.2.3.1 for missing data). For Grade 3, the duration will be calculated as the sum of individual days with the event reported as Grade 3 or reported as missing during the solicited event period.

For the duration of solicited AEs ongoing beyond the 4-day period:

- The duration of the event will be calculated as the difference between the start (during the solicited period) and end date (if known) plus one day regardless of the intensity. For Grade 3, the entire duration of symptoms with a maximum intensity equal to Grade 3 will be considered.

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:

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. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

Table 4 Intensity grading scale for solicited events

Event	Intensity Grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Erythema at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °C.
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

The route for measuring temperature can be oral or axillary. Fever is defined as temperature ≥38.0°C regardless of the location of measurement.

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

	Erythema/swelling	Fever
0:	≤20mm	< 38.0°C
1:	>20 - ≤50mm	≥38.0°C - ≤38.5°C
2:	> 50 - ≤100mm	>38.5°C - ≤39.0°C
3:	>100mm	>39.0°C

6.2.3.10. Counting rules for occurrence of unsolicited adverse events

Unsolicited AE summaries will include SAEs and pIMDs 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 will not contribute to the summaries of unsolicited AEs.

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.

6.2.4. 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. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (age at first vaccination 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.

6.2.4.4. Serological summary statistics

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

GMT CCI 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.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985;4,213-226.