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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, placebo-controlled, observer-blind, multicenter study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_E$ or $AS01_B$ or unadjuvanted) when administered intramuscularly according to a 0, 2 month schedule in adults aged 18-40 or 60-80 years.
eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
Scope:	All data pertaining to the above study (except IDMC analyses)
Date of Statistical Analysis Plan	Amendment 2: 17-Mar-2020
Co-ordinating author:	PPD (Statistician)
Reviewed by:	(Clinical and Epidemiology Project Lead) (Clinic) (Lead statistician) (Lead statistical analyst) (Scientific writer) PPD (Stat Peer Reviewer) (Regulatory Affairs) (SERM physician) PPD (Safety scientist) (Public disclosure representative) PPD (CLS – Clinical Read-outs) PPD (CMI Expert representative)
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 01NOV2018)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CD40L	Cluster of Differentiation 40 Ligand
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CMV	Cytomegalovirus
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
DLP	Data Lock Point
eCRF	electronic Case Report Form
eDiary	electronic Diary
ELU/ml	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
ES	Exposed Set
FDA	Food and Drug Administration
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Commitee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IL	Interleukin
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit Of Quantification
Mcg or µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities

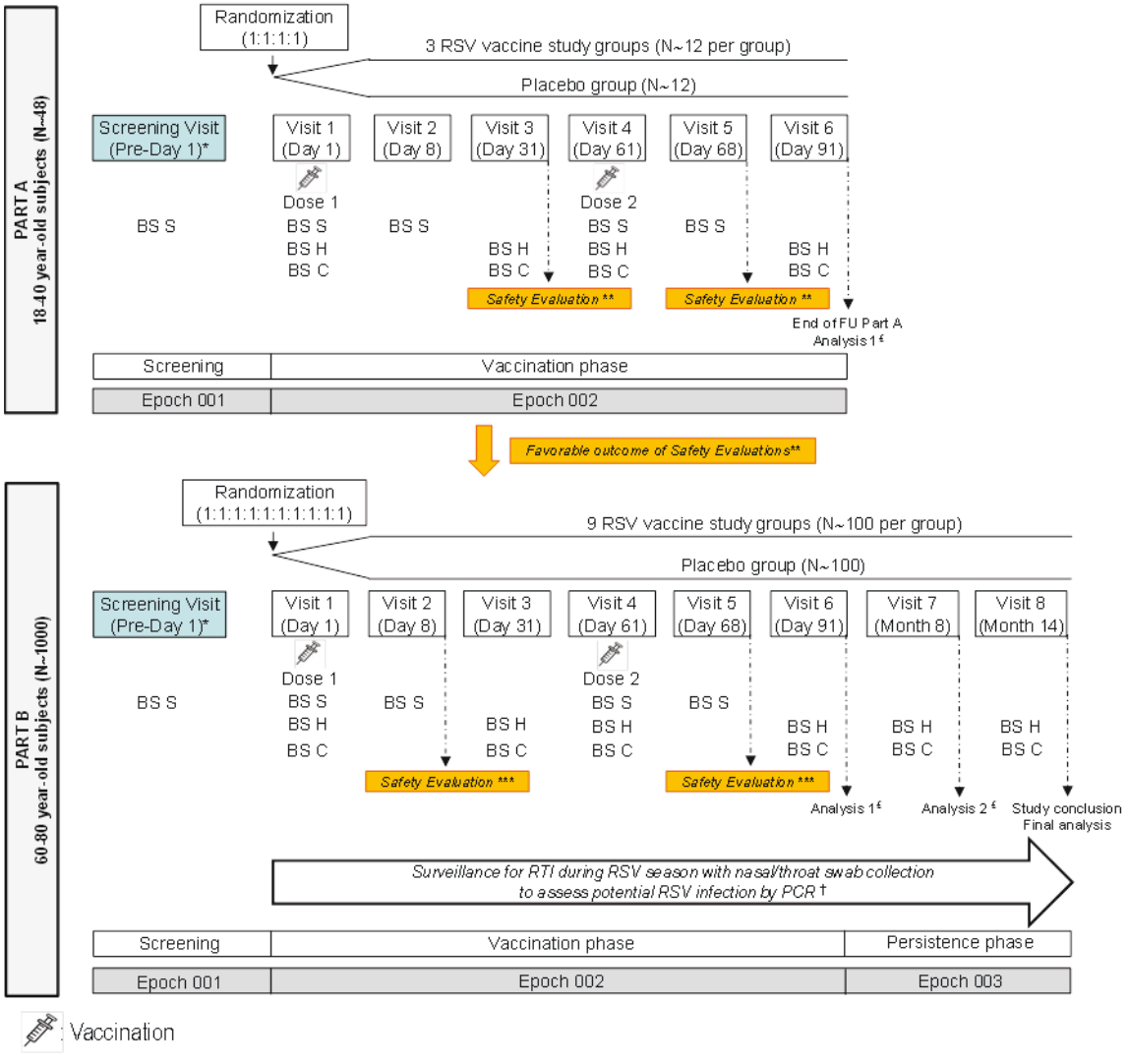
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncitial Virus
RTI	Respiratory Tract Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TNF-α	Tumor Necrosis Factor alpha
TOC	Table of Content
UL	Upper Limit of the confidence interval
WBC	White Blood cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
14-JAN-2019	first version	Final: 11 SEP 2018
27-JAN-2020	Amendment 1: implement changes discussed at the KOM Dry-run and progress meetings	Final: 11 SEP 2018
17-MAR-2020	Amendment 2: updates in CMI model notations following comments received by FDA	Final: 11 SEP 2018

2. STUDY DESIGN

Figure 1 Study design



BS S: Blood sample for safety (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
BS C: Blood sample for cell-mediated immune responses (for CD4+/CD8+ and/or memory B-cell testing)
FU: Follow-up; PCR: Polymerase Chain Reaction

* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.
** In Part A, a first IDMC evaluation of safety data up to Day 31 based on all subjects (~12 per group or at least 8 per group in case of slow recruitment) will be performed before proceeding with administration of Dose 2 in Part A and Dose 1 in Part B. A second IDMC evaluation will be performed based on safety data up to Day 68 for all subjects. Part B of the study can only be initiated upon favorable outcome of the first IDMC safety evaluation in Part A.
*** In Part B, a third and fourth IDMC evaluation of safety data up to Day 8 and Day 68, respectively, for the first enrolled and vaccinated subjects (~10 per group or at least 8 per group in case of slow recruitment) will be performed. Additional IDMC evaluations will happen during the conduct of the study.
† In case of RTI symptoms during the RSV seasons (approximately from October to March), the subject will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab at the site. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).
£ Analysis 1 will be performed on all data collected up to Day 91 for at least primary and secondary endpoints based on both study parts (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). Analysis 2 will be performed when all safety data up to Month 8 (Visit 7) are available. The analyses will be based on data as clean as possible.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-country study with 2 parts (i.e., Part A in young adults aged 18-40 years with 4 parallel groups and Part B in older adults aged 60-80 years with 10 parallel groups).
- **Primary Completion Date (PCD):** last visit of the vaccination phase in Part B (Visit 6 [Day 91]).
- **End of Study (EoS):** Last testing results released of samples collected up to Visit 8 in Part B (Month 14) (for assays related to primary and secondary endpoints only).
- **Treatment allocation:** Subjects will be randomized using a centralised randomization system on internet (SBIR) on Day 1.

  In Part A, the aim is to enrol approximately 48 subjects (~12 per group) aged 18-40 years. The randomization algorithm will use a minimisation procedure accounting for center and gender.

  In Part B, the aim is to enrol approximately 700 subjects (~70 per group) aged 60-69 years and approximately 300 subjects (~30 per group) aged 70-80 years. The randomization algorithm will use a minimisation procedure accounting for age, center and gender in each step.
- **Study groups:**

  For the investigational RSV vaccines in Part A and Step 1 in Part B, the RSVPreF3 high-dose formulation containing 120 μg RSVPreF3 will be used to prepare the vaccines for all dose groups (i.e., 30 μg, 60 μg and 120 μg dose groups). For Step 2 in Part B, the RSVPreF3 low-dose and mid-dose formulations (containing 30 μg and 60 μg RSVPreF3, respectively) will be used for the groups receiving 30 μg and 60 μg of RSVPreF3, respectively, and the RSVPreF3 high-dose formulation will be used for the 120 μg dose groups. As the reconstitution methods for the vaccines

administered to subjects enrolled in Step 1 and 2 of Part B will be different, separate study groups have been identified (referred to as B1 and B2). Throughout this document, the combined groups for Steps 1 and 2 are mentioned when referring to the number of groups in Part B (10 groups).

- **Control:** placebo.
- **Vaccination schedule:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Blinding**: observer-blind.

The vaccination phases of each study part (Epoch 002) will be observer-blind. A first statistical analysis will be performed on data available up to one month post-Dose 2 (Visit 6, Day 91). Given that summary safety results may unblind some specific subjects, the persistence phase of Part B (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Visit 8 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

- **RTI surveillance in Part B:** Active and passive surveillance will only be carried out during RSV seasons (approximately from October to March) throughout the entire Part B of the study:
  - **Active surveillance:** study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience an RTI.
  - **Passive surveillance:** study participants are instructed to contact the investigator/study staff as soon as they experience an RTI.

  At the beginning of RSV seasons, study participants will be reminded of the start of the RTI surveillance.
- **Sampling schedule:**

  In Part A:

  - At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the electronic Case Report Form (eCRF). The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
  - At Day 1 (Visit 1), a blood sample for cytomegalovirus (CMV) status determination will be drawn from all subjects.
  - **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

- **Blood samples for humoral immunogenicity and cell-mediated immunity (CMI)** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).

In Part B:

- At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
- At Day 1 (Visit 1), a blood sample for CMV status determination will be drawn from all subjects.
- **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects and on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).
- **Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91, Month 8 and Month 14 (Visits 1, 3, 4, 6, 7 and 8).
- **Nasal/throat swabs:** In case of RTI symptoms during the RSV season (approximately from October to March), the study participants will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).

- **Type of study:** self-contained.
- **Data collection:** eCRF. Solicited symptoms will be collected using an electronic subject Diary (eDiary). Unsolicited symptoms will be collected using a paper subject Diary.
- **Safety monitoring:** The study will be conducted in 2 parts with oversight by an IDMC. The investigator is not permitted to start vaccinating the subjects in the next step in each part until receipt of the favorable outcome of the respective safety evaluations by the IDMC.
  - **Part A:** Approximately 48 young adults aged 18-40 years will be enrolled and vaccinated with the first dose. If the IDMC evaluation on data up to 30 days post Dose 1 is favorable, the Part A study participants will be vaccinated with the second dose and Part B of the study will be initiated.

– **Part B:** This part will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. In Step 1, approximately 100 subjects will be enrolled and vaccinated. Safety evaluations based on unblinded data from those first 100 subjects will be performed by the IDMC to allow the start of Step 2. In Step 2, the remaining study participants (N≅900) will be recruited and vaccinated.

In total, 6 IDMC meetings for safety evaluation are foreseen in the vaccination phase of the study (Epoch 002), i.e., 2 meetings in Part A and 4 meetings in Part B.

During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

If any safety concern is identified by the investigator or the sponsor, *ad-hoc* safety evaluations by the IDMC may be performed.

Analysis planned for IDMC evaluations are described in a separate document (SAP for IDMC).

- **Group description for analysis:**

For analysis based on subjects in Part A and Part B Step 1 (B1), the group labels listed in table below will be used in the TFLs.

For final analysis based on subjects from Part B Steps 1 and 2, the groups will be pooled (B1 and B2) and the Pooled group labels will be used in the TFLs.

Table 1 Groups description

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
30-PLAIN_A	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part A	NA	
60-PLAIN_A	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part A	NA	
120-PLAIN_A	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part A	NA	
Placebo_A	subjects receiving Placebo in Part A	NA	
30-PLAIN_B1	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 1	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B
30-PLAIN_B2	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 2	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
60-PLAIN_B1	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 1	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B
60-PLAIN_B2	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 2	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B
120-PLAIN_B1	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 1	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
120-PLAIN_B2	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 2	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
30-AS01E_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B
30-AS01E_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
30-AS01B_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
30-AS01B_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
120-AS01B_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
120-AS01B_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
Placebo_B1	subjects receiving Placebo in Part B Step 1	Placebo_B	subjects receiving Placebo in Part B
Placebo_B2	subjects receiving Placebo in Part B Step 2	Placebo_B	subjects receiving Placebo in Part B

For some of the comparison analyses in Part B, the RSV vaccine groups will be pooled according to their adjuvant content and the following group names will be used in the TFLs:

Pooled Group label in tables	Pooled Group definition for footnote	Groups to be pooled
PLAIN_B	subjects receiving unadjuvanted RSVPreF3 in Part B (30, 60 or 120 μg)	30_PLAIN_B1, 30_PLAIN_B2, 60_PLAIN_B1, 60_PLAIN_B2, 120_PLAIN_B1, 120_PLAIN_B2
AS01E_B	subjects receiving RSVPreF3 adjuvanted with AS01E in Part B (30, 60 or 120 μg)	30_AS01E_B1, 30_ AS01E _B2, 60_ AS01E _B1, 60_ AS01E _B2, 120_ AS01E _B1, 120_ AS01E _B2
AS01B_B	subjects receiving RSVPreF3 adjuvanted with AS01B in Part B (30, 60 or 120 μg)	30_AS01B_B1, 30_ AS01B _B2, 60_ AS01B _B1, 60_ AS01B _B2, 120_ AS01B _B1, 120_ AS01B _B2

For the analysis by age category, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	60-69Y	60-69 years old subjects
2	70-80Y	70-80 years old subjects

For the analysis by CMV status before vaccination, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	CMV+	Subjects CMV positive before vaccination
2	CMV-	Subjects CMV negative before vaccination

3. OBJECTIVES/ENDPOINTS

3.1. Objectives

3.1.1. Primary objective

For Part A and Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

3.1.2. Secondary objectives

For Part A and Part B:

- To characterize the humoral immune responses (including dose-response) in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).
- To characterize the cell-mediated immune responses in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

For Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccines administered IM according to a 0, 2 month schedule, up to the end of follow-up (Month 14, Visit 8).
- To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

3.1.3. Tertiary objectives

For Part A and Part B:

- To further characterize the cell-mediated immune responses to investigational RSV vaccine formulations.

For Part B:

- To further characterize immune responses to investigational RSV vaccine formulations.
- To characterize persistence of immune responses to the investigational RSV vaccine formulations at Month 8 (Visit 7) and Month 14 (Visit 8).

- To further evaluate the occurrence of RSV-associated RTI (including co-infections with other respiratory viruses) during the RSV seasons in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.
- To evaluate the occurrence of RSV-associated RTI during the RSV season using self-collected nasal swabs.

3.2. Endpoints

3.2.1. Primary endpoints

For Part A and Part B:

- Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91):
  - Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination.
  - Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination.
  - Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68.
  - Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination.
  - Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

For Part B only:

  - Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

3.2.2. Secondary endpoints

For Part A and Part B:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro.

For Part B only:

- Occurrence of RSV-associated RTI (as measured by qRT-PCR in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
- Occurrence of SAEs from Dose 1 up to the end of follow-up.
- Occurrence of pIMDs from Dose 1 up to the end of follow-up.

3.2.3. Tertiary endpoints

For Part A and Part B:

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro.

For Part B only:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype B in all subjects.
  - RSVPreF3 site 0 specific antibody concentrations in a subset of subjects who received the selected vaccine formulation or placebo.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific memory B-cells in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Persistence of the humoral immune response with respect to components of the investigational vaccine at Months 8 and 14:
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.

- Persistence of the cell-mediated immune response profile with respect to components of the investigational vaccine:
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific memory B-cells at Month 14 in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:
  - Antibodies against specific protein F epitopes.
  - Potential new immunological markers for protection.
  - Cross-reactive neutralizing antibody titers against hMPV
- Occurrence of RSV-associated RTI, including co-infections with other respiratory viruses (as measured by multiplex PCR in self-collected nasal swab samples and nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons.
- Occurrence of RSV-associated RTI as measured by qRT-PCR in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

4. ANALYSIS SETS

4.1. Definition

4.1.1. Exposed Set

The Exposed Set (ES) will include all subjects with study vaccine administration documented.

A safety analysis based on the ES will include all vaccinated subjects.

An immunogenicity analysis based on ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at Dose 1.

4.1.2. Per-Protocol Set for analysis of immunogenicity

The Per-Protocol set (PPS) for analysis of immunogenicity will be defined by time point (and this to include all eligible subjects' data up to the time of important protocol deviations). The PPS will include all evaluable subjects in the ES:

- Meeting all eligibility criteria.
- For whom the administration route of the vaccine was as according to protocol.
- For whom the study vaccine was administered as per protocol.
- Who did not receive a concomitant medication/ product leading to exclusion from a PP analysis, as described in Section 6.6.2 of the protocol, up to the considered time point.
- Who did not present with a medical condition leading to exclusion from a PP analysis, as described in Section 6.7 of the protocol, up to the considered time point.
- Who complied with the vaccination schedule, as specified in the protocol.
- Who complied with the timings of the post-vaccination blood sampling for immune response evaluation, as specified in the protocol.
- For whom post-vaccination immunogenicity results are available for at least one assay component at the corresponding time points.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects eliminated from ES.

4.2.2. Elimination from Per-protocol analysis Set (PPS)

4.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions.

For codes 1040, 1070, 1080, 1090, 2040, 2060, 2080: subjects will be eliminated from the time at which the condition is met onwards.

For codes 2090, 2100, 2120: subjects will be eliminated at the specific visit at which the condition is met.

When applicable, codes will be allocated to subjects as long as they are included in the study. For example, withdrawals before the second dose will not be attributed a code 1070 because they missed a dose.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
900	Invalid informed consent or fraudulent data	All	All
1030	Study vaccine not administered at all	All	All
1040	Administration of concomitant vaccine(s) forbidden in the protocol: • Any investigational or non-registered vaccine other than the study vaccine used during the study period • A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last vaccine dose, except for inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each vaccination.	All	Immunology
1050	Randomisation failure	All	Immunology
1060	Randomisation code was broken	All	Immunology
1070	Vaccination not according to protocol: • Incomplete vaccination course • Subject 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 Visits 1 and 4	Immunology
1080	Vaccine temperature deviation → vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visits 1 and 4	Immunology

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
1090	Expired vaccine administered	Vaccination visits 1 and 4	Immunology
2010	Protocol violation (inclusion/exclusion criteria)	All	Immunology
2040	Administration of any medication forbidden by the protocol • Any investigational or non-registered medication used during the study period • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period • Long-acting immune-modifying drugs administered at any time during the study period • Immunoglobulins and/or any blood products administered during the study period	All	Immunology
2060	Intercurrent medical condition • Subjects may be eliminated from the PPS if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status (other than RSV infection).	All	Immunology
2080	Subjects did not comply with vaccination schedule: • **Part A**: number of days between dose 1 and dose 2 is outside [55-80 days] • **Part B**: number of days between dose 1 and dose 2 is outside [55-75 days]	Visit 4	Immunology

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule at a specific visit: • Number of days between dose 1 and visit 3 blood sample is outside [30-37 days] • Number of days between dose 1 and visit 4 blood sample is outside [55-80 days] for **Part A** or [55-75 days] for **Part B** • Number of days between dose 2 and visit 6 blood sample is outside [30-37 days] **Part B only:** • Number of days between dose 2 and visit 7 blood sample is outside [170-190 days] • Number of days between dose 2 and visit 8 blood sample is outside [350-395 days]	Visits 3, 4, 6, 7 and 8	Immunology
2100	Immunological results not available post-vaccination • No immunological result at visit x for all 3 following tests: RSV A Neutralising antibody titer, RSVPreF3-specific IgG antibody concentration and RSVPreF3-specific CD4+ T cells frequency	Visits 3, 4, 6, 7, 8	Immunology
2120	Obvious incoherence or abnormality or error in data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab	Visits 1, 3, 4, 6, 7, 8	Immunology

5. STATISTICAL ANALYSES

Note that standard data derivation rules and stat methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and stat methods will be described in section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (age at first vaccination in years, gender, race and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error and range will be provided for continuous data such as age.

The distribution of subjects will be tabulated as a whole and per group and for each age category (60-69 years and 70-80 years in Part B only).

Withdrawal status will be summarized by group using descriptive statistics:

- The number of subjects enrolled into the study as well as the number of subjects excluded from PP analyses will be tabulated.
- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal.

5.1.2. Additional considerations

The analysis of demographic characteristics by group will be performed on the ES and on the PPS.

Demography and baseline characteristics will also be summarized by country.

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure, pulse oximetry) and pre-vaccination temperature reported at visit 1 (Part A and Part B) will be summarized by group using descriptive statistics.

Subject disposition in the ES and PPS will be reported as a whole and per group, and for each age category (60-69 years and 70-80 years in Part B only).

Distribution of hematology and biochemistry parameters at baseline with respect to normal laboratory ranges will be tabulated by group.

For Part B only, the follow-up time in the study (in days) up to DLP for analysis or up to last contact will be described overall and by group using descriptive statistics.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

NA

5.2.2. Additional considerations

The number of doses of study vaccines administered will be tabulated by group and by vaccine.

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be performed on the PPS for immunogenicity in Part A and Part B.

In Part B only: if in any study group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is at least 10%, a second analysis will be performed on the ES.

5.3.1.1. Within groups evaluation - humoral immune response

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

In Part A and Part B:

- Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
- GMCs/GMTs and their 95% CI will be tabulated and represented graphically.
- Geometric mean of ratios of antibody titer/concentrations at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.
- Antibody titer/concentration will be displayed using reverse cumulative curves.
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will be computed and tabulated using descriptive statistics.

In Part B only:

- Individual post-vaccination results (at Days 31 and 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots. Results of the placebo group will be used as a reference.

- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers) will be tabulated.
- The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.

The immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The humoral immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.2. Within groups evaluation - Cell-mediated immune response

The following parameters will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI:

In Part A and Part B:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, upon in vitro stimulation and background substracted, measured by ICS using PBMCs.
- Frequency of CD4+ and/or CD8+ T-cells expressing **any combination of immune marker(s)** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs (see details in section 5.3.2.2).
- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ , as measured by ICS using PBMCs.

In Part B only:

- Frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.
- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

This will be displayed overall and by pre-vaccination category: <Q1, Q1-Q3, >Q3, where Q1/Q3 are respectively the 25th and the 75th percentiles of the results at pre-vaccination computed on pooled groups.

In addition, vaccine response in terms of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ, will be explored and summarised by group.

The descriptive immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The cell-mediated immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.3. Between groups evaluation (Part B only)

Statistical analyses will be performed to compare the 9 RSV investigational vaccine formulations in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

The between-groups analysis will be performed using an ANCOVA model, in several steps as follows:

1. The 9 RSV formulations will be first compared to the Placebo in order to identify groups whose means are significantly higher from the mean of the Placebo group, in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells at Day 31 and Day 91 (One-sided alpha=2.5%, Dunnett's adjustment test for multiplicity).
2. The effect of the second vaccination will be evaluated by comparing the means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31), of the groups pooled according to their adjuvant content ($AS01_B$, $AS01_E$ and Plain), in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibody titers (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose).

   Based on the results of this test, the next comparisons will be performed either at Day 91 or at Day 31.
3. Appropriate contrasts will be implemented to compare the RSV formulations as follows:
   - To demonstrate the adjuvant effect (on pooled groups according to their adjuvant content: $AS01_B$, $AS01_E$, Plain), by testing sequentially $AS01_B$ and $AS01_E$ versus Plain (One-sided alpha=2.5% for each superiority test: Adjuvant >Plain) in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibodies and, if applicable, by comparing $AS01_B$ vs $AS01_E$.
   - To demonstrate linearity of increase in immune response when increasing the antigen dose in each adjuvanted group in terms of RSV-A neutralizing antibody and/or RSVPreF3-specific CD4+ T-cells.
   - Further ANCOVA t-tests would demonstrate superiority of 120 µg or 60 µg, should a quadratic effect be demonstrated.

Similar exploratory comparisons might also be performed on the RSVPreF3 ELISA antibody concentrations if deemed necessary.

5.3.2. Additional considerations

5.3.2.1. Within groups – humoral immune response

- Correlations between assays of the humoral response will be investigated using scatter plots generated on pooled RSV groups in Part B:
  - RSVPreF3-specific IgG versus RSV A neutralizing antibody titer at each timepoint,
  - RSV A versus RSV B neutralizing antibody titer at Pre-vaccination and Day 91
  - RSVPreF3-specific IgG versus RSV-B neutralizing antibody titer at Pre-vaccination and Day 91

The same analysis will be performed on the fold increase post over pre-vaccination.

For each assay, values strictly below the cut-off and values strictly greater than the upper limit of quantification (ULOQ) will not be used for the scatter plots neither for the evaluation of the coefficients of correlation.

- The fold increase (post over pre-vaccination) of the RSVPreF3 IgG antibody concentrations versus the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will also be displayed graphically by group using scatter plots.

- The hMPV neutralizing antibody titers will also be tested at Day 1 and Day 91, on all subjects in Part A and on a subset of 40 subjects per group in Part B. The following analysis will be performed for each hMPV subtypes (A1, B1, A2, B2):
  - Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
  - GMTs and their 95% CI will be tabulated and represented graphically.
  - Geometric mean of ratios of antibody titer at post-vaccination time point (Day 91) over pre-vaccination (Day 1) will be tabulated with 95% CI.
  - Antibody titer will be displayed using reverse cumulative curves.
  - Distribution of the fold increase of the antibody titers (post- over pre-vaccination titers) will be tabulated.
  - Individual post-vaccination results (Day 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots for the selected RSV formulation and the placebo group as a reference.

5.3.2.2. Within groups – Cell-mediated immune response

Descriptive statistics of the cell-mediated immune response will be tabulated and displayed graphically using boxplots (min, Q1, median, Q3, max), by group and timepoint.

The RSVPreF3-specific CD4+/CD8+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geomean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+/CD8+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 cytokines [$Freq^{2+}$] will be computed as follows:

$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

And

$$Freq^{2+}_{Specific} = Freq^{2+}_{Induction} - Freq^{2+}_{Background}$$

where

$n^{2+}_{Background}$ = number of CD4+ T cells expressing at least 2 cytokines after stimulation with medium only (background)

$n^{2+}_{Induction}$ = number of CD4+ T cells expressing at least 2 cytokines after stimulation with a pool of peptides covering RSVPreF3 (induction)

$N^{CD4}_{Back/Ind}$ = Total number of CD4 T cells involved in the assay (background or induction)

Same computations will be done for all CMI responses that will be analysed, i.e.:

- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least 2 markers including at least 1 cytokine*** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.

  ** cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17*
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IFN-γ (Th1-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IL-13 (Th2-like response)**, as measured by ICS using PBMCs.

- Frequency of RSVPreF3-specific CD4+/ CD8+ T-cells expressing **at least IL-17 (Th17-like response)**, as measured by ICS using PBMCs.
- **Co-expression profile:** Frequency of RSVPreF3-specific CD4+ T-cells expressing **any combination of marker(s) among** CD40L, IL-2, TNF-α, IFN-γ, as measured by ICS using PBMCs, at Day 31 and Day 91 (→15 combinations).

Vaccine response in terms of RSVPreF3-specific CD4+ T cells frequencies expressing at least 2 markers among CD40L, IL-2, TNF-α, IFN-γ will be explored as follows:

- Distribution of the fold increase: the percentage of subjects with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

For the computation of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ, the results **below the LLOQ** of the assay will be replaced by the value of the LLOQ.

5.3.2.3. Between groups analysis

Statistical comparisons will be performed on the logarithm base 10 transformed results, in terms of RSV-A neutralizing antibody titers and frequency of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

a. Comparisons versus Placebo:

The 9 RSV formulations will be compared to the Placebo (control group) at Day 31 and Day 91 using an ANCOVA model with the Dunnett's adjustment method for multiplicity. The model will include the treatment group and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. Geometric mean ratios between groups and associated Dunnett's adjusted 95% CIs of the ratios will be tabulated.

The Dunnett's test is specifically designed for situations where all groups are to be compared against one "Reference" group. It is commonly used after ANCOVA has rejected the hypothesis of equality of the means of the distributions.

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test (where=(visit=D91));
 CLASS treatmnt Adj agecat;
 MODEL log(titer)=treatmnt baseline agecat / ddfm=KR DDFM=KR
outpm=pred_model cl;
 REPEATED / group=Adj ; /* test homogeneity of variances and consider
different variance by adjuvant content if appropriate */
 LSMEANS treatmnt / ALPHA=0.05 Adjust=Dunnett pdiff=control ("Placebo")
CL;
RUN;
```

b. Comparisons between RSV groups:

The difference between RSV groups will be evaluated using an ANCOVA model including the adjuvant content (AS01B, AS01E, Plain), the antigen dose (30, 60, 120 µg), the visit (Day 31, Day 91) and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. The adjuvant by antigen interaction will also be tested, and included in the model if significant at 10% (p-value <10%).

Based on this global model, appropriate contrasts will be used to perform the following comparisons:

1. Effect of the second vaccination:

   The means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31) will be compared within each pooled group according to adjuvant content (AS01B, AS01E and Plain) (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose). Geometric mean ratios and associated 95% CIs will be tabulated.

2. Adjuvant effect:

   The adjuvant effect will be tested sequentially as follow (One-sided alpha=2.5% for each superiority test):

   i. AS01B versus Plain
   ii. AS01E versus Plain
   iii. AS01B versus AS01E.

   Geometric mean ratios and their 95% CIs will be computed for each comparison.

   The same comparisons will also be performed by age category.

3. Antigen dose-response: test linear and quadratic effect of the antigen dose. Depending on significance of those 2 effects, ANCOVA t-tests might be done to demonstrate superiority of 120 µg or 60 µg.

   Geometric mean ratios and their 95% CIs will be computed for each pairwise comparison within each adjuvant content family (120 µg vs 60 µg, 120 µg vs 30 µg, 60 µg vs 30 µg for Plain, AS01E and AS01B groups).

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test;
 class Adj(1B, 1E, PL) Ag(30, 60, 120) visit(PD1, PD2) subject agecat;
 model log(titer) = Adj Ag visit Adj*Ag Adj*visit Ag*visit Adj*Ag*visit
baseline baseline*visit agecat / DDFM=KR S outpm=pred_model cl;
 REPEATED visit / SUBJECT=subject type=unr group=Adj;
 /* test homogeneity of variances and consider different variance by
adjuvant content if appropriate */

 LSMEANS Adj*visit /E slice=visit CL PDIFF ALPHA=0.05; /*option E to see
coefficients assigned to each effect */
 LSMEANS Adj*visit /E slice=Adj CL PDIFF ALPHA=0.05;
 LSMEANS Adj*Ag*visit / slice=visit CL PDIFF ALPHA=0.05;

/* contrasts to be added for each comparison of interest */
QUIT;
```

The inferential analysis on the RSVPreF3-specific CD4+ T cells will be performed on the log-transformation frequency of the CD4+ T cells expressing at least 2 markers (background or induction) computed by adding an offset of 0.5 cells to the number of activated CD4+ T cells (Delta method, see below). These transformations are deemed appropriate for further inferential analyses provided the incidence of activated CD4+ T-cells is below 4%.

Considering:

$X_{ijk} = \log\left(\frac{n^{2+}_{background} + 0.5}{N^{CD4}_{Background}}\right)$, the log background frequency, and

$Y_{ijk} = \log\left(\frac{n^{2+}_{Induction} + 0.5}{N^{CD4}_{Induction}}\right)$, the log induction frequency

As described for humoral response, the differences between RSV groups will be evaluated using an ANCOVA model including the adjuvant content (AS01B, AS01E, Plain), the antigen dose (30, 60, 120 µg), the visit (Day 31, Day 91) and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log-transformed CD4 T cell frequency following induction and the post-vaccination log-transformed CD4 T cell frequency under background condition as covariates.

All interactions will also be tested and included in the model if significant.

The following model will be used to analyse the log-transformed ratio between induction and background frequencies, and provide estimates of the RSVPreF3-specific CD4+ T cell frequency relative to background frequency. ***These estimates better represent the net effect of the vaccines over the CD4+ T cells frequency as the nuisance background frequency is subtracted from the induction frequency.***

$$\boldsymbol{Y_{ijk} - x_{ijk} = \mu_{jk} + \alpha_j . y_{i0k} + \beta . x_{ijk} + \varepsilon_{ijk},} \quad \textbf{\textit{with}}$$

$$\boldsymbol{\widehat{Y}_{jk} - x_{ijk}|_{\bar{y}_0, \bar{x}} = \mu_{jk} + \alpha_j . \bar{y}_0 + \beta . \bar{x},}$$

LS means conditional to $\bar{y}_0$ and $\bar{x}$, where:

i, j , k=subject *i*, visit j, group *k*; $\bar{y}_0$ = mean log induction frequency at pre-vaccination,

$\bar{x}$ = mean log background after vaccination.

Note: This analysis is assuming that the background is the same for all groups and all timepoints. This assumption will be checked during the analysis.

From that model, the least-squares means are then back-transformed into geometric means for the Induction / Background frequency ratio. The Background mean is then subtracted from the Induction mean and the fold-increase on that difference is calculated, as follows:

$$\hat{Z}_{jk} = 10\hat{}(\hat{Y}_{jk} - \bar{x}) - 1 = \frac{10\hat{}(\hat{Y}_{jk}) - 10\hat{}(\bar{x})}{10\hat{}(\bar{x})}$$, and

$$Log(\hat{W}_{jk}) = Log\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right) = Log\left(\frac{10\hat{}(\hat{Y}_{jk_2}) - 10\hat{}(\bar{x})}{10\hat{}(\hat{Y}_{jk_1}) - 10\hat{}(\bar{x})}\right)$$, where

$\hat{Z}_{jk}$ = mean increase from background to induction frequency relative to background frequency at visit *j* for treatment *k*, and

$\hat{W}_{jk}$ = vaccine effect on the antigen specific frequency following adjustment for background frequency.

The test and the 95% CIs for treatment comparisons will be calculated according to the delta method on the log-transformed ratio of RSVPref3-specific frequency relative to the background frequency estimates.

For each comparison, the covariance matrix of the means is pre multiplied and post-multiplied by the vector of partial derivative to provide the variance of the contrast:

$$Var\left(Log_{10}\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right)\right) = T\left(\nabla_{\hat{Y}_{jk\,1},\hat{Y}_{jk\,2}}(\bullet)\right) \cdot \sum \cdot \nabla_{\hat{Y}_{jk\,1},\hat{Y}_{jk\,2}}(\bullet)$$

Where

$\sum$ *is the covariance matrix, and*

$$\nabla_{\hat{Y}_{jk\,1},\hat{Y}_{jk\,2}}(\bullet) = \nabla_{\hat{Y}_{jk\,1},\hat{Y}_{jk\,2}}\left(Log_{10}\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right)\right) = \begin{pmatrix} -1 - \frac{1}{\hat{Z}_{jk1}} \\ 1 + \frac{1}{\hat{Z}_{jk2}} \end{pmatrix}$$

The Log10(W_{jk}) confidence interval is calculated based on the T-student percentile using the degrees of freedom provided by the MIXED procedure for the difference of means under consideration (eg Y_{jk2} and Y_{jk1}) and the standard error calculated above.

$$Log_{10}\left(LowerCI\left(W_{jk}\right)\right) = Log_{10}\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right) - TINV(1 - alpha/2, df) \bullet \sqrt{Var\left(Log_{10}\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right)\right)}$$

The confidence intervals are then back-transformed to the original units to provide the confidence intervals for W_{jk}. (Amendment 2 – 17 MAR 2020).

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 30-day 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 any AEs considered related to vaccination, for Grade 3 AEs considered related to vaccination and for Grade 3 non-serious AEs.

The percentage of subjects with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will also be tabulated after each dose and overall.

The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for Grade 3 (> 39.0°C/102.2°F) causally related fever.

For each group and for each hematology and biochemistry parameter:

- The percentage of subjects having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
- The summary of grading post-vaccination will be tabulated versus baseline. (Grades will be based on the FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”, see APPENDIX C in the protocol. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on 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 Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. SAEs will also be described in detail.

For Part A only, pregnancy and pregnancy outcomes will be listed (if applicable).

For Part B only, the percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. PIMDs will also be described in detail.

The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 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.

The analysis of safety will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years in Part B only).

5.4.2. Additional considerations

All analyses will be descriptive and will be based on the Exposed Set (ES).

Compliance in completing solicited adverse events information will be tabulated after each dose and overall.

The percentage of subjects with at least **one local solicited** AE, with at least **one general solicited** AE and with **any solicited** AE during the 7-day 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 any AEs considered related to vaccination, and for Grade 3 AEs considered related to vaccination.

The number of days with solicited symptoms reported during the **7-day follow-up period** will be tabulated for each solicited adverse event, after each dose using descriptive statistics (mean, min, Q1, median, Q3, maximum).

The same tabulation will be done for Grade 3 symptoms, and also during **the whole post-vaccination period** (to include the total number of days for symptoms ongoing beyond the follow-up period).

The incidence of each solicited symptom (any grade and grade 3) will also be represented graphically per group and per dose.

Analysis of solicited symptoms will also be done:

- on the **pooled groups according to adjuvant content** (AS01B, AS01E, Plain), overall and by age category.
- On symptoms reported during the 4-day period, i.e. on the day of vaccination and 3 subsequent days, for each group after each dose and overall.

5.4.2.1. Solicited Adverse Events

Solicited adverse events will be reported daily during the 7-day (from Day 1 to Day 7) follow up period after each vaccination, using structured diaries. Missing or non-evaluable measurements will not be replaced.

In order to summarize the data, the maximum intensity of local injection site redness/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity. Body temperature will also be summarized by 0.5°C increments as follows: ≥38.0, >38.5, >39.0, >39.5, >40.0 °C.

Each subject's data will be summarized according to the maximal severity observed during the follow-up period for each adverse event and each dose, followed by a summary across subjects and across doses.

5.4.2.2. Unsolicited Adverse Events

When an unsolicited adverse event occurs more than once for a subject, 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.

The analysis of unsolicited adverse events includes the following categories:

- Any unsolicited adverse event.
- Possibly related unsolicited adverse events.
- Grade 3 unsolicited adverse events
- Grade 3 possibly related unsolicited adverse events.
- Serious adverse events (SAEs)
- Possibly related SAEs.
- Potential Immune-Mediated disease (pIMDs, in Part B only)
- Medically attended adverse events

SAEs and pIMDs reported during the entire study period will be tabulated.

In addition, the following time periods will be considered to report SAEs/pIMDs at the first and second analyses (E1_02 and E1_03, see section 7.1):

- from Dose 1 up to 30 days post dose 2 (or up to 90 days post dose 1 for subjects who did not received the second dose)
- from Dose 1 up to 6 months* post dose 2 (or up to 8 months* post dose 1 for subjects who did not received the second dose).
- From Dose 1 up to Data lock point, in order to report all SAEs/pIMDs reported at the time of analysis.

* months will be converted in days in order to select the events for the output tables.

Listing of AEs/SAEs leading premature withdrawal from study or to interruption of vaccination will be described in detail.

5.4.2.3. Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes:

Solicited symptom	**Lower level term code**	**Corresponding Lower level term decode**
Pain	10022086	Injection site pain
Erythema	10015150	Erythema
Swelling	10053425	Swelling at injection site
Fatigue	10016256	Fatigue
Fever	10016558	Fever
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Headache	10019211	Headache
Myalgia	10028411	Myalgia
Shivering	10040558	Shivering
Arthralgia	10003239	Arthralgia

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.4.2.4. Clinical Safety Laboratory Investigations

In case of invalid or missing results or clinically significant grade 3 and above abnormal laboratory findings, a repeat testing may be done to confirm the first result (see Protocol section 7.1.4). For the analysis, the following rules will be applied:

- In general, the first result will be considered, except if this result is missing.
- In case of retesting for a grade 3 at pre-vaccination, the retesting will be considered if the result is < grade 3.
- If result at Visit 1 is missing, the result of the screening will be used as baseline in the analysis.

5.4.2.5. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.5. Analysis of RTI for Part B

5.5.1. Analysis of RTI planned in the protocol

The analysis will be performed on the ES.

Any RTI episode for which a visit for the assessment of potential RSV-RTI has been performed (with nasal/throat swab sampling) will be considered for the analysis. The assessment of RSV infection will be performed using qRT-PCR on nasal/throat swabs separately for samples collected by the subject and those collected by an appropriately qualified person (i.e., medical or nursing) at the assessment visit.

The proportion of subjects with at least one RSV-associated RTI (with 95 % CI) will be calculated by group.

Descriptive analyses (mean, median, min, max) of viral load assessed by quantitative PCR (RSV-A/B) of RSV-RTI will be performed by study group.

The incidence rate of all-cause RTI (with 95% CI) will be calculated by group. These will also be presented by co-infection identified by multiplex PCR.

5.5.2. Additional considerations

The mean viral load of the RSV positive-RTI samples will also be reported by collection method (at assessment visit or at home) and by collection time (0-2, 3-4, >4 days between RTI onset date of symptoms and collection date).

Information collected at assessment visit will be described for RSV RTI episodes versus Non-RSV RTI episodes, as tested by qRT-PCR on nasal/throat swabs collected at assessment visit. It will include: vital signs, clinical symptoms, self-collected nasal swab result, medically attended visit and SAE related to the episode.

RTI episodes will be described in detail in a listing. In addition, baseline RSV A Neutralizing antibody titer (GMT and 95% CIs) will be presented graphically by RTI episode status (RSV-RTI vs Non RSV-RTI vs No RTI).

6. ANALYSIS INTERPRETATION

All analyses will be descriptive with the aim to characterize the difference in safety/reactogenicity or immunogenicity between groups.

All comparisons will be exploratory. They should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons, except for the comparisons of all RSV formulations vs Placebo (Dunnett's adjustment).

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- **A first analysis** will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 91 are available (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). This will include results from all subjects in Part A and Part B. This analysis will be considered as final for those endpoints. A clinical study report will be written.

  At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available), but no individual listings will be provided to the study team. Given that summary safety results may unblind some specific subjects, the study will be considered as single-blind from this point onwards, with subjects remaining blinded up to study end (Visit 8, Month 14). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.
- **A second analysis** will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:
  - The safety analysis of data up to 6 months post-Dose 2.
  - The analysis of all qPCR data available at that time.
  - The analysis of laboratory results that may become available at that time.
- **A third immunogenicity analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 8 are available, to evaluate the persistence up to 6 months post-Dose 2 in Part B.

- **A fourth analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 14 (Visit 8) are available for the subjects enrolled in Step 1 of Part B. This analysis will include any additional laboratory results that may become available at that time.

  No individual listings will be provided before the final end of study analysis.

- **The final end of study analysis** will be performed when all data for at least primary and secondary endpoints up to study conclusion are available (Month 14). All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage. An integrated clinical study report containing all available data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Reference for TFL TOC
Final analysis	E1_01	SR, CTRS	See column A in TFL TOC
Analysis up to Day 91	E1_02	SR, CTRS	See column B in TFL TOC
Analysis up to Month 8 (safety and PCR)	E1_03	Internal	See column C in TFL TOC
Analysis up to Month 8 (immuno)	E1_04	Internal	See column D in TFL TOC
Analysis up to Month 14 (Part B Step 1)	E1_05	Internal	See column E in TFL TOC

7.2. Statistical considerations for interim analyses

All confirmatory analyses will be conducted on final data (as clean as possible) and therefore no statistical adjustment for interim analyses is required.

8. CHANGES FROM PLANNED ANALYSES

Statistical analyses

The fold-increase parameter for CMI (post over pre-vaccination) that will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI has been adapted as follows:

- ***Fold increase (Post over pre-vaccination)*** of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 marker(s) among IL-2, CD40L, TNF-α, IFN-γ , ***as measured by ICS using PBMCs.***

This analysis was also added for the Memory B cells:

- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

All additional analysis planned compared to protocol are described in the "Additional considerations sections". The mains ones to be included in the CSR are also described below (changes indicated in bold):

- Demography and baseline characteristics will be summarized ***by country***.
- Vital signs at baseline will be described by group using descriptive statistics.
- Exposure to study vaccine will be tabulated by group and by vaccine
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV neutralizing antibody titers will be reported for RSV-A ***and RSV B***.
- Comparisons with Placebo will be done ***at Day 31*** and Day 91, for both RSV A Neutralizing antibody ***and CD4+ T cells expressing at least 2 markers***.
- Analyses of solicited symptoms were added: incidence of any/local/general solicited AEs, number of days with solicited AEs, analysis on pooled groups according to adjuvant content.
- RTI episodes: analysis of viral load by collection method and collection time was added, as well as the description of signs and symptoms for RSV-RTI vs Non-RSV RTI cases.
- Analysis of hMPV neutralizing antibody titers on all subjects in Part A and on a subset of subjects in Part B.

Sequence of analyses

The wording of the 2nd analysis have been adapted as follows to allow the descriptive analysis of any additional immunogenicity results available for all subjects or for part of them:

- **A second analysis** will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:
  - The safety analysis of data up to 6 months post-Dose 2.
  - The analysis of all qPCR data available at that time.
  - ***The analysis of laboratory results that may become available at that time.***

Sensitivity analysis

An issue in the randomization was identified on 23rd of July, and was identified as Significant Quality Issue (SQI) on the 6th of November 2019.

Randomization were performed in SBIR to create "placeholders"

1. For subjects whose eligibility was not yet confirmed
2. For subjects who were identified and whose ICF was not yet signed
3. For subjects not yet identified

This was not allowed neither based on the protocol, nor by consulting the central team.

As this issue might have an impact on the randomization, a sensitivity analysis will be performed excluding subjects who were randomized after the 23rd of July (randomization date >= 23JUL2019), for immunogenicity secondary endpoints at the time of first analysis (table template 17 and 22).

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Handling of missing data

9.1.1. Dates

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 other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

9.2. Duration of events

When a solicited AE is ongoing at the end of the solicited follow up period (Day 7), the following rules will be applied:

- If the event is present at Day 7 and information is available at each day up to the end of the event: count number of days with event up to last day reported
- If information is missing at several days between the first day with the event and the end of event: count missing days as days with an event (worst case scenario)
- For Grade 3 AEs: take into account the grading of the last day with AE reported (last observation carried forward)

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject 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 CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day 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.

See also exceptions in section 9.1.

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited symptoms, symptoms will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. 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

Conversion of temperature from °Fahrenheit to °C will be performed according to SDTM specifications.

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	**Derived value**
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is > ULOQ	ULOQ*
All other cases	missing

*This rule will be used to computed descriptive statistics (GMTs, fold increase,etc). All values might be displayed in RCCs and scatter plots with individual results.

10.1.3.4. 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. Antibody titers or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

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

10.1.3.6. Duration of events

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

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

See also specific rules for ongoing symptoms in section 9.2.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse 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.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal.

Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22.2%
1/45	2.2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.

Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics 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 minima of transformed body temperatures will be displayed with one decimal.

10.1.4.3. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Adjusted GMT or GMC ratios

When between-group GMT or GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The TFL TOC provides the list of tables/figures/listings that will be generated at each analysis. It can be found in eTMF folder section 11.01.01.

The mock tables/figures referred under column named ‘layout’ can be found in section 12.

11. REFERENCES

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

12. STUDY MOCK TFLS

The following drafted standard and study specific mocks will be used. Note that standard templates might be updated based on the last version of the standard catalogue used at the time of analysis. Titles and footnotes will be adapted accordingly.

The data display, title and footnotes are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment.

12.1. Demography

Template Table 1 Summary of demography and baseline characteristics (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**
Age (years) at first vaccination				
N	xxx		xxx	
Mean	xxx.x		xxx.x	
Standard Deviation	xxx.x		xxx.x	
Median	xxx.x		xxx.x	
Minimum	xxx		xxx	
Maximum	xxx		xxx	
Sex				
Male	xxx	xx.x	xxx	xx.x
Female	xxx	xx.x	xxx	xx.x
Ethnicity				
<Each Ethnicity>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Race				
<Each Race>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Age category				
<Each Age category>	xxx	xx.x	xxx	xx.x
CMV status				
Positive	xxx	xx.x	xxx	xx.x
Equivocal	xxx	xx.x	xxx	xx.x
Negative	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template Table 2 Number of subjects by country and center (Exposed Set)

		<Each group> N=XXXX		Total N=XXXX	
Country	**Center-Investigator Name**	**n**	**%**	**n**	**%**
<each country>	<each center-investigator name>	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template Table 3 Number of subjects by study steps (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
Steps	**n**	**%**	**n**	**%**
Part A				
Part B Step 1				
Part B Step 2				

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template Table 4 Summary of vital signs (Exposed Set)

			<Each group> N=XXXX	Total N=XXXX
Visit	**Characteristics**	**Parameters**	**Value**	**Value**
<EACH VISIT>	Heart rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Respiratory rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Systolic Blood pressure (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Diastolic blood pressure (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Pulse oximetry (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Pre-vaccination Temperature (C)	n		
		Mean		
		SD		
		Median		
		Minimum		
		Maximum		

Short group label = long group label

N = total number of subjects

Value = value of the considered parameter

n = number of subjects in a given category

N with data = number of subjects with documentation of the corresponding data

SD = standard deviation

Template Table 5 Summary of study completion with reason for withdrawal (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	n	%	n	%
Completed the study	xxx	xx.x	xxx	xx.x
Withdrawn from the study	xxx	xx.x	xxx	xx.x
Primary reason for withdrawal :				
<Each reason>	xxx	xx.x	xxx	xx.x

Short group label = long group label

Template Table 6 Summary of visit attendance (Exposed Set)

		<EACH GROUP> N=XXXX		Total N=XXXX	
Visit	Status	n	%	n	%
<EACH VISIT>	Attended	xx	xx.x	xx	xx.x
	Did not attend yet	xx	xx.x	xx	xx.x
	Withdrawal at visit or earlier	xx	xx.x	xx	xx.x
	Did not attend	xx	xx.x	xx	xx.x

Short group label = long group label
N = Number of subjects in each group or in total
n/% = number / percentage of subjects in a given category

Template Table 7 Summary of important protocol deviations leading to elimination from any analyses (Enrolled Set)

Category Sub-category	<Each group> N=XXX			Total N=XXX		
	Occ	n	%	Occ	n	%
At least one Important Protocol Deviation						
< Each category >						
<each sub-category>						

Short group label = long group label
N = Total number of subjects
Occ = number of occurrences = number of important protocol deviations
n/% = number / percentage of subjects with important protocol deviations

Template Table 8 Summary of subject disposition from Enrolled set to Randomized set (Enrolled Set)

	Total N=	
	n	%
Withdrawals prior to randomization		
<withdrawal reason 1>		
<withdrawal reason 2>		
…		
Number of subjects included in randomized set		

N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 9 Summary of subject disposition from Randomized Set to Exposed set (Randomized set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Number of subjects included in the Exposed set				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 10 Summary of subject disposition from Exposed Set to Per Protocol Set at visit x (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Number of subjects included in the Per Protocol set at visit x				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 11 Summary of subject disposition from Exposed Set to End of study (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Number of subjects who completed the study				
Completed with 1 dose				
Completed with 2 doses				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 12 Deviations from protocol for age and intervals between study visits (Exposed set)

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
Age	<age range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	
<each interval between study visit>	<interval range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Template Table 13 Number of enrolled subjects by country

		<Each group> N = XXX	Total N = XXX
Characteristics	**Categories**	**n**	**n**
Country	<each country>		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given country or for all countries

Template Table 14 Number of enrolled subjects by age category

		<*each group*> N =	Total N =
Characteristics	**Categories**	**n**	**n**
Age category	Adults [18-64 years]		
	Adults [65-84 years]		
	Missing		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = age at study vaccination unknown

Template Table 15 Minimum and maximum visit dates <analysis set name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
< each informed consent>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
[Randomization]	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

12.2. Exposure

Template Table 16 Exposure to study vaccines by vaccine (Exposed Set)

		<Each group> N=XXXX		<Each group> N=XXXX	
Vaccine administered	**Number of subjects receiving**	**n**	**%**	**n**	**%**
< Vaccine A>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x
	Total number of doses administered during the study	xxx		xxx	
< Each vaccine>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x
	Total number of doses administered during the study	xxx		xxx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered analysis set
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

12.3. Immunogenicity

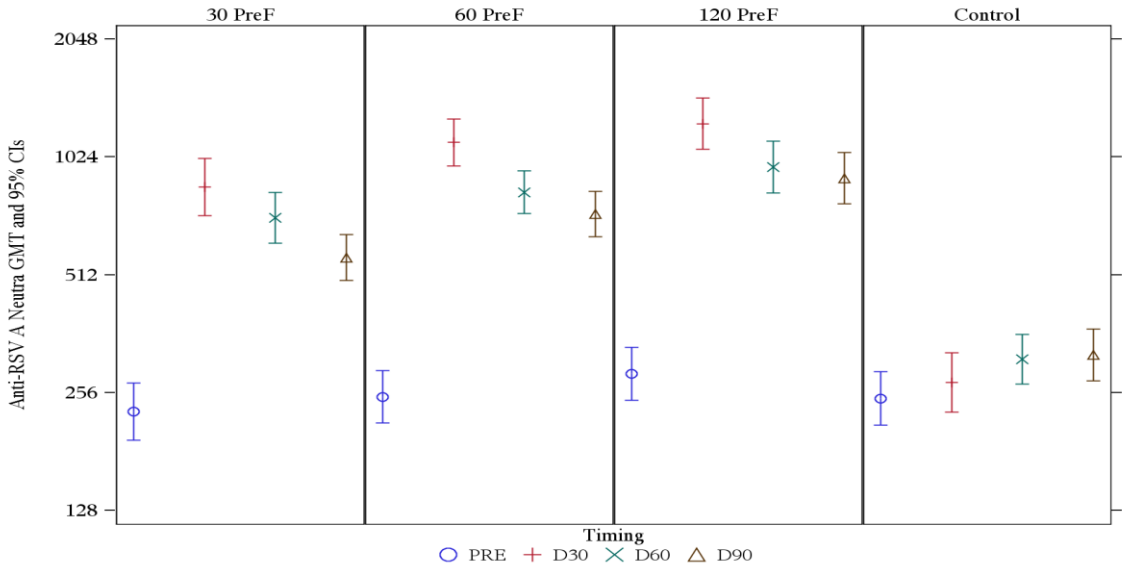
12.3.1. Within groups

Template Table 17 Number and percentage of subjects with <antibody titer /concentration> equal to or above <cut-off unit> and <GMT/Cs> <analysis set name>

				>=cut-off unit				GMT/C				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
<each antibody>	<each group>	<each timing>										

Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
N = Number of subjects with available results
n/% = number/percentage of subjects with titer/concentration equal to or above specified value
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Short timing label = long timing label

Template Figure 1 <GMT/Cs> and their 95% CIs for <antibody titers/ concentrations> <analysis set name>



Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
95% CI = 95% confidence interval
Short timing label = long timing label

Note: This graph is provided as an example.
For RSV A Nab and RSVPreF3- specific IgG Ab, it will be adapted to display: all the groups (4 groups for Part A, 10 groups for Part B) and all available timepoints (4 TPs up to Day 91, 6 TPs up to study end for Part B).
If needed for Part B, this graph might be split in several graphs: either by adjuvant content vs Placebo or by antigen content vs Placebo.

Same graph will be generated for RSV B NAb with 2 timepoints (10 groups, at Days 1 and 91), for RSVPreF3 site 0 Ab with 2 groups and 2 timepoints (selected formulation and Placebo groups, at Days 1 and 91), and for hMPV Nab (10 groups, at Days 1 and 91).

Template Table 18 Geometric mean of the individual ratio of <antibody titers/concentrations (units)> post-vaccination compared to pre-vaccination <Per Protocol Set>

						<GMT,C> ratio			
								95% CI	
Group	**N**	**Time point description**	**<GMT,C>**	**Time point description**	**<GMT,C>**	**Ratio order**	**Value**	**LL**	**UL**
<each group>	xxx	PI(D31)		PRE		PI(D31) / PRE			
		<Each time point>		PRE		<time point> / PRE			

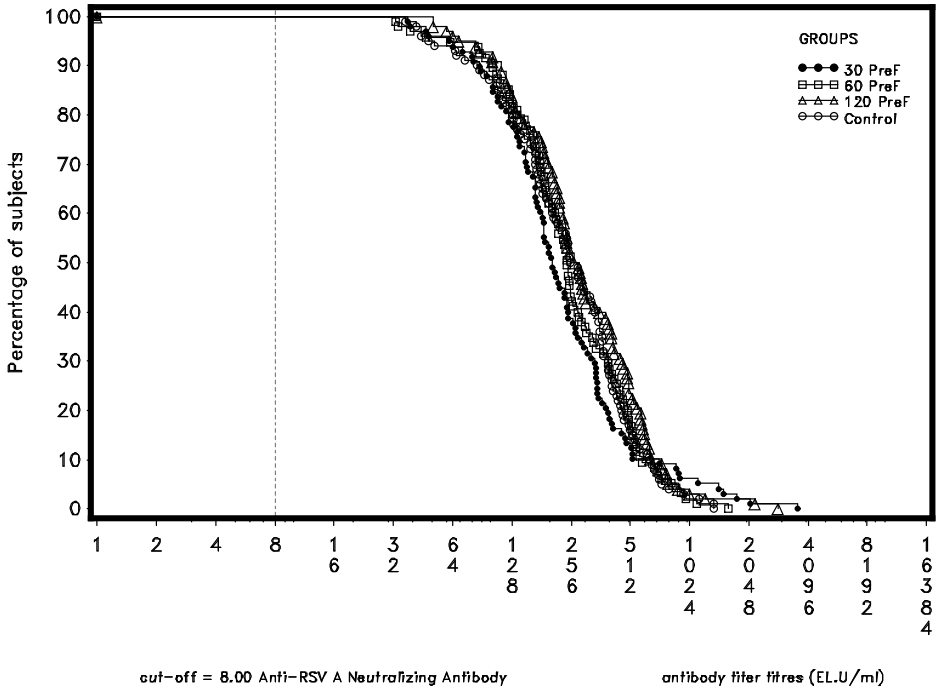
Short group label = long group label
<GMT,C> = geometric mean antibody <titer,concentration>
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template Table 19 Distribution of <antibody titers/concentrations> fold increase post-vaccination compared to pre-vaccination <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	**Timing**	**FI**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each antibody>	<each timing>	< 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
FI= Fold Increase post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with <titer, concentration> fold change meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template Figure 2 Reverse cumulative distribution curve of <antibody titers/concentrations> in the <group label> group <Per Protocol Set>

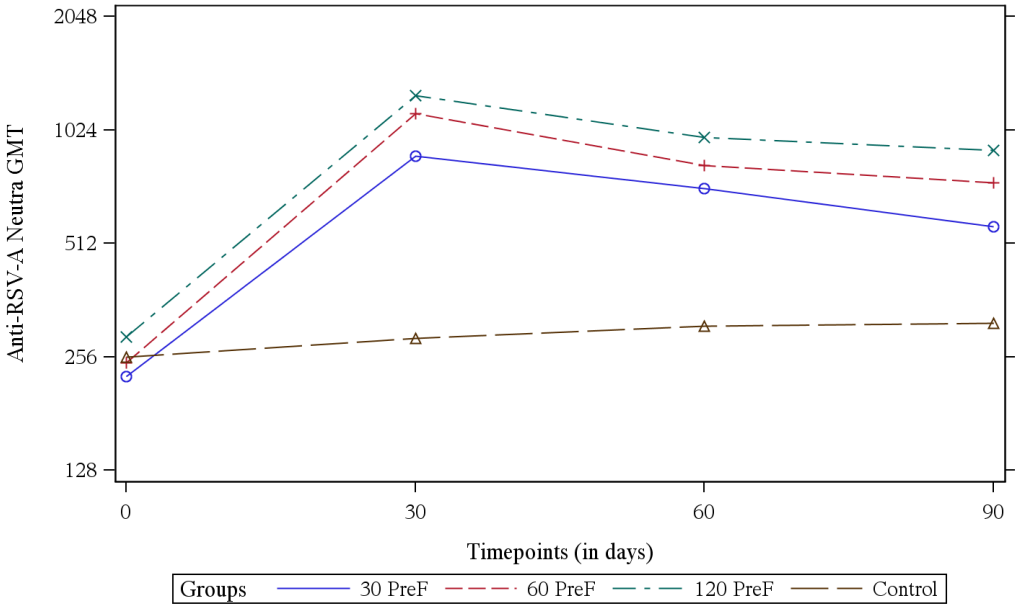


Short group label = long group label
Short timing label = long timing label

Note: this graph is provided as an example. It will be generated by group, and will be adapted to display the 4 timepoints (PRE, D31, D61, D91) for the considered group. For Part B, same graphs will also be generated at Day 91 with groups according to adjuvant content or antigen content vs Placebo. If applicable, the upper limit of quantification will be presented (similarly to the cut-off).

For RSV B Nab ,RSVPreF3 site 0 specific Ab and hMPV NAb, the figure will display only 2 timepoints (Days 1 and 91).

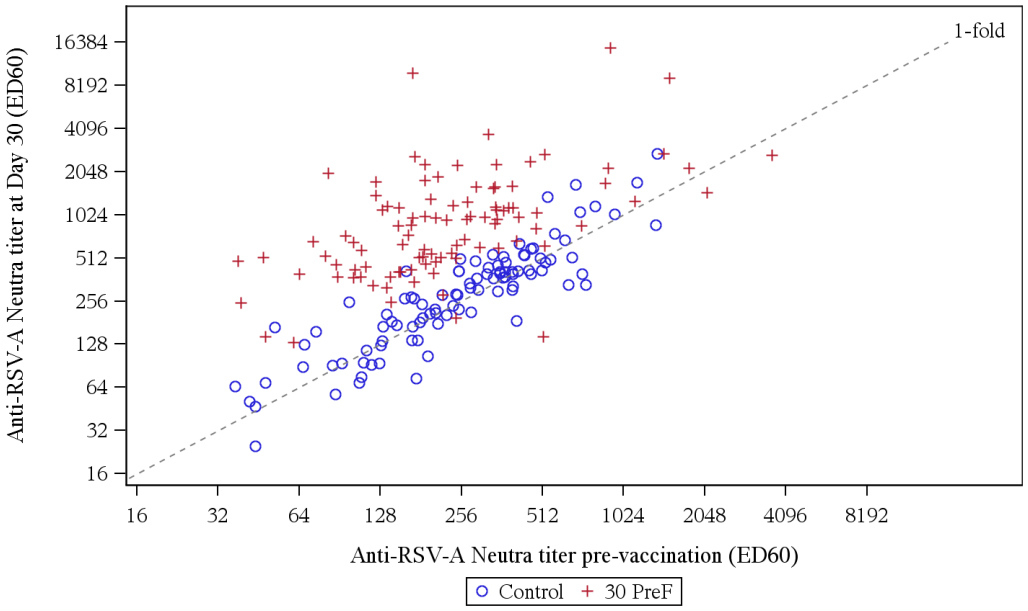
Template Figure 3 Kinetics of < antibody GMT/Cs> on subjects with results available at all timepoints up to <Day 91, Month 14> <Per protocol set>



Short group label = long group label
Short timing label = long timing label

Note: This graph is provided as an example. Template will be adapted to display all the groups (10 groups for Part B) and all the timepoints (4 TPs up to Day 91, 6 TPs up to study end).

Template Figure 4 Individual results of <RSV A Neutralizing antibody titer> at <time point> versus pre-vaccination in <group label> and Placebo_B groups <Per protocol set>

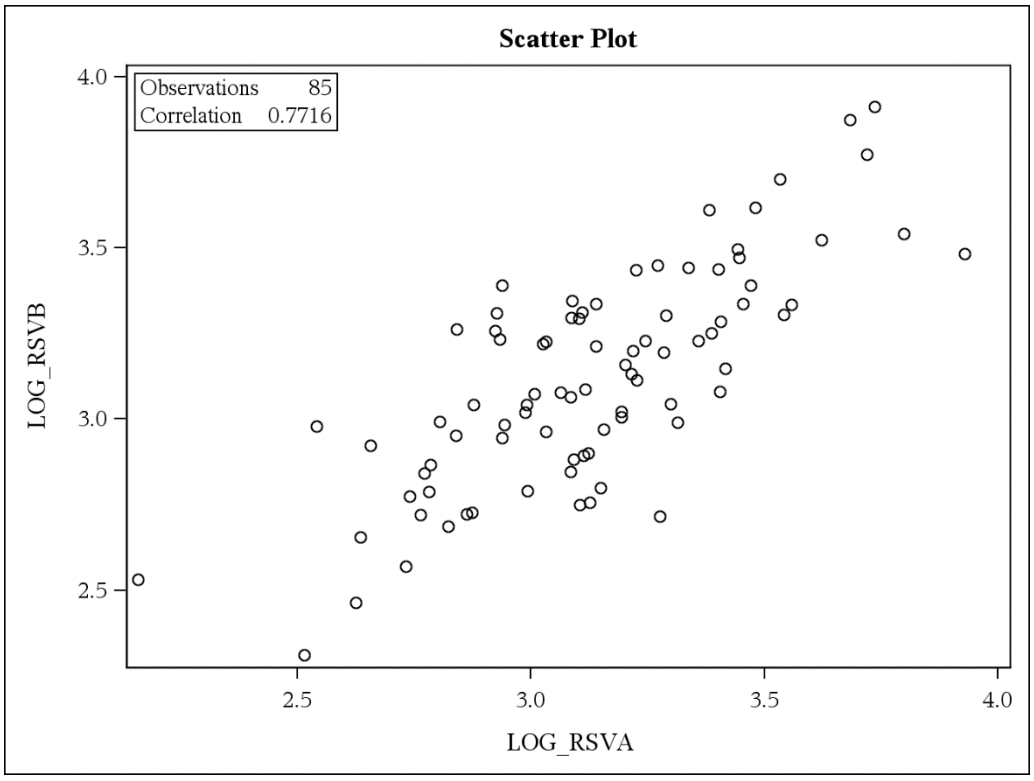


Short group label = long group label
Short timing label = long timing label

Note: This graph is provided as an example. It will be generated as follows:

- RSV A Nab at Day 31 and Day 91, for each RSV groups (18 graphs)
- RSVPref3 IgG at Day 31 and Day 91, for each RSV groups (18 graphs)
- RSV B Nab at Day 91, for the selected formulation (1 graph)

Template Figure 5 Individual results of <RSV A versus RSV B Neutralizing antibody titer> at <time point> , on pooled RSV groups <Per protocol set>



Note: this graph is provided as an example. It will be generated on pooled RSV groups as follows:

- RSV A Nab vs RSVPreF3 IgG at each timepoint
- RSV A Nab vs RSV B Nab at Pre and Day 91
- RSV B Nab vs RSVPreF3 IgG at Pre and Day 91

Correlation coefficient will be computed on Log10 transformed data.
Raw data will be presented on Log10 axes.

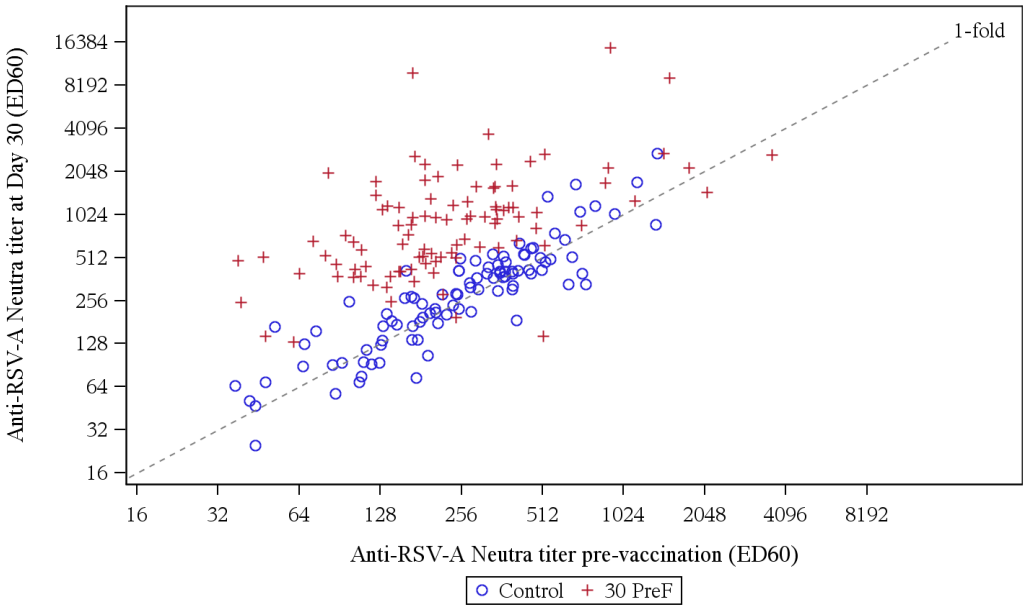
The same graphs will be generated on fold increase Post over Pre.

Template Table 20 Geometric mean ratios of the fold increase (Pre to Post - vaccination) between RSVPreF3 IgG antibody concentrations and <RSV-A, RSV-B> neutralising antibody titers <Per protocol set>

									GM ratio of FI		
										95% CI	
Timepoint	Group	N	RSVPref3 IgG GMF	95% CI		<*RSV-A, B*> Nab GMF	95%		Value	LL	UL
				LL	UL		LL	UL			
PI(D31)/PRE	<each group>										
<each timepoint>											

Short group label = long group label
N = Number of subjects with available results at the two considered time points (post and pre) for both RSVPreF3 IgG and <*RSV-A, B*> Nab
GMF = Geometric mean fold increase Pre to Post-vaccination
GM ratio of FI=Geometric mean ratio of fold increase (Pre to Post)
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template Figure 6 Individual results of the fold increase (post over pre-vaccination) of RSVPreF3 IgG antibody concentrations versus <RSV A, RSV B> neutralizing antibody titers at <time point> in <group label> <Per protocol set>



Short group label = long group label

Note: This graph is provided as an example. It will be generated as follows:

- Y axis=RSVPreF3 IgG vs X axis=RSV A Nab, at Days 31 and 91, for each RSV group (18 graphs)
- Y axis= RSVPreF3 IgG vs X axis=RSV B Nab at Day 91, for the selected formulation (1 graph)
- Axes will be in Log10.

Template Table 21 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

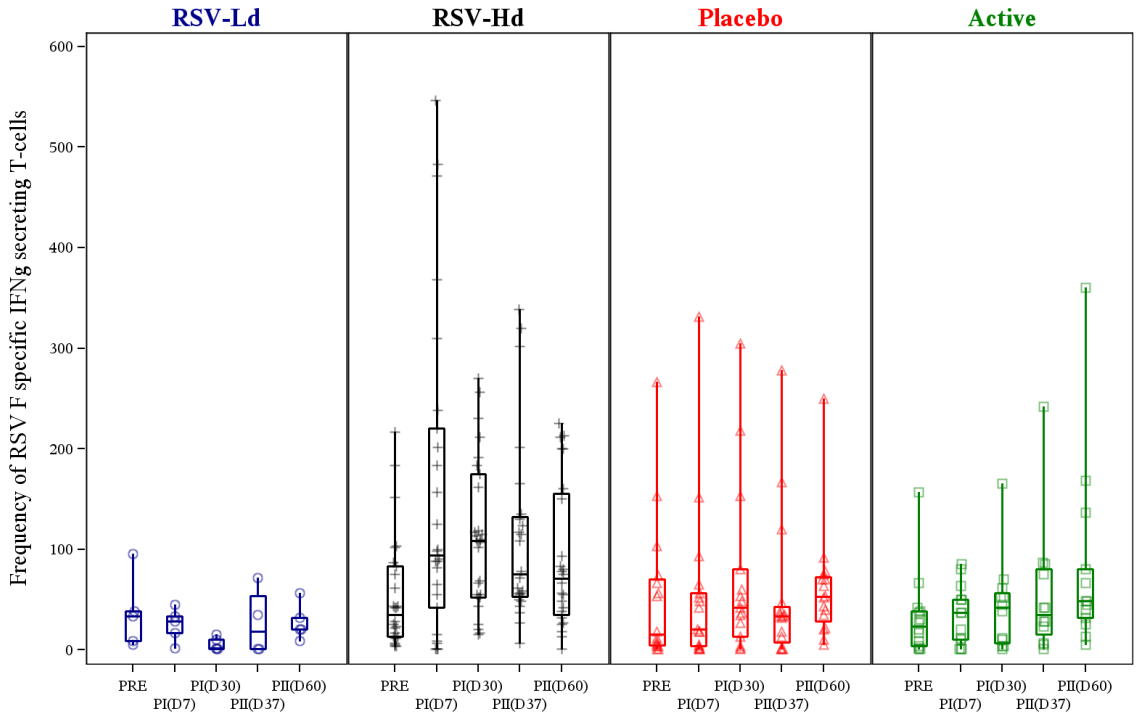
Note: this table will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).

Template Table 22 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS), by pre-vaccination category <Per Protocol Set>

				<Each group>	<Each group>
Immune Marker	**Pre-vaccination status**	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Q1	<Each timing>	N	xxxx	xxxx
			GM	xx.x	xx.x
			SD		
			Minimum	xx.x	xx.x
			Q1	xx.x	xx.x
			Median	xx.x	xx.x
			Q3	xx.x	xx.x
			Maximum	xx.x	xx.x
	[Q1-Q3]	<Each timing>	<each parameter>		
	>Q3				
	Total				

Short group label = long group label
<Q1= subjects with pre-vaccination frequency < Q1 of the frequencies at pre-vaccination computed on pooled groups
Q1-Q3= subjects with pre-vaccination frequency within [Q1-Q3] of the frequencies at pre-vaccination computed on pooled groups
>Q3=subjects with pre-vaccination frequency < Q3 of the frequencies at pre-vaccination computed on pooled groups
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Figure 7 Boxplots with individual data of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol set>



Short group label = long group label
Short timing label = long timing label

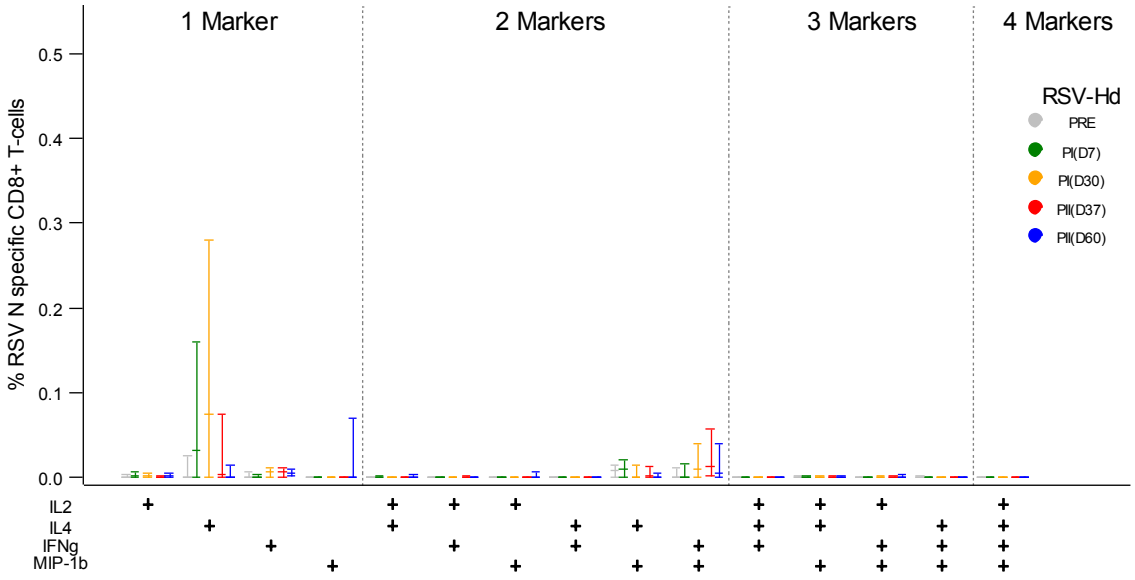
Note: This graph is provided as an example. Depending on the analysis, it will display groups and timepoints as follows:

- Part A: 1 graph with 4 groups and 3 (D1, D31, D91) or 4 timepoints (D1, D31, D61, D91)
- Part B: 3 graphs with 4 groups (either by adjuvant content or by antigen content vs Placebo), and 3 timepoints (D1, D31, D91) or 5 timepoints (up to Month 8) or 6 timepoints (up to Month 14, only for selected Ag dose and Placebo)

This graph will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).

For Part B, the same graph will be generated for memory B-cells, with 4 groups (selected Ag dose with Plain/AS01E/AS01B, and Placebo) and 4 timepoints (PRE, D31, D91, M14).

Template Figure 8 Frequency of RSVPreF3 specific CD4+ T-cells expressing any combination of markers among IL-2, CD40L, TNFa, IFNg in <group label> group at Day 31 and Day 91 (per million of CD4+ T cells, by ICS) <Per Protocol Set>



Short group label = long group label
Short timing label = long timing label

Note: This graph is provided as an example. It will be generated by group and will be adapted to display Q1-Median-Q3 for each combination of the markers (15) at Day 31 and Day 91.

Template Table 23 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**Value**
<At least 2 markers>	<Each timing post-vaccination>	N	xxxx	Xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results at both timepoints (pre and post)
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 24 Descriptive statistics of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 25 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing post-vaccination>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 26 Distribution of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Assay	Timing	FI	N	n	%	LL	UL	N	n	%	LL	UL
<assay name>	<each timing>	< 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
FI= Fold increase Post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with fold increase meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

12.3.2. Between groups

Template Table 27 Comparisons of the 9 RSV formulations versus Placebo in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at one month post <dose 1 (Day 31), dose 2 (Day 91)> (ANCOVA model, Dunnett's test) – Part B <Per Protocol set>

Assay	Timepoint	RSV group	N	GM<T,F> ratio (RSV over Placebo)	Dunnett's 95% CI		Dunnett's p-value
					LL	UL	
<assay name>	<Day 31, Day 91>	30-PLAIN_B					
		60-PLAIN_B					
		120-PLAIN_B					
		30-AS01E_B					
		60-AS01E_B					
		120-AS01E_B					
		30-AS01B_B					
		60-AS01B_B					
		120-AS01B_B					

Short group label = long group label
N= Number of subjects with both pre- and post-vaccination results available
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
RSV Vaccine is considered superior to Placebo if one-sided p-value <0.025
Dunnett's 95% CI = 95% confidence interval based on Dunnett's adjustment, LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment and age category as fixed effects

Template Table 28 Comparisons of the mean responses post dose 2 (Day 91) versus post dose 1 (Day 31) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> on pooled groups according to adjuvant content (ANCOVA model) – Part B <Per Protocol set >

Assay	RSV group	N	GM<T,F> ratio (D91/D31)	95% CI		p-value
				LL	UL	
<assay name>	PLAIN_B					
	AS01E_B					
	AS01B_B					

Short pooled group label = long pooled group label
N= Number of subjects with results available at both timepoints
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
PII D91 is considered as significantly higher to PI D31 if one-sided p-value <0.025
95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the adjuvant content, antigen dose and age category as fixed effects

Template Table 29 Comparisons of the RSV groups pooled according to their adjuvant content (Plain, AS01E, AS01B) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) - Part B <Per Protocol set>

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	Timepoint	Group 1	N	GM<T,F>	LL	UL	Group 2	N	GM<T,F>	LL	UL	Value	LL	UL	p-value
<assay name>	<each timing>	AS01B_B					PLAIN_B								
		AS01E_B					PLAIN_B								
		AS01B_B					AS01E_B								

Short group label = long group label
GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects
Group 1 is considered superior to Group 2 if one-sided p-value <0.025

Template Table 30 Comparisons of the RSV groups (by antigen dose level) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) – Part B <Per Protocol set >

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	Timepoint	Group 1	N	GM<T,F>	LL	UL	Group 2	N	GM<T,F>	LL	UL	Value	LL	UL	p-value
<assay name>	<each timing>	120-PLAIN_B					60-PLAIN_B								
		120-PLAIN_B					30-PLAIN_B								
		60-PLAIN_B					30-PLAIN_B								
		120-AS01E_B					60-AS01E_B								
		120-AS01E_B					30-AS01E_B								
		60-AS01E_B					30-AS01E_B								
		120-AS01B_B					60-AS01B_B								
		120-AS01B_B					30-AS01B_B								
		60-AS01B_B					30-AS01B_B								

Short group label = long group label

GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance);

LL = lower limit, UL = upper limit

ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment, age category and gender as fixed effects

Group 1 is considered superior to Group 2 if one-sided p-value <0.025

Template Table 31 Parameters of the ANCOVA model for the comparison between RSV groups in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg>– Part B <analysis set name>

Timepoint	Variable	DF	Fvalue	p-value
<each timepoint>	Pre-vaccination log <titer, frequency>			
	Age category			
	Adjuvant			
	Antigen			
	Visit			
	Linear effect of antigen			
	Quadratic effect of antigen			
	Antigen*Adjuvant			

Antigen = Antigen dose (3 levels: 30, 60, 120 mcg)
Adjuvant = Adjuvant content (3 levels: no adjuvant, AS01E, AS01B)
Antigen*Adjuvant = interaction between antigen dose and adjuvant
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects
DF = degrees of freedom
Interaction (Antigen * Adjuvant) considered as statistically significant if p-value <0.100
Main factors (Pre-vaccination, antigen, adjuvant) considered as statistically significant if p-value <0.050 (model including interaction)

12.4. Safety

Template Table 32 Compliance in completing solicited adverse events information (Exposed Set)

	<Each group>		
DOSE	**N**	**n**	**Compliance (%)**
Vaccination at Visit 1	xxx	xxx	xx.x
Vaccination at Visit 4	xxx	xxx	xx.x
TOTAL	xxx	xxx	xx.x

Short group label = long group label
N=Number of administered vaccinations
n = number of vaccinations with solicited symptom information completed
Compliance (%) = (n / N) X 100

Template Table 33 Incidence and nature of <grade 3> symptoms (solicited and unsolicited) <with causal relationship to vaccination> reported during the XX-day (Days 1-XX) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 34 Incidence of any symptoms (solicited and unsolicited) resulting in medically attended visit, reported during the 30-day (Days 1-30) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 35 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <analysis set name>

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
DOSE 2	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
OVERALL/DOSE	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
OVERALL/SUBJECT	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 36 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <cohort name>

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
DOSE 2	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/DOSE	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/SUBJECT	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					

Short group label = long group label

For each dose:

N = number of subjects with the corresponding documented dose

n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose

For Overall/dose:

N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom

For Overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting the type of symptom at least once

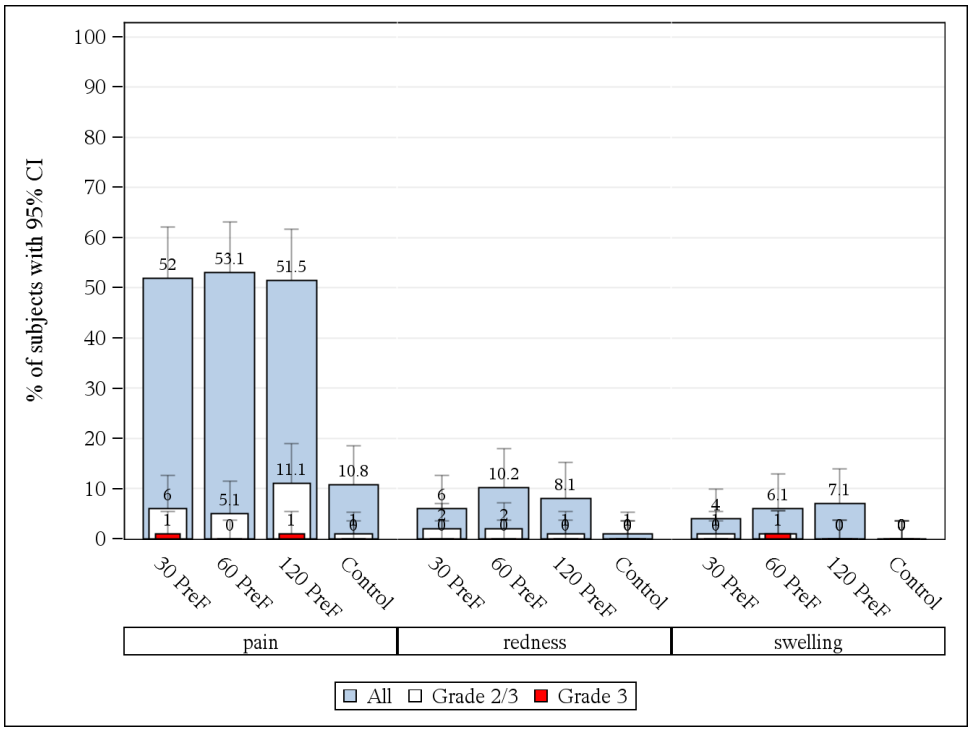
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 37 Number of days with <*local/general*> solicited symptoms during <the 7-day (Days 1-7), the whole> post-vaccination period <analysis set name>

			<Each group>
Dose	**Symptom**	**Statistic**	**Value**
DOSE 1	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
DOSE 2	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
OVERALL/DOSE	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	

Short group label = long group label
n = number of doses with the symptom
Q1 = 25th percentile
Q3= 75th percentile

Template Figure 9 Incidence of solicited <local, general> adverse events reported during the 7-day (Days 1-7) post-vaccination period following each dose <Exposed set>



Short group label = long group label

Note: this graph is provided as an example. It will be adapted to display the percentage of subjects reporting each local or general symptom, any grade and grade 3, by group and by dose. Template will be discussed at the time of the dry-run.

Template Table 38 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the 30-day (Days 1-30) post-vaccination period <analysis set name>

		<Each group> N=XXXX					Total N=XXXX				
					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	N	%	LL	UL
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
…	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
	…										

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects included in the considered analysis set in each group
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template Table 39 List of (S)AEs and solicited adverse events leading to study/treatment discontinuation <Exposed set>

Group	Sub. No	Country	Gender	Race	AE Description	Preferred Term	SAE	Causality	Outcome	Vaccination and visit	Type of discontinuation *

Short group label = long group label
* type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template Table 40 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<each group>								

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD source
<each group>										

Short group label = long group label

Template Table 41 Listing of SAEs <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>							

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>									

Short group label = long group label

Template Table 42 Listing of pregnancies reported during the study period in Part A <analysis set name>

Group	Sub. No.	Country	Race	Age at vaccination	Previous Dose	LMP date	Days between LMP-vacc	Age at delivery (Year)	Date of delivery	Pregnancy Outcome	Date of outcome	Gestational weeks at birth/miscarriage /termination

Short group label = long group label
LMP=Last Mentrual Period

Template Table 43 Number and percentage of subjects taking concomitant medication during the <XX>-day (Days 1-<XX>) post-vaccination period by dose and overall <analysis set name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**N**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = total number of subjects with the corresponding administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses after which the specified type of concomitant medication was taken at least once during the considered period
For overall/subject:
N = total number of subjects with at least one administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 44 Distribution of change from baseline in hematology and biochemistry with respect to normal laboratory ranges, 7 days post dose <1, 2> <analysis set name>

			<Each group>			<Each group>		
Laboratory parameter	Range indicator at Baseline (PRE)	Range indicator at post-vaccination	N	n	%	N	n	%
<Each parameter>	UNKNOWN	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	BELOW	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	WITHIN	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	ABOVE	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						

Short group label = long group label
N = number of subjects with available results for the specified laboratory parameter and timing in a given baseline category
n/% = number/percentage of subjects in the specified category
Below = below the normal laboratory range defined for the specified laboratory parameter
Within = within the normal laboratory range defined for the specified laboratory parameter
Above = above the normal laboratory range defined for the specified laboratory parameter

Baseline= Pre-vaccination at <Day 1, Day 61>
Post-vaccination= Post vaccination at <Day 8, Day 68>

Template Table 45 Summary of hematology and biochemistry results by grade at 7 days post dose <1, 2 > versus baseline (<Day 1, Day 61>) <analysis set name>

			<each group >		
Laboratory parameter	Baseline	Post-vaccination	N	n	%
<Each parameter>	Unknown	Unknown			
		<Each grade>			
	<Each grade>	Unknown			
		<Each grade>			
	Total	Unknown			
		<Each grade>			

Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
Baseline= Pre-vaccination at <Day 1, Day 61>
Post-vaccination= Post vaccination at <Day 8, Day 68>

Note: Templates 45 and 46 will be generated post dose 1 with results at Visit 2 (Day 8) versus baseline at Day 1, and post dose 2 with results at Visit 5 (Day 68) versus baseline at Day 61.

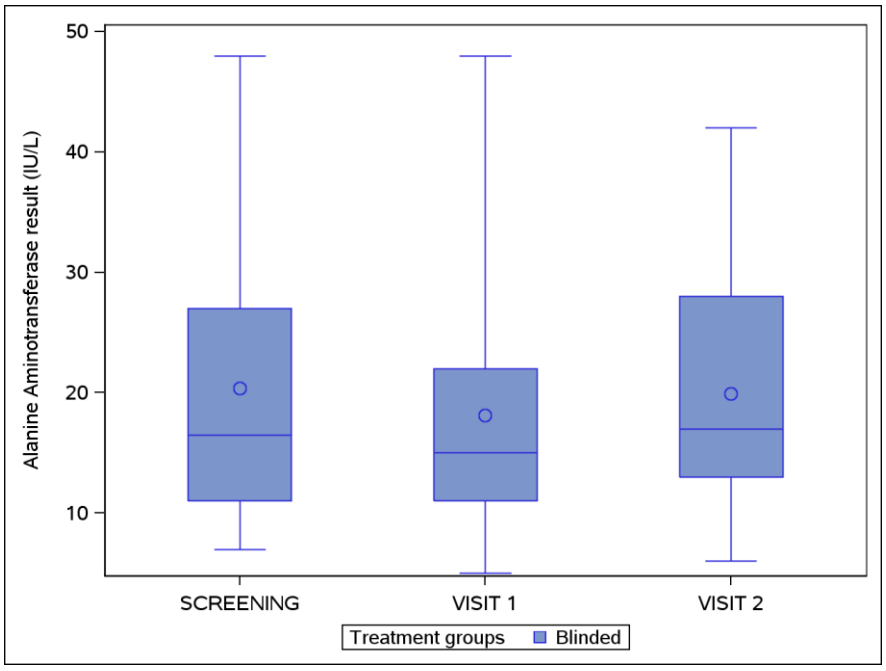
Template Table 46 Summary of hemoglobin change from baseline at 7 days post-dose <1, 2> (Exposed set)

		<Each group>		
Laboratory parameter		**N**	**n**	**%**
Hemoglobin - change from baseline	UNKNOWN			
	GRADE 0			
	GRADE 1			
	GRADE 2			
	GRADE 3			

Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Note:This table will be generated post dose 1 with results at Visit 2 (Day 8) and Day 1 as baseline, and post dose 2 with results at Visit 5 (Day 68) and Day 61 as baseline.

Template Figure 10 Boxplot of <each hematology/biochemistry parameter> (Exposed Set)



Note: This graph is given as an example. It will be adapted to display one boxplot per group and per timepoint, all timepoints available (5 TPs: Screening, Days 1, 8, 61, 68). For Part A, one graph will be generated displaying the 4 groups. For Part B, 3 graphs will be generated displaying 4 groups: 3 RSV groups (30/60/120 -Plain, - AS01E or - AS01B) and the Placebo group.

Template Table 47 Solicited and unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 1-30) post-vaccination period including number of events - SAE excluded <analysis set name>

		<Each group> N=XXXX			<Each group> N=XXXX		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
	At least one symptom	XXX	XXX	XX.X	XXX	XXX	XX.X
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	XXX	XXX	XX.X	XXX	XXX	XX.X
	<each PT (PT code)>	XXX	XXX	XX.X	XXX	XXX	XX.X
	…						

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects included in the considered analysis set in each group
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template Table 48 Number (%) of subjects with serious adverse events during the study period including number of events reported <analysis set name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

12.5. Analysis of RTI

Template Table 49 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal/throat swab at assessment visit	RSV+										
	RSV-										
	All										

Short group label = long group label

RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group or in Total
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 50 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal swab samples collected at home <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal swab at home	RSV+										
	RSV-										
	All										

Short group label = long group label

RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 51 Mean of the viral load of the RSV-confirmed RTI episodes, as measured by qRT-PCR on nasal/throat swabs, by collection time and collection method <Exposed set>

		RSV A +				RSV B +			
Days after RTI onset	**Swab**	**N**	**n**	**%**	**mean**	**N**	**n**	**%**	**mean**
0-2	Nasal swab at home								
	Nasal/throat swab at assessment visit								
3-4	Nasal swab at home								
	Nasal/throat swab at assessment visit								
>4	Nasal swab at home								
	Nasal/throat swab at assessment visit								

Days after RTI onset = number of days between start of RTI symptoms and collection date
N=Number of swabs with qRT-PCR results available
n/%= number/percentage of swabs tested as RSV A/B positive by qRT-PCR
mean= mean of the viral load computed on RSV A/B positive swabs

Template Table 52 Descriptive statistics of the viral load of the RSV- confirmed RTI episodes, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <at home> <Exposed Set>

		<Each group> N=	Total N=
Type	**Parameters**	**Value**	**Value**
RSV A +	n		
	Mean		
	Min		
	Q1		
	Median		
	Q3		
	Max		
RSV B +	…		
All RSV +			

Short group label = long group label
RSV A+= RSV A positive samples by qRT-PCR
RSV B+-= RSV B positive samples by qRT-PCR
All RSV += All RSV positive samples by qRT-PCR
N = Number of swabs with qRT-PCR results available
n= number/percentage of samples in each category
Q1 and Q3 = 25th and 75th percentiles
Min/Max = Minimum/Maximum

Template Table 53 Number and percentage of subjects reporting co-infections with respiratory viruses, as measured by multiplex PCR on RSV A/B positive RTI samples collected <at assessment visit, at home> <Exposed Set>

	RSV RTI N =			
			95% CI	
Categories	**n**	**%**	**LL**	**UL**
Influenza A Virus				
Influenza B Virus				
…				
<each virus>				
…				
Total				

N = number of swabs tested RSV positive by qRT-PCR
n/% = number/percentage of swabs tested positive by multiplex in a given category
Total= number of swabs tested positive for at least one virus
LL, UL= Exact 95% Lower and Upper confidence limits

Template Table 54 Clinical signs and symptoms associated with RTI episodes (Exposed set)

		RSV RTI N=XXXX		Non RSV RTI N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Heart Rate increase (beats/min)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Respiratory rate increase (breaths/min)	5-10						
	10-15						
	15-20						
	20-25						
	…						
Systolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Diastolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Oxygen saturation decrease (%)	1-2						
	3-4						
	5-6						
	7-8						

		RSV RTI N=XXXX		Non RSV RTI N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
	…						
Upper respiratory symptoms	<Each symptom>						
Lower respiratory symptoms	<Each symptom>						
qPCR result	RSV A+						
	RSV B+						
	RSV -						
Self-collected Nasal swab	RSV+						
	RSV-						
	NA						
Medically attended visit	Emergency room						
	Hospitalisation						
	Medical personnel						
	None						
SAE associated to the episode	Yes						
	No						

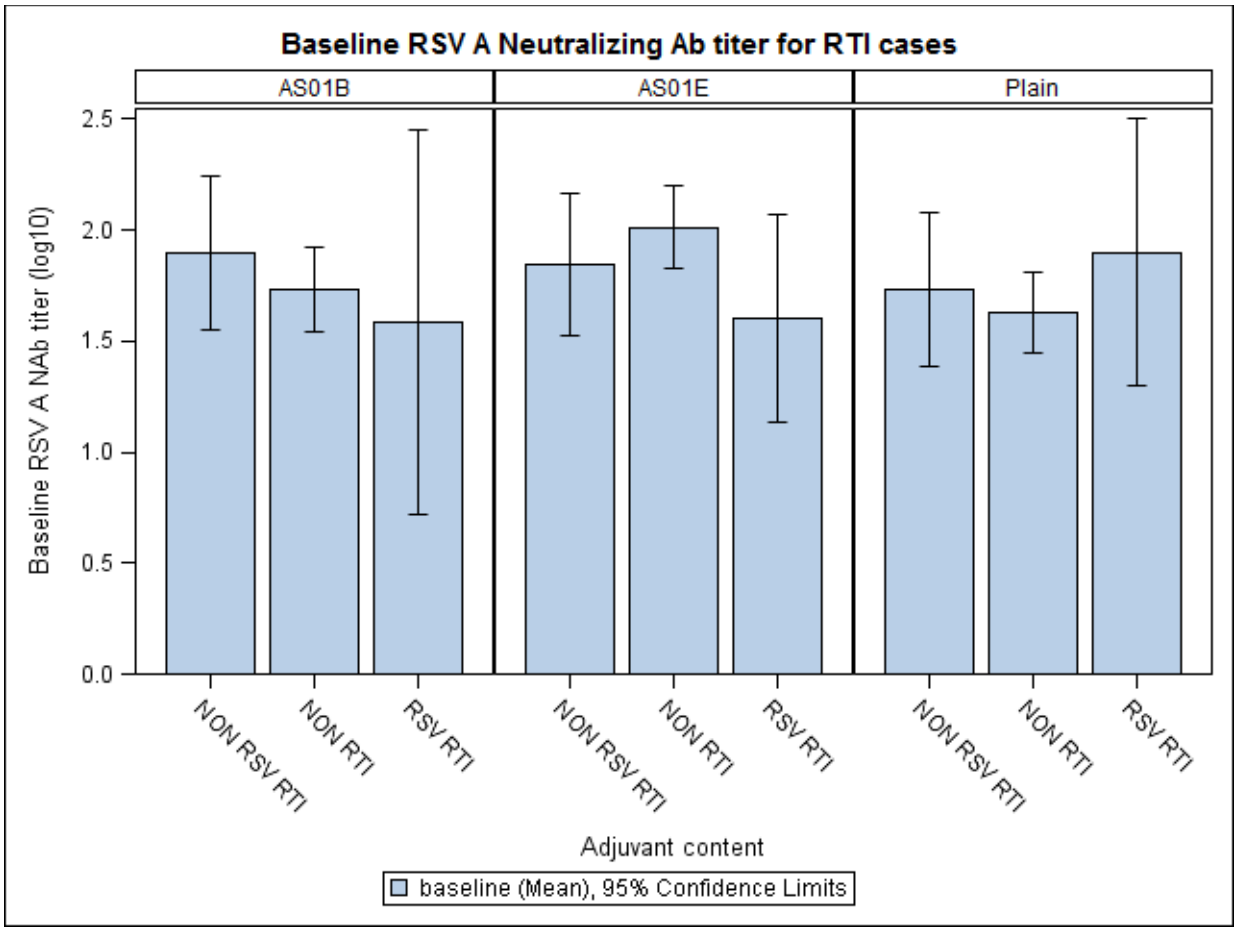
RSV RTI= RTI episode tested as RSV positive by qRT-PCR on nasal/throat swab collected at assessment visit
Non-RSV RTI= RTI episode tested as RSV negative by qRT-PCR on nasal/throat swab collected at assessment visit
N = number of RTI episodes in each category or in total
n = number of RTI episodes in the corresponding category
% = n / N x 100
For vital signs, change from baseline (increase/decrease) will be displayed by category: category of 10 units increase for heart rate, systolic and diastolic BP, 5 units increase for respiratory rate, and 1% decrease for oxygen saturation (to be adapted at the time of dry run if needed)

Template Table 55 Listing of RTI episodes reported during RTI surveillance in Part B (Exposed set)

Group	Sub. No.	Age at Dose 1	Sex	Episode nb	Start date of episode	End date of episode	Date of assessment visit	Nb of signs and symptoms	Date nasal swab on site	RSV A positive (site)	RSV B positive (site)	Date nasal swab at home	RSV-A positive (home)	RSV-B positive (home)	Medically attended visit	SAE related to RTI episode
										Yes/No	Yes/No		Yes/No	Yes/No		Yes/No

Short group label = long group label

Template Figure 11 GMTs and 95% CIs of RSV A Neutralizing antibody titer at baseline for subjects reporting RTI episodes (RSV RTI vs or non RSV RTI vs No RTI), by groups pooled according to the adjuvant content <Exposed Set>



This graph is provided as an example, template will be finalized at the time of the dry-run. It will display the GMTs and 95% CIs for subjects reporting confirmed RSV RTI episodes vs subjects reporting Non-RSV RTI episodes vs subjects who did not report any RTI episode (NON RTI), in the RSV groups pooled according to the adjuvant content (Plain, AS01E, AS01B).

12.6. Additional templates (Amendment 1)

Template Table 56 Distribution of hematology and biochemistry parameters at baseline with respect to normal laboratory ranges <analysis set name>

		<Each group>			<Each group>		
Laboratory parameter	**Range indicator at baseline**	**N**	**n**	**%**	**N**	**n**	**%**
<Each parameter>	UNKNOWN						
	BELOW						
	WITHIN						
	ABOVE						

Short group label = long group label
N = number of subjects with available results for the specified laboratory parameter in a given baseline category
n/% = number/percentage of subjects in the specified category
Below = below the normal laboratory range defined for the specified laboratory parameter
Within = within the normal laboratory range defined for the specified laboratory parameter
Above = above the normal laboratory range defined for the specified laboratory parameter

Template Table 57 Summary of follow-up time (in days) up to <DLP or last contact> (Exposed Set)

	<Each group> N=XXXX	Total N=XXXX
	Value	**Value**
Number of days in the study		
N	xxx	xxx
Mean	xxx.x	xxx.x
Median	xxx.x	xxx.x
Minimum	xxx	xxx
Maximum	xxx	xxx

Short group label = long group label
N = total number of subjects
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data

Template Table 58 Summary of subjects by unsolicited adverse event category

		<each group> N=XXXX
At least one unsolicited adverse event within 30-day of any vaccination	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one related unsolicited adverse event within 30-day of any vaccination	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one medically attended unsolicited adverse event within 30-day of any vaccination	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one serious unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one serious related unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one potential immune-mediated disorder (pIMD) <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one related potential immune-mediated disorder (pIMD) <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one fatal unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)

n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, placebo-controlled, observer-blind, multicenter study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_E$ or $AS01_B$ or unadjuvanted) when administered intramuscularly according to a 0, 2 month schedule in adults aged 18-40 or 60-80 years.
eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
Scope:	All data pertaining to the above study (except IDMC analyses)
Date of Statistical Analysis Plan	Amendment 1 Final: 27 January 2020
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD, PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Stat Peer Reviewer) PPD (Regulatory Affairs) PPD (SERM physician) PPD (Safety scientist) PPD (Public disclosure representative) PPD (CLS – Clinical Read-outs) PPD (CMI Expert representative)
Approved by:	PPD (Clinical and Epidemiology Project Lead) PPD (Lead statistician) PPD (Statistician) PPD (Lead Scientific writer) PPD (Lead stat Analyst)

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3 June 2019)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CD40L	Cluster of Differentiation 40 Ligand
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CMV	Cytomegalovirus
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
DLP	Data Lock Point
eCRF	electronic Case Report Form
eDiary	electronic Diary
ELISA	Enzyme-linked immunosorbent assay
ELU/ml	ELISA unit per milliliter
EoS	End of Study
ES	Exposed Set
FDA	Food and Drug Administration
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Commitee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IL	Interleukin
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit Of Quantification
Mcg or µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities

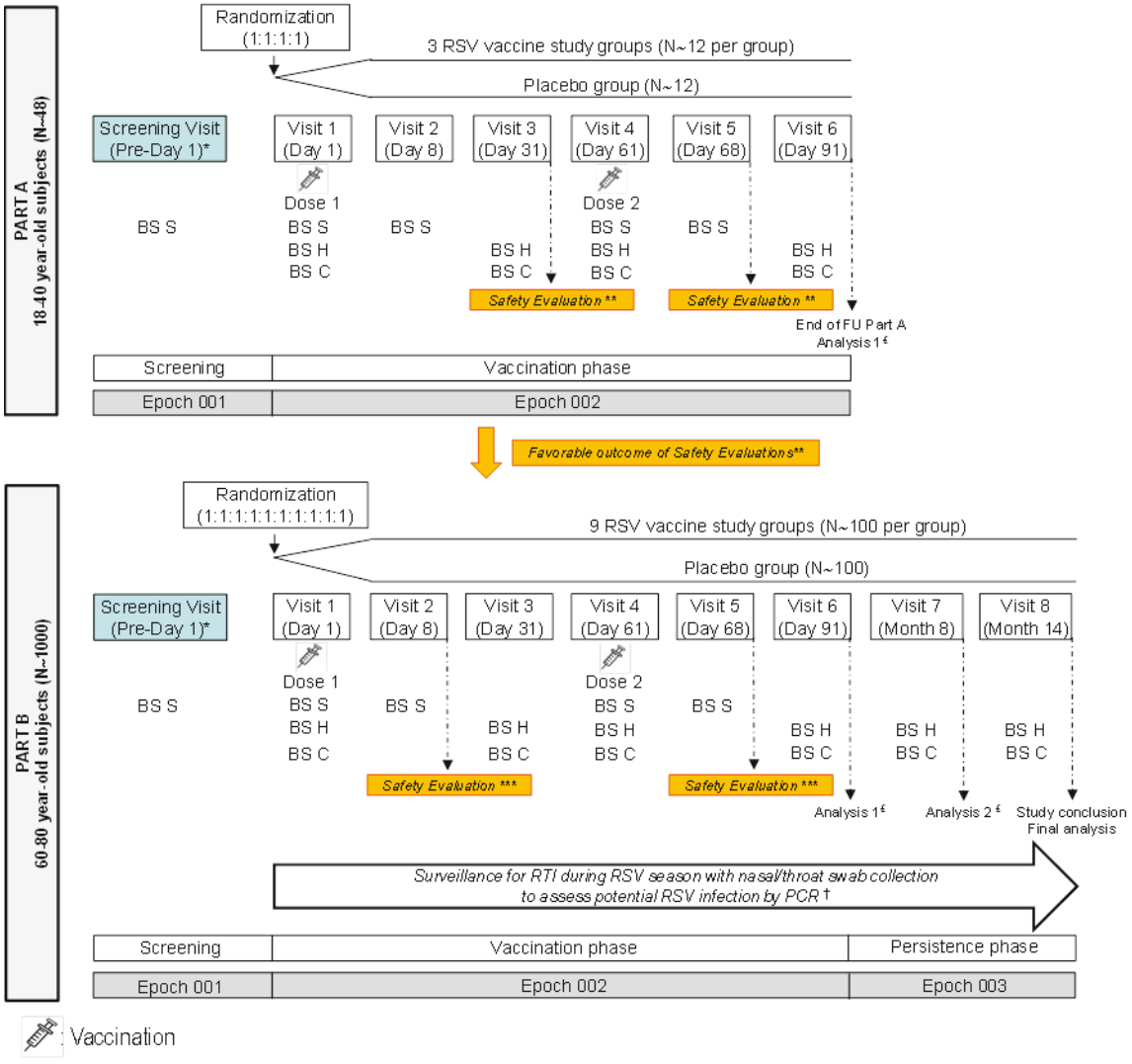
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncitial Virus
RTI	Respiratory Tract Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TNF-α	Tumor Necrosis Factor alpha
TOC	Table of Content
UL	Upper Limit of the confidence interval
WBC	White Blood cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
14-JAN-2019	first version	Final: 11 SEP 2018
27-JAN-2020	Amendment 1: implement changes discussed at the KOM Dry-run and progress meetings	Final: 11 SEP 2018

2. STUDY DESIGN

Figure 1 Study design



BS S: Blood sample for safety (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
BS C: Blood sample for cell-mediated immune responses (for CD4+/CD8+ and/or memory B-cell testing)
FU: Follow-up; PCR: Polymerase Chain Reaction
* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF.

Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

** In Part A, a first IDMC evaluation of safety data up to Day 31 based on all subjects (~12 per group or at least 8 per group in case of slow recruitment) will be performed before proceeding with administration of Dose 2 in Part A and Dose 1 in Part B. A second IDMC evaluation will be performed based on safety data up to Day 68 for all subjects. Part B of the study can only be initiated upon favorable outcome of the first IDMC safety evaluation in Part A.

*** In Part B, a third and fourth IDMC evaluation of safety data up to Day 8 and Day 68, respectively, for the first enrolled and vaccinated subjects (~10 per group or at least 8 per group in case of slow recruitment) will be performed. Additional IDMC evaluations will happen during the conduct of the study.

† In case of RTI symptoms during the RSV seasons (approximately from October to March), the subject will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab at the site. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).

£ Analysis 1 will be performed on all data collected up to Day 91 for at least primary and secondary endpoints based on both study parts (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). Analysis 2 will be performed when all safety data up to Month 8 (Visit 7) are available. The analyses will be based on data as clean as possible.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-country study with 2 parts (i.e., Part A in young adults aged 18-40 years with 4 parallel groups and Part B in older adults aged 60-80 years with 10 parallel groups).
- **Primary Completion Date (PCD):** last visit of the vaccination phase in Part B (Visit 6 [Day 91]).
- **End of Study (EoS):** Last testing results released of samples collected up to Visit 8 in Part B (Month 14) (for assays related to primary and secondary endpoints only).
- **Treatment allocation:** Subjects will be randomized using a centralised randomization system on internet (SBIR) on Day 1.

  In Part A, the aim is to enrol approximately 48 subjects (~12 per group) aged 18-40 years. The randomization algorithm will use a minimisation procedure accounting for center and gender.

  In Part B, the aim is to enrol approximately 700 subjects (~70 per group) aged 60-69 years and approximately 300 subjects (~30 per group) aged 70-80 years. The randomization algorithm will use a minimisation procedure accounting for age, center and gender in each step.

- **Study groups:**

  For the investigational RSV vaccines in Part A and Step 1 in Part B, the RSVPreF3 high-dose formulation containing 120 μg RSVPreF3 will be used to prepare the vaccines for all dose groups (i.e., 30 μg, 60 μg and 120 μg dose groups). For Step 2 in Part B, the RSVPreF3 low-dose and mid-dose formulations (containing 30 μg and 60 μg RSVPreF3, respectively) will be used for the groups receiving 30 μg and 60 μg of RSVPreF3, respectively, and the RSVPreF3 high-dose formulation will be used for the 120 μg dose groups. As the reconstitution methods for the vaccines administered to subjects enrolled in Step 1 and 2 of Part B will be different, separate study groups have been identified (referred to as B1 and B2). Throughout this

document, the combined groups for Steps 1 and 2 are mentioned when referring to the number of groups in Part B (10 groups).

- **Control:** placebo.
- **Vaccination schedule:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Blinding**: observer-blind.

The vaccination phases of each study part (Epoch 002) will be observer-blind. A first statistical analysis will be performed on data available up to one month post-Dose 2 (Visit 6, Day 91). Given that summary safety results may unblind some specific subjects, the persistence phase of Part B (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Visit 8 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

- **RTI surveillance in Part B:** Active and passive surveillance will only be carried out during RSV seasons (approximately from October to March) throughout the entire Part B of the study:
  - **Active surveillance:** study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience an RTI.
  - **Passive surveillance:** study participants are instructed to contact the investigator/study staff as soon as they experience an RTI.

  At the beginning of RSV seasons, study participants will be reminded of the start of the RTI surveillance.
- **Sampling schedule:**

  In Part A:

  - At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the electronic Case Report Form (eCRF). The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
  - At Day 1 (Visit 1), a blood sample for cytomegalovirus (CMV) status determination will be drawn from all subjects.
  - **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).

- **Blood samples for humoral immunogenicity and cell-mediated immunity (CMI)** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).

In Part B:

- At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
- At Day 1 (Visit 1), a blood sample for CMV status determination will be drawn from all subjects.
- **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects and on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).
- **Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91, Month 8 and Month 14 (Visits 1, 3, 4, 6, 7 and 8).
- **Nasal/throat swabs:** In case of RTI symptoms during the RSV season (approximately from October to March), the study participants will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).

- **Type of study:** self-contained.
- **Data collection:** eCRF. Solicited symptoms will be collected using an electronic subject Diary (eDiary). Unsolicited symptoms will be collected using a paper subject Diary.
- **Safety monitoring:** The study will be conducted in 2 parts with oversight by an IDMC. The investigator is not permitted to start vaccinating the subjects in the next step in each part until receipt of the favorable outcome of the respective safety evaluations by the IDMC.
  - **Part A:** Approximately 48 young adults aged 18-40 years will be enrolled and vaccinated with the first dose. If the IDMC evaluation on data up to 30 days post Dose 1 is favorable, the Part A study participants will be vaccinated with the second dose and Part B of the study will be initiated.

– **Part B:** This part will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. In Step 1, approximately 100 subjects will be enrolled and vaccinated. Safety evaluations based on unblinded data from those first 100 subjects will be performed by the IDMC to allow the start of Step 2. In Step 2, the remaining study participants (N≅900) will be recruited and vaccinated.

In total, 6 IDMC meetings for safety evaluation are foreseen in the vaccination phase of the study (Epoch 002), i.e., 2 meetings in Part A and 4 meetings in Part B.

During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

If any safety concern is identified by the investigator or the sponsor, *ad-hoc* safety evaluations by the IDMC may be performed.

Analysis planned for IDMC evaluations are described in a separate document (SAP for IDMC).

- **Group description for analysis:**

For analysis based on subjects in Part A and Part B Step 1 (B1), the group labels listed in table below will be used in the TFLs.

For final analysis based on subjects from Part B Steps 1 and 2, the groups will be pooled (B1 and B2) and the Pooled group labels will be used in the TFLs.

Table 1 Groups description

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
30-PLAIN_A	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part A	NA	
60-PLAIN_A	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part A	NA	
120-PLAIN_A	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part A	NA	
Placebo_A	subjects receiving Placebo in Part A	NA	
30-PLAIN_B1	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 1	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B
30-PLAIN_B2	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 2	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B
60-PLAIN_B1	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 1	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B
60-PLAIN_B2	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 2	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
120-PLAIN_B1	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 1	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
120-PLAIN_B2	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 2	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
30-AS01E_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B
30-AS01E_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
30-AS01B_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
30-AS01B_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B
120-AS01B_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
120-AS01B_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
Placebo_B1	subjects receiving Placebo in Part B Step 1	Placebo_B	subjects receiving Placebo in Part B
Placebo_B2	subjects receiving Placebo in Part B Step 2	Placebo_B	subjects receiving Placebo in Part B

For some of the comparison analyses in Part B, the RSV vaccine groups will be pooled according to their adjuvant content and the following group names will be used in the TFLs:

Pooled Group label in tables	Pooled Group definition for footnote	Groups to be pooled
PLAIN_B	subjects receiving unadjuvanted RSVPreF3 in Part B (30, 60 or 120 μg)	30_PLAIN_B1, 30_PLAIN_B2, 60_PLAIN_B1, 60_PLAIN_B2, 120_PLAIN_B1, 120_PLAIN_B2
AS01E_B	subjects receiving RSVPreF3 adjuvanted with AS01E in Part B (30, 60 or 120 μg)	30_AS01E_B1, 30_ AS01E _B2, 60_ AS01E _B1, 60_ AS01E _B2, 120_ AS01E _B1, 120_ AS01E _B2
AS01B_B	subjects receiving RSVPreF3 adjuvanted with AS01B in Part B (30, 60 or 120 μg)	30_AS01B_B1, 30_ AS01B _B2, 60_ AS01B _B1, 60_ AS01B _B2, 120_ AS01B _B1, 120_ AS01B _B2

For the analysis by age category, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	60-69Y	60-69 years old subjects
2	70-80Y	70-80 years old subjects

For the analysis by CMV status before vaccination, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	CMV+	Subjects CMV positive before vaccination
2	CMV-	Subjects CMV negative before vaccination

3. OBJECTIVES/ENDPOINTS

3.1. Objectives

3.1.1. Primary objective

For Part A and Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

3.1.2. Secondary objectives

For Part A and Part B:

- To characterize the humoral immune responses (including dose-response) in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).
- To characterize the cell-mediated immune responses in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

For Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccines administered IM according to a 0, 2 month schedule, up to the end of follow-up (Month 14, Visit 8).
- To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

3.1.3. Tertiary objectives

For Part A and Part B:

- To further characterize the cell-mediated immune responses to investigational RSV vaccine formulations.

For Part B:

- To further characterize immune responses to investigational RSV vaccine formulations.
- To characterize persistence of immune responses to the investigational RSV vaccine formulations at Month 8 (Visit 7) and Month 14 (Visit 8).
- To further evaluate the occurrence of RSV-associated RTI (including co-infections with other respiratory viruses) during the RSV seasons in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

- To evaluate the occurrence of RSV-associated RTI during the RSV season using self-collected nasal swabs.

3.2. Endpoints

3.2.1. Primary endpoints

For Part A and Part B:

- Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91):
  - Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination.
  - Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination.
  - Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68.
  - Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination.
  - Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

For Part B only:

  - Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

3.2.2. Secondary endpoints

For Part A and Part B:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro.

For Part B only:

- Occurrence of RSV-associated RTI (as measured by qRT-PCR in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
- Occurrence of SAEs from Dose 1 up to the end of follow-up.
- Occurrence of pIMDs from Dose 1 up to the end of follow-up.

3.2.3. Tertiary endpoints

For Part A and Part B:

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro.

For Part B only:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype B in all subjects.
  - RSVPreF3 site 0 specific antibody concentrations in a subset of subjects who received the selected vaccine formulation or placebo.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific memory B-cells in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Persistence of the humoral immune response with respect to components of the investigational vaccine at Months 8 and 14:
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Persistence of the cell-mediated immune response profile with respect to components of the investigational vaccine:
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).

  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific memory B-cells at Month 14 in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:
  - Antibodies against specific protein F epitopes.
  - Potential new immunological markers for protection.
  - Cross-reactive neutralizing antibody titers against hMPV
- Occurrence of RSV-associated RTI, including co-infections with other respiratory viruses (as measured by multiplex PCR in self-collected nasal swab samples and nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons.
- Occurrence of RSV-associated RTI as measured by qRT-PCR in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

4. ANALYSIS SETS

4.1. Definition

4.1.1. Exposed Set

The Exposed Set (ES) will include all subjects with study vaccine administration documented.

A safety analysis based on the ES will include all vaccinated subjects.

An immunogenicity analysis based on ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at Dose 1.

4.1.2. Per-Protocol Set for analysis of immunogenicity

The Per-Protocol set (PPS) for analysis of immunogenicity will be defined by time point (and this to include all eligible subjects' data up to the time of important protocol deviations). The PPS will include all evaluable subjects in the ES:

- Meeting all eligibility criteria.
- For whom the administration route of the vaccine was as according to protocol.

- For whom the study vaccine was administered as per protocol.
- Who did not receive a concomitant medication/ product leading to exclusion from a PP analysis, as described in Section 6.6.2 of the protocol, up to the considered time point.
- Who did not present with a medical condition leading to exclusion from a PP analysis, as described in Section 6.7 of the protocol, up to the considered time point.
- Who complied with the vaccination schedule, as specified in the protocol.
- Who complied with the timings of the post-vaccination blood sampling for immune response evaluation, as specified in the protocol.
- For whom post-vaccination immunogenicity results are available for at least one assay component at the corresponding time points.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects eliminated from ES.

4.2.2. Elimination from Per-protocol analysis Set (PPS)

4.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions.

For codes 1040, 1070, 1080, 1090, 2040, 2060, 2080: subjects will be eliminated from the time at which the condition is met onwards.

For codes 2090, 2100, 2120: subjects will be eliminated at the specific visit at which the condition is met.

When applicable, codes will be allocated to subjects as long as they are included in the study. For example, withdrawals before the second dose will not be attributed a code 1070 because they missed a dose.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
900	Invalid informed consent or fraudulent data	All	All
1030	Study vaccine not administered at all	All	All
1040	Administration of concomitant vaccine(s) forbidden in the protocol: • Any investigational or non-registered vaccine other than the study vaccine used during the study period • A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last vaccine dose, except for inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each vaccination.	All	Immunology
1050	Randomisation failure	All	Immunology
1060	Randomisation code was broken	All	Immunology
1070	Vaccination not according to protocol: • Incomplete vaccination course • Subject 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 Visits 1 and 4	Immunology
1080	Vaccine temperature deviation • vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visits 1 and 4	Immunology
1090	Expired vaccine administered	Vaccination visits 1 and 4	Immunology
2010	Protocol violation (inclusion/exclusion criteria)	All	Immunology

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2040	Administration of any medication forbidden by the protocol • Any investigational or non-registered medication used during the study period • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period • Long-acting immune-modifying drugs administered at any time during the study period • Immunoglobulins and/or any blood products administered during the study period	All	Immunology
2060	Intercurrent medical condition • Subjects may be eliminated from the PPS if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status (other than RSV infection).	All	Immunology
2080	Subjects did not comply with vaccination schedule: • **Part A**: number of days between dose 1 and dose 2 is outside [55-80 days] • **Part B**: number of days between dose 1 and dose 2 is outside [55-75 days]	Visit 4	Immunology
2090	Subjects did not comply with blood sample schedule at a specific visit: • Number of days between dose 1 and visit 3 blood sample is outside [30-37 days] • Number of days between dose 1 and visit 4 blood sample is outside [55-80 days] for **Part A** or [55-75 days] for **Part B** • Number of days between dose 2 and visit 6 blood sample is outside [30-37 days] • **Part B only:** • Number of days between dose 2 and visit 7 blood sample is outside [170-190 days] • Number of days between dose 2 and visit 8 blood sample is outside [350-395 days]	Visits 3, 4, 6, 7 and 8	Immunology

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2100	Immunological results not available post-vaccination • No immunological result at visit x for all 3 following tests: RSV A Neutralising antibody titer, RSVPreF3-specific IgG antibody concentration and RSVPreF3-specific CD4+ T cells frequency	Visits 3, 4, 6, 7, 8	Immunology
2120	Obvious incoherence or abnormality or error in data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab	Visits 1, 3, 4, 6, 7, 8	Immunology

5. STATISTICAL ANALYSES

Note that standard data derivation rules and stat methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and stat methods will be described in section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (age at first vaccination in years, gender, race and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error and range will be provided for continuous data such as age.

The distribution of subjects will be tabulated as a whole and per group and for each age category (60-69 years and 70-80 years in Part B only).

Withdrawal status will be summarized by group using descriptive statistics:

- The number of subjects enrolled into the study as well as the number of subjects excluded from PP analyses will be tabulated.
- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal.

5.1.2. Additional considerations

The analysis of demographic characteristics by group will be performed on the ES and on the PPS.

Demography and baseline characteristics will also be summarized by country.

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure, pulse oximetry) and pre-vaccination temperature reported at visit 1 (Part A and Part B) will be summarized by group using descriptive statistics.

Subject disposition in the ES and PPS will be reported as a whole and per group, and for each age category (60-69 years and 70-80 years in Part B only).

Distribution of hematology and biochemistry parameters at baseline with respect to normal laboratory ranges will be tabulated by group.

For Part B only, the follow-up time in the study (in days) up to DLP for analysis or up to last contact will be described overall and by group using descriptive statistics.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

NA

5.2.2. Additional considerations

The number of doses of study vaccines administered will be tabulated by group and by vaccine.

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be performed on the PPS for immunogenicity in Part A and Part B.

In Part B only: if in any study group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is at least 10%, a second analysis will be performed on the ES.

5.3.1.1. Within groups evaluation - humoral immune response

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

In Part A and Part B:

- Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
- GMCs/GMTs and their 95% CI will be tabulated and represented graphically.
- Geometric mean of ratios of antibody titer/concentrations at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.
- Antibody titer/concentration will be displayed using reverse cumulative curves.
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will be computed and tabulated using descriptive statistics.

In Part B only:

- Individual post-vaccination results (at Days 31 and 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots. Results of the placebo group will be used as a reference.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers) will be tabulated.
- The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.

The immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The humoral immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.2. Within groups evaluation - Cell-mediated immune response

The following parameters will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI:

In Part A and Part B:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, upon in vitro stimulation and background substracted, measured by ICS using PBMCs.
- Frequency of CD4+ and/or CD8+ T-cells expressing **any combination of immune marker(s)** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs (see details in section 5.3.2.2).
- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ , as measured by ICS using PBMCs.

In Part B only:

- Frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.
- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

This will be displayed overall and by pre-vaccination category: <Q1, Q1-Q3, >Q3, where Q1/Q3 are respectively the 25th and the 75th percentiles of the results at pre-vaccination computed on pooled groups.

In addition, vaccine response in terms of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ, will be explored and summarised by group.

The descriptive immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The cell-mediated immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.3. Between groups evaluation (Part B only)

Statistical analyses will be performed to compare the 9 RSV investigational vaccine formulations in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

The between-groups analysis will be performed using an ANCOVA model, in several steps as follows:

1. The 9 RSV formulations will be first compared to the Placebo in order to identify groups whose means are significantly higher from the mean of the Placebo group, in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells at Day 31 and Day 91 (One-sided alpha=2.5%, Dunnett's adjustment test for multiplicity).

2. The effect of the second vaccination will be evaluated by comparing the means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31), of the groups pooled according to their adjuvant content ($AS01_B$, $AS01_E$ and Plain), in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibody titers (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose).

   Based on the results of this test, the next comparisons will be performed either at Day 91 or at Day 31.

3. Appropriate contrasts will be implemented to compare the RSV formulations as follows:

   - To demonstrate the adjuvant effect (on pooled groups according to their adjuvant content: $AS01_B$, $AS01_E$, Plain), by testing sequentially $AS01_B$ and $AS01_E$ versus Plain (One-sided alpha=2.5% for each superiority test: Adjuvant >Plain) in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibodies and, if applicable, by comparing $AS01_B$ vs $AS01_E$.
   - To demonstrate linearity of increase in immune response when increasing the antigen dose in each adjuvanted group in terms of RSV-A neutralizing antibody and/or RSVPreF3-specific CD4+ T-cells.
   - Further ANCOVA t-tests would demonstrate superiority of 120 µg or 60 µg, should a quadratic effect be demonstrated.

Similar exploratory comparisons might also be performed on the RSVPreF3 ELISA antibody concentrations if deemed necessary.

5.3.2. Additional considerations

5.3.2.1. Within groups – humoral immune response

- Correlations between assays of the humoral response will be investigated using scatter plots generated on pooled RSV groups in Part B:
  - RSVPreF3-specific IgG versus RSV A neutralizing antibody titer at each timepoint,
  - RSV A versus RSV B neutralizing antibody titer at Pre-vaccination and Day 91
  - RSVPreF3-specific IgG versus RSV-B neutralizing antibody titer at Pre-vaccination and Day 91

The same analysis will be performed on the fold increase post over pre-vaccination.

For each assay, values strictly below the cut-off and values strictly greater than the upper limit of quantification (ULOQ) will not be used for the scatter plots neither for the evaluation of the coefficients of correlation.

- The fold increase (post over pre-vaccination) of the RSVPreF3 IgG antibody concentrations versus the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will also be displayed graphically by group using scatter plots.

- The hMPV neutralizing antibody titers will also be tested at Day 1 and Day 91, on all subjects in Part A and on a subset of 40 subjects per group in Part B. The following analysis will be performed for each hMPV subtypes (A1, B1, A2, B2):

  – Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.

  – GMTs and their 95% CI will be tabulated and represented graphically.

  – Geometric mean of ratios of antibody titer at post-vaccination time point (Day 91) over pre-vaccination (Day 1) will be tabulated with 95% CI.

  – Antibody titer will be displayed using reverse cumulative curves.

  – Distribution of the fold increase of the antibody titers (post- over pre-vaccination titers) will be tabulated.

  – Individual post-vaccination results (Day 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots for the selected RSV formulation and the placebo group as a reference.

5.3.2.2. Within groups – Cell-mediated immune response

Descriptive statistics of the cell-mediated immune response will be tabulated and displayed graphically using boxplots (min, Q1, median, Q3, max), by group and timepoint.

The RSVPreF3-specific CD4+/CD8+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geomean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+/CD8+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 cytokines [$Freq^{2+}$] will be computed as follows:

$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

And

$$Freq^{2+}_{Specific} = Freq^{2+}_{Induction} - Freq^{2+}_{Background}$$

where

$n^{2+}_{Background}$= number of CD4+ T cells expressing at least 2 cytokines after stimulation with medium only (background)

$n^{2+}_{Induction}$= number of CD4+ T cells expressing at least 2 cytokines after stimulation with a pool of peptides covering RSVPreF3 (induction)

$N^{CD4}_{Back/Ind}$ = Total number of CD4 T cells involved in the assay (background or induction)

Same computations will be done for all CMI responses that will be analysed, i.e.:

- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least 2 markers including at least 1 cytokine*** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.
- ** cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17*
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IFN-γ (Th1-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IL-13 (Th2-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/ CD8+ T-cells expressing **at least IL-17 (Th17-like response)**, as measured by ICS using PBMCs.
- **Co-expression profile:** Frequency of RSVPreF3-specific CD4+ T-cells expressing **any combination of marker(s) among** CD40L, IL-2, TNF-α, IFN-γ, as measured by ICS using PBMCs, at Day 31 and Day 91 (→15 combinations).

Vaccine response in terms of RSVPreF3-specific CD4+ T cells frequencies expressing at least 2 markers among CD40L, IL-2, TNF-α, IFN-γ will be explored as follows:

- Distribution of the fold increase: the percentage of subjects with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

For the computation of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ, the results **below the LLOQ** of the assay will be replaced by the value of the LLOQ.

5.3.2.3. Between groups analysis

Statistical comparisons will be performed on the logarithm base 10 transformed results, in terms of RSV-A neutralizing antibody titers and frequency of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

a. Comparisons versus Placebo:

The 9 RSV formulations will be compared to the Placebo (control group) at Day 31 and Day 91 using an ANCOVA model with the Dunnett's adjustment method for multiplicity. The model will include the treatment group and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. Geometric mean ratios between groups and associated Dunnett's adjusted 95% CIs of the ratios will be tabulated.

The Dunnett's test is specifically designed for situations where all groups are to be compared against one "Reference" group. It is commonly used after ANCOVA has rejected the hypothesis of equality of the means of the distributions.

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test (where=(visit=D91));
 CLASS treatmnt Adj agecat;
 MODEL log(titer)=treatmnt baseline agecat / ddfm=KR DDFM=KR
outpm=pred_model cl;
 REPEATED / group=Adj ; /* test homogeneity of variances and consider
different variance by adjuvant content if appropriate */
 LSMEANS treatmnt / ALPHA=0.05 Adjust=Dunnett pdiff=control ("Placebo")
CL;
RUN;
```

b. Comparisons between RSV groups:

The difference between RSV groups will be evaluated using an ANCOVA model including the adjuvant content (AS01B, AS01E, Plain), the antigen dose (30, 60, 120 µg), the visit (Day 31, Day 91) and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. The adjuvant by antigen interaction will also be tested, and included in the model if significant at 10% (p-value <10%).

Based on this global model, appropriate contrasts will be used to perform the following comparisons:

1. Effect of the second vaccination:

The means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31) will be compared within each pooled group according to adjuvant content (AS01B, AS01E and Plain) (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose). Geometric mean ratios and associated 95% CIs will be tabulated.

2. Adjuvant effect:

The adjuvant effect will be tested sequentially as follow (One-sided alpha=2.5% for each superiority test):

1. AS01B versus Plain
2. AS01E versus Plain
3. AS01B versus AS01E.

Geometric mean ratios and their 95% CIs will be computed for each comparison.

The same comparisons will also be performed by age category.

3. Antigen dose-response: test linear and quadratic effect of the antigen dose. Depending on significance of those 2 effects, ANCOVA t-tests might be done to demonstrate superiority of 120 µg or 60 µg.

Geometric mean ratios and their 95% CIs will be computed for each pairwise comparison within each adjuvant content family (120 µg vs 60 µg, 120 µg vs 30 µg, 60 µg vs 30 µg for Plain, AS01E and AS01B groups).

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test;
 class Adj(1B, 1E, PL) Ag(30, 60, 120) visit(PD1, PD2) subject agecat;
 model log(titer) = Adj Ag visit Adj*Ag Adj*visit Ag*visit Adj*Ag*visit
baseline baseline*visit agecat / DDFM=KR S outpm=pred_model cl;
 REPEATED visit / SUBJECT=subject type=unr group=Adj;
 /* test homogeneity of variances and consider different variance by
adjuvant content if appropriate */

 LSMEANS Adj*visit /E slice=visit CL PDIFF ALPHA=0.05; /*option E to see
coefficients assigned to each effect */
 LSMEANS Adj*visit /E slice=Adj CL PDIFF ALPHA=0.05;
 LSMEANS Adj*Ag*visit / slice=visit CL PDIFF ALPHA=0.05;

/* contrasts to be added for each comparison of interest */
QUIT;
```

The inferential analysis on the RSVPreF3-specific CD4+ T cells will be performed on the log-transformation frequency of the CD4+ T cells expressing at least 2 markers (background or induction) computed by adding an offset of 0.5 cells to the number of activated CD4+ T cells (Delta method, see below). These transformations are deemed appropriate for further inferential analyses provided the incidence of activated CD4+ T-cells is below 4%.

Considering:

$X_{ijk} = \log\left(\frac{n^{2+}_{background} + 0.5}{N^{CD4}_{Background}}\right)$, the log background frequency, and

$Y_{ijk} = \log\left(\frac{n^{2+}_{Induction} + 0.5}{N^{CD4}_{Induction}}\right)$, the log induction frequency

The following model can be used to analyse the log-transformed ratio between induction and background frequencies, and provide estimates of the RSVPreF3-specific frequency (Delta Method- Inference on Induction/background data):

$Y_{ijk} = \mu_{jk} + \alpha_j . y_{i0k} + \beta . x_{ijk} + \varepsilon_{ijk}$, with

$(\overline{Y_{jk} - x_{jk}})\Big|_{\bar{y}_0, \bar{x}} = \mu_{jk} + \alpha_j . \bar{y}_0 + \beta . \bar{x}$, LS means conditional to $\bar{y}_0$ and $\bar{x}$

where:

i, j , k=subject *i*, visit j, group *k*; $\bar{y}_0$= mean log induction frequency at pre-vaccination,

$\bar{x}$= mean log background after vaccination.

Note: This analysis is assuming that the background is the same for all groups and all timepoints. This assumption will be checked during the analysis.

Geometric means (GMs) of post-vaccination RSVPreF3-specific CD4+ T cell frequency and 95% CIs, will be calculated conditionally to the means of the pre-vaccination log-transformed CD4+ T cell frequency following induction with RSVPreF3 and the post-vaccination log-transformed CD4+ T cell frequency under background conditions.

The test and the 95% CIs for treatment comparisons will be calculated according to the delta method on the log-transformed ratio of RSVPref3-specific frequency relative to the background frequency estimates:

$$\hat{Z}_{jk} = 10\text{^}(\hat{Y}_{jk} - \bar{x}) - 1 = \frac{10\text{^}(\hat{Y}_{jk}) - 10\text{^}(\bar{x})}{10\text{^}(\bar{x})}, \text{ and}$$

$$Log(\hat{W}_{jk}) = Log\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right) = Log\left(\frac{10\text{^}(\hat{Y}_{jk_2}) - 10\text{^}(\bar{x})}{10\text{^}(\hat{Y}_{jk_1}) - 10\text{^}(\bar{x})}\right), \text{ where}$$

$\hat{Z}_{jk}$= mean increase from background to induction frequency relative to background frequency at visit *j* for treatment *k*, and

$\hat{W}_{jk}$= vaccine effect on the antigen specific frequency following adjustment for background frequency.

Algorithm for calculations of Confidence Intervals of antigen-specific CMI response using the Delta-Method

Analysis results transformations:

1. The LSM and CI are back-transformed on the original scale to provide Geometric Mean Ratios of the induction frequency over background frequency.
   (Induction_freq GM / Background_freq GM)
2. Unity is removed from the Geometric Mean Ratios & CI
   ((Induction_freq GM – Background_freq GM) / Background_freq GM)
3. The result in 2 is multiplied by the geometric mean of background frequency used to calculate the LSM to provide the geometric means for the antigen-specific frequency.
   (Induction_freq GM – Background_freq GM)

4. The log-transformed of the result in 2 is calculated and the difference between test group and control group is calculated.
   Log(Induction_freq GM_test – Background_freq GM) -
   Log(Induction_freq GM_control – Background_freq GM)
5. The confidence interval of the result in 4 is calculated through the delta-method, using student-t distribution and the number of degree of freedom provided by MIXED for the difference in LSM.
6. The result in 4 is back-transformed to original scale to provide the fold-increase in the frequency of antigen-specific frequency.
   (Induction_freq GM_t – Background_freq GM) /
   (Induction_freq GM_c – Background_freq GM)

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 30-day 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 any AEs considered related to vaccination, for Grade 3 AEs considered related to vaccination and for Grade 3 non-serious AEs.

The percentage of subjects with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will also be tabulated after each dose and overall.

The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for Grade 3 (> 39.0°C/102.2°F) causally related fever.

For each group and for each hematology and biochemistry parameter:

- The percentage of subjects having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
- The summary of grading post-vaccination will be tabulated versus baseline. (Grades will be based on the FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”, see APPENDIX C in the protocol. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on 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 Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. SAEs will also be described in detail.

For Part A only, pregnancy and pregnancy outcomes will be listed (if applicable).

For Part B only, the percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. PIMDs will also be described in detail.

The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 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.

The analysis of safety will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years in Part B only).

5.4.2. Additional considerations

All analyses will be descriptive and will be based on the Exposed Set (ES).

Compliance in completing solicited adverse events information will be tabulated after each dose and overall.

The percentage of subjects with at least **one local solicited** AE, with at least **one general solicited** AE and with **any solicited** AE during the 7-day 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 any AEs considered related to vaccination, and for Grade 3 AEs considered related to vaccination.

The number of days with solicited symptoms reported during the **7-day follow-up period** will be tabulated for each solicited adverse event, after each dose using descriptive statistics (mean, min, Q1, median, Q3, maximum).

The same tabulation will be done for Grade 3 symptoms, and also during **the whole post-vaccination period** (to include the total number of days for symptoms ongoing beyond the follow-up period).

The incidence of each solicited symptom (any grade and grade 3) will also be represented graphically per group and per dose.

Analysis of solicited symptoms will also be done:

- on the **pooled groups according to adjuvant content** (AS01B, AS01E, Plain), overall and by age category.
- On symptoms reported during the 4-day period, i.e. on the day of vaccination and 3 subsequent days, for each group after each dose and overall.

5.4.2.1. Solicited Adverse Events

Solicited adverse events will be reported daily during the 7-day (from Day 1 to Day 7) follow up period after each vaccination, using structured diaries. Missing or non-evaluable measurements will not be replaced.

In order to summarize the data, the maximum intensity of local injection site redness/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity. Body temperature will also be summarized by 0.5°C increments as follows: ≥38.0, >38.5, >39.0, >39.5, >40.0 °C.

Each subject's data will be summarized according to the maximal severity observed during the follow-up period for each adverse event and each dose, followed by a summary across subjects and across doses.

5.4.2.2. Unsolicited Adverse Events

When an unsolicited adverse event occurs more than once for a subject, 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.

The analysis of unsolicited adverse events includes the following categories:

- Any unsolicited adverse event.
- Possibly related unsolicited adverse events.

- Grade 3 unsolicited adverse events
- Grade 3 possibly related unsolicited adverse events.
- Serious adverse events (SAEs)
- Possibly related SAEs.
- Potential Immune-Mediated disease (pIMDs, in Part B only)
- Medically attended adverse events
- SAEs and pIMDs reported during the entire study period will be tabulated.
- In addition, the following time periods will be considered to report SAEs/pIMDs at the first and second analyses (E1_02 and E1_03, see section 7.1):
- from Dose 1 up to 30 days post dose 2 (or up to 90 days post dose 1 for subjects who did not received the second dose)
- from Dose 1 up to 6 months* post dose 2 (or up to 8 months* post dose 1 for subjects who did not received the second dose).
- From Dose 1 up to Data lock point, in order to report all SAEs/pIMDs reported at the time of analysis.

  * months will be converted in days in order to select the events for the output tables.
- Listing of AEs/SAEs leading premature withdrawal from study or to interruption of vaccination will be described in detail.

5.4.2.3. Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10015150	Erythema
Swelling	10053425	Swelling at injection site
Fatigue	10016256	Fatigue
Fever	10016558	Fever
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Headache	10019211	Headache
Myalgia	10028411	Myalgia
Shivering	10040558	Shivering
Arthralgia	10003239	Arthralgia

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.4.2.4. Clinical Safety Laboratory Investigations

In case of invalid or missing results or clinically significant grade 3 and above abnormal laboratory findings, a repeat testing may be done to confirm the first result (see Protocol section 7.1.4). For the analysis, the following rules will be applied:

- In general, the first result will be considered, except if this result is missing.
- In case of retesting for a grade 3 at pre-vaccination, the retesting will be considered if the result is < grade 3.
- If result at Visit 1 is missing, the result of the screening will be used as baseline in the analysis.

5.4.2.5. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.5. Analysis of RTI for Part B

5.5.1. Analysis of RTI planned in the protocol

The analysis will be performed on the ES.

Any RTI episode for which a visit for the assessment of potential RSV-RTI has been performed (with nasal/throat swab sampling) will be considered for the analysis. The assessment of RSV infection will be performed using qRT-PCR on nasal/throat swabs separately for samples collected by the subject and those collected by an appropriately qualified person (i.e., medical or nursing) at the assessment visit.

The proportion of subjects with at least one RSV-associated RTI (with 95 % CI) will be calculated by group.

Descriptive analyses (mean, median, min, max) of viral load assessed by quantitative PCR (RSV-A/B) of RSV-RTI will be performed by study group.

The incidence rate of all-cause RTI (with 95% CI) will be calculated by group. These will also be presented by co-infection identified by multiplex PCR.

5.5.2. Additional considerations

The mean viral load of the RSV positive-RTI samples will also be reported by collection method (at assessment visit or at home) and by collection time (0-2, 3-4, >4 days between RTI onset date of symptoms and collection date).

Information collected at assessment visit will be described for RSV RTI episodes versus Non-RSV RTI episodes, as tested by qRT-PCR on nasal/throat swabs collected at assessment visit. It will include: vital signs, clinical symptoms, self-collected nasal swab result, medically attended visit and SAE related to the episode.

RTI episodes will be described in detail in a listing. In addition, baseline RSV A Neutralizing antibody titer (GMT and 95% CIs) will be presented graphically by RTI episode status (RSV-RTI vs Non RSV-RTI vs No RTI).

6. ANALYSIS INTERPRETATION

All analyses will be descriptive with the aim to characterize the difference in safety/reactogenicity or immunogenicity between groups.

All comparisons will be exploratory. They should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons, except for the comparisons of all RSV formulations vs Placebo (Dunnett's adjustment).

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- **A first analysis** will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 91 are available (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). This will include results from all subjects in Part A and Part B. This analysis will be considered as final for those endpoints. A clinical study report will be written.

  At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available), but no individual listings will be provided to the study team. Given that summary safety results may unblind some specific subjects, the study will be considered as single-blind from this point onwards, with subjects remaining blinded up to study end (Visit 8, Month 14). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

- **A second analysis** will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:

  – The safety analysis of data up to 6 months post-Dose 2.

  – The analysis of all qPCR data available at that time.

  – The analysis of laboratory results that may become available at that time.

- **A third immunogenicity analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 8 are available, to evaluate the persistence up to 6 months post-Dose 2 in Part B.

- **A fourth analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 14 (Visit 8) are available for the subjects enrolled in Step 1 of Part B. This analysis will include any additional laboratory results that may become available at that time.

  No individual listings will be provided before the final end of study analysis.

- **The final end of study analysis** will be performed when all data for at least primary and secondary endpoints up to study conclusion are available (Month 14). All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage. An integrated clinical study report containing all available data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Reference for TFL TOC
Final analysis	E1_01	SR, CTRS	See column A in TFL TOC
Analysis up to Day 91	E1_02	SR, CTRS	See column B in TFL TOC
Analysis up to Month 8 (safety and PCR)	E1_03	Internal	See column C in TFL TOC
Analysis up to Month 8 (immuno)	E1_04	Internal	See column D in TFL TOC
Analysis up to Month 14 (Part B Step 1)	E1_05	Internal	See column E in TFL TOC

7.2. Statistical considerations for interim analyses

All confirmatory analyses will be conducted on final data (as clean as possible) and therefore no statistical adjustment for interim analyses is required.

8. CHANGES FROM PLANNED ANALYSES

Statistical analyses

The fold-increase parameter for CMI (post over pre-vaccination) that will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI has been adapted as follows:

- ~~Geometric mean ratios~~ ***Fold increase (Post over pre-vaccination)*** of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 marker(s) among IL-2, CD40L, TNF-α, IFN-γ , ~~at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI~~ ***as measured by ICS using PBMCs.***

This analysis was also added for the Memory B cells:

- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

All additional analysis planned compared to protocol are described in the "Additional considerations sections". The mains ones to be included in the CSR are also described below (changes indicated in bold):

- Demography and baseline characteristics will be summarized ***by country***.
- Vital signs at baseline will be described by group using descriptive statistics.
- Exposure to study vaccine will be tabulated by group and by vaccine
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV neutralizing antibody titers will be reported for RSV-A ***and RSV B***.
- Comparisons with Placebo will be done ***at Day 31*** and Day 91, for both RSV A Neutralizing antibody ***and CD4+ T cells expressing at least 2 markers***.
- Analyses of solicited symptoms were added: incidence of any/local/general solicited AEs, number of days with solicited AEs, analysis on pooled groups according to adjuvant content.
- RTI episodes: analysis of viral load by collection method and collection time was added, as well as the description of signs and symptoms for RSV-RTI vs Non-RSV RTI cases.
- Analysis of hMPV neutralizing antibody titers on all subjects in Part A and on a subset of subjects in Part B.

Sequence of analyses

The wording of the 2nd analysis have been adapted as follows to allow the descriptive analysis of any additional immunogenicity results available for all subjects or for part of them:

- **A second analysis** will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:
  - The safety analysis of data up to 6 months post-Dose 2.
  - The analysis of all qPCR data available at that time.
  - ***The analysis of laboratory results that may become available at that time.***

Sensitivity analysis

An issue in the randomization was identified on 23rd of July, and was identified as Significant Quality Issue (SQI) on the 6th of November 2019.

Randomization were performed in SBIR to create "placeholders"

1. For subjects whose eligibility was not yet confirmed
2. For subjects who were identified and whose ICF was not yet signed
3. For subjects not yet identified

This was not allowed neither based on the protocol, nor by consulting the central team.

As this issue might have an impact on the randomization, a sensitivity analysis will be performed excluding subjects who were randomized after the 23rd of July (randomization date >= 23JUL2019), for immunogenicity secondary endpoints at the time of first analysis (table template 17 and 22).

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Handling of missing data

9.1.1. Dates

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 other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

9.2. Duration of events

When a solicited AE is ongoing at the end of the solicited follow up period (Day 7), the following rules will be applied:

- If the event is present at Day 7 and information is available at each day up to the end of the event: count number of days with event up to last day reported
- If information is missing at several days between the first day with the event and the end of event: count missing days as days with an event (worst case scenario)
- For Grade 3 AEs: take into account the grading of the last day with AE reported (last observation carried forward)

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject 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 CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day 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.

See also exceptions in section 9.1.

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited symptoms, symptoms will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. 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

Conversion of temperature from °Fahrenheit to °C will be performed according to SDTM specifications.

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is > ULOQ	ULOQ*
All other cases	missing

*This rule will be used to computed descriptive statistics (GMTs, fold increase,etc). All values might be displayed in RCCs and scatter plots with individual results.

10.1.3.4. 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. Antibody titers or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

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

10.1.3.6. Duration of events

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

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

See also specific rules for ongoing symptoms in section 9.2.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse 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.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal.

Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22.2%
1/45	2.2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.

Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics 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 minima of transformed body temperatures will be displayed with one decimal.

10.1.4.3. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Adjusted GMT or GMC ratios

When between-group GMT or GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The TFL TOC provides the list of tables/figures/listings that will be generated at each analysis. It can be found in eTMF folder section 11.01.01.

The mock tables/figures referred under column named ‘layout’ can be found in section 12.

11. REFERENCES

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

12. STUDY MOCK TFLS

The following drafted standard and study specific mocks will be used. Note that standard templates might be updated based on the last version of the standard catalogue used at the time of analysis. Titles and footnotes will be adapted accordingly.

The data display, title and footnotes are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment.

12.1. Demography

Template Table 1 Summary of demography and baseline characteristics (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**
Age (years) at first vaccination				
N	xxx		xxx	
Mean	xxx.x		xxx.x	
Standard Deviation	xxx.x		xxx.x	
Median	xxx.x		xxx.x	
Minimum	xxx		xxx	
Maximum	xxx		xxx	
Sex				
Male	xxx	xx.x	xxx	xx.x
Female	xxx	xx.x	xxx	xx.x
Ethnicity				
<Each Ethnicity>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Race				
<Each Race>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Age category				
<Each Age category>	xxx	xx.x	xxx	xx.x
CMV status				
Positive	xxx	xx.x	xxx	xx.x
Equivocal	xxx	xx.x	xxx	xx.x
Negative	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template Table 2 Number of subjects by country and center (Exposed Set)

		<Each group> N=XXXX		Total N=XXXX	
Country	**Center-Investigator Name**	**n**	**%**	**n**	**%**
<each country>	<each center-investigator name>	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template Table 3 Number of subjects by study steps (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
Steps	**n**	**%**	**N**	**%**
Part A				
Part B Step 1				
Part B Step 2				

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template Table 4 Summary of vital signs (Exposed Set)

			<Each group> N=XXXX	Total N=XXXX
Visit	**Characteristics**	**Parameters**	**Value**	**Value**
<EACH VISIT>	Heart rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Respiratory rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Systolic Blood pressure (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	Xxx
		Maximum	xxx	Xxx
	Diastolic blood pressure (<unit>)	n	xxx	Xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	Xxx
		Maximum	xxx	Xxx

			<Each group> N=XXXX	Total N=XXXX
Visit	**Characteristics**	**Parameters**	**Value**	**Value**
	Pulse oximetry (<unit>)	n	xxx	Xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	Xxx
		Maximum	xxx	Xxx
	Pre-vaccination Temperature (C)	n		
		Mean		
		SD		
		Median		
		Minimum		
		Maximum		

Short group label = long group label

N = total number of subjects

Value = value of the considered parameter

n = number of subjects in a given category

N with data = number of subjects with documentation of the corresponding data

SD = standard deviation

Template Table 5 Summary of study completion with reason for withdrawal (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Completed the study	xxx	xx.x	xxx	xx.x
Withdrawn from the study	xxx	xx.x	xxx	xx.x
Primary reason for withdrawal :				
<Each reason>	xxx	xx.x	xxx	xx.x

Short group label = long group label

Template Table 6 Summary of visit attendance (Exposed Set)

		<EACH GROUP> N=XXXX		Total N=XXXX	
Visit	**Status**	**n**	**%**	**n**	**%**
<EACH VISIT>	Attended	xx	xx.x	xx	xx.x
	Did not attend yet	xx	xx.x	xx	xx.x
	Withdrawal at visit or earlier	xx	xx.x	xx	xx.x
	Did not attend	xx	xx.x	xx	xx.x

Short group label = long group label

N = Number of subjects in each group or in total

n/% = number / percentage of subjects in a given category

Template Table 7 Summary of important protocol deviations leading to elimination from any analyses (Enrolled Set)

Category Sub-category	<Each group> N=XXX			Total N=XXX		
	Occ	n	%	Occ	n	%
At least one Important Protocol Deviation						
< Each category >						
<each sub-category>						

Short group label = long group label
N = Total number of subjects
Occ = number of occurrences = number of important protocol deviations
n/% = number / percentage of subjects with important protocol deviations

Template Table 8 Summary of subject disposition from Enrolled set to Randomized set (Enrolled Set)

	Total N=	
	n	%
Withdrawals prior to randomization		
<withdrawal reason 1>		
<withdrawal reason 2>		
…		
Number of subjects included in randomized set		

N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 9 Summary of subject disposition from Randomized Set to Exposed set (Randomized set)

	<Each group> N=XXXX		Total N=XXXX	
	N	%	n	%
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Number of subjects included in the Exposed set				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 10 Summary of subject disposition from Exposed Set to Per Protocol Set at visit x (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Number of subjects included in the Per Protocol set at visit x				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 11 Summary of subject disposition from Exposed Set to End of study (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	**%**	**n**	**%**
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
…				
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
…				
Number of subjects who completed the study				
Completed with 1 dose				
Completed with 2 doses				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template Table 12 Deviations from protocol for age and intervals between study visits (Exposed set)

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
Age	<age range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	
<each interval between study visit>	<interval range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Template Table 13 Number of enrolled subjects by country

		<Each group> N = XXX	Total N = XXX
Characteristics	**Categories**	**N**	**n**
Country	<each country>		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given country or for all countries

Template Table 14 Number of enrolled subjects by age category

		<each group> N =	Total N =
Characteristics	**Categories**	**n**	**n**
Age category	Adults [18-64 years]		
	Adults [65-84 years]		
	Missing		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = age at study vaccination unknown

Template Table 15 Minimum and maximum visit dates <analysis set name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
< each informed consent>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
[Randomization]	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

12.2. Exposure

Template Table 16 Exposure to study vaccines by vaccine (Exposed Set)

		<Each group> N=XXXX		<Each group> N=XXXX	
Vaccine administered	**Number of subjects receiving**	**n**	**%**	**n**	**%**
< Vaccine A>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x
	Total number of doses administered during the study	xxx		xxx	
< Each vaccine>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x
	Total number of doses administered during the study	xxx		xxx	

Short group label = long group label
N = number of subjects in each group or in total included in the considered analysis set
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

12.3. Immunogenicity

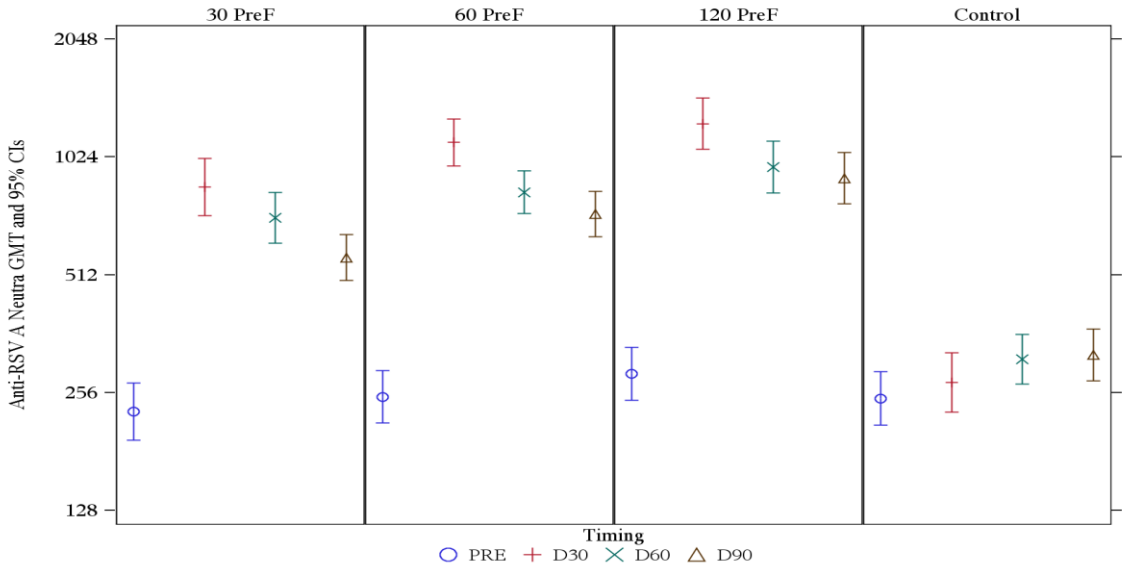
12.3.1. Within groups

Template Table 17 Number and percentage of subjects with <antibody titer /concentration> equal to or above <cut-off unit> and <GMT/Cs> <analysis set name>

				>=cut-off unit				GMT/C				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
<each antibody>	<each group>	<each timing>										

Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
N = Number of subjects with available results
n/% = number/percentage of subjects with titer/concentration equal to or above specified value
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Short timing label = long timing label

Template Figure 1 <GMT/Cs> and their 95% CIs for <antibody titers/ concentrations> <analysis set name>



Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
95% CI = 95% confidence interval
Short timing label = long timing label
Note: This graph is provided as an example.
For RSV A Nab and RSVPreF3- specific IgG Ab, it will be adapted to display: all the groups (4 groups for Part A, 10 groups for Part B) and all available timepoints (4 TPs up to Day 91, 6 TPs up to study end for Part B).
If needed for Part B, this graph might be split in several graphs: either by adjuvant content vs Placebo or by antigen content vs Placebo.
Same graph will be generated for RSV B NAb with 2 timepoints (10 groups, at Days 1 and 91), for RSVPreF3 site 0 Ab with 2 groups and 2 timepoints (selected formulation and Placebo groups, at Days 1 and 91), and for hMPV Nab (10 groups, at Days 1 and 91).

Template Table 18 Geometric mean of the individual ratio of <antibody titers/concentrations (units)> post-vaccination compared to pre-vaccination <Per Protocol Set>

						<GMT,C> ratio			
								95% CI	
Group	**N**	**Time point description**	**<GMT,C>**	**Time point description**	**<GMT,C>**	**Ratio order**	**Value**	**LL**	**UL**
<each group>	xxx	PI(D31)		PRE		PI(D31) / PRE			
		<Each time point>		PRE		<time point> / PRE			

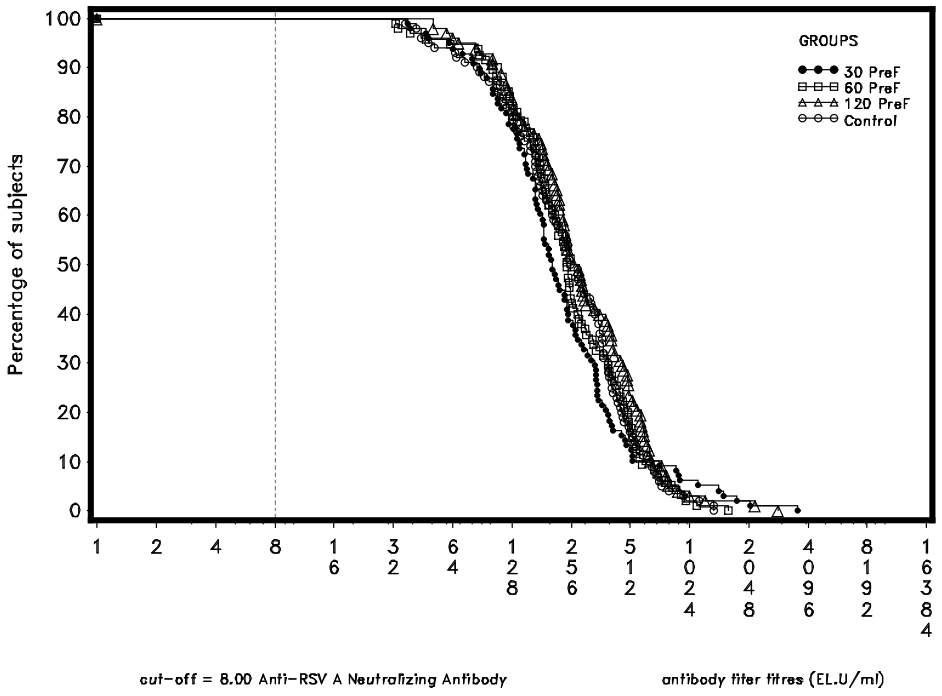
Short group label = long group label
<GMT,C> = geometric mean antibody <titer,concentration>
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template Table 19 Distribution of <antibody titers/concentrations> fold increase post-vaccination compared to pre-vaccination <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	**Timing**	**FI**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each antibody>	<each timing>	< 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

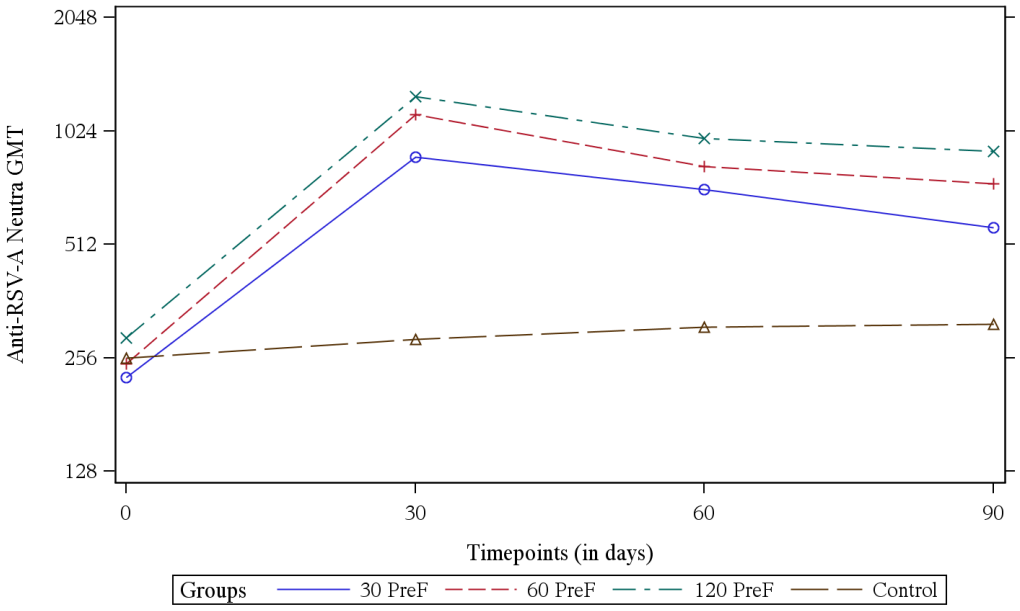
Short group label = long group label
FI= Fold Increase post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with <titer, concentration> fold change meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template Figure 2 Reverse cumulative distribution curve of <antibody titers/concentrations> in the <group label> group <Per Protocol Set>



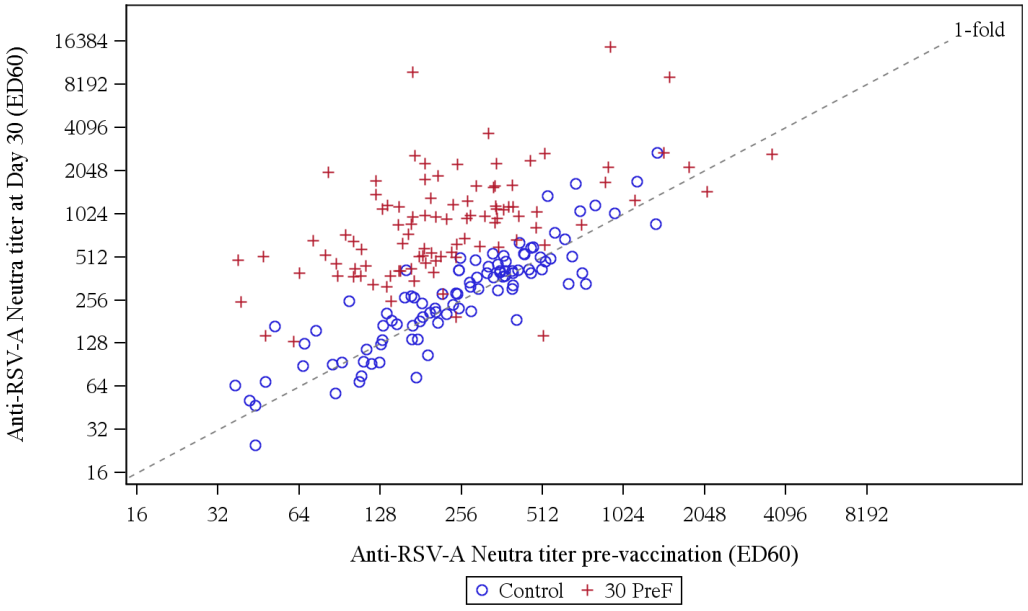
Short group label = long group label
Short timing label = long timing label
Note: this graph is provided as an example. It will be generated by group, and will be adapted to display the 4 timepoints (PRE, D31, D61, D91) for the considered group. For Part B, same graphs will also be generated at Day 91 with groups according to adjuvant content or antigen content vs Placebo. If applicable, the upper limit of quantification will be presented (similarly to the cut-off).
For RSV B Nab ,RSVPreF3 site 0 specific Ab and hMPV NAb, the figure will display only 2 timepoints (Days 1 and 91).

Template Figure 3 Kinetics of < antibody GMT/Cs> on subjects with results available at all timepoints up to <Day 91, Month 14> <Per protocol set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. Template will be adapted to display all the groups (10 groups for Part B) and all the timepoints (4 TPs up to Day 91, 6 TPs up to study end).

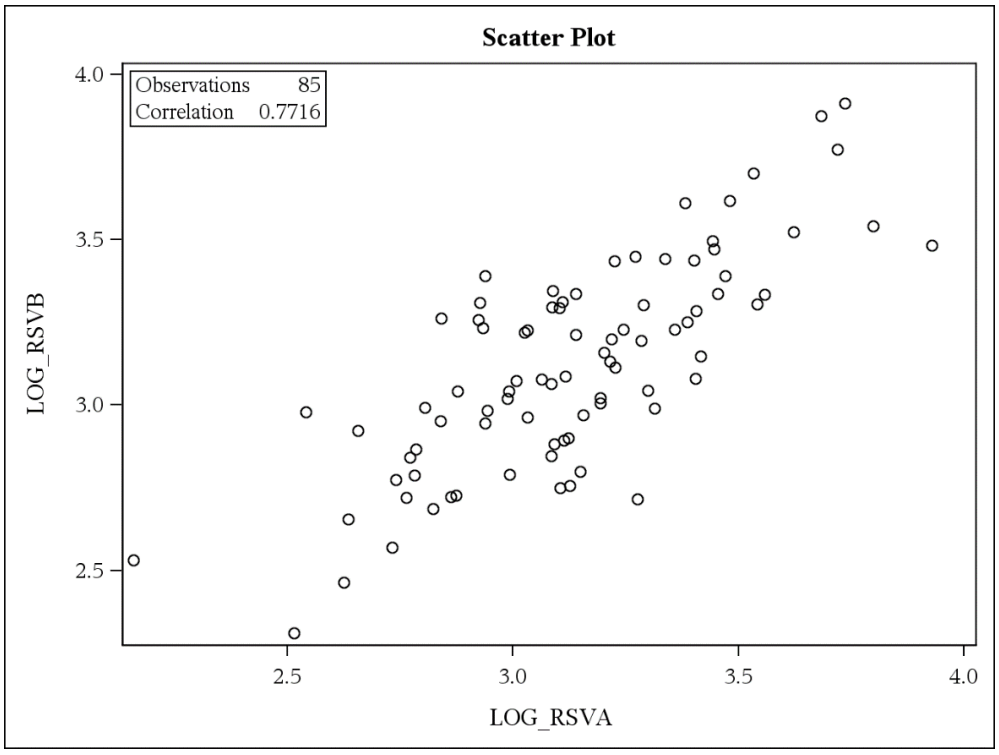
Template Figure 4 Individual results of <RSV A Neutralizing antibody titer> at <time point> versus pre-vaccination in <group label> and Placebo_B groups <Per protocol set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. It will be generated as follows:

- RSV A Nab at Day 31 and Day 91, for each RSV groups (18 graphs)
- RSVPref3 IgG at Day 31 and Day 91, for each RSV groups (18 graphs)
- RSV B Nab at Day 91, for the selected formulation (1 graph)

Template Figure 5 Individual results of <RSV A versus RSV B Neutralizing antibody titer> at <time point> , on pooled RSV groups <Per protocol set>



Note: this graph is provided as an example. It will be generated on pooled RSV groups as follows:

- RSV A Nab vs RSVPreF3 IgG at each timepoint
- RSV A Nab vs RSV B Nab at Pre and Day 91
- RSV B Nab vs RSVPreF3 IgG at Pre and Day 91

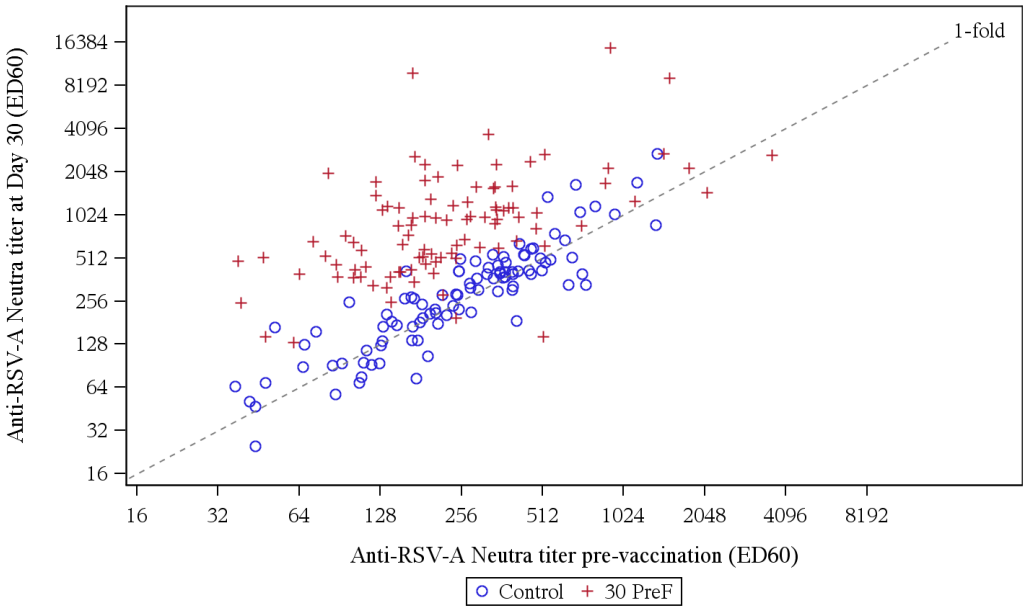
Correlation coefficient will be computed on Log10 transformed data.
Raw data will be presented on Log10 axes.
The same graphs will be generated on fold increase Post over Pre.

Template Table 20 Geometric mean ratios of the fold increase (Pre to Post - vaccination) between RSVPreF3 IgG antibody concentrations and <RSV-A, RSV-B> neutralising antibody titers <Per protocol set>

									GM ratio of FI		
										95% CI	
Timepoint	**Group**	**N**	**RSVPref3 IgG GMF**	**95% CI**		***<RSV-A, B>* Nab GMF**	**95%**		**Value**	**LL**	**UL**
				LL	**UL**		**LL**	**UL**			
PI(D31)/PRE	<each group>										
<each timepoint>											

Short group label = long group label
N = Number of subjects with available results at the two considered time points (post and pre) for both RSVPreF3 IgG and <*RSV-A, B*> Nab
GMF = Geometric mean fold increase Pre to Post-vaccination
GM ratio of FI=Geometric mean ratio of fold increase (Pre to Post)
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template Figure 6 Individual results of the fold increase (post over pre-vaccination) of RSVPreF3 IgG antibody concentrations versus <RSV A, RSV B> neutralizing antibody titers at <time point> in <group label> <Per protocol set>



Short group label = long group label
Note: This graph is provided as an example. It will be generated as follows:

- Y axis=RSVPreF3 IgG vs X axis=RSV A Nab, at Days 31 and 91, for each RSV group (18 graphs)
- Y axis= RSVPreF3 IgG vs X axis=RSV B Nab at Day 91, for the selected formulation (1 graph)
- Axes will be in Log10.

Template Table 21 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

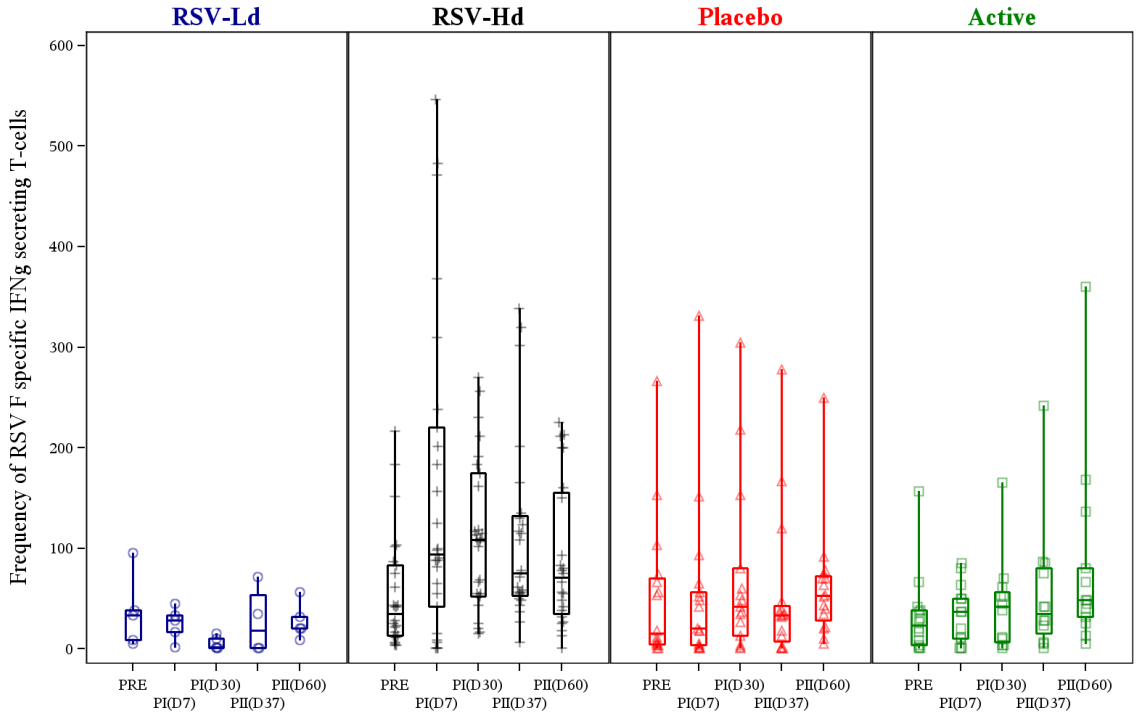
Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label
Note: this table will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).

Template Table 22 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS), by pre-vaccination category <Per Protocol Set>

				<Each group>	<Each group>
Immune Marker	**Pre-vaccination status**	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Q1	<Each timing>	N	xxxx	xxxx
			GM	xx.x	xx.x
			SD		
			Minimum	xx.x	xx.x
			Q1	xx.x	xx.x
			Median	xx.x	xx.x
			Q3	xx.x	xx.x
			Maximum	xx.x	xx.x
	[Q1-Q3]	<Each timing>	<each parameter>		
	>Q3				
	Total				

Short group label = long group label
<Q1= subjects with pre-vaccination frequency < Q1 of the frequencies at pre-vaccination computed on pooled groups
Q1-Q3= subjects with pre-vaccination frequency within [Q1-Q3] of the frequencies at pre-vaccination computed on pooled groups
>Q3=subjects with pre-vaccination frequency < Q3 of the frequencies at pre-vaccination computed on pooled groups
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Figure 7 Boxplots with individual data of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol set>

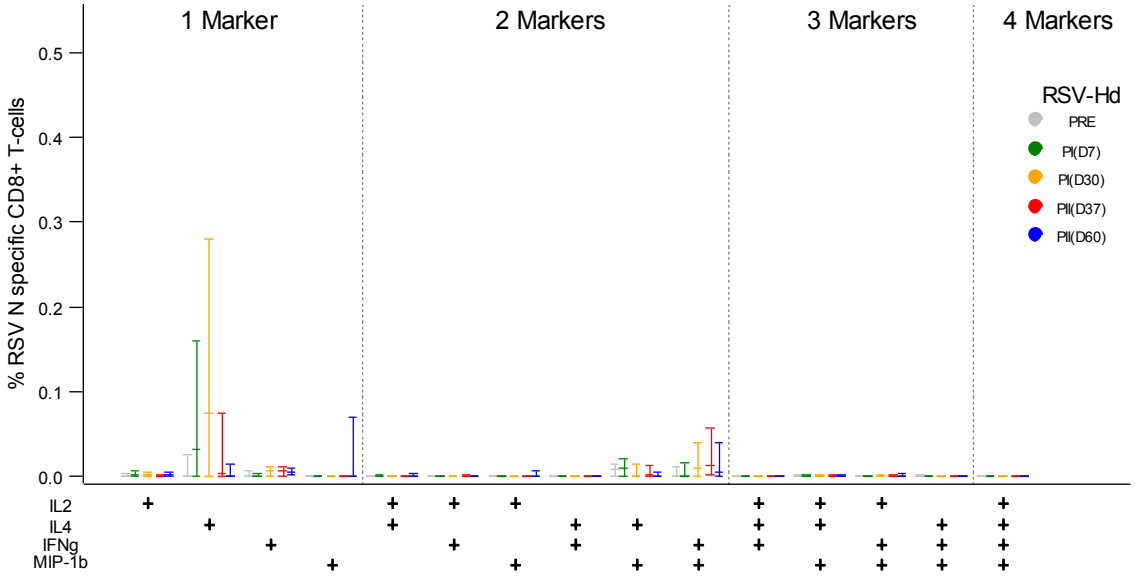


Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. Depending on the analysis, it will display groups and timepoints as follows:

- Part A: 1 graph with 4 groups and 3 (D1, D31, D91) or 4 timepoints (D1, D31, D61, D91)
- Part B: 3 graphs with 4 groups (either by adjuvant content or by antigen content vs Placebo), and 3 timepoints (D1, D31, D91) or 5 timepoints (up to Month 8) or 6 timepoints (up to Month 14, only for selected Ag dose and Placebo)

This graph will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).
For Part B, the same graph will be generated for memory B-cells, with 4 groups (selected Ag dose with Plain/AS01E/AS01B, and Placebo) and 4 timepoints (PRE, D31, D91, M14).

Template Figure 8 Frequency of RSVPreF3 specific CD4+ T-cells expressing any combination of markers among IL-2, CD40L, TNFa, IFNg in <group label> group at Day 31 and Day 91 (per million of CD4+ T cells, by ICS) <Per Protocol Set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. It will be generated by group and will be adapted to display Q1-Median-Q3 for each combination of the markers (15) at Day 31 and Day 91.

Template Table 23 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**Value**
<At least 2 markers>	<Each timing post-vaccination>	N	xxxx	Xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results at both timepoints (pre and post)
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 24 Descriptive statistics of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 25 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing post-vaccination>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template Table 26 Distribution of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Assay	**Timing**	**FI**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<assay name>	<each timing>	< 2	Xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	Xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
FI= Fold increase Post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with fold increase meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

12.3.2. Between groups

Template Table 27 Comparisons of the 9 RSV formulations versus Placebo in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at one month post <dose 1 (Day 31), dose 2 (Day 91)> (ANCOVA model, Dunnett's test) – Part B <Per Protocol set>

Assay	**Timepoint**	**RSV group**	**N**	**GM<T,F> ratio (RSV over Placebo)**	**Dunnett's 95% CI**		**Dunnett's p-value**
					LL	**UL**	
<assay name>	<Day 31, Day 91>	30-PLAIN_B					
		60-PLAIN_B					
		120-PLAIN_B					
		30-AS01E_B					
		60-AS01E_B					
		120-AS01E_B					
		30-AS01B_B					
		60-AS01B_B					
		120-AS01B_B					

Short group label = long group label
N= Number of subjects with both pre- and post-vaccination results available
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
RSV Vaccine is considered superior to Placebo if one-sided p-value <0.025
Dunnett's 95% CI = 95% confidence interval based on Dunnett's adjustment, LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment and age category as fixed effects

Template Table 28 Comparisons of the mean responses post dose 2 (Day 91) versus post dose 1 (Day 31) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> on pooled groups according to adjuvant content (ANCOVA model) – Part B <Per Protocol set >

Assay	RSV group	N	GM<T,F> ratio (D91/D31)	95% CI		p-value
				LL	UL	
<assay name>	PLAIN_B					
	AS01E_B					
	AS01B_B					

Short pooled group label = long pooled group label
N= Number of subjects with results available at both timepoints
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
PII D91 is considered as significantly higher to PI D31 if one-sided p-value <0.025
95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the adjuvant content, antigen dose and age category as fixed effects

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Template Table 29 Comparisons of the RSV groups pooled according to their adjuvant content (Plain, AS01E, AS01B) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) - Part B <Per Protocol set>

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	**Timepoint**	**Group 1**	**N**	**GM<T,F>**	**LL**	**UL**	**Group 2**	**N**	**GM<T,F>**	**LL**	**UL**	**Value**	**LL**	**UL**	**p-value**
<assay name>	<each timing>	AS01B_B					PLAIN_B								
		AS01E_B					PLAIN_B								
		AS01B_B					AS01E_B								

Short group label = long group label

GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance); LL = lower limit, UL = upper limit

ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects

Group 1 is considered superior to Group 2 if one-sided p-value <0.025

Template Table 30 Comparisons of the RSV groups (by antigen dose level) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) – Part B <Per Protocol set >

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	Timepoint	Group 1	N	GM<T,F>	LL	UL	Group 2	N	GM<T,F>	LL	UL	Value	LL	UL	p-value
<assay name>	<each timing>	120-PLAIN_B					60-PLAIN_B								
		120-PLAIN_B					30-PLAIN_B								
		60-PLAIN_B					30-PLAIN_B								
		120-AS01E_B					60-AS01E_B								
		120-AS01E_B					30-AS01E_B								
		60-AS01E_B					30-AS01E_B								
		120-AS01B_B					60-AS01B_B								
		120-AS01B_B					30-AS01B_B								
		60-AS01B_B					30-AS01B_B								

Short group label = long group label

GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance); LL = lower limit, UL = upper limit

ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment, age category and gender as fixed effects

Group 1 is considered superior to Group 2 if one-sided p-value <0.025

Template Table 31 Parameters of the ANCOVA model for the comparison between RSV groups in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg>– Part B <analysis set name>

Timepoint	Variable	DF	Fvalue	p-value
<each timepoint>	Pre-vaccination log <titer, frequency>			
	Age category			
	Adjuvant			
	Antigen			
	Visit			
	Linear effect of antigen			
	Quadratic effect of antigen			
	Antigen*Adjuvant			

Antigen = Antigen dose (3 levels: 30, 60, 120 mcg)
Adjuvant = Adjuvant content (3 levels: no adjuvant, AS01E, AS01B)
Antigen*Adjuvant = interaction between antigen dose and adjuvant
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects
DF = degrees of freedom
Interaction (Antigen * Adjuvant) considered as statistically significant if p-value <0.100
Main factors (Pre-vaccination, antigen, adjuvant) considered as statistically significant if p-value <0.050 (model including interaction)

12.4. Safety

Template Table 32 Compliance in completing solicited adverse events information (Exposed Set)

	<Each group>		
DOSE	**N**	**n**	**Compliance (%)**
Vaccination at Visit 1	xxx	xxx	xx.x
Vaccination at Visit 4	xxx	xxx	xx.x
TOTAL	xxx	xxx	xx.x

Short group label = long group label
N=Number of administered vaccinations
n = number of vaccinations with solicited symptom information completed
Compliance (%) = (n / N) X 100

Template Table 33 Incidence and nature of <grade 3> symptoms (solicited and unsolicited) <with causal relationship to vaccination> reported during the XX-day (Days 1-XX) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 34 Incidence of any symptoms (solicited and unsolicited) resulting in medically attended visit, reported during the 30-day (Days 1-30) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 35 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <analysis set name>

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
DOSE 2	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
OVERALL/DOSE	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					
OVERALL/SUBJECT	<*Each symptom*>	All					
		Grade ≥2					
		Grade 3					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 36 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <cohort name>

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
DOSE 2	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/DOSE	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/SUBJECT	*<Each symptom – except fever>*	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					

Short group label = long group label

For each dose:

N = number of subjects with the corresponding documented dose

n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose

For Overall/dose:

N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom

For Overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting the type of symptom at least once

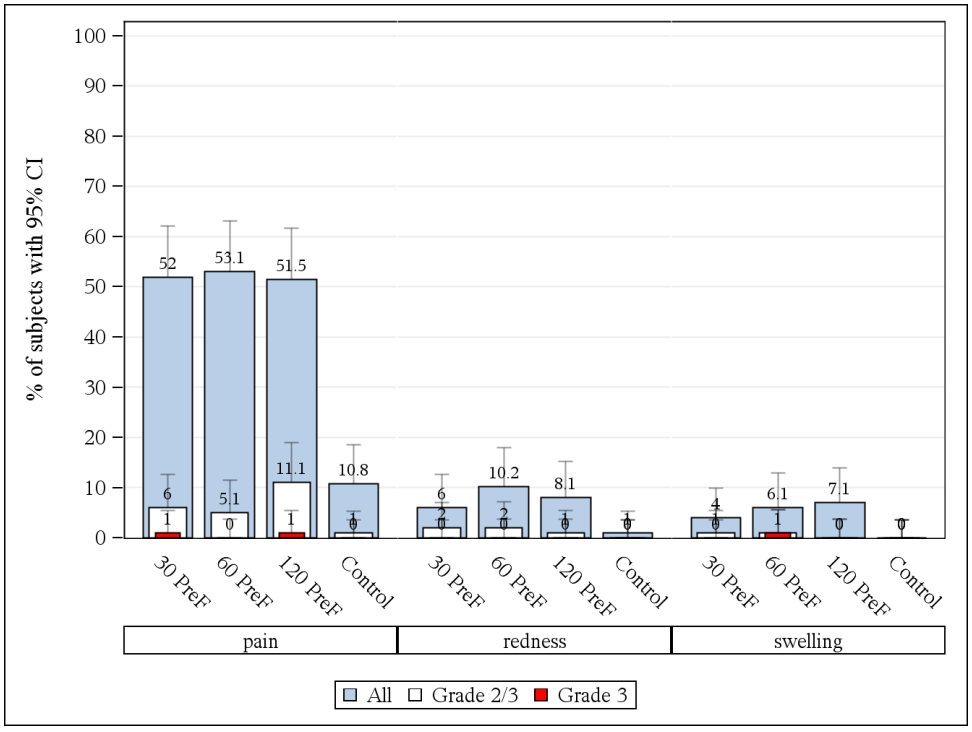
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 37 Number of days with <*local/general*> solicited symptoms during <the 7-day (Days 1-7), the whole> post-vaccination period <analysis set name>

			<Each group>
Dose	**Symptom**	**Statistic**	**Value**
DOSE 1	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
DOSE 2	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
OVERALL/DOSE	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	

Short group label = long group label
n = number of doses with the symptom
Q1 = 25th percentile
Q3= 75th percentile

Template Figure 9 Incidence of solicited <local, general> adverse events reported during the 7-day (Days 1-7) post-vaccination period following each dose <Exposed set>



Short group label = long group label
Note: this graph is provided as an example. It will be adapted to display the percentage of subjects reporting each local or general symptom, any grade and grade 3, by group and by dose. Template will be discussed at the time of the dry-run.

Template Table 38 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the 30-day (Days 1-30) post-vaccination period <analysis set name>

		<Each group> N=XXXX					Total N=XXXX				
					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	N	%	LL	UL
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
…	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
	…										

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects included in the considered analysis set in each group
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template Table 39 List of (S)AEs and solicited adverse events leading to study/treatment discontinuation <Exposed set>

Group	Sub. No	Country	Gender	Race	AE Description	Preferred Term	SAE	Causality	Outcome	Vaccination and visit	Type of discontinuation*

Short group label = long group label
* type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template Table 40 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<each group>								

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD source
<each group>										

Short group label = long group label

Template Table 41 Listing of SAEs <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>							

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>									

Short group label = long group label

Template Table 42 Listing of pregnancies reported during the study period in Part A <analysis set name>

Group	Sub. No.	Country	Race	Age at vaccination	Previous Dose	LMP date	Days between LMP-vacc	Age at delivery (Year)	Date of delivery	Pregnancy Outcome	Date of outcome	Gestational weeks at birth/miscarriage /termination

Short group label = long group label
LMP=Last Mentrual Period

Template Table 43 Number and percentage of subjects taking concomitant medication during the <XX>-day (Days 1-<XX>) post-vaccination period by dose and overall <analysis set name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		**N**	**n**	**%**	**LL**	**UL**	**N**	**N**	**%**	**LL**	**UL**
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = total number of subjects with the corresponding administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses after which the specified type of concomitant medication was taken at least once during the considered period
For overall/subject:

N = total number of subjects with at least one administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 44 Distribution of change from baseline in hematology and biochemistry with respect to normal laboratory ranges, 7 days post dose <1, 2> <analysis set name>

			<Each group>			<Each group>		
Laboratory parameter	**Range indicator at Baseline (PRE)**	**Range indicator at post-vaccination**	**N**	**n**	**%**	**N**	**n**	**%**
<Each parameter>	UNKNOWN	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	BELOW	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	WITHIN	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						
	ABOVE	UNKNOWN						
		BELOW						
		WITHIN						
		ABOVE						

Short group label = long group label
N = number of subjects with available results for the specified laboratory parameter and timing in a given baseline category
n/% = number/percentage of subjects in the specified category
Below = below the normal laboratory range defined for the specified laboratory parameter
Within = within the normal laboratory range defined for the specified laboratory parameter
Above = above the normal laboratory range defined for the specified laboratory parameter
Baseline= Pre-vaccination at <Day 1, Day 61>
Post-vaccination= Post vaccination at <Day 8, Day 68>

Template Table 45 Summary of hematology and biochemistry results by grade at 7 days post dose <1, 2 > versus baseline (<Day 1, Day 61>) <analysis set name>

			<each group >		
Laboratory parameter	**Baseline**	**Post-vaccination**	**N**	**n**	**%**
<Each parameter>	Unknown	Unknown			
		<Each grade>			
	<Each grade>	Unknown			
		<Each grade>			
	Total	Unknown			
		<Each grade>			

Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
Baseline= Pre-vaccination at <Day 1, Day 61>
Post-vaccination= Post vaccination at <Day 8, Day 68>

Note: Templates 45 and 46 will be generated post dose 1 with results at Visit 2 (Day 8) versus baseline at Day 1, and post dose 2 with results at Visit 5 (Day 68) versus baseline at Day 61.

Template Table 46 Summary of hemoglobin change from baseline at 7 days post-dose <1, 2> (Exposed set)

		<Each group>		
Laboratory parameter		**N**	**n**	**%**
Hemoglobin - change from baseline	UNKNOWN			
	GRADE 0			
	GRADE 1			
	GRADE 2			
	GRADE 3			

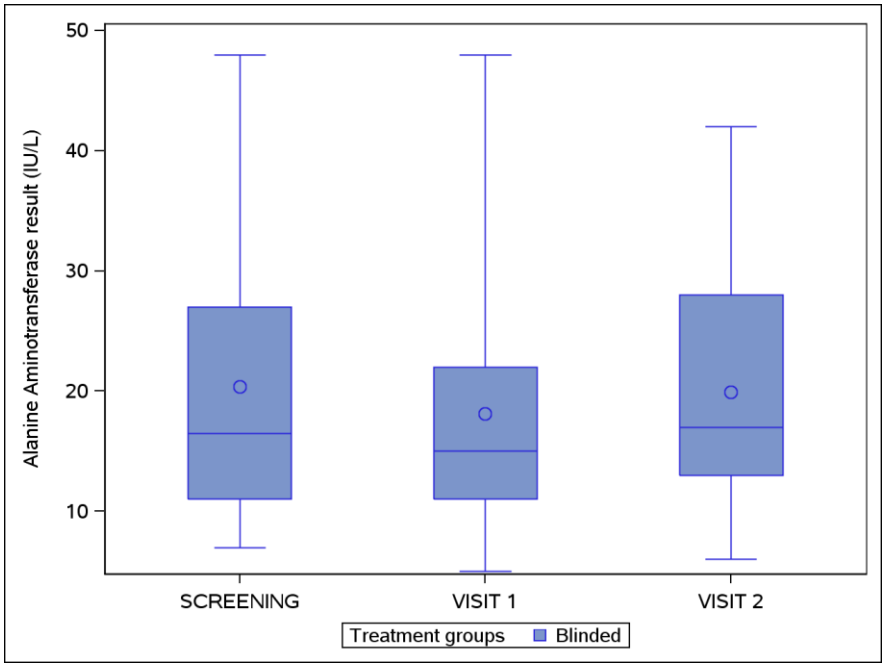
Short group label = long group label

N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period

n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Note:This table will be generated post dose 1 with results at Visit 2 (Day 8) and Day 1 as baseline, and post dose 2 with results at Visit 5 (Day 68) and Day 61 as baseline.

Template Figure 10 Boxplot of <each hematology/biochemistry parameter> (Exposed Set)



Note: This graph is given as an example. It will be adapted to display one boxplot per group and per timepoint, all timepoints available (5 TPs: Screening, Days 1, 8, 61, 68). For Part A, one graph will be generated displaying the 4 groups. For Part B, 3 graphs will be generated displaying 4 groups: 3 RSV groups (30/60/120 -Plain, - AS01E or - AS01B) and the Placebo group.

Template Table 47 Solicited and unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 1-30) post-vaccination period including number of events - SAE excluded <analysis set name>

		<Each group> N=XXXX			<Each group> N=XXXX		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
	At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each PT (PT code)> …	xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects included in the considered analysis set in each group
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template Table 48 Number (%) of subjects with serious adverse events during the study period including number of events reported <analysis set name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

12.5. Analysis of RTI

Template Table 49 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal/throat swab at assessment visit	RSV+										
	RSV-										
	All										

Short group label = long group label

RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group or in Total
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 50 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal swab samples collected at home <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal swab at home	RSV+										
	RSV-										
	All										

Short group label = long group label

RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template Table 51 Mean of the viral load of the RSV-confirmed RTI episodes, as measured by qRT-PCR on nasal/throat swabs, by collection time and collection method <Exposed set>

		RSV A +				RSV B +			
Days after RTI onset	**Swab**	**N**	**n**	**%**	**mean**	**N**	**n**	**%**	**mean**
0-2	Nasal swab at home								
	Nasal/throat swab at assessment visit								
3-4	Nasal swab at home								
	Nasal/throat swab at assessment visit								
>4	Nasal swab at home								
	Nasal/throat swab at assessment visit								

Days after RTI onset = number of days between start of RTI symptoms and collection date
N=Number of swabs with qRT-PCR results available
n/%= number/percentage of swabs tested as RSV A/B positive by qRT-PCR
mean= mean of the viral load computed on RSV A/B positive swabs

Template Table 52 Descriptive statistics of the viral load of the RSV- confirmed RTI episodes, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <at home> <Exposed Set>

		<Each group> N=	Total N=
Type	**Parameters**	**Value**	**Value**
RSV A +	N		
	Mean		
	Min		
	Q1		
	Median		
	Q3		
	Max		
RSV B +	…		
All RSV +			

Short group label = long group label
RSV A+= RSV A positive samples by qRT-PCR
RSV B+-= RSV B positive samples by qRT-PCR
All RSV += All RSV positive samples by qRT-PCR
N = Number of swabs with qRT-PCR results available
n= number/percentage of samples in each category
Q1 and Q3 = 25th and 75th percentiles
Min/Max = Minimum/Maximum

Template Table 53 Number and percentage of subjects reporting co-infections with respiratory viruses, as measured by multiplex PCR on RSV A/B positive RTI samples collected <at assessment visit, at home> <Exposed Set>

	RSV RTI N =			
			95% CI	
Categories	**n**	**%**	**LL**	**UL**
Influenza A Virus				
Influenza B Virus				
…				
<each virus>				
…				
Total				

N = number of swabs tested RSV positive by qRT-PCR
n/% = number/percentage of swabs tested positive by multiplex in a given category
Total= number of swabs tested positive for at least one virus
LL, UL= Exact 95% Lower and Upper confidence limits

Template Table 54 Clinical signs and symptoms associated with RTI episodes (Exposed set)

		RSV RTI N=XXXX		Non RSV RTI N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**N**	**%**	**n**	**%**	**n**	**%**
Heart Rate increase (beats/min)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Respiratory rate increase (breaths/min)	5-10						
	10-15						
	15-20						
	20-25						
	…						
Systolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Diastolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Oxygen saturation decrease (%)	1-2						
	3-4						
	5-6						
	7-8						
	…						
Upper respiratory symptoms	<Each symptom>						
Lower respiratory symptoms	<Each symptom>						

		RSV RTI N=XXXX		Non RSV RTI N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**N**	**%**	**n**	**%**	**n**	**%**
qPCR result	RSV A+						
	RSV B+						
	RSV -						
Self-collected Nasal swab	RSV+						
	RSV-						
	NA						
Medically attended visit	Emergency room						
	Hospitalisation						
	Medical personnel						
	None						
SAE associated to the episode	Yes						
	No						

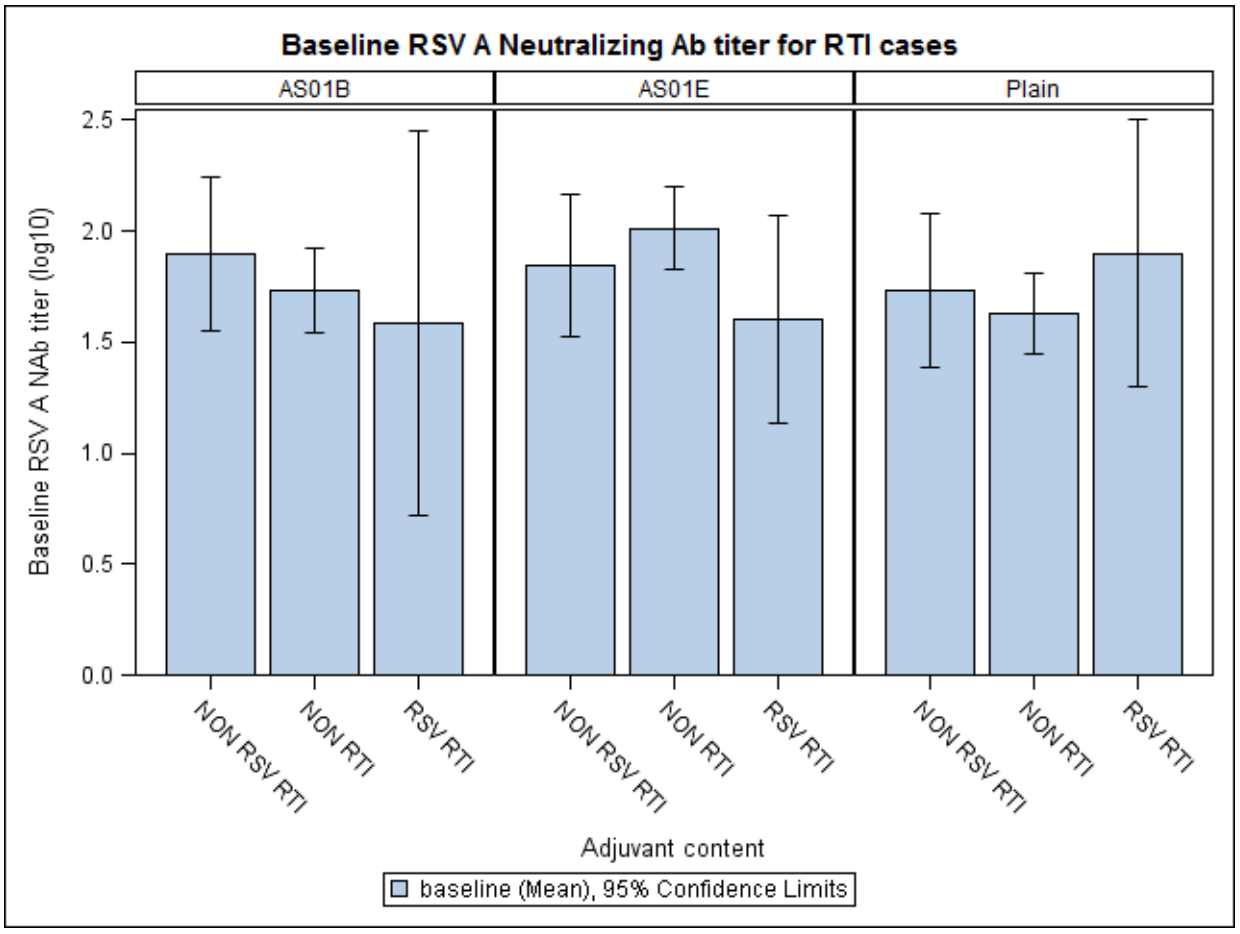
RSV RTI= RTI episode tested as RSV positive by qRT-PCR on nasal/throat swab collected at assessment visit
Non-RSV RTI= RTI episode tested as RSV negative by qRT-PCR on nasal/throat swab collected at assessment visit
N = number of RTI episodes in each category or in total
n = number of RTI episodes in the corresponding category
% = n / N x 100
For vital signs, change from baseline (increase/decrease) will be displayed by category: category of 10 units increase for heart rate, systolic and diastolic BP, 5 units increase for respiratory rate, and 1% decrease for oxygen saturation (to be adapted at the time of dry run if needed)

Template Table 55 Listing of RTI episodes reported during RTI surveillance in Part B (Exposed set)

Group	Sub. No.	Age at Dose 1	Sex	Episode nb	Start date of episode	End date of episode	Date of assessment visit	Nb of signs and symptoms	Date nasal swab on site	RSV A positive (site)	RSV B positive (site)	Date nasal swab at home	RSV-A positive (home)	RSV-B positive (home)	Medically attended visit	SAE related to RTI episode
										Yes/No	Yes/No		Yes/No	Yes/No		Yes/No

Short group label = long group label

Template Figure 11 GMTs and 95% CIs of RSV A Neutralizing antibody titer at baseline for subjects reporting RTI episodes (RSV RTI vs or non RSV RTI vs No RTI), by groups pooled according to the adjuvant content <Exposed Set>



This graph is provided as an example, template will be finalized at the time of the dry-run. It will display the GMTs and 95% CIs for subjects reporting confirmed RSV RTI episodes vs subjects reporting Non-RSV RTI episodes vs subjects who did not report any RTI episode (NON RTI), in the RSV groups pooled according to the adjuvant content (Plain, AS01E, AS01B).

12.6. Additional templates (Amendment 1)

Template Table 56 Distribution of hematology and biochemistry parameters at baseline with respect to normal laboratory ranges <analysis set name>

		<Each group>			<Each group>		
Laboratory parameter	**Range indicator at baseline**	**N**	**n**	**%**	**N**	**n**	**%**
<Each parameter>	UNKNOWN						
	BELOW						
	WITHIN						
	ABOVE						

Short group label = long group label
N = number of subjects with available results for the specified laboratory parameter in a given baseline category
n/% = number/percentage of subjects in the specified category
Below = below the normal laboratory range defined for the specified laboratory parameter
Within = within the normal laboratory range defined for the specified laboratory parameter
Above = above the normal laboratory range defined for the specified laboratory parameter

Template Table 57 Summary of follow-up time (in days) up to <DLP or last contact> (Exposed Set)

	<Each group> N=XXXX	Total N=XXXX
	Value	**Value**
Number of days in the study		
N	xxx	Xxx
Mean	xxx.x	xxx.x
Median	xxx.x	xxx.x
Minimum	xxx	Xxx
Maximum	xxx	Xxx

Short group label = long group label
N = total number of subjects
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data

Template Table 58 Summary of subjects by unsolicited adverse event category

	<each group> N=XXXX	
At least one unsolicited adverse event within 30-day of any vaccination	n*	Xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one related unsolicited adverse event within 30-day of any vaccination	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one medically attended unsolicited adverse event within 30-day of any vaccination	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one serious unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one serious related unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one potential immune-mediated disorder (pIMD) <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one related potential immune-mediated disorder (pIMD) <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)
At least one fatal unsolicited adverse event <up to DLP or study end>	n*	xxx
	n	xxx
	%	xx.x
	95% CI	(xx.x ; xx.x)

n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase I/II, randomized, placebo-controlled, observer-blind, multicenter study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_E$ or $AS01_B$ or unadjuvanted) when administered intramuscularly according to a 0, 2 month schedule in adults aged 18-40 or 60-80 years.
eTrack study number and Abbreviated Title	208851 (RSV OA=ADJ-002)
Scope:	All data pertaining to the above study (except IDMC analyses)
Date of Statistical Analysis Plan	Final: 14 January 2019
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Stat Peer Reviewer) PPD (Regulatory Affairs) PPD (SERM physician) PPD (Safety scientist) PPD (Public disclosure representative) PPD (CLS – Clinical Read-outs) PPD (CMI Expert representative)
Approved by:	PPD (Clinical and Epidemiology Project Lead) PPD (Lead statistician) PPD (Statistician) PPD (Lead Scientific writer) PPD (Lead stat Analyst)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 12 November 2018)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CD40L	Cluster of Differentiation 40 Ligand
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CMV	Cytomegalovirus
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
eCRF	electronic Case Report Form
eDiary	electronic Diary
ELU/ml	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
ES	Exposed Set
FDA	Food and Drug Administration
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Commitee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IL	Interleukin
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit Of Quantification
Mcg or µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	Peripheral Blood Mononuclear Cells

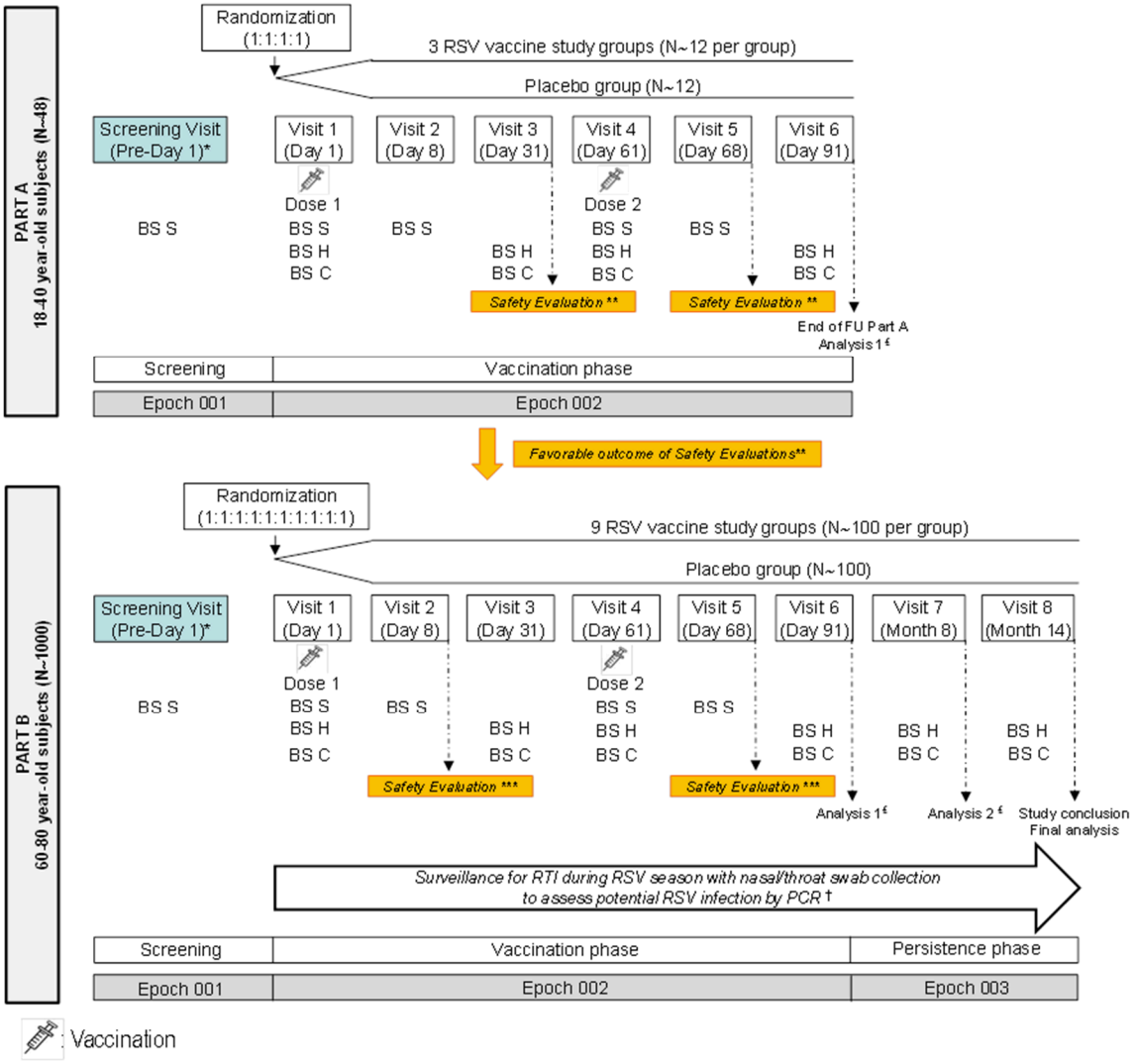
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncitial Virus
RTI	Respiratory Tract Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TNF-α	Tumor Necrosis Factor alpha
TOC	Table of Content
UL	Upper Limit of the confidence interval
WBC	White Blood cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
14-JAN-2019	Final version	Final: 11 SEP 2018

2. STUDY DESIGN

Figure 1 Study design



BS S: Blood sample for safety (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
BS C: Blood sample for cell-mediated immune responses (for CD4+/CD8+ and/or memory B-cell testing)
FU: Follow-up; PCR: Polymerase Chain Reaction
* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

** In Part A, a first IDMC evaluation of safety data up to Day 31 based on all subjects (~12 per group or at least 8 per group in case of slow recruitment) will be performed before proceeding with administration of Dose 2 in Part A and Dose 1 in Part B. A second IDMC evaluation will be performed based on safety data up to Day 68 for all subjects. Part B of the study can only be initiated upon favorable outcome of the first IDMC safety evaluation in Part A.
*** In Part B, a third and fourth IDMC evaluation of safety data up to Day 8 and Day 68, respectively, for the first enrolled and vaccinated subjects (~10 per group or at least 8 per group in case of slow recruitment) will be performed. Additional IDMC evaluations will happen during the conduct of the study.
† In case of RTI symptoms during the RSV seasons (approximately from October to March), the subject will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab at the site. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).
£ Analysis 1 will be performed on all data collected up to Day 91 for at least primary and secondary endpoints based on both study parts (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). Analysis 2 will be performed when all safety data up to Month 8 (Visit 7) are available. The analyses will be based on data as clean as possible.

- **Experimental design:** Phase I/II, observer-blind, randomized, controlled, multi-country study with 2 parts (i.e., Part A in young adults aged 18-40 years with 4 parallel groups and Part B in older adults aged 60-80 years with 10 parallel groups).
- **Primary Completion Date (PCD):** last visit of the vaccination phase in Part B (Visit 6 [Day 91]).
- **End of Study (EoS):** Last testing results released of samples collected up to Visit 8 in Part B (Month 14) (for assays related to primary and secondary endpoints only).
- **Treatment allocation:** Subjects will be randomized using a centralised randomization system on internet (SBIR) on Day 1.

  In Part A, the aim is to enrol approximately 48 subjects (~12 per group) aged 18-40 years. The randomization algorithm will use a minimisation procedure accounting for center and gender.

  In Part B, the aim is to enrol approximately 700 subjects (~70 per group) aged 60-69 years and approximately 300 subjects (~30 per group) aged 70-80 years. The randomization algorithm will use a minimisation procedure accounting for age, center and gender in each step.

- **Study groups:**

  For the investigational RSV vaccines in Part A and Step 1 in Part B, the RSVPreF3 high-dose formulation containing 120 μg RSVPreF3 will be used to prepare the vaccines for all dose groups (i.e., 30 μg, 60 μg and 120 μg dose groups). For Step 2 in Part B, the RSVPreF3 low-dose and mid-dose formulations (containing 30 μg and 60 μg RSVPreF3, respectively) will be used for the groups receiving 30 μg and 60 μg of RSVPreF3, respectively, and the RSVPreF3 high-dose formulation will be used for the 120 μg dose groups. As the reconstitution methods for the vaccines administered to subjects enrolled in Step 1 and 2 of Part B will be different, separate study groups have been identified (referred to as B1 and B2). Throughout this document, the combined groups for Steps 1 and 2 are mentioned when referring to the number of groups in Part B (10 groups).

- **Control:** placebo**.**
- **Vaccination schedule:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Blinding: observer-blind.**

The vaccination phases of each study part (Epoch 002) will be observer-blind. A first statistical analysis will be performed on data available up to one month post-Dose 2 (Visit 6, Day 91). Given that summary safety results may unblind some specific subjects, the persistence phase of Part B (Epoch 003) will be considered as single-blind with subjects remaining blinded up to study end (Visit 8 [Month 14]). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

- **RTI surveillance in Part B:** Active and passive surveillance will only be carried out during RSV seasons (approximately from October to March) throughout the entire Part B of the study:
  - **Active surveillance:** study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experience an RTI.
  - **Passive surveillance:** study participants are instructed to contact the investigator/study staff as soon as they experience an RTI.

  At the beginning of RSV seasons, study participants will be reminded of the start of the RTI surveillance.
- **Sampling schedule:**

  In Part A:

  - At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the electronic Case Report Form (eCRF). The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
  - At Day 1 (Visit 1), a blood sample for cytomegalovirus (CMV) status determination will be drawn from all subjects.
  - **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).
  - **Blood samples for humoral immunogenicity and cell-mediated immunity (CMI)** testing will be drawn from all subjects at Days 1, 31, 61 and 91 (Visits 1, 3, 4 and 6).

In Part B:

- At Screening (Pre-Day 1), a blood sample for eligibility assessment will be drawn from all subjects. In case Visit 1 occurs more than 30 days after the Screening visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection must be repeated (maximum one re-screening per subject is allowed). Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. Only data from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The subject can however only be randomized once the investigator receives the safety assessment results and confirms the eligibility criteria.
- At Day 1 (Visit 1), a blood sample for CMV status determination will be drawn from all subjects.
- **Blood samples for safety assessment** (hematology/biochemistry) will be drawn from all subjects and on Days 1, 8, 61 and 68 (Visits 1, 2, 4 and 5).
- **Blood samples for humoral immunogenicity and CMI** testing will be drawn from all subjects at Days 1, 31, 61, 91, Month 8 and Month 14 (Visits 1, 3, 4, 6, 7 and 8).
- **Nasal/throat swabs:** In case of RTI symptoms during the RSV season (approximately from October to March), the study participants will be asked to collect a nasal swab at home and contact the investigator/study staff to schedule an assessment visit for collection of an additional nasal/throat swab by qualified staff from the study team. The assessment visit should take place as soon as possible after the start of symptoms (ideally within 48 hours, but no later than 7 days).

- **Type of study:** self-contained.
- **Data collection:** eCRF. Solicited symptoms will be collected using an electronic subject Diary (eDiary). Unsolicited symptoms will be collected using a paper subject Diary.
- **Safety monitoring:** The study will be conducted in 2 parts with oversight by an IDMC. The investigator is not permitted to start vaccinating the subjects in the next step in each part until receipt of the favorable outcome of the respective safety evaluations by the IDMC.
  - **Part A:** Approximately 48 young adults aged 18-40 years will be enrolled and vaccinated with the first dose. If the IDMC evaluation on data up to 30 days post Dose 1 is favorable, the Part A study participants will be vaccinated with the second dose and Part B of the study will be initiated.
  - **Part B:** This part will be conducted in a 2-step staggered design to ensure maximum safety of the participating subjects. In Step 1, approximately 100 subjects will be enrolled and vaccinated. Safety evaluations based on unblinded data from those first 100 subjects will be performed by the IDMC to allow the start of Step 2. In Step 2, the remaining study participants (N≅900) will be recruited and vaccinated.

In total, 6 IDMC meetings for safety evaluation are foreseen in the vaccination phase of the study (Epoch 002), i.e., 2 meetings in Part A and 4 meetings in Part B.

During the persistence phase of Part B (Epoch 003), 2 IDMC meetings will be planned with an interval of approximately 6 months.

If any safety concern is identified by the investigator or the sponsor, *ad-hoc* safety evaluations by the IDMC may be performed.

Analysis planned for IDMC evaluations are described in a separate document (SAP for IDMC).

- **Group description for analysis:**

For analysis based on subjects in Part A and Part B Step 1 (B1), the group labels listed in table below will be used in the TFLs.

For final analysis based on subjects from Part B Steps 1 and 2, the groups will be pooled (B1 and B2) and the Pooled group labels will be used in the TFLs.

Table 1 Groups description

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
30-PLAIN_A	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part A	NA	
60-PLAIN_A	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part A	NA	
120-PLAIN_A	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part A	NA	
Placebo_A	subjects receiving Placebo in Part A	NA	
30-PLAIN_B1	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 1	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B
30-PLAIN_B2	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B Step 2	30-PLAIN_B	subjects receiving unadjuvanted 30 mcg RSVPreF3 in Part B
60-PLAIN_B1	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 1	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B
60-PLAIN_B2	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B Step 2	60-PLAIN_B	subjects receiving unadjuvanted 60 mcg RSVPreF3 in Part B
120-PLAIN_B1	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 1	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
120-PLAIN_B2	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B Step 2	120-PLAIN_B	subjects receiving unadjuvanted 120 mcg RSVPreF3 in Part B
30-AS01E_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B

Group label in tables	Group definition for footnote	Pooled Group label in tables	Pooled Group definition for footnote
30-AS01E_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	30-AS01E_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
60-AS01E_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	60-AS01E_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 1	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
120-AS01E_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B Step 2	120-AS01E_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01E in Part B
30-AS01B_B1	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
30-AS01B_B2	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	30-AS01B_B	subjects receiving 30 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B1	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B
60-AS01B_B2	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	60-AS01B_B	subjects receiving 60 mcg RSVPreF3 adjuvanted with AS01B in Part B
120-AS01B_B1	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 1	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
120-AS01B_B2	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B Step 2	120-AS01B_B	subjects receiving 120 mcg RSVPreF3 adjuvanted with AS01B in Part B
Placebo_B1	subjects receiving Placebo in Part B Step 1	Placebo_B	subjects receiving Placebo in Part B
Placebo_B2	subjects receiving Placebo in Part B Step 2	Placebo_B	subjects receiving Placebo in Part B

For some of the comparison analyses in Part B, the RSV vaccine groups will be pooled according to their adjuvant content and the following group names will be used in the TFLs:

Pooled Group label in tables	Pooled Group definition for footnote	Groups to be pooled
PLAIN_B	subjects receiving unadjuvanted RSVPreF3 in Part B (30, 60 or 120 μg)	30_PLAIN_B1, 30_PLAIN_B2, 60_PLAIN_B1, 60_PLAIN_B2, 120_PLAIN_B1, 120_PLAIN_B2
AS01E_B	subjects receiving RSVPreF3 adjuvanted with AS01E in Part B (30, 60 or 120 μg)	30_AS01E_B1, 30_ AS01E _B2, 60_ AS01E _B1, 60_ AS01E _B2, 120_ AS01E _B1, 120_ AS01E _B2
AS01B_B	subjects receiving RSVPreF3 adjuvanted with AS01B in Part B (30, 60 or 120 μg)	30_AS01B_B1, 30_ AS01B _B2, 60_ AS01B _B1, 60_ AS01B _B2, 120_ AS01B _B1, 120_ AS01B _B2

For the analysis by age category, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	60-69Y	60-69 years old subjects
2	70-80Y	70-80 years old subjects

For the analysis by CMV status before vaccination, the following sub-group names will be used in the TFLs:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	CMV+	Subjects CMV positive before vaccination
2	CMV-	Subjects CMV negative before vaccination

3. OBJECTIVES/ENDPOINTS

3.1. Objectives

3.1.1. Primary objective

For Part A and Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

3.1.2. Secondary objectives

For Part A and Part B:

- To characterize the humoral immune responses (including dose-response) in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).
- To characterize the cell-mediated immune responses in relation to the investigational RSV vaccine formulations administered IM according to a 0, 2 month schedule, up to one month after the last dose (Day 91, Visit 6).

For Part B:

- To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccines administered IM according to a 0, 2 month schedule, up to the end of follow-up (Month 14, Visit 8).
- To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

3.1.3. Tertiary objectives

For Part A and Part B:

- To further characterize the cell-mediated immune responses to investigational RSV vaccine formulations.

For Part B:

- To further characterize immune responses to investigational RSV vaccine formulations.
- To characterize persistence of immune responses to the investigational RSV vaccine formulations at Month 8 (Visit 7) and Month 14 (Visit 8).
- To further evaluate the occurrence of RSV-associated RTI (including co-infections with other respiratory viruses) during the RSV seasons in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI.

- To evaluate the occurrence of RSV-associated RTI during the RSV season using self-collected nasal swabs.

3.2. Endpoints

3.2.1. Primary endpoints

For Part A and Part B:

- Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91):
  - Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination.
  - Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination.
  - Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68.
  - Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination.
  - Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

For Part B only:

  - Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).

3.2.2. Secondary endpoints

For Part A and Part B:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro.

For Part B only:

- Occurrence of RSV-associated RTI (as measured by qRT-PCR in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons, up to the end of follow-up.
- Occurrence of SAEs from Dose 1 up to the end of follow-up.
- Occurrence of pIMDs from Dose 1 up to the end of follow-up.

3.2.3. Tertiary endpoints

For Part A and Part B:

- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (Day 61) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro.

For Part B only:

- Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91):
  - Neutralizing antibody titers against RSV serotype B in all subjects.
  - RSVPreF3 site 0 specific antibody concentrations in a subset of subjects who received the selected vaccine formulation or placebo.
- Cell-mediated immune response profile with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31) and 30 days post-Dose 2 (Day 91):
  - Frequency of RSVPreF3-specific memory B-cells in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Persistence of the humoral immune response with respect to components of the investigational vaccine at Months 8 and 14:
  - Neutralizing antibody titers against RSV serotype A.
  - RSVPreF3-specific IgG antibody concentrations.
- Persistence of the cell-mediated immune response profile with respect to components of the investigational vaccine:
  - Frequency of RSVPreF3-specific CD4+ and/or CD8+ T-cells identified as expressing one or any combination of immune marker(s) in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).

  - Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro, in all subjects (Month 8) and in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo (Month 14).
  - Frequency of RSVPreF3-specific memory B-cells at Month 14 in a subset of subjects who received the selected level of antigen dose (3 RSV vaccine formulations) or placebo.
- Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to:
  - Antibodies against specific protein F epitopes.
  - Potential new immunological markers for protection.
  - Cross-reactive neutralizing antibody titters against hMPV
- Occurrence of RSV-associated RTI, including co-infections with other respiratory viruses (as measured by multiplex PCR in self-collected nasal swab samples and nasal/throat swab samples collected during the assessment visit for potential RSV-RTI) during the RSV seasons.
- Occurrence of RSV-associated RTI as measured by qRT-PCR in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

4. ANALYSIS SETS

4.1. Definition

4.1.1. Exposed Set

The Exposed Set (ES) will include all subjects with study vaccine administration documented.

A safety analysis based on the ES will include all vaccinated subjects.

An immunogenicity analysis based on ES will include all vaccinated subjects for whom immunogenicity data are available.

The ES analysis will be performed per treatment actually administered at Dose 1.

4.1.2. Per-Protocol Set for analysis of immunogenicity

The Per-Protocol set (PPS) for analysis of immunogenicity will be defined by time point (and this to include all eligible subjects' data up to the time of important protocol deviations). The PPS will include all evaluable subjects in the ES:

- Meeting all eligibility criteria.
- For whom the administration route of the vaccine was as according to protocol.

- For whom the study vaccine was administered as per protocol.
- Who did not receive a concomitant medication/ product leading to exclusion from a PP analysis, as described in Section 6.6.2 of the protocol, up to the considered time point.
- Who did not present with a medical condition leading to exclusion from a PP analysis, as described in Section 6.7 of the protocol, up to the considered time point.
- Who complied with the vaccination schedule, as specified in the protocol.
- Who complied with the timings of the post-vaccination blood sampling for immune response evaluation, as specified in the protocol.
- For whom post-vaccination immunogenicity results are available for at least one assay component at the corresponding time points.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects eliminated from ES.

4.2.2. Elimination from Per-protocol analysis Set (PPS)

4.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions.

For codes 1040, 1070, 1080, 1090, 2040, 2060, 2080: subjects will be eliminated from a specific visit (at which the condition is met) onwards.

For codes 2090, 2100, 2120: subjects will be eliminated at the specific visit at which the condition is met.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
900	Invalid informed consent or fraudulent data	All	All
1030	Study vaccine not administered at all	All	All
1040	Administration of concomitant vaccine(s) forbidden in the protocol: Any investigational or non-registered vaccine other than the study vaccine used during the study period A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last vaccine dose, except for inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each vaccination.	All	Immunology
1050	Randomisation failure	All	Immunology
1060	Randomisation code was broken	All	Immunology
1070	Vaccination not according to protocol: Incomplete vaccination course Subject 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	All	Immunology
1080	Vaccine temperature deviation vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visits 1 and 4	Immunology
1090	Expired vaccine administered	Vaccination visits 1 and 4	Immunology
2010	Protocol violation (inclusion/exclusion criteria)	All	Immunology
2040	Administration of any medication forbidden by the protocol Any investigational or non-registered medication used during the study period Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period Long-acting immune-modifying drugs administered at any time during the study period Immunoglobulins and/or any blood products administered during the study period	All	Immunology
2060	Intercurrent medical condition Subjects may be eliminated from the PPS if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status (other than RSV infection).	All	Immunology
2080	Subjects did not comply with vaccination schedule: **Part A**: number of days between dose 1 and dose 2 is outside [55-80 days] **Part B**: number of days between dose 1 and dose 2 is outside [55-75 days]	Visit 4	Immunology

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule at a specific visit: Number of days between dose 1 and visit 3 blood sample is outside [30-37 days] Number of days between dose 2 and visit 6 blood sample is outside [30-37 days] **Part B only:** Number of days between dose 2 and visit 7 blood sample is outside [170-190 days] Number of days between dose 2 and visit 8 blood sample is outside [350-395 days]	Visits 3, 6, 7 and 8	Immunology
2100	Immunological results not available post-vaccination No immunological result at visit x for all 3 following tests: RSV A Neutralising antibody titer, RSVPreF3-specific IgG antibody concentration and RSVPreF3-specific CD4+ T cells frequency	Visits 3, 4, 6, 7, 8	Immunology
2120	Obvious incoherence or abnormality or error in data Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab	Visits 1, 3, 4, 6, 7, 8	Immunology

5. STATISTICAL ANALYSES

Note that standard data derivation rules and stat methods are described in "business rules document" and will not be repeated below. The study specific data derivation rules and stat methods will be described in section 9.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (age at first vaccination in years, gender, race and ethnicity) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error and range will be provided for continuous data such as age.

The distribution of subjects will be tabulated as a whole and per group and for each age category (60-69 years and 70-80 years in Part B only).

Withdrawal status will be summarized by group using descriptive statistics:

- The number of subjects enrolled into the study as well as the number of subjects excluded from PP analyses will be tabulated.
- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal.

5.1.2. Additional considerations

The analysis of demographic characteristics by group will be performed on the ES and on the PPS.

Demography and baseline characteristics will also be summarized by country.

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure, pulse oximetry) reported at visit 1 (Part A and Part B) will be summarized by group using descriptive statistics.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

NA

5.2.2. Additional considerations

The number of doses of study vaccines administered will be tabulated by group and by vaccine.

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be performed on the PPS for immunogenicity and, if in any study group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is at least 10%, a second analysis will be performed on the ES.

5.3.1.1. Within groups evaluation - humoral immune response

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

In Part A and Part B:

- Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
- GMCs/GMTs and their 95% CI will be tabulated and represented graphically.
- Geometric mean of ratios of antibody titer/concentrations at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.
- Antibody titer/concentration will be displayed using reverse cumulative curves.
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will be computed and tabulated using descriptive statistics.

In Part B only:

- The distributions of antibody titers/concentrations will be tabulated.
- Individual post-vaccination results (at Days 31 and 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots. Results of the placebo group will be used as a reference.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers) will be tabulated.
- The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.

The immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The humoral immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.2. Within groups evaluation - Cell-mediated immune response

The following parameters will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI:

In Part A and Part B:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, upon in vitro stimulation and background substracted, measured by ICS using PBMCs.
- Frequency of CD4+ and/or CD8+ T-cells expressing **any combination of immune marker(s)** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs (see details in section 5.3.2.2).

- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ , as measured by ICS using PBMCs.

In Part B only:

- Frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

This will be displayed overall and by pre-vaccination category: <Q1, Q1-Q3, >Q3, where Q1/Q3 are respectively the 25th and the 75th percentiles of the results at pre-vaccination computed on pooled groups.

In addition, vaccine response in terms of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ, will be explored and summarised by group.

The descriptive immunogenicity analysis will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years) in Part B only.

The cell-mediated immune response by CMV status before vaccination might be explored in Parts A and B. This will be done if at least 10% of the subjects are included in each CMV status category (CMV positive and CMV negative).

5.3.1.3. Between groups evaluation (Part B only)

Statistical analyses will be performed to compare the 9 RSV investigational vaccine formulations in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

The between-groups analysis will be performed using an ANCOVA model, in several steps as follows:

1. The 9 RSV formulations will be first compared to the Placebo in order to identify groups whose means are significantly higher from the mean of the Placebo group, in terms of RSV-A neutralizing antibody titers and RSVPreF3-specific CD4+ T-cells at Day 31 and Day 91 (One-sided alpha=2.5%, Dunnett's adjustment test for multiplicity).
2. The effect of the second vaccination will be evaluated by comparing the means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31), of the groups pooled according to their adjuvant content ($AS01_B$, $AS01_E$ and Plain), in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibody titers (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose).

   Based on the results of this test, the next comparisons will be performed either at Day 91 or at Day 31.

3. Appropriate contrasts will be implemented to compare the RSV formulations as follows:

   – To demonstrate the adjuvant effect (on pooled groups according to their adjuvant content: AS01B, AS01E, Plain), by testing sequentially AS01B and AS01E versus Plain (One-sided alpha=2.5% for each superiority test: Adjuvant >Plain) in terms of RSVPreF3-specific CD4+ T-cells and RSV-A neutralizing antibodies and, if applicable, by comparing AS01B vs AS01E.

   – To demonstrate linearity of increase in immune response when increasing the antigen dose in each adjuvanted group in terms of RSV-A neutralizing antibody and/or RSVPreF3-specific CD4+ T-cells.

   – Further ANCOVA t-tests would demonstrate superiority of 120 µg or 60 µg, should a quadratic effect be demonstrated.

   – Similar exploratory comparisons might also be performed on the RSVPreF3 ELISA antibody concentrations if deemed necessary.

5.3.2. Additional considerations

5.3.2.1. Within groups – humoral immune response

- Correlations between assays of the humoral response will be investigated using scatter plots generated on pooled RSV groups:

  – RSVPreF3-specific IgG versus RSV A neutralizing antibody titer at each timepoint,

  – RSV A versus RSV B neutralizing antibody titer at Pre-vaccination and Day 91

  – RSVPreF3-specific IgG versus RSV-B neutralizing antibody titer at Pre-vaccination and Day 91

The same analysis will be performed on the fold increase post over pre-vaccination.

- The fold increase (post over pre-vaccination) of the RSVPreF3 IgG antibody concentrations versus the fold increase (post over pre-vaccination) of RSV-A and RSV B neutralizing antibody titers will also be displayed graphically by group using scatter plots.

5.3.2.2. Within groups – Cell-mediated immune response

Descriptive statistics of the cell-mediated immune response will be tabulated and displayed graphically using boxplots (min, Q1, median, Q3, max), by group and timepoint.

The RSVPreF3-specific CD4+/CD8+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geomean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+/CD8+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 cytokines [$Freq^{2+}$] will be computed as follows:

$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

And

$$Freq^{2+}_{Specific} = Freq^{2+}_{Induction} - Freq^{2+}_{Background}$$

where

$n^{2+}_{Background}$= number of CD4+ T cells expressing at least 2 cytokines after stimulation with medium only (background)

$n^{2+}_{Induction}$= number of CD4+ T cells expressing at least 2 cytokines after stimulation with a pool of peptides covering RSVPreF3 (induction)

$N^{CD4}_{Back/Ind}$= Total number of CD4 T cells involved in the assay (background or induction)

Same computations will be done for all CMI responses that will be analysed, i.e.:

- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least 2 markers including at least 1 cytokine*** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.

  ** cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17*
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IFN-γ (Th1-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/CD8+ T-cells expressing **at least IL-13 (Th2-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+/ CD8+ T-cells expressing **at least IL-17 (Th17-like response)**, as measured by ICS using PBMCs.
- **Co-expression profile:** Frequency of RSVPreF3-specific CD4+ T-cells expressing **any combination of marker(s) among** CD40L, IL-2, TNF-α, IFN-γ, as measured by ICS using PBMCs, at Day 31 and Day 91 (15 combinations).

Vaccine response in terms of RSVPreF3-specific CD4+ T cells frequencies expressing at least 2 markers among CD40L, IL-2, TNF-α, IFN-γ will be explored as follows:

- Distribution of the fold increase: the percentage of subjects with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

For the computation of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ, the results **below the LLOQ** of the assay will be replaced by the value of the LLOQ.

5.3.2.3. Between groups analysis

Statistical comparisons will be performed on the logarithm base 10 transformed results, in terms of RSV-A neutralizing antibody titers and frequency of RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ.

a. Comparisons versus Placebo:

The 9 RSV formulations will be compared to the Placebo (control group) at Day 31 and Day 91 using an ANCOVA model with the Dunnett's adjustment method for multiplicity. The model will include the treatment group and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. Geometric mean ratios between groups and associated Dunnett's adjusted 95% CIs of the ratios will be tabulated.

The Dunnett's test is specifically designed for situations where all groups are to be compared against one "Reference" group. It is commonly used after ANCOVA has rejected the hypothesis of equality of the means of the distributions.

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test (where=(visit=D91));
 CLASS treatmnt Adj agecat;
 MODEL log(titer)=treatmnt baseline agecat / ddfm=KR DDFM=KR
outpm=pred_model cl;
 REPEATED / group=Adj ; /* test homogeneity of variances and consider
different variance by adjuvant content if appropriate */
 LSMEANS treatmnt / ALPHA=0.05 Adjust=Dunnett pdiff=control ("Placebo")
CL;
RUN;
```

b. Comparisons between RSV groups:

The difference between RSV groups will be evaluated using an ANCOVA model including the adjuvant content (AS01B, AS01E, Plain), the antigen dose (30, 60, 120 µg), the visit (Day 31, Day 91) and the age category (age at Dose 1: 60-69 or 70-80 years) as fixed effects, and the pre-vaccination log10-transformed titer as covariate. The adjuvant by antigen interaction will also be tested, and included in the model if significant at 10% (p-value <10%).

Based on this global model, appropriate contrasts will be used to perform the following comparisons:

1. Effect of the second vaccination:

The means one month post-Dose 2 (Day 91) and one month post-Dose 1 (Day 31) will be compared within each pooled group according to adjuvant content (AS01B, AS01E and Plain) (One-sided alpha=2.5% for each superiority test: 2 doses> 1 dose). Geometric mean ratios and associated 95% CIs will be tabulated.

1. Adjuvant effect:

The adjuvant effect will be tested sequentially as follow (One-sided alpha=2.5% for each superiority test):

1. AS01B versus Plain
2. AS01E versus Plain
3. AS01B versus AS01E.

Geometric mean ratios and their 95% CIs will be computed for each comparison.

The same comparisons will also be performed by age category.

1. Antigen dose-response: test linear and quadratic effect of the antigen dose. Depending on significance of those 2 effects, ANCOVA t-tests might be done to demonstrate superiority of 120 µg or 60 µg.

Geometric mean ratios and their 95% CIs will be computed for each pairwise comparison within each adjuvant content family (120 µg vs 60 µg, 120 µg vs 30 µg, 60 µg vs 30 µg for Plain, AS01E and AS01B groups).

Here is an example of SAS code that will be used:

```
PROC MIXED DATA=test;
 class Adj(1B, 1E, PL) Ag(30, 60, 120) visit(PD1, PD2) subject agecat;
 model log(titer) = Adj Ag visit Adj*Ag Adj*visit Ag*visit Adj*Ag*visit
baseline baseline*visit agecat / DDFM=KR S outpm=pred_model cl;
 REPEATED visit / SUBJECT=subject type=unr group=Adj;
 /* test homogeneity of variances and consider different variance by
adjuvant content if appropriate */
 LSMEANS Adj*visit /E slice=visit CL PDIFF ALPHA=0.05; /*option E to see
coefficients assigned to each effect */
 LSMEANS Adj*visit /E slice=Adj CL PDIFF ALPHA=0.05;
 LSMEANS Adj*Ag*visit / slice=visit CL PDIFF ALPHA=0.05;
/* contrasts to be added for each comparison of interest */
QUIT;
```

The inferential analysis on the RSVPreF3-specific CD4+ T cells will be performed on the log-transformation frequency of the CD4+ T cells expressing at least 2 markers (background or induction) computed by adding an offset of 0.5 cells to the number of activated CD4+ T cells (Delta method, see below). These transformations are deemed appropriate for further inferential analyses provided the incidence of activated CD4+ T-cells is below 4%.

Considering:

$X_{ijk} = \log\left(\frac{n^{2+}_{background} + 0.5}{N^{CD4}_{Background}}\right)$, the log background frequency, and

$Y_{ijk} = \log\left(\frac{n^{2+}_{Induction} + 0.5}{N^{CD4}_{Induction}}\right)$, the log induction frequency

The following model can be used to analyse the log-transformed ratio between induction and background frequencies, and provide estimates of the RSVPreF3-specific frequency (Delta Method- Inference on Induction/background data):

$Y_{ijk} = \mu_{jk} + \alpha_j . y_{i0k} + \beta . x_{ijk} + \varepsilon_{ijk}$, with

$(\overline{Y_{jk} - x_{jk}})\Big|_{\bar{y}_0, \bar{x}} = \mu_{jk} + \alpha_j . \bar{y}_0 + \beta . \bar{x}$, LS means conditional to $\bar{y}_0$ and $\bar{x}$

where:

i, j , k=subject *i*, visit j, group *k*; $\bar{y}_0$= mean log induction frequency at pre-vaccination,

$\bar{x}$= mean log background after vaccination.

Note: This analysis is assuming that the background is the same for all groups and all timepoints. This assumption will be checked during the analysis.

Geometric means (GMs) of post-vaccination RSVPreF3-specific CD4+ T cell frequency and 95% CIs, will be calculated conditionally to the means of the pre-vaccination log-transformed CD4+ T cell frequency following induction with RSVPreF3 and the post-vaccination log-transformed CD4+ T cell frequency under background conditions.

The test and the 95% CIs for treatment comparisons will be calculated according to the delta method on the log-transformed ratio of RSVPref3-specific frequency relative to the background frequency estimates:

$\hat{Z}_{jk} = 10\hat{}(\hat{Y}_{jk} - \bar{x}) - 1 = \frac{10\hat{}(\hat{Y}_{jk}) - 10\hat{}(\bar{x})}{10\hat{}(\bar{x})}$, and

$Log(\hat{W}_{jk}) = Log\left(\frac{\hat{Z}_{jk_2}}{\hat{Z}_{jk_1}}\right) = Log\left(\frac{10\hat{}(\hat{Y}_{jk_2}) - 10\hat{}(\bar{x})}{10\hat{}(\hat{Y}_{jk_1}) - 10\hat{}(\bar{x})}\right)$, where

$\hat{Z}_{jk}$= mean increase from background to induction frequency relative to background frequency at visit *j* for treatment *k*, and

$\hat{W}_{jk}$ = vaccine effect on the antigen specific frequency following adjustment for background frequency.

Algorithm for calculations of Confidence Intervals of antigen-specific CMI response using the Delta-Method

Analysis results transformations:

1. The LSM and CI are back-transformed on the original scale to provide Geometric Mean Ratios of the induction frequency over background frequency.(Induction_freq GM / Background_freq GM)
2. Unity is removed from the Geometric Mean Ratios & CI ((Induction_freq GM – Background_freq GM) / Background_freq GM)
3. The result in 2 is multiplied by the geometric mean of background frequency used to calculate the LSM to provide the geometric means for the antigen-specific frequency.(Induction_freq GM – Background_freq GM)
4. The log-transformed of the result in 2 is calculated and the difference between test group and control group is calculated.Log(Induction_freq GM_test – Background_freq GM) - Log(Induction_freq GM_control – Background_freq GM)
5. The confidence interval of the result in 4 is calculated through the delta-method, using student-t distribution and the number of degree of freedom provided by MIXED for the difference in LSM.
6. The result in 4 is back-transformed to original scale to provide the fold-increase in the frequency of antigen-specific frequency.(Induction_freq GM_t – Background_freq GM) / (Induction_freq GM_c – Background_freq GM)

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 30-day 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 any AEs considered related to vaccination, for Grade 3 AEs considered related to vaccination and for Grade 3 non-serious AEs.

The percentage of subjects with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will also be tabulated after each dose and overall.

The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.

Similar tabulations will be performed for any fever with a causal relationship to vaccination and for Grade 3 (> 39.0°C/102.2°F) causally related fever.

For each group and for each hematology and biochemistry parameter:

- The percentage of subjects having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
- The summary of grading post-vaccination will be tabulated versus baseline. (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX C in the protocol. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on 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 Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. SAEs will also be described in detail.

For Part A only, pregnancy and pregnancy outcomes will be listed (if applicable).

For Part B only, the percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. PIMDs will also be described in detail.

The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 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.

The analysis of safety will also be performed by age category (age at Dose 1: 60-69 years and 70-80 years in Part B only).

5.4.2. Additional considerations

All analyses will be descriptive and will be based on the Exposed Set (ES).

Compliance in completing solicited adverse events information will be tabulated after each dose and overall.

The percentage of subjects with at least **one local solicited** AE, with at least **one general solicited** AE and with **any solicited** AE during the 7-day 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 any AEs considered related to vaccination, and for Grade 3 AEs considered related to vaccination.

The number of days with solicited symptoms reported during the **7-day follow-up period** will be tabulated for each solicited adverse event, after each dose using descriptive statistics (mean, min, Q1, median, Q3, maximum).

The same tabulation will be done for Grade 3 symptoms, and also during **the whole post-vaccination period** (to include the total number of days for symptoms ongoing beyond the follow-up period).

The incidence of each solicited symptom (any grade and grade 3) will also be represented graphically per group and per dose.

Analysis of solicited symptoms will also be done on the **pooled groups according to adjuvant content** (AS01B, AS01E, Plain), overall and by age category.

5.4.2.1. Solicited Adverse Events

Solicited adverse events will be reported daily during the 7-day (from Day 1 to Day 7) follow up period after each vaccination, using structured diaries. Missing or non-evaluable measurements will not be replaced.

In order to summarize the data, the maximum intensity of local injection site redness/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Redness/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity. Body temperature will also be summarized by 0.5°C increments as follows: ≥38.0, >38.5, >39.0, >39.5, >40.0 °C.

Each subject's data will be summarized according to the maximal severity observed during the follow-up period for each adverse event and each dose, followed by a summary across subjects and across doses.

5.4.2.2. Unsolicited Adverse Events

When an unsolicited adverse event occurs more than once for a subject, 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.

The analysis of unsolicited adverse events includes the following categories:

- Any unsolicited adverse event.
- Possibly related unsolicited adverse events.
- Grade 3 unsolicited adverse events
- Grade 3 possibly related unsolicited adverse events.
- Serious adverse events (SAEs)
- Possibly related SAEs.
- Potential Immune-Mediated disease (pIMDs, in Part B only)
- Medically attended adverse events

SAEs and pIMDs reported during the entire study period will be tabulated.

In addition, the following time periods will be considered to report SAEs/pIMDs at the first and second analyses (E1_02 and E1_03, see section 7.1):

- from Dose 1 up to 30 days post dose 2 (or up to 90 days post dose 1 for subjects who did not received the second dose)
- from Dose 1 up to 6 months* post dose 2 (or up to 8 months* post dose 1 for subjects who did not received the second dose).

  * months will be converted in days in order to select the events for the output tables.
- Listing of AEs/SAEs leading premature withdrawal from study or to interruption of vaccination will be described in detail.

5.4.2.3. Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10015150	Erythema
Swelling	10053425	Swelling at injection site
Fatigue	10016256	Fatigue
Fever	10016558	Fever
Gastrointestinal symptoms	10017944	Gastrointestinal disorder
Headache	10019211	Headache
Myalgia	10028411	Myalgia
Shivering	10040558	Shivering
Arthralgia	10003239	Arthralgia

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.4.2.4. Clinical Safety Laboratory Investigations

In case of invalid or missing results or clinically significant grade 3 and above abnormal laboratory findings, a repeat testing may be done to confirm the first result (see Protocol section 7.1.4). For the analysis, the following rules will be applied:

- In general, the first result will be considered, except if this result is missing.
- In case of retesting for a grade 3 at pre-vaccination, the retesting will be considered if the result is < grade 3.

5.4.2.5. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.5. Analysis of RTI for Part B

5.5.1. Analysis of RTI planned in the protocol

The analysis will be performed on the ES.

Any RTI episode for which a visit for the assessment of potential RSV-RTI has been performed (with nasal/throat swab sampling) will be considered for the analysis. The assessment of RSV infection will be performed using qRT-PCR on nasal/throat swabs separately for samples collected by the subject and those collected by an appropriately qualified person (i.e., medical or nursing) at the assessment visit.

The proportion of subjects with at least one RSV-associated RTI (with 95 % CI) will be calculated by group.

Descriptive analyses (mean, median, min, max) of viral load assessed by quantitative PCR (RSV-A/B) of RSV-RTI will be performed by study group.

The incidence rate of all-cause RTI (with 95% CI) will be calculated by group. These will also be presented by co-infection identified by multiplex PCR.

5.5.2. Additional considerations

The mean viral load of the RSV positive-RTI samples will also be reported by collection method (at assessment visit or at home) and by collection time (0-2, 3-4, >4 days between RTI onset date of symptoms and collection date).

Information collected at assessment visit will be described for RSV RTI episodes versus Non-RSV RTI episodes, as tested by qRT-PCR on nasal/throat swabs collected at assessment visit. It will include: vital signs, clinical symptoms, self-collected nasal swab result, medically attended visit and SAE related to the episode.

RTI episodes will be described in detail in a listing. In addition, baseline RSV A Neutralizing antibody titer (GMT and 95% CIs) will be presented graphically by RTI episode status (RSV-RTI vs Non RSV-RTI vs No RTI).

6. ANALYSIS INTERPRETATION

All analyses will be descriptive with the aim to characterize the difference in safety/reactogenicity or immunogenicity between groups.

All comparisons will be exploratory. They should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons, except for the comparisons of all RSV formulations vs Placebo (Dunnett's adjustment).

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- **A first analysis** will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 91 are available (except for cell-mediated immune response at pre-Dose 2 [Day 61] in Part A and Part B and the occurrence of RSV RTI in Part B). This will include results from all subjects in Part A and Part B. This analysis will be considered as final for those endpoints. A clinical study report will be written.

At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available), but no individual listings will be provided to the study team. Given that summary safety results may unblind some specific subjects, the study will be considered as single-blind from this point onwards, with subjects remaining blinded up to study end (Visit 8, Month 14). The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

- **A second analysis** will be performed when all safety data up to Month 8 (Visit 7) are available (data as clean as possible). At this time, the following analyses will be performed:
  - The safety analysis of data up to 6 months post-Dose 2.
  - The analysis of all qPCR data available at that time.
  - The analysis of any additional laboratory results up to one month post-Dose 2 that may become available for all planned subjects in Part B.
- **A third immunogenicity analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 8 are available, to evaluate the persistence up to 6 months post-Dose 2 in Part B.
- **A fourth analysis** will be performed when data for at least tertiary immunogenicity endpoints related to persistence (humoral and cell-mediated immunogenicity) up to Month 14 (Visit 8) are available for the subjects enrolled in Step 1 of Part B. This analysis will include any additional laboratory results that may become available at that time.

  No individual listings will be provided before the final end of study analysis.
- **The final end of study analysis** will be performed when all data for at least primary and secondary endpoints up to study conclusion are available (Month 14). All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage. An integrated clinical study report containing all available data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Reference for TFL TOC
Final analysis	E1_01	SR, CTRS	See column A in TFL TOC
Analysis up to Day 91	E1_02	SR, CTRS	See column B in TFL TOC
Analysis up to Month 8 (safety and PCR)	E1_03	Internal	See column C in TFL TOC
Analysis up to Month 8 (immuno)	E1_04	Internal	See column D in TFL TOC
Analysis up to Month 14 (Part B Step 1)	E1_05	Internal	See column E in TFL TOC

7.2. Statistical considerations for interim analyses

All analyses will be conducted on final data (as clean as possible) and therefore no statistical adjustment for interim analyses is required.

8. CHANGES FROM PLANNED ANALYSES

The fold-increase parameter for CMI (post over pre-vaccination) that will be summarised by group using descriptive statistics (N, geometric mean [GM], min, Q1, median, Q3, max) at each time point during which blood samples are collected for CMI has been adapted as follows:

- ***Fold increase (Post over pre-vaccination)*** of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 marker(s) among IL-2, CD40L, TNF-α, IFN-γ , ***as measured by ICS using PBMCs.***

This analysis was also added for the Memory B cells:

- Fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific memory B-cells, as measured by ELISpot using PBMCs.

All additional analysis planned compared to protocol are described in the "Additional considerations sections". The mains ones to be included in the CSR are also described below (changes indicated in bold):

- Demography and baseline characteristics will be summarized ***by country***.
- Vital signs at baseline will be described by group using descriptive statistics.
- Exposure to study vaccine will be tabulated by group and by vaccine
- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV neutralizing antibody titers will be reported for RSV-A ***and RSV B***.
- Comparisons with Placebo will be done ***at Day 31*** and Day 91, for both RSV A Neutralizing antibody ***and CD4+ T cells expressing at least 2 markers***.

- Analyses of solicited symptoms were added: incidence of any/local/general solicited AEs, number of days with solicited AEs, analysis on pooled groups according to adjuvant content.
- RTI episodes: analysis of viral load by collection method and collection time was added, as well as the description of signs and symptoms for RSV-RTI vs Non-RSV RTI cases.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1).

9.1. Handling of missing data

9.1.1. Dates

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 other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject 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 CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day 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.

See also exceptions in section 9.1.

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited symptoms

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited symptoms, symptoms will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = 10SEP1983, Date of vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of vaccination = 10SEP2018 -> Age = 35 years

10.1.3.2. 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

Conversion of temperature from °Fahrenheit to °C will be performed according to SDTM specifications.

10.1.3.3. 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
All other cases	missing

10.1.3.4. 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. Antibody titers or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.5. Onset day

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

10.1.3.6. Duration of events

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

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

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse 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.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

- Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics 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 minima of transformed body temperatures will be displayed with one decimal.

10.1.4.3. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Adjusted GMT or GMC ratios

When between-group GMT or GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

10.2. TFL ToC

The TFL TOC provides the list of tables/figures/listings that will be generated at each analysis. It can be found in eTMF folder section 11.01.01.

The mock tables/figures referred under column named ‘layout’ can be found in section 12.

11. REFERENCES

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

12. STUDY MOCK TFLS

The following drafted standard and study specific mocks will be used. Note that standard templates might be updated based on the last version of the standard catalogue used at the time of analysis. Titles and footnotes will be adapted accordingly.

The data display, title and footnotes are for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment.

12.1. Demography

Template 1 Summary of demography and baseline characteristics (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	Value or n	**%**	**Value or n**	**%**
Age (years) at first vaccination				
N	xxx		xxx	
Mean	xxx.x		xxx.x	
Standard Deviation	xxx.x		xxx.x	
Median	xxx.x		xxx.x	
Minimum	xxx		xxx	
Maximum	xxx		xxx	
Sex				
Male	xxx	xx.x	xxx	xx.x
Female	xxx	xx.x	xxx	xx.x
Ethnicity				
<Each Ethnicity>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Race				
<Each Race>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x
Age category				
<Each Age category>	xxx	xx.x	xxx	xx.x
…	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template 2 Number of subjects by country and center (Exposed Set)

		<Each group> N=XXXX		Total N=XXXX	
Country	**Center-Investigator Name**	**n**	**%**	**n**	**%**
<each country>	<each center-investigator name>	XXX	XX.X	XXX	XX.X
	All	XXX	XX.X	XXX	XX.X

Short group label = long group label
N = total number of subjects
n = number of subjects in a given center or country
% = (n/N) x 100

Template 3 Number of subjects by study steps (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
Steps	**n**	**%**	**n**	**%**
Part A				
Part B Step 1				
Part B Step 2				

Short group label = long group label
N = total number of subjects
n = number of subjects in a given category
% = (n/N) x 100

Template 4 Summary of vital signs (Exposed Set)

			<Each group> N=XXXX	Total N=XXXX
Visit	**Characteristics**	**Parameters**	**Value**	**Value**
<EACH VISIT>	Heart rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Respiratory rate (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Systolic Blood pressure (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Diastolic blood pressure (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Pulse oximetry (<unit>)	n	xxx	xxx
		Mean	xxx.x	xxx.x
		SD	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Minimum	xxx	xxx
		Maximum	xxx	xxx
	Pre-vaccination Temperature (C)	n		
		Mean		
		SD		
		Median		
		Minimum		
		Maximum		

Short group label = long group label
N = total number of subjects
Value = value of the considered parameter
n = number of subjects in a given category
N with data = number of subjects with documentation of the corresponding data
SD = standard deviation

Template 5 Summary of study completion with reason for withdrawal (Exposed Set)

	<Each group> N=XXXX		Total N=XXXX	
	n	%	n	%
Completed the study	xxx	xx.x	xxx	xx.x
Withdrawn from the study	xxx	xx.x	xxx	xx.x
Primary reason for withdrawal :				
<Each reason>	xxx	xx.x	xxx	xx.x

Short group label = long group label

Template 6 Summary of visit attendance (Exposed Set)

		<EACH GROUP> N=XXXX		Total N=XXXX	
Visit	Status	n	%	n	%
<EACH VISIT>	Attended	xx	xx.x	xx	xx.x
	Did not attend yet	xx	xx.x	xx	xx.x
	Withdrawal at visit or earlier	xx	xx.x	xx	xx.x
	Did not attend	xx	xx.x	xx	xx.x

Short group label = long group label
N = Number of subjects in each group or in total
n/% = number / percentage of subjects in a given category

Template 7 Summary of important protocol deviations leading to elimination from any analyses (Enrolled Set)

Category Sub-category	<Each group> N=XXX			Total N=XXX		
	Occ	n	%	Occ	n	%
At least one Important Protocol Deviation						
< Each category >						
<each sub-category>						

Short group label = long group label
N = Total number of subjects
Occ = number of occurrences = number of important protocol deviations
n/% = number / percentage of subjects with important protocol deviations

Template 8 Summary of subject disposition from Enrolled set to Randomized set (Enrolled Set)

	Total N=	
	n	%
Withdrawals prior to randomization		
<withdrawal reason 1>		
<withdrawal reason 2>		
Number of subjects included in randomized set		

N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template 9 Summary of subject disposition from Randomized Set to Exposed set (Randomized set)

	<Each group> N=XXXX		Total N=XXXX	
	n	%	n	%
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
Number of subjects included in the Exposed set				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template 10 Summary of subject disposition from Exposed Set to Per Protocol Set at visit x (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	%	n	%
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
Number of subjects included in the Per Protocol set at visit x				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template 11 Summary of subject disposition from Exposed Set to End of study (Exposed set)

	<Each group> N=XXXX		Total N=XXXX	
	n	%	n	%
Eliminations				
<Elimination reason 1 (code)>				
<Elimination reason 2 (code)>				
Withdrawals				
<withdrawal reason 1>				
<withdrawal reason 2>				
Number of subjects who completed the study				
Completed with 1 dose				
Completed with 2 doses				

Short group label = long group label
N = Number of subjects
n = number of subjects enrolled by center
% = n / Number of subjects with available results x 100

Template 12 Deviations from protocol for age and intervals between study visits (Exposed set)

			<each group>		<each group>	
Type of interval	**Interval range**		**Value or n**	**%**	**Value or n**	**%**
Age	<age range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	
<each interval between study visit>	<interval range>	N	xxx		xxx	
		n	xxx	xx.x	xxx	xx.x
		Minimum	xxx		xxx	
		Maximum	xxx		xxx	

Template 13 Number of enrolled subjects by country

		<Each group> N = XXX	Total N = XXX
Characteristics	**Categories**	**n**	**n**
Country	<each country>		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given country or for all countries

Template 14 Number of enrolled subjects by age category

		<*each group*> N =	Total N =
Characteristics	**Categories**	**n**	**n**
Age category	Adults [18-64 years]		
	Adults [65-84 years]		
	Missing		

Short group label = long group label
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = age at study vaccination unknown

Template 15 Minimum and maximum visit dates <analysis set name>

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
< each informed consent>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
[Randomization]	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

12.2. Exposure

Template 16 Exposure to study vaccines by vaccine (Exposed Set)

		<Each group>N=XXXX		<Each group> N=XXXX	
Vaccine administered	**Number of subjects receiving**	**n**	**%**	**n**	**%**
< Vaccine A>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x
< Each vaccine>	Exactly 1 vaccination	xxx	xx.x	xxx	xx.x
	Exactly 2 vaccinations	xxx	xx.x	xxx	xx.x
	At least 1 vaccination	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = number of subjects in each group or in total included in the considered analysis set
n = number of subjects/doses in the given category
% = percentage of subjects in the given category

12.3. Immunogenicity

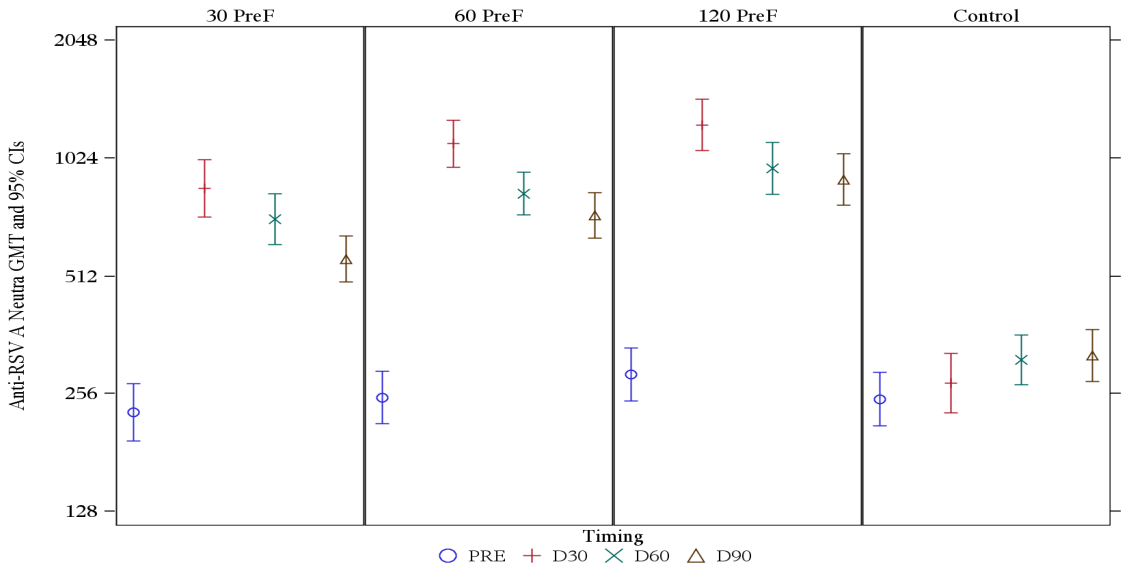
12.3.1. Within groups

Template 17 Number and percentage of subjects with <antibody titer /concentration> equal to or above <cut-off unit> and <GMT/Cs> <analysis set name>

				>=cut-off unit				GMT/C				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
<each antibody>	<each group>	<each timing>										

Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
N = Number of subjects with available results
n/% = number/percentage of subjects with titer/concentration equal to or above specified value
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
MIN/MAX = Minimum/Maximum
Short timing label = long timing label

Template 18 <GMT/Cs> and their 95% CIs for <antibody titers/ concentrations> <analysis set name>



Short group label = long group label
GMT/C = geometric mean antibody titer/concentration
95% CI = 95% confidence interval
Short timing label = long timing label
Note: This graph is provided as an example.
For RSV A Nab and RSVPreF3- specific IgG Ab, it will be adapted to display all the groups (4 groups for Part A, 10 groups for Part B) and all available timepoints (4 TPs up to Day 91, 6 TPs up to study end for Part B).
If needed for Part B, this graph might be split in several graphs: either by adjuvant content vs Placebo or by antigen content vs Placebo.
Same graph will be generated for RSV B NAb with 2 timepoints (10 groups, at Days 1 and 91), and for RSVPreF3 site 0 Ab with 2 groups and 2 timepoints (selected formulation and Placebo groups, at Days 1 and 91).

Template 19 Geometric mean of the individual ratio of <antibody titers/concentrations (units)> post-vaccination compared to pre-vaccination <Per Protocol Set>

						<GMT,C> ratio			
								95% CI	
Group	**N**	**Time point description**	**<GMT,C>**	**Time point description**	**<GMT,C>**	**Ratio order**	**Value**	**LL**	**UL**
<each group>	xxx	PI(D31)		PRE		PI(D31) / PRE			
		<Each time point>		PRE		<time point> / PRE			

Short group label = long group label
<GMT,C> = geometric mean antibody <titer,concentration>
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template 20 Distribution of <antibody titers/concentrations> <Per Protocol Set>

			<Each group>					<Each group>				
						<95>% CI					<95>% CI	
Antibody	Timing	<Titer/Concentration>	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	< cut-off1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= cut-off1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= cut-off2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= cut-off3	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

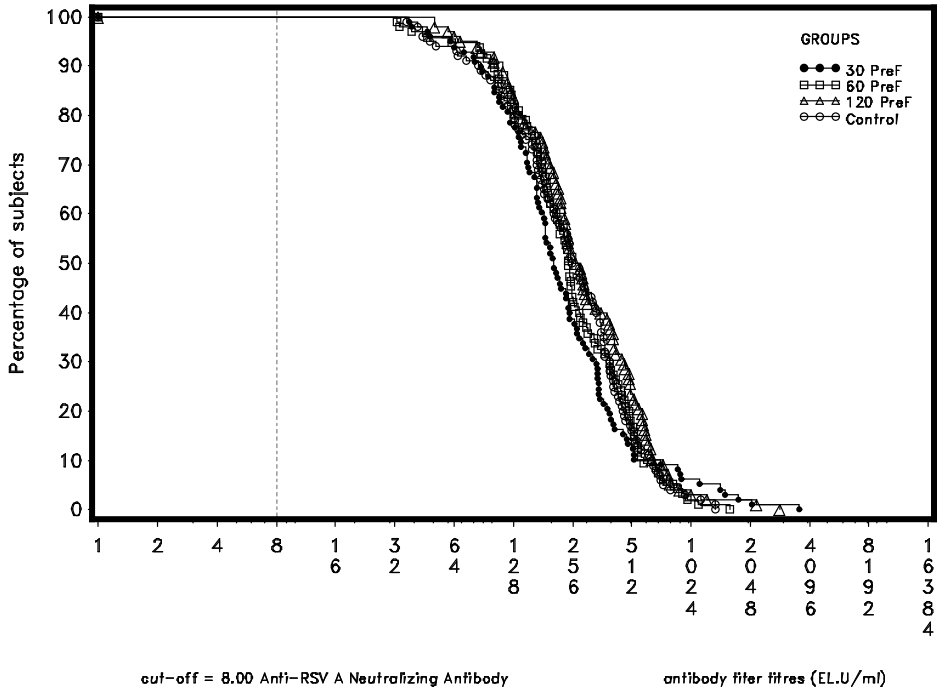
Short group label = long group label
N = number of subjects with available results
n/% = number/percentage of subjects with <titer, concentration> within the specified criterion
<95>% CI = <95>% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 21 Distribution of <antibody titers/concentrations> fold increase post-vaccination compared to pre-vaccination <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Antibody	Timing	FI	N	n	%	LL	UL	N	n	%	LL	UL
<each antibody>	<each timing>	< 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 1	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

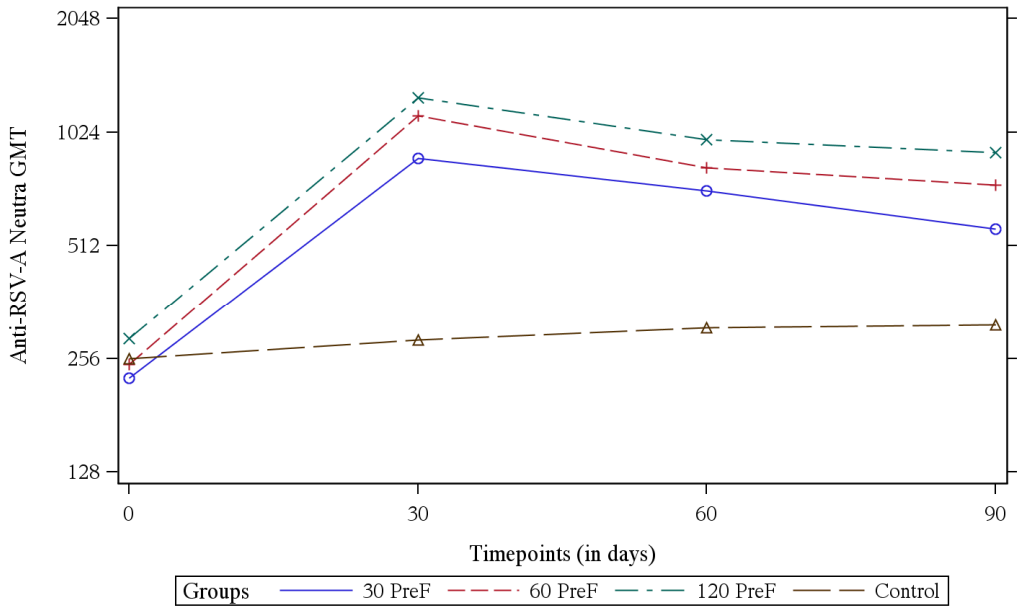
Short group label = long group label
FI= Fold Increase post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with <titer, concentration> fold change meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

Template 22 Reverse cumulative distribution curve of <antibody titers/concentrations> in the <group label> group <Per Protocol Set>



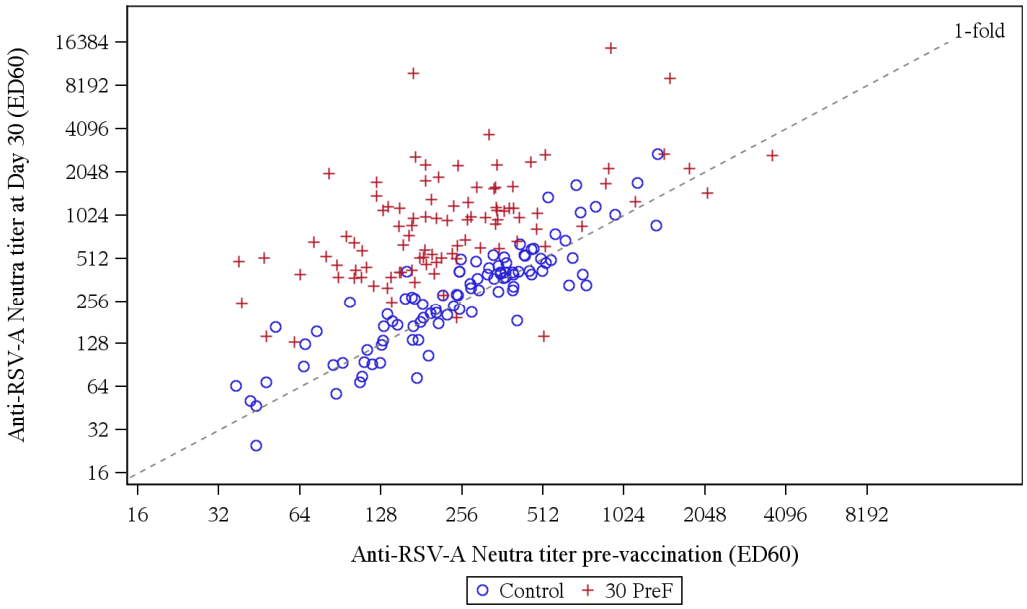
Short group label = long group label
Short timing label = long timing label
Note: this graph is provided as an example. It will be generated by group, and will be adapted to display the 4 timepoints (PRE, D31, D61, D91) for the considered group. For Part B, same graphs will also be generated at Day 91 with groups according to adjuvant content or antigen content vs Placebo.
For RSV B Nab and RSVPreF3 site 0 specific Ab, the figure will display only 2 timepoints (Days 1 and 91).

Template 23 Kinetics of < antibody GMT/Cs> on subjects with results available at all timepoints up to <Day 91, Month 14> <Per protocol set>



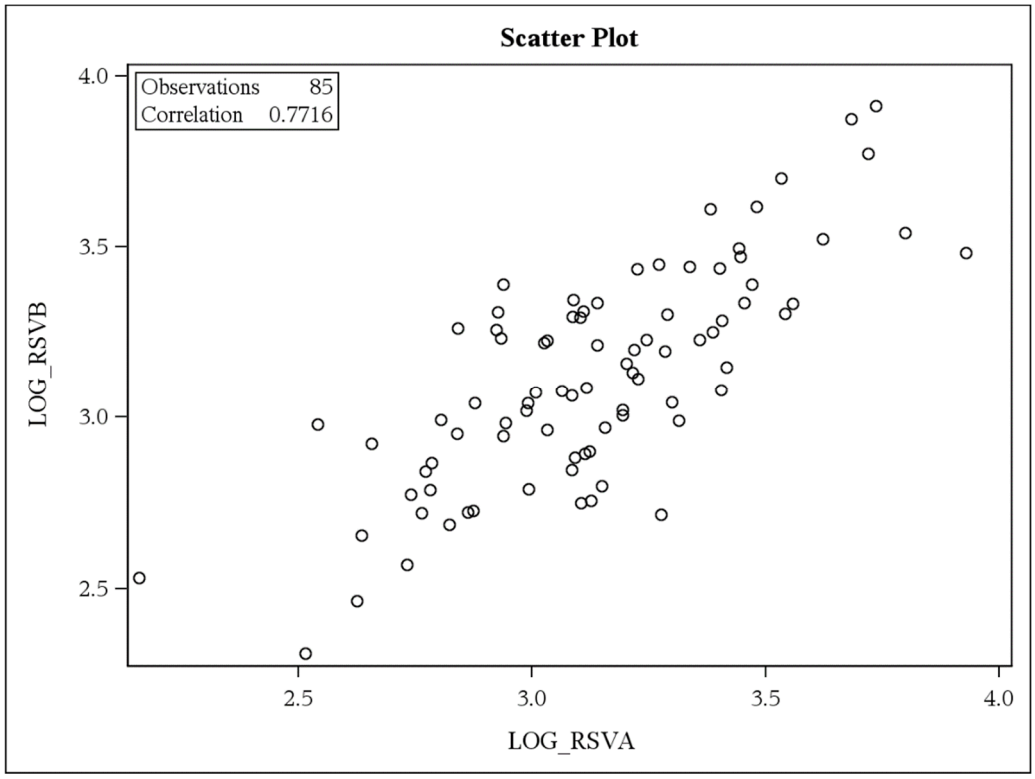
Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. Template will be adapted to display all the groups (10 groups for Part B) and all the timepoints (4 TPs up to Day 91, 6 TPs up to study end).

Template 24 Individual results of <RSV A Neutralizing antibody titer> at <time point> versus pre-vaccination in <group label> and Placebo_B groups <Per protocol set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. It will be generated as follows:
RSV A Nab at Day 31 and Day 91, for each RSV groups (18 graphs)
RSVPref3 IgG at Day 31 and Day 91, for each RSV groups (18 graphs)
RSV B Nab at Day 91, for the selected formulation (1 graph)

Template 25 Individual results of <RSV A versus RSV B Neutralizing antibody titer> at <time point> , on pooled RSV groups <Per protocol set>



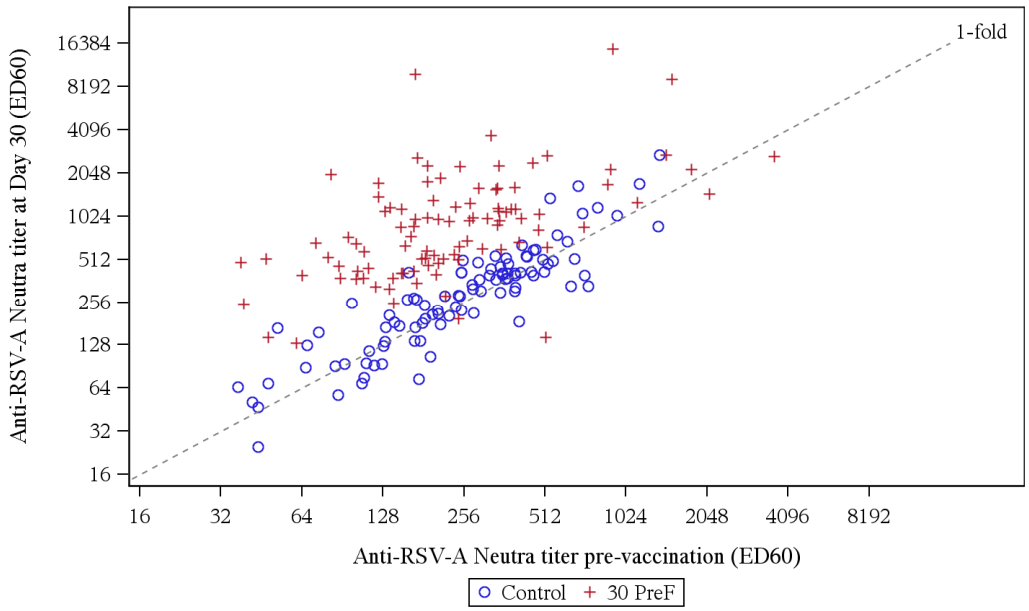
Note: this graph is provided as an example. It will be generated on pooled RSV groups as follows:
RSV A Nab vs RSVPreF3 IgG at each timepoint
RSV A Nab vs RSV B Nab at Pre and Day 91
RSV B Nab vs RSVPreF3 IgG at Pre and Day 91
The same graphs will be generated on fold increase Post over Pre.

Template 26 Geometric mean ratios of the fold increase (Pre to Post -vaccination) between RSVPreF3 IgG antibody concentrations and <RSV-A, RSV-B> neutralising antibody titers <Per protocol set>

									GM ratio of FI		
										95% CI	
Timepoint	Group	N	RSVPref3 IgG GMF	95% CI		<RSV-A, B> Nab GMF	95%		Value	LL	UL
				LL	UL		LL	UL			
PI(D31)/PRE	<each group>										
<each timepoint>											

Short group label = long group label
N = Number of subjects with available results at the two considered time points (post and pre) for both RSVPreF3 IgG and <RSV-A, B> Nab
GMF = Geometric mean fold increase Pre to Post-vaccination
GM ratio of FI=Geometric mean ratio of fold increase (Pre to Post)
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Short timing label = long timing label

Template 27 Individual results of the fold increase (post over pre-vaccination) of RSVPreF3 IgG antibody concentrations versus <RSV A, RSV B> neutralizing antibody titers at <time point> in <group label> <Per protocol set>



Short group label = long group label
Note: This graph is provided as an example. It will be generated as follows:
Y axis=RSVPreF3 IgG vs X axis=RSV A Nab, at Days 31 and 91, for each RSV group (18 graphs)
Y axis= RSVPreF3 IgG vs X axis=RSV B Nab at Day 91, for the selected formulation (1 graph)

Template 28 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

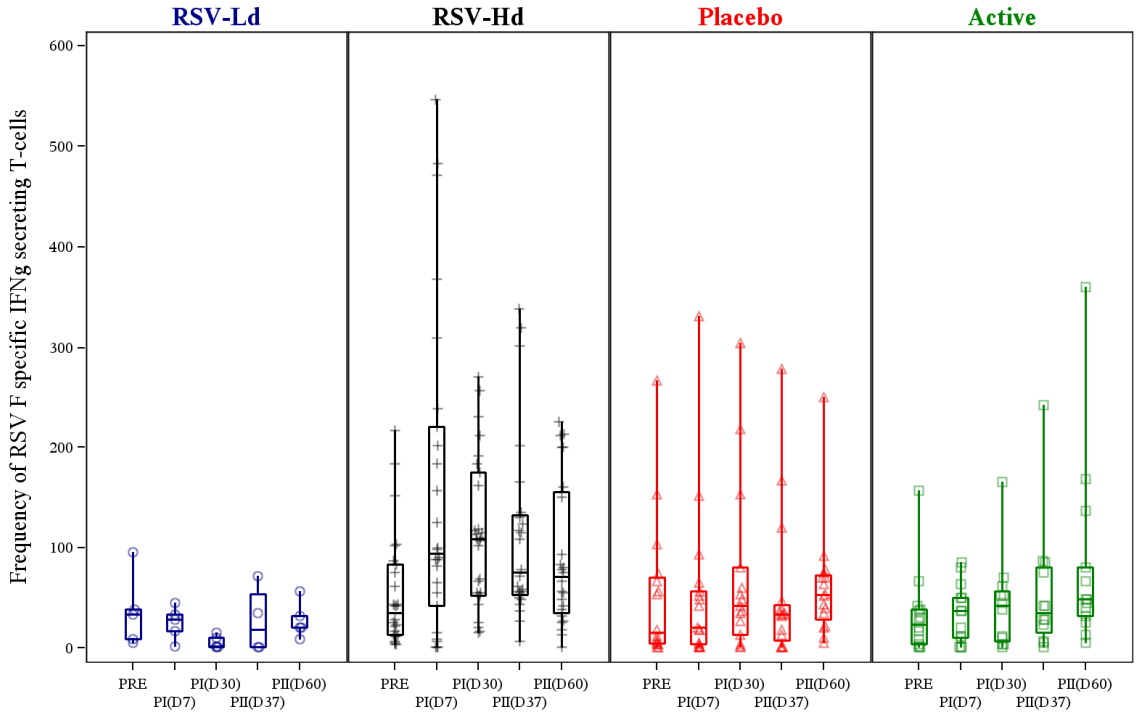
Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label
Note: this table will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).

Template 29 Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS), by pre-vaccination category <Per Protocol Set>

				<Each group>	<Each group>
Immune Marker	**Pre-vaccination status**	**Timing**	**Statistic**	**value**	**value**
<At least 2 markers>	<Q1	<Each timing>	N	xxxx	xxxx
			GM	xx.x	xx.x
			SD		
			Minimum	xx.x	xx.x
			Q1	xx.x	xx.x
			Median	xx.x	xx.x
			Q3	xx.x	xx.x
			Maximum	xx.x	xx.x
	[Q1-Q3]	<Each timing>	<each parameter>		
	>Q3				
	Total				

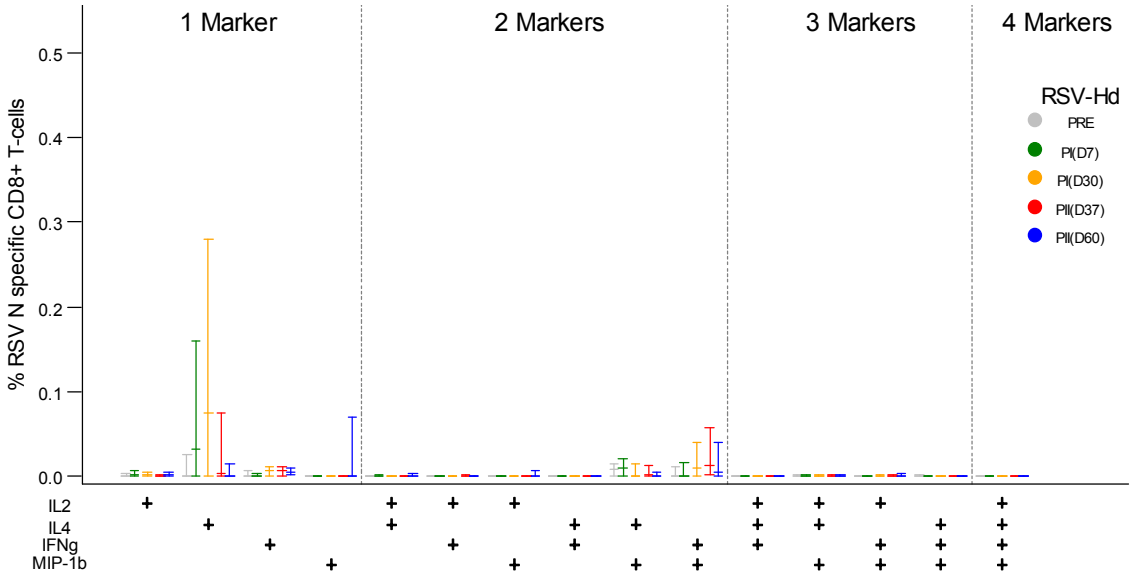
Short group label = long group label
<Q1= subjects with pre-vaccination frequency < Q1 of the frequencies at pre-vaccination computed on pooled groups
Q1-Q3= subjects with pre-vaccination frequency within [Q1-Q3] of the frequencies at pre-vaccination computed on pooled groups
>Q3=subjects with pre-vaccination frequency < Q3 of the frequencies at pre-vaccination computed on pooled groups
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template 30 Boxplots with individual data of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. Depending on the analysis, it will display groups and timepoints as follows:
Part A: 1 graph with 4 groups and 3 (D1, D31, D91) or 4 timepoints (D1, D31, D61, D91)
Part B: 3 graphs with 4 groups (either by adjuvant content or by antigen content vs Placebo), and 3 timepoints (D1, D31, D91) or 5 timepoints (up to Month 8) or 6 timepoints (up to Month 14, only for selected Ag dose and Placebo)
This graph will be generated for each CMI response defined in section 5.3.2.2 (see TFL TOC).
For Part B, the same graph will be generated for memory B-cells, with 4 groups (selected Ag dose with Plain/AS01E/AS01B, and Placebo) and 4 timepoints (PRE, D31, D91, M14).

Template 31 Frequency of RSVPreF3 specific CD4+ T-cells expressing any combination of markers among IL-2, CD40L, TNFa, IFNg in <group label> group at Day 31 and Day 91 (per million of CD4+ T cells, by ICS) <Per Protocol Set>



Short group label = long group label
Short timing label = long timing label
Note: This graph is provided as an example. It will be generated by group and will be adapted to display Q1-Median-Q3 for each combination of the markers (15) at Day 31 and Day 91.

Template 32 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least <2 markers among IL-2, CD40L, TNFa, IFNg> (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>	<Each group>
Immune Marker	**Timing**	**Statistic**	**value**	**Value**
<At least 2 markers>	<Each timing post-vaccination>	N	xxxx	Xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results at both timepoints (pre and post)
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template 33 Descriptive statistics of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template 34 Descriptive statistics of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-memory B-cells (per million of memory B cells, by Elispot) – Part B <Per Protocol Set>

			<Each group>	<Each group>
Immuno assay	**Timing**	**Statistic**	**value**	**value**
Memory B cells	<Each timing post-vaccination>	N	xxxx	xxxx
		GM	xx.x	xx.x
		SD		
		Minimum	xx.x	xx.x
		Q1	xx.x	xx.x
		Median	xx.x	xx.x
		Q3	xx.x	xx.x
		Maximum	xx.x	xx.x

Short group label = long group label
N= Number of subjects with available results
GM= Geometric mean
SD= Standard Deviation
Q1 and Q3= 25th and 75th percentiles
Short timing label = long timing label

Template 35 Distribution of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T cells, by ICS) <Per Protocol Set>

			<Each group>					<Each group>				
						95% CI					95% CI	
Assay	**Timing**	**FI**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<assay name>	<each timing>	< 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 2	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 4	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 6	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 8	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x
		>= 10	xx	xx	xx.x	xx.x	xx.x	xx	xx	xx.x	xx.x	xx.x

Short group label = long group label
FI= Fold increase Post over pre-vaccination result
N = number of subjects with pre and corresponding post-vaccination results available
n/% = number/percentage of subjects with fold increase meeting the specified criterion
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Short timing label = long timing label

12.3.2. Between groups

Template 36 Comparisons of the 9 RSV formulations versus Placebo in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at one month post <dose 1 (Day 31), dose 2 (Day 91)> (ANCOVA model, Dunnett's test) – Part B <Per Protocol set>

Assay	Timepoint	RSV group	N	GM<T,F> ratio (RSV over Placebo)	Dunnett's 95% CI		Dunnett's p-value
					LL	UL	
<assay name>	<Day 31, Day 91>	30-PLAIN_B					
		60-PLAIN_B					
		120-PLAIN_B					
		30-AS01E_B					
		60-AS01E_B					
		120-AS01E_B					
		30-AS01B_B					
		60-AS01B_B					
		120-AS01B_B					

Short group label = long group label
N= Number of subjects with both pre- and post-vaccination results available
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
RSV Vaccine is considered superior to Placebo if one-sided p-value <0.025
Dunnett's 95% CI = 95% confidence interval based on Dunnett's adjustment, LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment and age category as fixed effects

Template 37 Comparisons of the mean responses post dose 2 (Day 91) versus post dose 1 (Day 31) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> on pooled groups according to adjuvant content (ANCOVA model) – Part B <Per Protocol set >

Assay	RSV group	N	GM<T,F> ratio (D91/D31)	95% CI		p-value
				LL	UL	
<assay name>	PLAIN_B					
	AS01E_B					
	AS01B_B					

Short pooled group label = long pooled group label
N= Number of subjects with results available at both timepoints
GM<T,F>= = Geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)
PII D91 is considered as significantly higher to PI D31 if one-sided p-value <0.025
95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance); LL = lower limit, UL = upper limit
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the adjuvant content, antigen dose and age category as fixed effects

Template 38 Comparisons of the RSV groups pooled according to their adjuvant content (Plain, AS01E, AS01B) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) - Part B <Per Protocol set>

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	Timepoint	Group 1	N	GM<T,F>	LL	UL	Group 2	N	GM<T,F>	LL	UL	Value	LL	UL	p-value
<assay name>	<each timing>	AS01B_B					PLAIN_B								
		AS01E_B					PLAIN_B								
		AS01B_B					AS01E_B								

Short group label = long group label

GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance);
LL = lower limit, UL = upper limit

ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects

Group 1 is considered superior to Group 2 if one-sided p-value <0.025

Template 39 Comparisons of the RSV groups (by antigen dose level) in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg> at Day 91 (ANCOVA model) – Part B <Per Protocol set >

		Group 1					Group 2					GM<T,F> ratio (Group 1 / Group 2)			
					95% CI					95% CI			95% CI		
Assay	Timepoint	Group 1	N	GM<T,F>	LL	UL	Group 2	N	GM<T,F>	LL	UL	Value	LL	UL	p-value
<assay name>	<each timing>	120-PLAIN_B					60-PLAIN_B								
		120-PLAIN_B					30-PLAIN_B								
		60-PLAIN_B					30-PLAIN_B								
		120-AS01E_B					60-AS01E_B								
		120-AS01E_B					30-AS01E_B								
		60-AS01E_B					30-AS01E_B								
		120-AS01B_B					60-AS01B_B								
		120-AS01B_B					30-AS01B_B								
		60-AS01B_B					30-AS01B_B								

Short group label = long group label

GM<T,F> = geometric mean antibody <titer, frequency> adjusted for covariates (ANCOVA model)

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT (Ancova model: adjustment for covariates - pooled variance); LL = lower limit, UL = upper limit

ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and the treatment, age category and gender as fixed effects

Group 1 is considered superior to Group 2 if one-sided p-value <0.025Template

Template 40 Parameters of the ANCOVA model for the comparison between RSV groups in terms of <RSV A Neutralizing antibody titers, RSVPreF3-specific CD4 T cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg>– Part B <analysis set name>

Timepoint	Variable	DF	Fvalue	p-value
<each timepoint>	Pre-vaccination log <titer, frequency>			
	Age category			
	Adjuvant			
	Antigen			
	Visit			
	Linear effect of antigen			
	Quadratic effect of antigen			
	Antigen*Adjuvant			

Antigen = Antigen dose (3 levels: 30, 60, 120 mcg)
Adjuvant = Adjuvant content (3 levels: no adjuvant, AS01E, AS01B)
Antigen*Adjuvant = interaction between antigen dose and adjuvant
ANCOVA model on the log-transformed <titers, frequencies> with the pre-vaccination log-transformed <titer,frequency> as covariate, and adjuvant content, antigen dose and age category as fixed effects
DF = degrees of freedom
Interaction (Antigen * Adjuvant) considered as statistically significant if p-value <0.100
Main factors (Pre-vaccination, antigen, adjuvant) considered as statistically significant if p-value <0.050 (model including interaction)

12.4. Safety

Template 41 Compliance in completing solicited adverse events information (Exposed Set)

	<Each group>		
DOSE	N	n	Compliance (%)
Vaccination at Visit 1	xxx	xxx	xx.x
Vaccination at Visit 4	xxx	xxx	xx.x
TOTAL	xxx	xxx	xx.x

Short group label = long group label
N=Number of administered vaccinations
n = number of vaccinations with solicited symptom information completed
Compliance (%) = (n / N) X 100

Template 42 Incidence and nature of <grade 3> symptoms (solicited and unsolicited) <with causal relationship to vaccination> reported during the XX-day (Days 1-XX) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	General symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
	Local symptoms	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 43 Incidence of any symptoms (solicited and unsolicited) resulting in medically attended visit, reported during the 30-day (Days 1-30) post-vaccination period following each dose and overall <analysis set name>

		<Each group>					<Each group>				
					95% CI					95% CI	
Dose	**Symptoms**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
DOSE 2	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = number of subjects with the corresponding administered dose
n/% = number/percentage of subjects presenting at least one type of symptom following the corresponding dose
For overall/dose:
N = number of administered dose
n/% = number/percentage of doses followed by at least one type of symptom
For overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 44 Incidence of solicited local symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <analysis set name>

			<Each group>				
						95 % CI	
Dose	Symptom	Type	N	n	%	LL	UL
DOSE 1	<Each symptom>	All					
		Grade ≥2					
		Grade 3					
DOSE 2	<Each symptom>	All					
		Grade ≥2					
		Grade 3					
OVERALL/DOSE	<Each symptom>	All					
		Grade ≥2					
		Grade 3					
OVERALL/SUBJECT	<Each symptom>	All					
		Grade ≥2					
		Grade 3					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 45 Incidence of solicited general symptoms reported during the 7-day (Days 1-7) post-vaccination period following each dose and overall <cohort name>

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
DOSE 1	<Each symptom – except fever>	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
DOSE 2	<Each symptom – except fever>	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/DOSE	<Each symptom – except fever>	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					

			<Each group>				
						95 % CI	
Dose	**Symptom**	**Type**	**N**	**n**	**%**	**LL**	**UL**
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					
OVERALL/SUBJECT	<Each symptom – except fever>	All					
		Grade ≥2					
		Grade 3					
		Related					
		Grade ≥2 Related					
		Grade 3 Related					
	Fever (°C)	All					
		≥38.0					
		>38.5					
		>39.0					
		>39.5					
		>40.0					
		Related					
		≥38.0 Related					
		>38.5 Related					
		>39.0 Related					
		>39.5 Related					
		>40.0 Related					

Short group label = long group label
For each dose:
N = number of subjects with the corresponding documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once following the corresponding dose
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the type of symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 46 Number of days with <*local/general*> solicited symptoms during <the 7-day (Days 1-7), the whole> post-vaccination period <analysis set name>

			<Each group>
Dose	**Symptom**	**Statistic**	**Value**
DOSE 1	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
DOSE 2	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	
OVERALL/DOSE	<Each symptom>	n	
		Mean	
		Minimum	
		Q1	
		Median	
		Q3	
		Maximum	

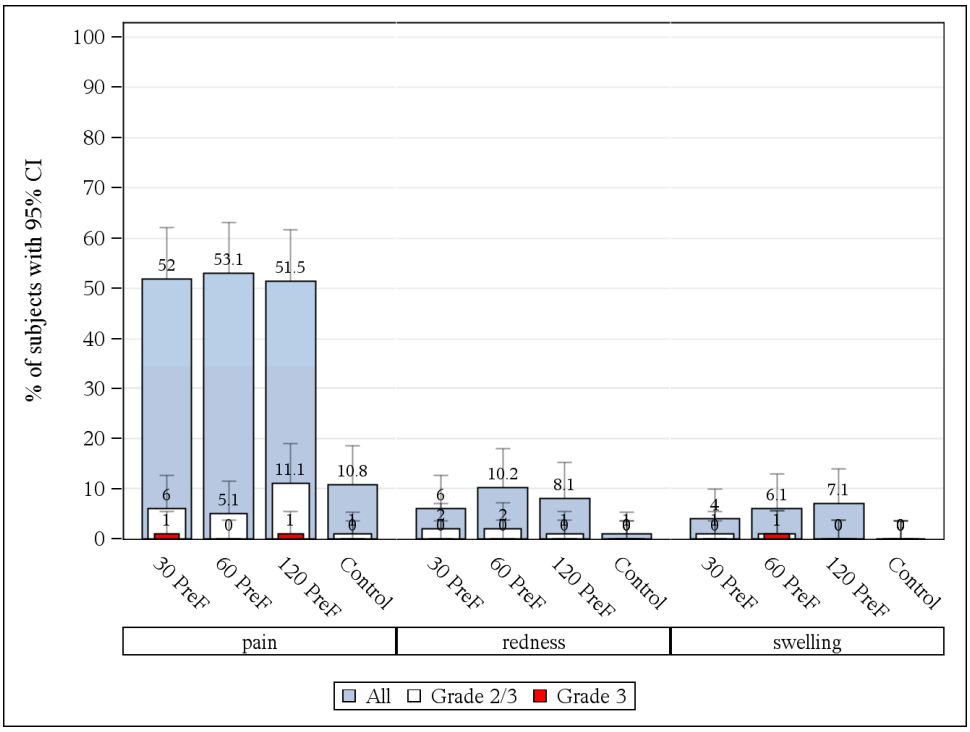
Short group label = long group label

n = number of doses with the symptom

Q1 = 25th percentile

Q3= 75th percentile

Template 47 Incidence of solicited <local, general> adverse events reported during the 7-day (Days 1-7) post-vaccination period following each dose <Exposed set>



Short group label = long group label

Note: this graph is provided as an example. It will be adapted to display the percentage of subjects reporting each local or general symptom, any grade and grade 3, by group and by dose. Template will be discussed at the time of the dry-run.

Template 48 Percentage of subjects reporting the occurrence of <grade 3> unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term <with causal relationship to vaccination> within the 30-day (Days 1-30) post-vaccination period <analysis set name>

		<Each group> N=XXXX					Total N=XXXX				
					95% CI					95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	LL	UL	n*	N	%	LL	UL
	At least one symptom	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
<each SOC (SOC code)>	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
…	<each PT (PT code)>	xxx	xxx	xx.x	xx.x	xx.x	xxx	Xxx	xx.x	xx.x	xx.x
	…										

Short group label = long group label

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects included in the considered analysis set in each group

n* = number of events reported

n/% = number/percentage of subjects reporting the symptom at least once

95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 49 List of (S)AEs and solicited adverse events leading to study/treatment discontinuation <Exposed set>

Group	Sub. No	Country	Gender	Race	AE Description	Preferred Term	SAE	Causality	Outcome	Vaccination and visit	Type of discontinuation *

Short group label = long group label

* type of discontinuation refers to whether the discontinuation is a treatment discontinuation or study follow-up discontinuation

Template 50 Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term	Primary System Organ Class
<each group>								

Group	Sub. No.	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome	SAE (Y/N)	pIMD source
<each group>										

Short group label = long group label

Template 51 Listing of SAEs <analysis set name>

Group	Sub. No.	Gender	Country	Race	Age at onset (Year)	Verbatim	Preferred Term
<each group>							

Group	Sub. No.	Primary System Organ Class	Medical visit type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>									

Short group label = long group label

Template 52 Listing of pregnancies reported during the study period in Part A <analysis set name>

Group	Sub. No.	Country	Race	Age at vaccination	Previous Dose	LMP date	Days between LMP-vacc	Age at delivery (Year)	Date of delivery	Pregnancy Outcome	Date of outcome	Gestational weeks at birth/miscarriage /termination

Short group label = long group label
LMP=Last Mentrual Period

Template 53 Number and percentage of subjects taking concomitant medication during the <XX>-day (Days 1-<XX>) post-vaccination period by dose and overall <analysis set name>

		<Each group>					<Each group>				
					<95>% CI					<95>% CI	
Dose		N	n	%	LL	UL	N	N	%	LL	UL
DOSE x	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/DOSE	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
OVERALL/SUBJECT	Any	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x
	Antipyretics										
	Prophylactic antipyretics	xx	xx	xx.x	xx.x	xx.x	xx	Xx	xx.x	xx.x	xx.x

Short group label = long group label
For each dose:
N = total number of subjects with the corresponding administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
For overall/dose:
N = number of administered doses
n/% = number/percentage of doses after which the specified type of concomitant medication was taken at least once during the considered period
For overall/subject:
N = total number of subjects with at least one administered dose
n/% = number/percentage of subjects who took the specified type of concomitant medication at least once during the considered period
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 54 Distribution of change from baseline in hematology and biochemistry with respect to normal laboratory ranges <analysis set name>

				<Each group>			<Each group>		
Laboratory parameter	**Timing**	**Range indicator at Baseline (PRE)**	**Range indicator at timing**	**N**	**n**	**%**	**N**	**n**	**%**
<Each parameter>	<Each timing>	UNKNOWN	UNKNOWN						
			BELOW						
			WITHIN						
			ABOVE						
		BELOW	UNKNOWN						
			BELOW						
			WITHIN						
			ABOVE						
		WITHIN	UNKNOWN						
			BELOW						
			WITHIN						
			ABOVE						
		ABOVE	UNKNOWN						
			BELOW						
			WITHIN						
			ABOVE						

Short group label = long group label
N = number of subjects with available results for the specified laboratory parameter and timing in a given baseline category
n/% = number/percentage of subjects in the specified category
Below = below the normal laboratory range defined for the specified laboratory parameter
Within = within the normal laboratory range defined for the specified laboratory parameter
Above = above the normal laboratory range defined for the specified laboratory parameter
Short timing label = long timing label

Template 55 Summary of hematology and biochemistry results by maximum grade at <Visit 2 (Day 8), Visit 5 (Day 68)> versus baseline (<Day 1, Day 61>) <analysis set name>

			<*each group* >		
Laboratory parameter	**Baseline (<Day 1, Day 61>)**	**Visit <2,5> (<Day 8, Day 68>)**	**N**	**n**	**%**
<Each parameter>	Unknown	Unknown			
		<Each grade>			
	<Each grade>	Unknown			
		<Each grade>			
	Total	Unknown			
		<Each grade>			

Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Note: This table will be generated post dose 1 at Visit 2 (Day 8) versus baseline at Day 1, and also post dose 2 at Visit 5 (Day 68) versus baseline at Day 61.

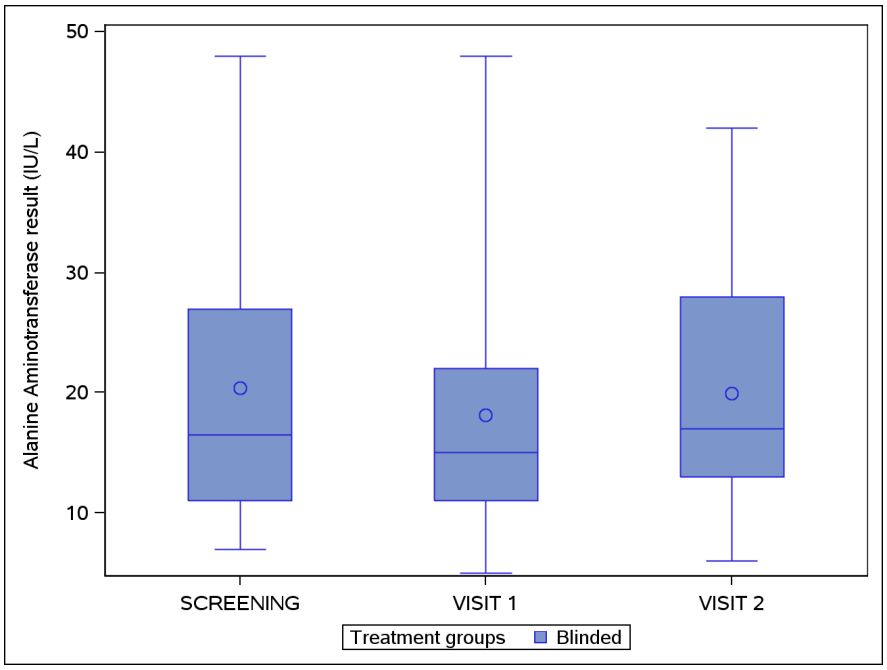
Template 56 Summary of maximum hemoglobin change from baseline at <Visit 2 (Day 8), Visit 5 (Day 68)> (Exposed set)

		<Each group>		
Laboratory parameter		**N**	**n**	**%**
Hemoglobin - change from baseline	UNKNOWN			
	GRADE 0			
	GRADE 1			
	GRADE 2			
	GRADE 3			

Short group label = long group label
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Note: This table will be generated post dose 1 at Visit 2 (Day 8) with Day 1 as baseline, and also post dose 2 at Visit 5 (Day 68) with Day 61 as baseline.

Template 57 Boxplot of <each hematology/biochemistry parameter> (Exposed Set)



Note: This graph is given as an example. It will be adapted to display one boxplot per group and per timepoint, all timepoints available (5 TPs: Screening, Days 1, 8, 61, 68). For Part A, one graph will be generated displaying the 4 groups. For Part B, 3 graphs will be generated displaying 4 groups: 3 RSV groups (30/60/120 -Plain, - AS01E or -AS01B) and the Placebo group.

Template 58 Solicited and unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 1-30) post-vaccination period including number of events - SAE excluded <analysis set name>

		<Each group> N=XXXX			<Each group> N=XXXX		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
<each SOC (SOC code)>	At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	At least one PT related to the corresponding SOC	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
	…						

Short group label = long group label
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects included in the considered analysis set in each group
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 59 Number (%) of subjects with serious adverse events during the study period including number of events reported <analysis set name>

			<Each group> N=XXXX			<Each group> N=XXXX		
Type of Event	**Primary System Organ Class (CODE)**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**
SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x
Related Fatal SAE		At least one symptom	xxx	xxx	xx.x	xxx	xxx	xx.x
	<each SOC (SOC code)>	<each PT (PT code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
			xxx	xxx	xx.x	xxx	xxx	xx.x

Short group label = long group label
N = number of subjects with administered dose
n/% = number/percentage of subjects reporting the symptom at least once
n* = Number of events reported
Related = assessed by the investigator as related

12.5. Analysis of RTI

Template 60 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal/throat swab at assessment visit	RSV+										
	RSV-										
	All										

Short group label = long group label
RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group or in Total
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 61 Number and percentages of subjects with at least one RSV-confirmed RTI episode post-vaccination, as measured by qRT-PCR in nasal swab samples collected at home <analysis set name>

		<Each group>					Total				
					95% CI					95% CI	
Samples	**RSV status**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Nasal swab at home	RSV+										
	RSV-										
	All										

Short group label = long group label
RSV+= subjects tested RSV positive by qRT-PCR at least once
RSV-= subjects tested as RSV negative by qRT-PCR
All= subjects with at least one qRT-PCR result available
N = number of subjects in each group
n/%= number/percentage of subjects in each category
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 62 Mean of the viral load of the RSV-confirmed RTI episodes, as measured by qRT-PCR on nasal/throat swabs, by collection time and collection method <Exposed set>

		RSV A +				RSV B +			
Days after RTI onset	**Swab**	**N**	**n**	**%**	**mean**	**N**	**n**	**%**	**mean**
0-2	Nasal swab at home								
	Nasal/throat swab at assessment visit								
3-4	Nasal swab at home								
	Nasal/throat swab at assessment visit								
>4	Nasal swab at home								
	Nasal/throat swab at assessment visit								

Days after RTI onset = number of days between start of RTI symptoms and collection date
N=Number of swabs with qRT-PCR results available
n/%= number/percentage of swabs tested as RSV A/B positive by qRT-PCR
mean= mean of the viral load computed on RSV A/B positive swabs

Template 63 Descriptive statistics of the viral load of the RSV- confirmed RTI episodes, as measured by qRT-PCR in nasal/throat swab samples collected at assessment visit <at home> <Exposed Set>

		<Each group> N=	Total N=
Type	**Parameters**	**Value**	**Value**
RSV A +	n		
	Mean		
	Min		
	Q1		
	Median		
	Q3		
	Max		
RSV B +	…		
All RSV +			

Short group label = long group label
RSV A+= RSV A positive samples by qRT-PCR
RSV B+-= RSV B positive samples by qRT-PCR
All RSV += All RSV positive samples by qRT-PCR
N = Number of swabs with qRT-PCR results available
n= number/percentage of samples in each category
Q1 and Q3 = 25th and 75th percentiles
Min/Max = Minimum/Maximum

Template 64 Number and percentage of subjects reporting co-infections with respiratory viruses, as measured by multiplex PCR on RSV A/B positive RTI samples collected <at assessment visit, at home> <Exposed Set>

	RSV RTI N =			
			95% CI	
Categories	**n**	**%**	**LL**	**UL**
Influenza A Virus				
Influenza B Virus				
…				
<each virus>				
…				
Total				

N = number of swabs tested RSV positive by qRT-PCR
n/% = number/percentage of swabs tested positive by multiplex in a given category
Total= number of swabs tested positive for at least one virus
LL, UL= Exact 95% Lower and Upper confidence limits

Template 65 Clinical signs and symptoms associated with RTI episodes (Exposed set)

		RSV RTI N=XXXX		Non RSV RTI N=XXXX		Total N=XXXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Heart Rate increase (beats/min)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Respiratory rate increase (breaths/min)	5-10						
	10-15						
	15-20						
	20-25						
	…						
Systolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Diastolic blood pressure increase (mmHg)	10-20						
	20-30						
	30-40						
	40-50						
	…						
Oxygen saturation decrease (%)	1-2						
	3-4						
	5-6						
	7-8						
	…						
Upper respiratory symptoms	<Each symptom>						
Lower respiratory symptoms	<Each symptom>						
qPCR result	RSV A+						
	RSV B+						
	RSV -						
Self-collected Nasal swab	RSV+						
	RSV-						
	NA						
Medically attended visit	Emergency room						
	Hospitalisation						
	Medical personnel						
	None						
SAE associated to the episode	Yes						
	No						

RSV RTI= RTI episode tested as RSV positive by qRT-PCR on nasal/throat swab collected at assessment visit
Non-RSV RTI= RTI episode tested as RSV negative by qRT-PCR on nasal/throat swab collected at assessment visit
N = number of RTI episodes in each category or in total
n = number of RTI episodes in the corresponding category

% = n / N x 100

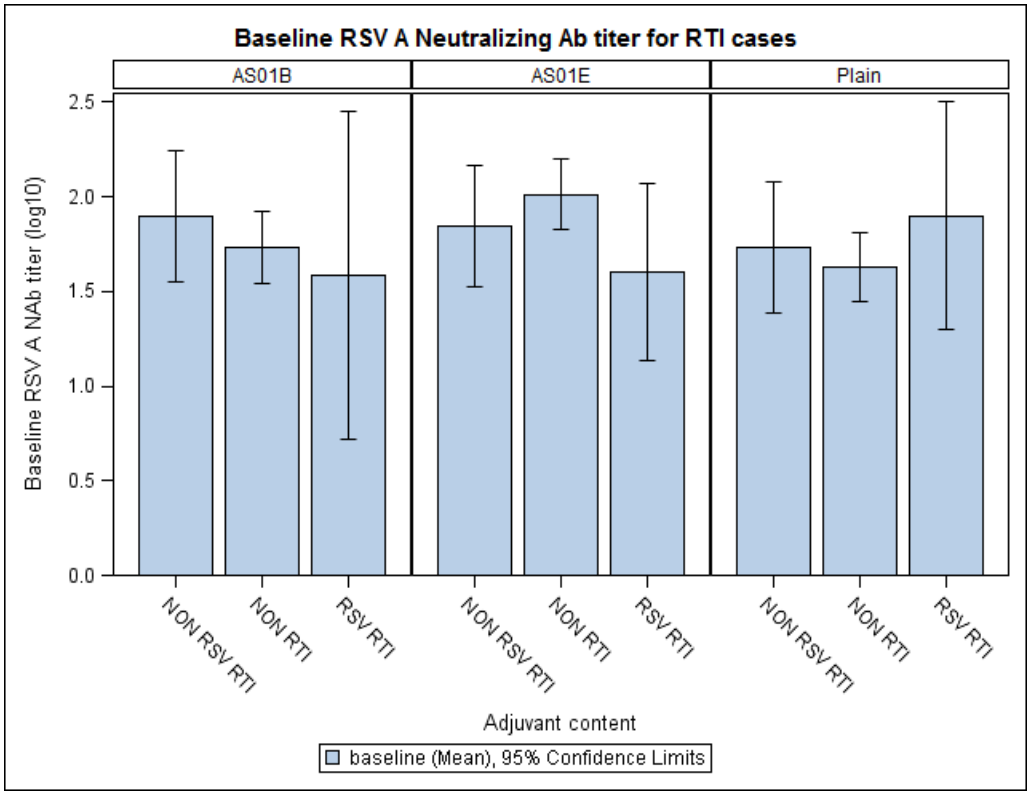
For vital signs, change from baseline (increase/decrease) will be displayed by category: category of 10 units increase for heart rate, systolic and diastolic BP, 5 units increase for respiratory rate, and 1% decrease for oxygen saturation (to be adapted at the time of dry run if needed)

Template 66 Listing of RTI episodes reported during RTI surveillance in Part B (Exposed set)

Group	Sub. No.	Age at Dose 1	Sex	Episode nb	Start date of episode	End date of episode	Date of assessment visit	Nb of signs and symptoms	Date nasal swab on site	RSV A positive (site)	RSV B positive (site)	Date nasal swab at home	RSV-A positive (home)	RSV-B positive (home)	Medically attended visit	SAE related to RTI episode
										Yes/No	Yes/No		Yes/No	Yes/No		Yes/No

Short group label = long group label

Template 67 GMTs and 95% CIs of RSV A Neutralizing antibody titer at baseline for subjects reporting RTI episodes (RSV RTI vs or non RSV RTI vs No RTI), by groups pooled according to the adjuvant content <Exposed Set>



This graph is provided as an example, template will be finalized at the time of the dry-run. It will display the GMTs and 95% CIs for subjects reporting confirmed RSV RTI episodes vs subjects reporting Non-RSV RTI episodes vs subjects who did not report any RTI episode (NON RTI), in the RSV groups pooled according to the adjuvant content (Plain, AS01E, AS01B).