Statistical Analysis Plan

Study alias & e-track number(s): 204812 (RSV F-021)

Version: DRAFT1 Date:10-NOV-2016

Detailed Title:	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 – 45 years.
Scope:	All data pertaining to the above study.
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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	According-to-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
eCRF	Electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
MA-RTI	Medically Attended Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities

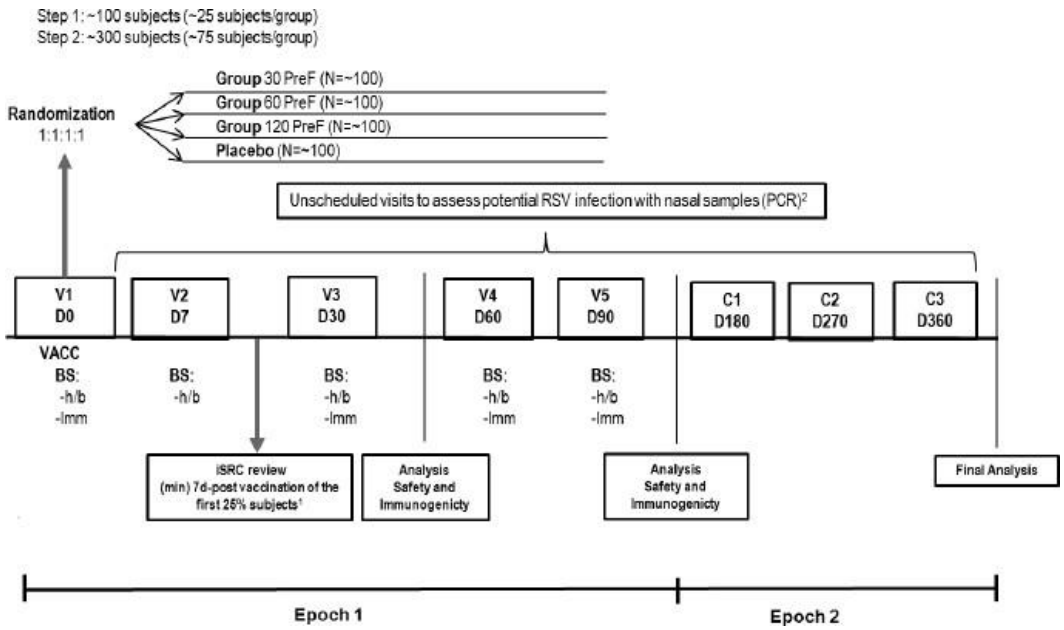
NEO	Neogenin
PCA	Palivizumab Competing Antibodies
PCD	Primary completion Date
PCR	Polymerase Chain Reaction
PPS	Per Protocol Set
PreF	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
RSV	Respiratory syncytial virus
RTI	Respiratory Track Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	(GSK) Biological's Internet Randomization System
SRT	Safety Review Team
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
WBC	White Blood Cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25-AUG-2016	Version 1: first version	Final – 20-JUL-2016

2. STUDY DESIGN

Figure 1. Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.
1 Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.
2 In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of an event related eCRF and the collection of a nasal swab within 72h after the medical attendance.
Vertical lines stand for analysis on all subjects.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.

- **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
  - Epoch 002: Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Primary completion Date (PCD)**: Visit 3 (Day 30).
- **End of Study (EoS)**: Last testing results released of samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).
- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30	X			
	NaCl				
60 µg PreF	PreF-60		X		
	NaCl				
120 µg PreF	PreF-120			X	
	NaCl				
Placebo	Formulation buffer S9b				X

- **Control**: Placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.

- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.

The following group and sub-group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	30 PreF	30 mcg PreF
2	60 PreF	60 mcg PreF
3	120 PreF	120 mcg PreF
4	Control	Placebo

Some tables might be presented by age category according to the following description:

Sub-group	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Age	1	18-32Y	18-32 years old subjects
	2	33-45Y	33-45 years old subjects

- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule:**
  - Blood samples for haematology/biochemistry will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - Blood samples for humoral immune response evaluation will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and at Visit 5 (Day 90).
  - Nasal swabs will be collected from subjects in case of a medically attended respiratory tract infection from enrolment (Visit 1) until study end (Contact 3).

- **Type of study**: self-contained
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring**: When the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) have been vaccinated, enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC). Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' Safety Review Team (SRT) on a regular basis throughout the study. Analyses related to iSRC evaluation will be described in a separate document (SAP/TFL for ISRC).
- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

3. OBJECTIVES

3.1 Primary Objective

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

3.2 Secondary objectives

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30).
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

3.3 Tertiary objective

- If deemed necessary, to further characterize the immune response of a single intramuscular dose of the RSV investigational vaccines.

Refer to Section 5.7.3 Laboratory assays of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

4. ENDPOINTS

4.1 Primary

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);

  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of any vaccine-related SAE.

- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group

4.2 Secondary

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;
  - Occurrence of any SAE, for all subjects in all groups.
- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day 30) for all subjects in all groups.

  - Antibody concentrations against NEO

- Occurrence of medically attended RSV-associated RTIs up to study conclusion

4.3 Tertiary

See section 5.7.3 of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

5. ANALYSIS SETS

5.1. Definition

In order to align to ICH and CDISC terminology, the Total Vaccinated Cohort (TVC) and the According To Protocol cohort (ATP) have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively. Two cohorts will be defined for the purpose of the analysis: the Exposed Set (ES) and the Per-Protocol Set (PPS) for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

5.1.1. Exposed Set (ES)

The 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 the ES will include all vaccinated subjects for whom immunogenicity data are available.

5.1.2. Per-Protocol Set (PPS) for analysis of immunogenicity

The PPS for immunogenicity will be defined by time point and will include all vaccinated subjects.

- Meeting all eligibility criteria (i.e. no protocol violation linked to the inclusion/ exclusion criteria, including age).
- Who received the study vaccine according to protocol procedures.

- Who did not receive a concomitant vaccination/medication/product leading to exclusion from the PPS analysis up to the corresponding timepoint as described in Section 6.6.2 of the Protocol.
- Who did not present with an intercurrent medical condition leading to exclusion from the PPS analysis up to the corresponding timepoint, as described in Section 6.7 of the Protocol.
- Who complied with the post-vaccination blood sampling schedule at the corresponding timepoint, as specified in Table 5 of the Protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding timepoint.

When presenting different timepoints, the PPS for immunogenicity will be adapted for each timepoint (up to D30 and up to D90).

5.2. 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.

5.2.1. Elimination from Exposed Set (ES)

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

5.2.2. Full Analysis Set (FAS)

NA

5.2.3. Elimination from Per-protocol analysis Set (PPS) for analysis of immunogenicity

A subject will be excluded from the PPS for analysis of immunogenicity analysis under the following conditions

Table 4 Elimination code from PPS for analysis of immunogenicity

Code Eli Type =M1/M2	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine dose not administered at all but subject number allocated
1040	Administration of concomitant vaccine(s) forbidden in the protocol up to blood sample at Visit 3/Visit 5
1050	Randomisation failure
1060	Randomisation code broken at the investigator site OR at GSK Safety department
1070	Study vaccine dose not administered according to protocol: - Site or route of study vaccine administration wrong or unknown - Administration not according to protocol for reason specified by the investigator other than side, site and route - Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)
1080	Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use
1090	Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration
2010	Protocol violation linked to the inclusion/exclusion criteria
2030	Biochemistry, haematology and other laboratory values outside normal range before any vaccination
2040	Administration of any medication forbidden by the protocol up to blood sample at Visit 3/Visit 5
2050	Underlying medical condition forbidden by the protocol up to blood sample at Visit 3/Visit 5
2060	Concomitant infection related to the vaccine which may influence the immune response up to blood sample at Visit 3/Visit 5
2070	Concomitant infection not related to the vaccine which may influence the immune response up to blood sample at Visit 3/Visit 5
2090	Non compliance with blood sample schedule at Visit 3/Visit 5
2100	Essential serological data missing: serological data missing for all antigens at both sampling time points at Visit 3/Visit 5
2120	Obvious incoherence, abnormal serology evolution or error in data (Eg; incoherence between CRF and results, wrong sample labelling)

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

- Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.
- Manual randomization: In case of the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.
- Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and statistical methods are described in Annex 1 and will not be repeated below.

6.1. Demography

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

The analysis of demography will be performed on the ES and on the PPS for immunogenicity.

Demographic characteristics such as age at vaccination in years, race, ethnicity, vital signs and cohort description will be summarised 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 (18 - 32 years and 33 - 45 years).

Withdrawal status will be summarised by group using descriptive statistics:

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

6.2. Analysis of immunogenicity

The analysis will be performed on the applicable PPS cohort for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is ≥5%, a second analysis will be performed on the ES.

Within group evaluation

Humoral Immune response to RSV vaccine

For each group, at each timepoint that blood samples are collected and for each assay (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI based on log-transformed values and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.

  Percentage of subjects above the seropositivity threshold and GMTs/GMCs will also be tabulated by group for each age category (18 - 32 years and 33 - 45 years).
- Pre- and post-vaccination antibody titres/concentrations will be displayed using reverse cumulative curves.

- The distributions of **neutralising** antibody titres will be tabulated in the tables with log2 scale (< 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 log2).
- Percentage of responders in terms of **neutralising** antibody titres will be tabulated with exact 95% CI.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- Distribution of the fold increase of **neutralising** antibody titres will be tabulated: by pre-vaccination titre category: < 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 (log2), and by cumulative categories: < 7, ≥ 7, ≥ 8, ≥ 9, ≥ 10, ≥ 11, ≥ 12 (log2).
- The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all timepoints.
- An analysis of variance model for repeated measures will be fitted to calculate GMTs/GMCs using mixed model with treatment group, visit and their interaction as fixed effects.

If deemed necessary, the same analyses may be done by age category (18 - 32 years and 33 - 45 years).

Between group evaluation

Exploratory comparisons will be performed for **RSV neutralising** antibody titres and PCA concentrations post-vaccination (Day 30, Day 60 and Day 90) between the different RSV vaccine groups.

- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment. This model includes:
    - The vaccine group as the fixed effect
    - The pre-vaccination titre/concentration as the covariate
    - Age groups (18-32 years and 33-45 years) and center as the categorical covariate

- GMT/GMC ratios with corresponding 95% CI will be computed between the RSV vaccine groups
    - PreF-120 *minus* PreF-30
    - PreF-120 *minus* PreF-60
    - PreF-60 *minus* PreF-30

6.3. Analysis of safety

The analysis of safety will be performed on the ES.

Within group evaluation

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 after vaccination will be tabulated with exact 95% CI. The same computations will be done for ≥ Grade 2 and Grade 3 AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for AEs resulting in medically attended visit.

The percentage of subjects reporting each individual **solicited local AE** (any grade, ≥ Grade 2, Grade 3, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each study vaccine for each group. The percentage of subjects reporting each individual **solicited general AE** (any grade, ≥ Grade 2, Grade 3, any related, ≥ Grade 2 related, Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each group.

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting fever will be reported by half degree (°C) cumulative increments. Similar tabulations will be performed for causally related fever, Grade 3 (> 39.5°C) causally related fever and fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination.

The percentage of subjects with any **unsolicited** symptoms within 30 days after vaccination 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 symptoms, for any causally related unsolicited symptoms, for Grade

3 causally related unsolicited symptoms and for unsolicited symptoms resulting in a medically attended visit (The verbatim reports of unsolicited symptoms 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).

SAEs reported throughout the study will be described in detail.

Pregnancy exposures throughout the study and pregnancy outcomes will be described in detail (if applicable).

The percentage of subjects using **concomitant medication** (any medication, any antipyretic and any antipyretic taken prophylactically) during the 7-day (Day 0 to Day 6) or 30-day (Day 0 to Day 29) follow-up period after vaccination will be summarised by group.

For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated for each timepoint.
- The maximum grading post-vaccination (from Day 7 to Day 90) versus baseline (Day 0) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 will be tabulated (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX D of the Protocol: FDA toxicity grading scale. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

Assessment of anti-NEO immune response at Day 30 post-vaccination for each group:

- GMCs pre-and post-vaccination will be tabulated with 95% CI and represented graphically.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody concentrations at Day 30 over pre-vaccination will be tabulated with 95% CI.
- Distribution of the antibody concentrations pre-and post-vaccination and of fold increase after vaccination will be tabulated.

Between group evaluation

Exploratory comparisons between each investigational RSV vaccine group and (minus) the control group (*placebo*), and between the RSV vaccine groups will be done in terms of the percentage of subjects reporting any ≥ Grade 2, Grade 3 AE (solicited and unsolicited), and/or any fever > 38.5°C, and/or any vaccine-related SAE during the 7-day follow-up period after vaccination.

- PreF-30 *minus placebo*
- PreF-60 *minus placebo*
- PreF-120 *minus placebo*
- PreF-120 *minus* PreF-30
- PreF-120 *minus* PreF-60
- PreF-60 *minus* PreF-30

The standardised asymptotic 95% CI for the difference between the investigational RSV vaccine groups as well as between the investigational RSV groups and (minus) the control group will be computed.

6.4. Analysis for ranking RSV formulations

The totality of data and sum total of evidence for particular dose(s) in terms of safety and immunogenicity will be evaluated by study team in addition to the analyses described in section 6.1 and 6.3 of this document on formulation selection. The desirability index approach described in the section below will be used as a descriptive tool to guide the formulation selection. In addition, any pertinent information from outside this study will be evaluated and may be used by the study team to help to make the final decision on a dose/formulation.

6.4.1. Definition of desirability in the context of Simulations

A desirability approach will be based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination.

This method is a multi-criteria decision making approach based on desirability functions. The main idea is to identify for each endpoint a desirability function that associates any value to another one between 0 and 1 depending on its desirability ('0' being considered as not desirable at all and '1' as the most desirable). An index with values between 0 and 1 will be created for each endpoint. An overall desirability index can be calculated by computing a weighted geometric mean of the endpoint indexes. By definition, this overall index also takes values between 0 and 1 and characterises the level of desirability of any candidate formulation by a single value [Dewé, 2015].

The desirability index calculations will include reactogenicity and safety data up to Day 7 post vaccination (on the TVC) and immunogenicity data at 30 days post-vaccination (on the ATP cohort for immunogenicity up to Day 30). The formulations will be ranked based on the values obtained with this overall desirability index.

6.4.2. Derived endpoints

The following endpoints will be computed and taken into account in the desirability analysis:

1. Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
2. Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
3. Geometric mean of neutralising antibody titres against RSV-A at Day 30 adjusted for pre-vaccination titres.
4. Geometric mean of PCA concentrations at Day 30 adjusted for pre-vaccination titres.

Each individual desirability index will be calculated based on data and tabulated by the treatment group and endpoints above. The details on how to calculate individual desirability index in terms of reactogenicity and immunogenicity and overall desirability index are elaborated in Annex 2.

6.5. Analysis of medically attended RTIs

The analysis will be performed on the ES by study group.

The proportion of subjects with at least one medically attended RSV-associated RTI identified by multiplex PCR with 95 % CI will be calculated.

Descriptive analyses (mean, median, min, max, standard deviation) of viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be tabulated for any cases where this assay is performed.

Medically attended RSV-associated RTI co-infected or colonisation with another viral etiology identified by multiplex PCR will be described.

Medically attended RTI with any viral etiology identified by multiplex PCR will be described.

The proportion of subjects with 95% CI with at least one medically attended RTI (all causes) will be calculated by group.

7. ANALYSIS INTERPRETATION

All comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The statistical analyses will be performed in several steps:

- In preparation of the planned iSRC evaluation, analysis of safety and reactogenicity data up to at least 7 days post-vaccination of the first 25% of all subjects will be performed (see Section 8.10.2 of the Protocol for more information).

- The first main analysis on all subjects will be performed when all data up to 30 days post-vaccination are available (primary endpoints). In order to maintain the blind, this analysis by group will be performed by an independent statistician and the results which would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). No individual data listings will be provided.
- A second analysis will be performed when all data up to 90 days post-vaccination are available (secondary endpoints). At this point, the GSK statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided. Given that summary results may unblind some specific subjects, the study will be conducted in a single-blind manner from this point onwards, with subjects remaining blinded up to study conclusion and the investigators will not have access to the treatment allocation up to study conclusion.
- The final analysis will be performed when all data up to study conclusion are available. All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage.
- An integrated study report presenting all analyses will be written and made available to the investigators at the time of final analysis.
- If 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=web posting, SR=study report, internal)**	**Dry run review needed (Y/N)**	***Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)**	**Reference for TFL**
Final Analysis	E1_01	Study report CTRS	N	Yes	All tables E1_01 identified in TFL dated xxxxxx

ISRC Day 7 safety on 25% of subjects	E1_02	Internal	N	Yes	All tables E1_01 identified in TFL for ISRC dated xxxxxx
Analysis of Day 30	E1_03	Internal CTRS	N	Yes	All tables E1_03 identified in TFL dated xxxxxx
Analysis of Day 90	E1_04	Internal	N	Yes	All tables E1_04 identified in TFL dated xxxxxx

8.2. Statistical considerations for interim analyses

No interim analysis will be performed.

9. CHANGES FROM PLANNED ANALYSES

In order to align to ICH and CDISC terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS,…)

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STAT METHODS

11.1. Statistical method references

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper:Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

Dewé W, Durand Ch, Marion S *et al*. A multi-criteria decision making approach to identify a vaccine formulation. *Journal of Biopharmaceutical Statistics*, 2015; epublication ahead of print: DOI: 10.1080/10543406.2015.1008517.

11.2. Standard data derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day and month are missing, 30 June is used.
- Onset day: The onset day for an event will be the number of days between the most recent vaccination and the start of the event. Events occurring on the day of vaccination will have an onset day of 0.
- Duration of events: The duration of an event will be the number of days between the start and stop dates + 1, e.g. an event which starts on 01DEC2014 and ends on 10DEC2014 will have duration of 10 days.

11.2.1. Demography

For a given subject and a given demographic variable, missing measurements will not be replaced.

- Age at vaccination - Age will be calculated as the number of complete months between the date of birth and the date of vaccination.
- Height - Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows: Height in centimeters = Height in inches * 2.54 (rounded to the unit - no decimal places)
- Weight - Weight will be presented in kilograms. Weights reported in pounds will be converted as follows: Weight in kilograms = Weight in pounds / 2.2 (rounded to 2 decimal places).

11.2.2. Immunogenicity

- Any missing or non-evaluable immunogenicity measurement will not be replaced:
  - For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
  - For the between group assessments, the Analysis of Covariance (ANCOVA) model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.
- A seronegative subject will be defined as a subject whose antibody titre/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre/concentration is greater than or equal to the cut-off value of the assay
- The geometric mean titres (GMTs)/geometric mean concentrations (GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the log10 transformed titres/concentrations.
  - The 95% CI for the mean of log-transformed titer will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.
- Vaccine response in terms of RSV neutralising antibodies will be defined as:
  - At least a 4-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre <7 log2 (<128).

  - At least a 3-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in [7-8] log2 ([128-256]).
  - At least a 2.5-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in >8-10 log2 (>256-1024).
  - At least 1-fold from pre-vaccination if pre-vaccination neutralising antibody titre >10 log2 (>1024).

- In order to compute fold increase of antibody titres/concentrations (ratio) between post-vaccination and pre-vaccination titres/concentrations, antibody titres/concentrations below the assay cut-off will be given an arbitrary value of half the cut-off.
- For neutralising antibody against RSV-A, the following rules will be applied:

Raw result	Derivation for seropositivity status	Derivation for GMT calculation	Derivation for fold-increase between Post and Pre-vaccination titres
<8	NEG	4	LLOQ/2
[8-LLOQ[	POS	8	LLOQ/2
≥LLOQ	POS	Exact value	Exact value

11.2.3. Safety

- Temperature conversion: The conversion of temperature (Fahrenheit to Celsius) will be done as follows and rounded to 1 decimal place:

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

- Handling of missing data: subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications/vaccinations) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications/vaccinations, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.

- For a given subject and the analysis of solicited symptoms during the 7-day follow-up period after vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will

include only vaccinated subjects with documented safety data (i.e., symptom screen completed).

- For analysis of unsolicited AEs, SAEs and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report an event or concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- For the summary of fever, the occurrence of fever will be reported per 0.5°C cumulative increments starting from 38°C by any route. "All" will including all subjects with a documented temperature of ≥ 38°C/100.4°F by any route and all subjects reporting temperature < 38°C but with missing values (MC) for at least one day during the solicited period).

The preferred route for recording temperature in this study will be oral. For the analysis, temperatures will be coded as follows:

Grade	Temperature for oral, axillary or tympanic route	Temperature for rectal route
0	< 37.5°C	< 38.0°C
1	≥ 37.5°C - ≤ 38.5°C	≥ 38.0°C - ≤ 39.0°C
2	> 38.5°C - ≤ 39.5°C	> 39.0°C - ≤ 40.0°C
3	> 39.5°C	> 40.0°C

For the analysis, the intensity scale for the following solicited AEs will be assessed as described:

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults:

0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

For clintrial.gov and EudraCT posting purposes, 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 name	Lower level term code	Corresponding Primary Term code
Pain	Pain	10033371	10033371
Redness	Erythema	10015150	10015150
Swelling	Swelling	10042674	10042674
Fatigue	Fatigue	10016256	10016256
Fever	Fever	10016558	10037660
Gastroinstestinal symptoms	Gastroinstestinal disorder	10017944	10017944
Headache	Headache	10019211	10019211

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

11.3. Number of decimals displayed:

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age, SD (age)	1
Immunogenicity	Ratio of GMT/GMC	2

12. ANNEX 2 CALCULATION OF INDIVIDUAL AND OVERALL DESIRABILITY INDEX

The section below provide the details on how to calculate individual desirability index and overall desirability index score based on Annex E in the Protocol.

Reactogenicity

A logistic regression model will be fitted on each reactogenicity endpoint (any Grade 2/3 general AE and any related SAE, Grade 2/3 fever) reported during the 7-day follow-up period after vaccination, including all RSV formulations.

- The vaccine group as the fixed effect
- The age groups (18-32 years and 33-45 years) as the categorical covariant.

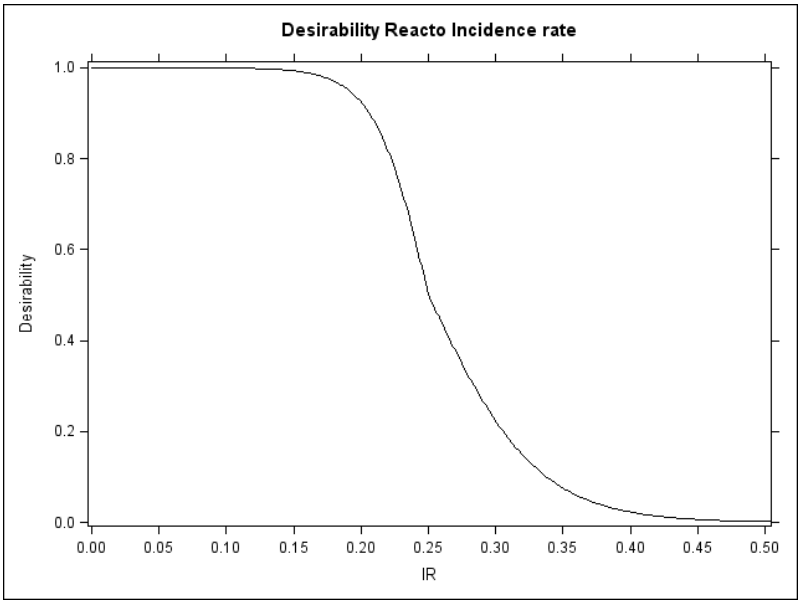
The estimation of indication rate will be tabulated by treatment group.

For any Grade 2/3 general AEs and any related SAEs, the incidence rate estimate ($\hat{IR}$) will be transformed in a [0,1] desirability index using the following function:

$$DR1 = \begin{cases} \dfrac{1}{1+\exp -50 * 0.25 - \hat{IR}}, & if\ \hat{IR} \leq 0.25 \\ \dfrac{1}{1+\exp -25 * 0.25 - \hat{IR}}, & if\ \hat{IR} \geq 0.25 \end{cases}$$

where $\hat{IR}$ is the incidence rate estimated by the model. This function will allocate a desirability value of 1, 0.5 and 0 to incidence rate equal to 0.1, 0.25 and 0.5 respectively (see **Error! Reference source not found.**). But the calculation equally weights Grade 2/3 general AEs and any related SAEs.

Figure 2 **Desirability function for the incidence rate of Grade 2/3 general AEs and related SAEs - for each investigational RSV vaccine formulation**

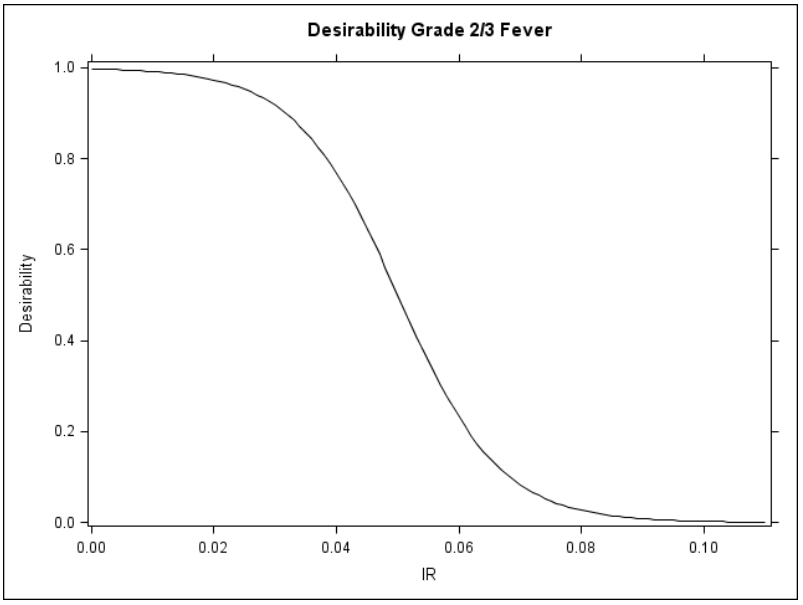


For Grade 2/3 fever, the incidence rate estimate ($\hat{}R$) will be transformed in a [0,1] desirability index using the following function:

$$DR2 = \frac{1}{1 + \exp(-120 * (0.05 - \hat{}R))}$$

where $\hat{}R$ is the incidence rate estimated by the model. As illustrated in **Error! Reference source not found.**, the function will allocate desirability values of 1, 0.5 and 0 to incidence rate equal to 0, 0.05 and 0.1 respectively.

Figure 3 Desirability function for the incidence rate of Grade 2/3 fever - for each investigational RSV vaccine formulation



Finally, the reactogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DR = \overline{DR1 * DR2}$$

Immunogenicity

The ANCOVA model will be fitted on the log-transformed titre for each immune response of neutralising anti-RSV-A and PCA separately including

- The vaccine group as the fixed effect
- The pre-vaccination titre/concentration and age groups (18-32 years and 33-45 years) as the covariates

The mean estimations of GMTs/GMCs for each treatment group at Day 30 and its 95% CI will be provided for immunogenicity desirability calculation. The estimated GMT and LL will be tabulated by treatment group.

As formulations inducing a high immune response will be considered suitable, the lower limit (LL) of the estimated GMT/C adjusted for pre-vaccination titres will be the statistical criterion considered for decision making.

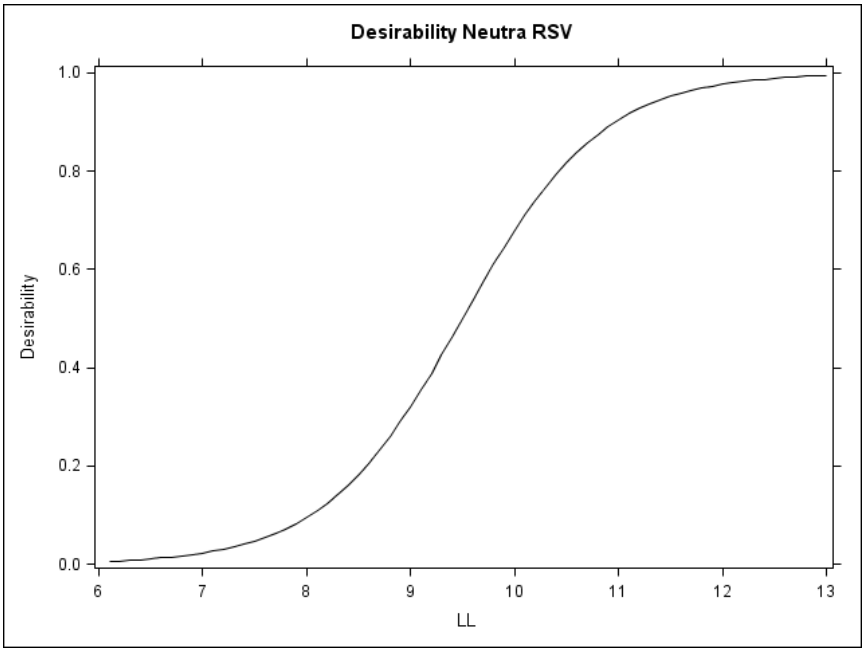
Neutralising anti-RSV-A titres

The LL of the GMT estimate will be transformed into a [0, 1] desirability index using the function:

$$DI1 = \frac{1}{1 + \exp(1.5 * (9.5 - LL))}$$

where LL is the lower limit of the 95% confidence interval of the GMT adjusted for pre-vaccination titres in log base 2. The function was chosen to have a desirability of 0 at LL value ≤ 6 log2 (=128), and a desirability of 1 at LL value ≥ 13 log2. This function is illustrated in **Error! Reference source not found.**.

Figure 4 Desirability function for neutralising anti-RSV-A GMTs - for each investigational RSV vaccine formulation



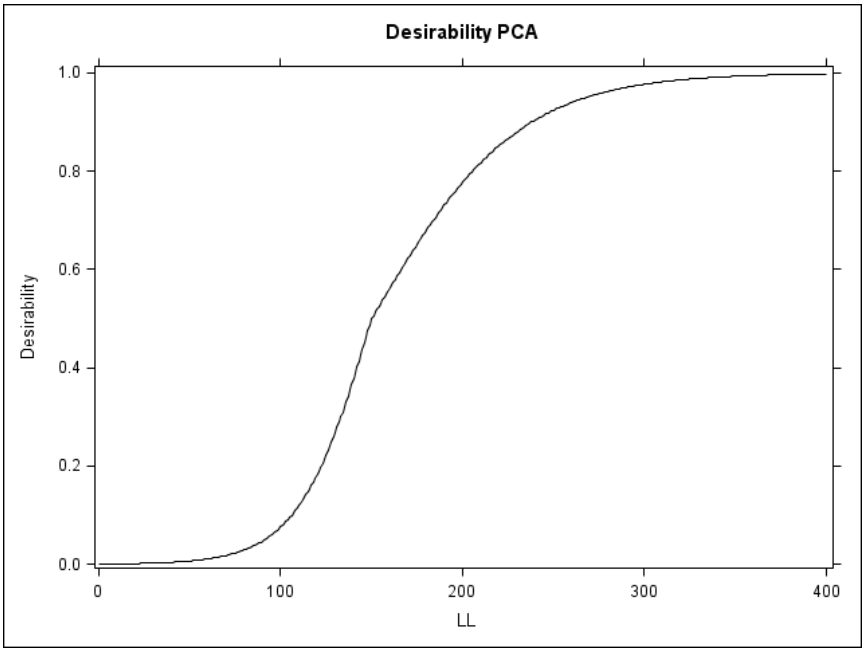
PCA concentrations

The LL of the GMC adjusted for pre-vaccination titres estimate will be transformed using the following function:

$$DI2 = \begin{cases} \frac{1}{1 + \exp 0.05 * 150 - LL}, & if\ LL \leq 150 \\ \frac{1}{1 + \exp 0.025 * 150 - LL}, & if\ LL \geq 150 \end{cases}$$

As illustrated in **Error! Reference source not found.**, a PCA response of 25, 150 and 400 µg/mL will have a desirability value of 0, 0.5 and 1 respectively.

Figure 5 Desirability function for PCA concentrations - for each investigational RSV vaccine formulation



Finally, the immunogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DI = \overline{DI1 * DI2}$$

Overall desirability index

The overall desirability index will be obtained by computing the following weighted geometric mean: $D = DR^{0.4} * DI^{0.6}$.

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

Template 46 Descriptive statistics of the viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases (Total vaccinated cohort)

		<each group> N =	Total N =
Visit	**Parameters**	**Value**	**Value**
	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		

<each group>:
30 PreF = 30 mcg PreF Plain
60 PreF = 60 mcg PreF Plain
120 PreF = 120 mcg PreF Plain
Control = Placebo

Template 47 Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (ATP cohort for immunogenicity)

Group	GMT	LL	DI1	DI2	DI
<each group>					

<each group>:
30 PreF = 30 mcg PreF Plain
60 PreF = 60 mcg PreF Plain
120 PreF = 120 mcg PreF Plain
GMT = estimated GMT adjusted for pre-vaccination titres LL
= estimated lower limit adjusted for pre-vaccination titres
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 48 Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Total vaccination cohort)

Group	Incidence Rate (IR)	DR1	DR2	DR

<each group>				

<each group>:
30 PreF = 30 mcg PreF Plain
60 PreF = 60 mcg PreF Plain
120 PreF = 120 mcg PreF Plain
$\hat{IR}$ = incidence rate estimated by the model
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index

Template 49 Desirability index based on reactogenicity and safety (TVC cohort up to Day 7) and immunogenicity (ATP cohort for immunogenicity up to Day 30)

Group	Reactogenicity Index		Immunogenicity Index		Overall Desirability Index $DR^{0.4} * DI^{0.6}$
<each group>	DR1		DI1		
	DR2		DI2		
	DR		DI		

<each group>:
30 PreF = 30 mcg PreF Plain
60 PreF = 60 mcg PreF Plain
120 PreF = 120 mcg PreF Plain
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 – 45 years.
eTrack study number and Abbreviated	204812 (RSV F-021)
Scope:	All data pertaining to the above study for review by the IDMC on all subjects with at least Day30 safety and reactogenicity data
Date of Statistical Analysis Plan	***Amendment 1: 02-May-2017*** ***Version 1: 21-Apr-2017***
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (SERM physician) PPD (Independent Statistician)
Approved by:	PPD (Clinical & Epidemiological Projects Lead) PPD (Lead statistician) PPD (Lead stat analyst) PPD (Lead scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
CEPL:	Clinical and Epidemiology Project Lead
CI:	Confidence Interval
CRDL:	Clinical Research and Development Lead
eCRF:	electronic Case Report Form
GP:	General Practitioner
GSK:	GlaxoSmithKline
iSRC:	Internal Safety Review Committee
IDMC:	Independent Data Monitor Committe
LL:	Lower Limit of the confidence interval
MA-RTI:	Medically Attended Respiratory Tract Infection
MedDRA:	Medical Dictionary for Regulatory Activities
PCR:	Polymerase Chain Reaction
PreF:	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
RSV:	Respiratory syncytial virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Randomisation System on Internet
SRT:	Safety Review Team
TFL:	Tables Figures and Listing template annexed to SAP
TVC:	Total Vaccinated Cohort
UL:	Upper Limit of the confidence interval
WBC:	White Blood Cells

1. DOCUMENT HISTORY

Date	Version	Description	Protocol Version
21APR2017	First Version	Enhanced respiratory disease risk review by IDMC	RSV F-021 (204812) Protocol (20-Jul-2016)
02MAY2017	***Amendment 1***	***Amendment 1: Description of changes from First Version are as below,*** ***- Individual results of levels outside of the normal ranges in each group are generated for all six lab parameters, including hemoglobin, platelets counts, white blood cells counts, ALT, AST, and creatinine to replace individual results of levels in the normal range*** ***- Add two tables for AE using maximum grading per subject for each grade*** ***- Add two tables for AE on all grades for duration***	***RSV F-021 (204812) Protocol (20-Jul-2016)***

2. INTRODUCTION

This SAP and TFL document presents the analyses of the data of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo.

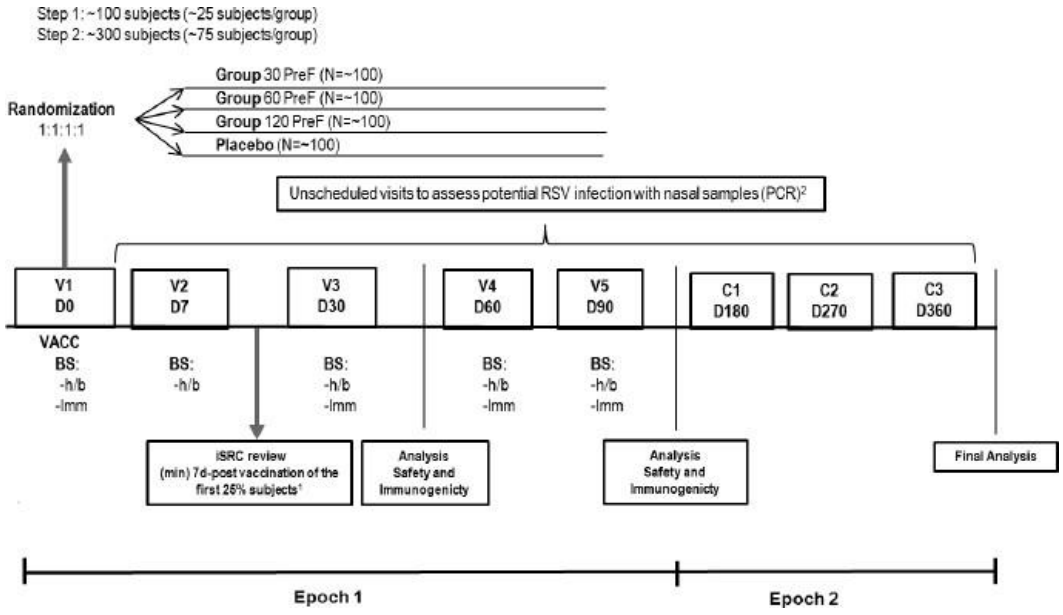
- the unblinded analyses and data displays presenting each study group for the Independent Data Monitoring Committee (IDMC).
- the blinded analyses and data displays presenting all groups pooled for the review of safety data by the GSK Safety Review Team (SRT) involved in the project.

Statistical analyses and data displays for the iSRC review, other study analyses and the end of study reporting are not covered in this SAP and will be described in a separate document.

The list of tables, figures and listings to be produced are shown in section 11.

3. STUDY DESIGN

Figure 1 Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.

1 Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.

2 In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of an event related eCRF and the collection of a nasal swab within 72h after the medical attendance.

Vertical lines stand for analysis on all subjects.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
- **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
- Epoch 002: Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Study groups**:

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.
- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.
- **Sampling schedule:**
  - **Blood samples for haematology/biochemistry** will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Blood samples for humoral immune response evaluation** will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Nasal swabs** will be collected from subjects in case of a MA-RTI from enrolment (Visit 1) until study end (Contact 3).
- **Type of study**: self-contained
- **Data collection**: Electronic Case Report Form (eCRF).
- **Safety monitoring**:
  - When the first 25% of subjects are vaccinated in the study, enrolment will be paused until completion of an unblinded review by a GSK iSRC. Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' SRT on a regular basis throughout the study.
  - IDMC will review all available safety and reactogenicity data (including haematology/biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo. The blinded safety data will also be reviewed by the GSK Biologicals' SRT.
- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

4. OBJECTIVES

This document does not describe the analyses relative to study objectives. This analysis is performed to support the IDMC and SRT reviews of at least Day 30 safety data for all subjects enrolled.

5. ENDPOINTS

- Occurrence of AEs from vaccination up to **Day 7**, for all subjects in all groups:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);
  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of each solicited local and general AE.
- Occurrence of AEs from vaccination up to **data lock point**, for all subjects in all groups:
  - Occurrence of any unsolicited AE;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7 and Day 30 for all subjects in all groups and at Day 60 and Day 90 for all available subjects in all groups.
- Occurrence of medically attended respiration tract infections (MA-RTIs) up to the data lock point
- Occurrence of any vaccine-related SAE up to the data lock point

6. STUDY POPULATION

6.1. Study cohorts to be evaluated

The statistical analyses that are described in the document are based on the Total Vaccinated Cohort; i.e. on subjects with at least one vaccine administration.

7. STATISTICAL METHODS

7.1. Data to be reviewed

The IDMC will review, in an unblinded manner, all available safety and reactogenicity data (including haematology/biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo and all SAEs reported up to the data lock point.

The following data will be reviewed during the IDMC meeting:

- Demographic characteristics.
- Summary tables containing information on events of interest (any Serious Adverse Events [SAE], any death or life-threatening SAE, any missed visits due to vaccine-related Adverse Event [AE], any AEs causing study withdrawal).

- Incidence of solicited local AEs (pain, redness, swelling): any, each grade (7-day follow-up period after vaccination).
- Incidence of solicited general AE (fever, headache, fatigue, gastrointestinal symptoms): any, each grade, any related, any Grade 2 related, any Grade 3 related (7-day follow-up period after vaccination).
- Incidence of unsolicited AE: any, Grade 3, any related, Grade 3 related (7-day and 30-day follow-up period after each vaccination).
- Any abnormality in haematological (haemoglobin level, leukocyte, neutrophil, lymphocyte, eosinophil and platelet count) and biochemical (ALT, AST and creatinine) parameters: number and percentage of subjects with parameters outside of the normal ranges, the maximum grading post-vaccination (from Day 7 to data lock point) versus baseline (Day 0) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 (Grades will be based on the Food & Drug Administration [FDA] Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials").
- Additional parameters of interest may be tabulated.

7.2. Group description

For the blinded report, the analyses will be presented as one group (RSV groups and Placebo group being pooled) as described in Table 2.

For the unblinded report, the analyses will be presented by group as described in Table 2.

Table 2 Group order and group label for the blinded and unblinded tables

Study groups	Blinded report			Unblinded report		
	Pooled group order	Pooled group label	Pooled group definition for footnote	Group order	Group label	Group definition for footnote
30 PreF	1	Step 1	RSV + Placebo	1	30 PreF	30 mcg PreF
60 PreF				2	60 PreF	60 mcg PreF
120 PreF				3	120 PreF	120 mcg PreF

8. STATISTICAL CALCULATIONS

8.1. Derived and transformed data

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:

- Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.
- For analyses of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- For the analysis, temperatures, redness and swellings will be coded as follows:

Table 3 Grading scales for temperatures, redness and swellings parameters applicable for this study

Grade	Temperature		Redness and swelling
	Oral, axillary or tympanic route	Rectal route	
0	< 37.5°C	< 38.0°C	≤ 20 mm
1	≥ 37.5°C to ≤ 38.5°C	≥ 38.0°C to ≤ 39.0°C	> 20 mm to ≤ 50 mm
2	> 38.5°C to ≤ 39.5°C	> 39.0°C to ≤ 40.0°C	> 50 mm to ≤ 100 mm
3	> 39.5°C	> 40.0°C	> 100 mm

- Haematology/biochemistry parameters will be graded according to FDA toxicity grading scales

Table 4 Toxicity grading scales for hematology and biochemistry parameters applicable for this study

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests -ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease - 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

ULN = upper limit of the normal range.

- Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered

8.2. Methodology for computing CI

All CI computed will be two-sided 95% CI.

The exact 95% CIs for a proportion within a group will be calculated from Proc StatXact [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika.* 1934; 26:404-413].

9. CONDUCT OF ANALYSES

This unblinded analysis will be done by an independent statistician outside GSK to maintain the study team blinded.

Description	Analysis ID	Disclosure Purpose
IDMC Analysis of Day30	E1_03	IDMC

One unblinded analysis is planned to be reviewed by the IDMC and one blinded analysis is planned to be reviewed by the GSK SRT for the project on all available safety and reactogenicity data (including all available haematology/biochemistry parameters at data lock point) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo.

10. REFERENCES

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika.* 1934; 26:404-413

11. LIST OF TABLES AND LISTINGS

11.1. List of tables

The tables and figures presented in this section will be created for the unblinded report.

For the blinded report, similar tables/figures will be presented with RSV and Placebo groups being pooled and presented as one group as described in Table 2.

Template #	Table Title	Output destination	Macro
Template 1	Summary of demographic characteristics (Total Vaccinated Cohort)	Annex	%DEMOGRA
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (**Day 30)** (Total Vaccinated Cohort)	Annex	%DROP_SUM (OTH=0)
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (**Day 60)** (Total Vaccinated Cohort)	Annex	%DROP_SUM (OTH=0)
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (**Day 90)** (Total Vaccinated Cohort)	Annex	%DROP_SUM (OTH=0)
Template 3	Compliance in returning symptom information (Total Vaccinated Cohort)	Annex	%COMPLI
Template 4	Incidence of solicited **local** symptoms reported during the 7-day (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%FREQ
Template 5	*Incidence of solicited **local** symptoms reported during the 7-day (day 0-6) post-vaccination period **by duration** (Total Vaccinated Cohort)*	***Annex***	***%FREQ***
Template 6	Incidence of solicited **general** symptoms reported during the 7-day (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%FREQ
Template 7	*Incidence of solicited **general** symptoms reported during the 7-day (day 0-6) post-vaccination period **by duration** (Total Vaccinated Cohort)*	***Annex***	***%FREQ***
Template 8	Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of symptoms (solicited and unsolicited) **considered related to vaccination** reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of symptoms (solicited and unsolicited) **with medically attended visit**, reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN

Template #	Table Title	Output destination	Macro
Template 8	Incidence and nature of **grade 3** symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of **grade 3** symptoms (solicited and unsolicited) **considered related to vaccination** reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of **grade 2/3** symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of symptoms (solicited and unsolicited) **considered related to vaccination** reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of symptoms (solicited and unsolicited) **with medically attended visit**, reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of **grade 3** symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of **grade 3** symptoms (solicited and unsolicited) **considered related to vaccination** reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 8	Incidence and nature of **grade 2/3** symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)	Annex	%LOCGEN
Template 9	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **7-day** (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL

Template #	Table Title	Output destination	Macro
Template 9	Percentage of subjects reporting the occurrence of **grade 3** unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **7-day** (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, **considered related to vaccination**, during the **7-day** (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of **grade 3** unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, **considered related to vaccination**, during the **7-day** (day 0-6) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **30-day** (day 0-29) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of **grade 3** unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **30-day** (day 0-29) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, **considered related to vaccination**, during the **30-day** (day 0-29) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of **grade 3** unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, **considered related to vaccination**, during the **30-day** (day 0-29) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of **medically attended respiration tract infections (MA-RTIs)**, during the **30-day** (day 0-29) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 9	Percentage of subjects reporting the occurrence of **medically attended respiration tract infections (MA-RTIs)**, during the **60-day** (day 0-59) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL

Template #	Table Title	Output destination	Macro
Template 9	Percentage of subjects reporting the occurrence of **medically attended respiration tract infections (MA-RTIs)**, during the **90-day** (day 0-89) post-vaccination period (Total Vaccinated Cohort)	Annex	%UNSOL
Template 10	Number and percentage of subjects taking a **concomitant medication** during the 7- day (Days 0-6) post -vaccination period (Total vaccinated cohort)	Annex	%CMED_INC
Template 10	Number and percentage of subjects taking a **concomitant medication** during the 30- day (Days 0-29) post -vaccination period (Total vaccinated cohort)	Annex	%CMED_INC
Template 11	Listing of **SAEs** reported up to data lock point (Total vaccinated cohort)	Annex	%SAE
Template 12	Listing of adverse events, SAEs and solicited symptoms leading to withdrawal from the treatment/study (Total Vaccinated Cohort)	Annex	%DISC_AE
Template 13	Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges (Total vaccinated cohort)	Annex	%HAEMATO_BIOCH
Template 14	Summary of haematology and biochemistry results by maximum grade from VISIT 2 (D7) up to VISIT 5 (D90) versus baseline (Total vaccinated cohort)	Annex	%HAEMATO_BIOCH_GR_CHANGE
Template 15	Summary of haematology change from baseline by maximum grade from VISIT2 (D7) up to VISIT5 (D90) (Total vaccinated cohort)	Annex	%HAEMATO_BIOCH_GR_CHANGE
Template 16	*Individuals results of **hemoglobin levels** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **hemoglobin levels** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **hemoglobin levels** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **hemoglobin levels** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **platelets counts** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***

Template #	Table Title	Output destination	Macro
Template 16	*Individuals results of **platelets counts** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **platelets counts** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **platelets counts** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **white blood cells counts** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **white blood cells counts** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **white blood cells counts** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **white blood cells counts** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **ALT levels** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **ALT levels** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **ALT levels** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **ALT levels** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **AST levels** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **AST levels** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **AST levels** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **AST levels** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **creatinine levels** outside of the normal ranges in **30** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***

Template #	Table Title	Output destination	Macro
Template 16	*Individuals results of **creatinine levels** outside of the normal ranges in **60** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **creatinine levels** outside of the normal ranges in **120** PreF group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***
Template 16	*Individuals results of **creatinine levels** outside of the normal ranges in **Control** group (Total vaccinated cohort)*	***Annex***	***%HB_PROFIL***

11.2. List of listings

The listings will present data reported up to the data lock point, of which may be after Visit 3 (Day 30) for some subjects.

For the blinded report, individual data listings are not including the group information.

For the unblinded report individual data listings are including the group in formation (XLS documents).

- APPENDIX TABLE IB - DEMOGRAPHY
- APPENDIX TABLE ICII - REASON FOR VISIT NOT DONE
- APPENDIX TABLE ID - GENERAL MEDICAL HISTORY - EXAMINATION
- APPENDIX TABLE II - REASON FOR VACCINE NOT ADMINISTERED
- APPENDIX TABLE IIA - SOLICITED LOCAL ADVERSE EVENTS
- APPENDIX TABLE IIB - SOLICITED GENERAL ADVERSE EVENTS
- APPENDIX TABLE IIC - UNSOLICITED ADVERSE EVENTS
- APPENDIX TABLE IID – MEDICATION
- APPENDIX TABLE IIEi - MA-RTI VISIT INFORMATION
- APPENDIX TABLE IIEii - MA-RTI SYMPTOMS INFORMATION
- APPENDIX TABLE IIEiii - MA-RTI MICROBIOLOGICAL WORKUP INFORMATION
- APPENDIX TABLE IIEiv - CHEST X-RAY OBSERVATIONS AT MA-RTI VISIT
- APPENDIX TABLE IVA - HAEMATOLOGY AND BIOCHEMISTRY (ALL VALUES)
- APPENDIX TABLE IVBi - RSV
- APPENDIX TABLE IVBii - PREGNANCY TEST

12. TEMPLATE OF TABLES

Template 1 Summary of demographic characteristics (Total vaccinated cohort)

		<each group> (N=)		Total (N=)	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at dose 1	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Ethnicity	American Hispanic or Latino				
	Not American Hispanic or Latino				
Geographic Ancestry	African Heritage / African American				
	American Indian or Alaskan Native				
	Asian - Central/South Asian Heritage				
	Asian - East Asian Heritage				
	Asian - Japanese Heritage				
	Asian - South East Asian Heritage				
	Native Hawaiian or Other Pacific Islander				
	White - Arabic / North African Heritage				
	White - Caucasian / European Heritage				
	Other				

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Day 30) (Total vaccinated cohort)

	<each group>	**Total**
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdraw:		
Serious Adverse Event		
Non-serious adverse event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Other - <reason>		
Other - <reason>		

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed up to Day30
withdrawn = number of subjects who did not come up to Day30

Template 3 Compliance in returning symptom information (Total vaccinated cohort)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
<each group>						

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 4 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Onset ≤48h * Grade 2					
	Onset ≤48h * Grade 3					
Redness (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Onset ≤48h * >50 and ≤ 100					
	Onset ≤48h * >100					
Swelling (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Onset ≤48h * >50 and ≤ 100					
	Onset ≤48h * >100					

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: $\leq$ 20 mm
1: > 20 mm to $\leq$ 50 mm
2: > 50 mm to $\leq$ 100 mm
3: > 100 mm

Note: this template is also for the summary by maximum intensity

Template 5 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period by duration (Total vaccinated cohort)

			<each group>				
						95 % CI	
Symptom	**Duration**	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	=<3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
	> 3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
	Total	All					
		Grade 1					
		Grade 2					
		Grade 3					
Redness (mm)	=<3 days	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					
	> 3 days	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					
	Total	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					
Swelling (mm)	=<3 days	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					
	> 3 days	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					
	Total	All					
		> 20 and ≤ 50					
		> 50 and ≤ 100					
		> 100					

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

Template 6 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2*Related					
	Grade 3*Related					
	Onset ≤48h					
	Onset ≤48h *Grade 2					
	Onset ≤48h *Grade 3					
Temperature (Oral) (°C)	All (≥37.5)					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related					
	>38.5*Related					
	>39.5*Related					
	Onset ≤48h					
	Onset ≤48h *>38.5					
	Onset ≤48h *>39.5					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2*Related					
	Grade 3*Related					
	Onset ≤48h					
	Onset ≤48h *Grade 2					
	Onset ≤48h *Grade 3					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2*Related					
	Grade 3*Related					
	Onset ≤48h					
	Onset ≤48h *Grade 2					
	Onset ≤48h *Grade 3					

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Note: this template is also for the summary by maximum intensity

Template 7 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period by duration (Total vaccinated cohort)

			<each group>				
						95 % CI	
Symptom	**Duration**	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	=<3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	> 3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	Total	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
Temperature (Oral) (°C)	=<3 days	All (≥37.5)					
		>38.0					
		>38.5					
		>39.0					
		>39.5					
		Related					
		>38.5*Related					
		>39.5*Related					
	> 3 days	All (≥37.5)					
		>38.0					
		>38.5					
		>39.0					
		>39.5					
		Related					
		>38.5*Related					
		>39.5*Related					
	Total	All (≥37.5)					
		>38.0					
		>38.5					
		>39.0					
		>39.5					
		Related					
		>38.5*Related					
		>39.5*Related					
Gastrointestinal symptoms	=<3 days	All					
		Grade 1					
		Grade 2					

			<each group>				
						95 % CI	
Symptom	**Duration**	**Type**	**N**	**n**	**%**	**LL**	**UL**
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	> 3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	Total	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
Headache	=<3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	> 3 days	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					
	Total	All					
		Grade 1					
		Grade 2					
		Grade 3					
		Related					
		Grade 2*Related					
		Grade 3*Related					

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:
0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 8 Incidence and nature of symptoms (solicited and unsolicited reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each group>															

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N = number of subjects with the administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 9 Percentage of subjects reporting the occurrence of unsolicited classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Total vaccinated cohort)

		<each group> **N =**			
				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**
At least one symptom					
<each SOC (code)>	<each PT (code)>				
...	..				
...	...				

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 10 Number and percentage of subjects taking a concomitant medication during the 7- day (Days 0-6) post -vaccination period (Total vaccinated cohort)

	<each group>				
				95% CI	
	N	**n**	**%**	**LL**	**UL**
Any					
Any antipyretics					
Prophylactic antipyretics					

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo
N= number of administered doses
n/%= number/percentage of subjects who took the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 11 Listing of SAEs reported up to data lock point (Total vaccinated cohort)

Group	Sub.No.	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo

Template 12 Listing of adverse events, SAEs and solicited symptoms leading to withdrawal from the treatment/study (Total Vaccinated Cohort)

Group	Study-Subject No.	Country	Gender	Race	AE Description	SAE	Causality	Outcome	Type of discontinuation

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF =120 mcg PreF
Control = Placebo

Template 13 Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges (Total vaccinated cohort)

			<each group >								
				Unknown		**Below**		**Within**		**Above**	
Laboratory parameter	**Timing**	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT)	PI (D7)	Unknown									
		Below									
		Within									
		Above									
	PI (D30)	…									
	PI (D60)	…									
	PI (D90)	…									
Aspartate Aminotransferase (AST)	PI (D7)	Unknown									
		Below									
		Within									
		Above									
	PI (D30)	…									
	PI (D60)	…									
	PI (D90)	…									
Creatinine	…	…									
Eosinophil	…	…									
Haemoglobin	…	…									
Lymphocyte	…	…									
Neutrophil	…	…									
Platelet count	…	…									
White Blood Cells (WBC)	…	…									

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF = 120 mcg PreF
Control = Placebo
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
PI (D7): 7 days post dose 1
PI (D30): 30 days post dose 1
PI(D60) = 60 days post dose 1
PI(D90) = 90 days post dose 1

Template 14 Summary of haematology and biochemistry results by maximum grade from VISIT 2 (D7) up to VISIT 5 (D90) versus baseline (Total vaccinated cohort)

		VISIT2 (D7) up to VISIT5 (D90)												
		<each group >												
			Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT) increase by factor	Unknown													
	Grade 0													
	Grade 1													
	Grade 2													
	Grade 3													
	Grade 4													
	Total													
Aspartate Aminotransferase (AST) increase by factor	…													
Creatinine	…													
Eosinophils increase	…													
Hemoglobin decrease	…													
Lymphocytes decrease	…													
Neutrophils decrease	…													
Platelet count decrease	…													
White Blood Cells (WBC) decrease	…													
White Blood Cells (WBC) increase	…													

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF = 120 mcg PreF
Control = Placebo
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of patients reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 15 Summary of haematology change from baseline by maximum grade from VISIT2 (D7) up to VISIT5 (D90) (Total vaccinated cohort)

	VISIT2 (D7) up to VISIT5 (D90)												
	<each group >												
		Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hemoglobin (Change from baseline)													

<each group>:
30 PreF = 30 mcg PreF
60 PreF = 60 mcg PreF
120 PreF = 120 mcg PreF
Control = Placebo
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

Template 16 Individuals results of hemoglobin levels outside of the normal ranges in < *group*> (Total vaccinated cohort)

Note: This figure is shown as an example. For the unblinded report, one figure per group will be performed. For the blinded report, 4 graphs will be performed each of them presenting PPD subjects regardless of treatment (the first PPD subjects, from the PPD to the PPD h subject…).The X axis will include Day 0, Day 7 and Day 30. The Y axis will be adapted according to each parameter.

	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 – 45 years.
eTrack study number and Abbreviated	204812 (RSV F-021)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	***Final: Amendment 2 (09-Nov-2017)*** ***Amendment 1 (21-Jul-2017)*** ***Version 2.0 (10-Nov-2016)*** ***Version 1.0 (25-Aug-2016***
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 (Regulatory Affair) PPD (SERM physician) PPD (Public disclosure representative)
Approved by:	PPD ***(Clinical Research and Development Lead)*** PPD (Lead statistician) PPD (Lead stat analyst) PPD (Lead scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	According-to-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
eCRF	Electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
MA-RTI	Medically Attended Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
NEO	Neogenin
PCA	Palivizumab Competing Antibodies
PCD	Primary completion Date
PCR	Polymerase Chain Reaction
PPS	Per Protocol Set
PreF	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
RSV	Respiratory syncytial virus

RTI	Respiratory Track Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	(GSK) Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
WBC	White Blood Cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25-AUG-2016	Version1: first version	RSV F-021 (204812) Protocol (20-Jul-2016)
10-NOV-2016	***Version2.0: Description of changes from Version 1.0 are as below*** – ***The table of elimination code has been modified*** – ***Algorithm for handling of data of PCA neutralising antibody concentrations between the LOB and LLOQ was added***	***RSV F-021 (204812) Protocol (20-Jul-2016)***
21-JUL-2017	***Amendment 1: Description of changes from Version 2.0 are as below:*** – ***Use of new template for SAP (Default-APP 9000058193 Statistical Analysis Plan_v1)*** – ***In section 6. Statistical Analyses, immunogenicity was moved before safety*** – ***For the sequence of analysis, IDMC analysis up to at least Day 30 including haematology and biochemistry parameters was newly-added*** – ***The table of elimination code has been modified for more clarity*** – ***In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A/B and concentrations against NEO have been added*** – ***In the analysis of safety section, the percentage of subjects reporting each individual solicited local/general AE during the 7-day follow-up period post vaccination based on maximum intensity per subject has been added*** – ***Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs*** – ***The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL).***	***RSV F-021 (204812) Protocol (20-Jul-2016)***

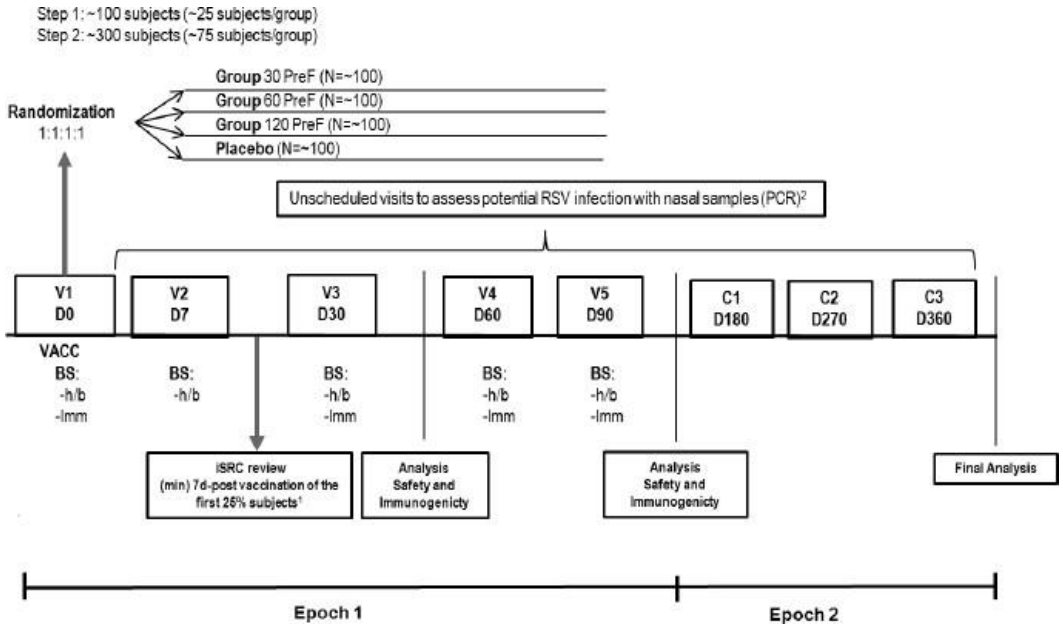
	– ***Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV A by considering the LOB for RSV-B is 6*** – ***Addition of analysis of the IgG total and IgG1 subclass*** – ***Addition of analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available*** – ***Changes of TFL/TOC*** • ***In the analysis of safety section, analysis on 'Individuals results of haematological and biochemical parameters outside of the normal ranges in each group' will be reported*** • ***In the analysis of safety section, the titles in all tables reporting 'incidence and nature of solicited and unsolicited symptoms' have been changed from 'with causal relationship to' to 'considered related to vaccination'*** • ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will also be reported based on maximum intensity per subject for each grade*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects with SAE or SAE considered related to vaccination during the study period' will not be reported*** • ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30/60/90-day post-vaccination period and up to study end' will be reported***	

	• ***In the analysis of medically attended RTIs, analysis on 'viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases' will be only listed in the individual listings*** • ***In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added*** • ***In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added*** • ***In the analysis of immunogenicity section, tables/figures related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added***	
09-NOV-2017	***Amendment 2: Description of changes from Amendment 1 are as below:*** – PPD ***(Clinical Research and Development Lead) was added*** – ***In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added*** – ***In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added*** – ***Changes of TFL/TOC*** • ***In the analysis of safety section, analysis on 'Individual results of hemoglobin levels beyond grade 2' have been added*** • ***In the analysis of safety section, analysis on 'Individual results of white blood cells counts levels lower than LL' and the figures of 'Individual results of white blood cells counts levels higher than UL' have been added***	***RSV F-021 (204812) Protocol Amendment 1 (21-Aug-2017)***

	• ***In the analysis of immunogenicity section, one new template of "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)"has been added*** • ***In the analysis of immunogenicity section, one new template of "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added***	

2. STUDY DESIGN

Figure 1. Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.

1 Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.

2 In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of an event related eCRF and the collection of a nasal swab within 72h after the medical attendance.

Vertical lines stand for analysis on all subjects.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
  - **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
  - Epoch 002: Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Primary Completion Date (PCD)**: Visit 3 (Day 30).
- **End of Study (EoS)**: Last testing results released of samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).
- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30 NaCl	X			
60 µg PreF	PreF-60 NaCl		X		
120 µg PreF	PreF-120 NaCl			X	
Placebo	Formulation buffer S9b				X

- **Control**: Placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.
- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.

The following group and sub-group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	30 PreF	30 µg PreF
2	60 PreF	60 µg PreF
3	120 PreF	120 µg PreF
4	Control	Placebo

Some tables might be presented by age category according to the following description:

Sub-group	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Age	1	18-32Y	18-32 years old subjects
	2	33-45Y	33-45 years old subjects

- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule:**
  - **Blood samples for haematology/biochemistry** will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Blood samples for humoral immune response evaluation** will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and at Visit 5 (Day 90).
  - **Nasal swabs** will be collected from subjects in case of a medically attended respiratory tract infection from enrolment (Visit 1) until study end (Contact 3).
- **Type of study**: self-contained
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring**:
  - When the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) have been vaccinated, enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC). Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' Safety Review Team (SRT) on a regular basis throughout the study. Analyses related to iSRC evaluation will be described in a separate document (SAP/TFL for iSRC).
  - ***When all subjects have been vaccinated, IDMC will review all available safety and reactogenicity data (including haematology/ biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo. The blinded safety data will be reviewed by the GSK Biologicals' SRT. Analyses related to IDMC evaluation will be described in a separate document (SAP/TFL for IDMC).***
- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

3. OBJECTIVES

3.1. Primary Objective

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

3.2. Secondary objectives

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30).
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

3.3. Tertiary objective

- If deemed necessary, to further characterize the immune response of a single intramuscular dose of the RSV investigational vaccines.

Refer to Section 5.7.3 Laboratory assays of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

4. ENDPOINTS

4.1. Primary

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);
  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of any vaccine-related SAE.
- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group

4.2. Secondary

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;
  - Occurrence of any SAE, for all subjects in all groups.
- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day 30) for all subjects in all groups.
  - Antibody concentrations against NEO
- Occurrence of medically attended RSV-associated RTIs up to study conclusion

4.3. Tertiary

See section 5.7.3 of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

5. ANALYSIS SETS

5.1. Definition

In order to align to ICH and CDISC terminology, the Total Vaccinated Cohort (TVC) and the According To Protocol cohort (ATP) have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively. Two cohorts will be defined for the purpose of the analysis: the Exposed Set (ES) and the Per-Protocol Set (PPS) for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

5.1.1. Exposed Set (ES)

The 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 the ES will include all vaccinated subjects for whom immunogenicity data are available.

5.1.2. Per-Protocol Set (PPS) for analysis of immunogenicity

The PPS for immunogenicity will be defined by time point and will include all vaccinated subjects.

- Meeting all eligibility criteria (i.e. no protocol violation linked to the inclusion/ exclusion criteria, including age).
- Who received the study vaccine according to protocol procedures.
- Who did not receive a concomitant vaccination/medication/product leading to exclusion from the PPS analysis up to the corresponding timepoint as described in Section 6.6.2 of the Protocol.
- Who did not present with an intercurrent medical condition leading to exclusion from the PPS analysis up to the corresponding timepoint, as described in Section 6.7 of the Protocol.
- Who complied with the post-vaccination blood sampling schedule at the corresponding timepoint, as specified in Table 5 of the Protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding timepoint.

When presenting different timepoints, the PPS for immunogenicity will be adapted for each timepoint (up to D30 and up to D90).

5.2. 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 sets.

5.2.1. Elimination from Exposed Set (ES)

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

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

5.2.2.1. Excluded subjects

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

Code	*Condition under which the code is used*	*Applicable Eli Type*	
		'M1' (Applicable up to Visit 3 - Day 30)	*'M2' (Applicable up to Visit 5 - Day 90)*
900	*Invalid informed consent or fraud data (Subjects receiving a code 900 should not receive any other elimination codes)*	*Applicable*	*Applicable*
1030	*Study vaccine not administered at all (Subjects receiving a code 1030 should not receive any other elimination codes)*	*Applicable*	*Applicable*
*1040**	*Administration of concomitant vaccine(s) forbidden in the protocol*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
1050	*Randomization failure (subject not randomized in the correct group)*	*Applicable*	*Applicable*
1060	*Randomization code was broken*	*Applicable*	*Applicable*
*1070***	*Subjects got vaccinated with the correct vaccine but containing a lower volume*	*Applicable*	*Applicable*
*1070***	*Administration not according to protocol for reason specified by the investigator other than site and route*	*Applicable*	*Applicable*
*1070***	*Site or route of study vaccine administration wrong or unknown*	*Applicable*	*Applicable*
*1070***	*Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)*	*Applicable*	*Applicable*

1070**	***Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number***	***Applicable***	***Applicable***
1080	***Vaccine temperature deviation***	***Applicable***	***Applicable***
1090	***Expired vaccine administered***	***Applicable***	***Applicable***
2010	***Protocol violation (inclusion/exclusion criteria)***	***Applicable*** ***DOB-VAC=18-45 years***	***Applicable*** ***DOB-VAC=18-45 years***
2040*	***Administration of any medication forbidden by the protocol***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2050*	***Underlying medical condition forbidden by the protocol***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2060*	***Concomitant infection related to the vaccine which may influence the immune response***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2070*	***Concomitant infection not related to the vaccine which may influence the immune response***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2090	***Subjects did not comply with blood sample schedule***	***Applicable*** ***VAC_1 to SER_2 = 30-44 (days)***	***Applicable*** ***VAC_1 to SER_3 = 56-70 (days)*** ***VAC_1 to SER_4 = 86-100 (days)***
2100	***Serological results not available post-vaccination***	***All assay for Day 30*** ***elimination code if ALL are missing*** ***v_ID for Neutra RSV-A=3240.001*** ***v_ID for Neutra RSV-B=3240.002*** ***v_ID for Neutra***	***All assay for Day60 and Day90*** ***elimination code if ALL are missing*** ***v_ID for Neutra RSV-A=3240.001*** ***v_ID for Neutra RSV-B=3240.002*** ***v_ID for Neutra***

		PCA=3241.009 ***v_ID for IgG total=3241.002*** ***v_ID for IgG 1=3241.005***	***PCA=3241.009*** ***v_ID for IgG total=3241.002*** ***v_ID for IgG 1=3241.005***
2120*	***Obvious incoherence or abnormality or error in data******	***All assay for Day 30***	***All assay for Day 60 and Day90***

**** Attribution of these elimcodes to subject need CRDL review of individual data listings***
***** Attribution of code 1070 to a subject requires CRDL confirmation***
****** Elimination criteria for implausible RSV serum immune responses (neut and/or ELISA): More than 4 fold decrease from pre-vaccination to Day 30; After Day 30, more than 4 fold increase or more than 8 fold decrease within a 30 day period***
Eli type is Internal GSK database code for type of elimination code
M1 for Visit 3 (Day30) analysis; M2 for Visit 5 (Day 90) analysis;

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

Manual randomization: In case of the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.

Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Annex 1 and will not be repeated below.

6.1. Demography

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

The analysis of demography will be performed on the ES and on the PPS for immunogenicity.

Demographic characteristics such as age at vaccination in years, race, ethnicity, vital signs and cohort description will be summarised 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 (18 - 32 years and 33 - 45 years).

Withdrawal status will be summarised by group using descriptive statistics:

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

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis will be performed on the applicable PPS cohort for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is ≥5%, a second analysis will be performed on the ES.

6.2.1.1. Within group analysis

Humoral Immune response to RSV vaccine

For each group, at each timepoint that blood samples are collected and for each assay (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI based on log-transformed values and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.

  Percentage of subjects above the seropositivity threshold and GMTs/GMCs will also be tabulated by group for each age category (18 - 32 years and 33 - 45 years).
- Pre- and post-vaccination antibody titres/concentrations will be displayed using reverse cumulative curves.
- The distributions of **neutralising** antibody titres will be tabulated in the tables with log2 scale (< 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 log2).
- Percentage of responders in terms of **neutralising** antibody titres will be tabulated with exact 95% CI.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- ***Distribution of the fold increase of the antibody titres/concentrations will be tabulated:***
  - ***For neutralising antibody titres against RSV-A and RSV-B: percentage of subjects with a fold increase equal to or above 1, 2, 2.5, 3, 4, 6, 8 10, 11 and 12 by pre-vaccination titre category: <7, 7-8,]8-9,]9-10,]10-11,]11-12, >12 log2, and cumulative: <7, ≥7, ≥8, ≥9, ≥10, ≥11, ≥12 log2.***
  - ***For antibody concentrations against NEO: percentage of subjects with a fold increase equal to or above 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5.***
- The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all timepoints.
- An analysis of variance model for repeated measures will be fitted to calculate GMTs/GMCs with treatment group, visit and their interaction as fixed effects if necessary.

If deemed necessary, the same analyses may be done by age category (18 - 32 years and 33 - 45 years).

6.2.1.2. Between group assessment

Exploratory comparisons will be performed for RSV neutralising antibody titres and PCA concentrations post-vaccination (Day 30, Day 60 and Day 90) between the different RSV vaccine groups.

- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment. This model includes:
  - The vaccine group as the fixed effect
  - The pre-vaccination titre/concentration as the covariate
  - Age groups (18-32 years and 33-45 years) and center as the categorical covariate if deemed necessary
- GMT/GMC ratios with corresponding 95% CI will be computed between the RSV vaccine groups
  - PreF-120 *minus* PreF-30
  - PreF-120 *minus* PreF-60
  - PreF-60 *minus* PreF-30

6.2.2. Additional considerations

In order to add the analysis of the <u>anti-RSV F IgG Total and IgG1 subclass</u> tested at Day 0 and Day 30 in a random subset of 50 subjects per group. The following analysis will be performed on the ATP cohort for immunogenicity analysis for each group and for both assays:

- ***GMCs with 95% CI will be tabulated.***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.***
- ***Geometric mean of ratios of antibody concentrations at each post-vaccination timepoint over pre-vaccination (fold increase) will be tabulated with 95% CI, and represented graphically.***
- ***Individual ratios of antibody concentrations will be displayed using reverse cumulative curves.***
- ***Exploratory comparisons between groups: geometric mean ratios and 95% CIs of fold increase post/pre between the RSV groups:***
  - ***120 PreF versus 60 PreF***
  - ***120 PreF versus 30 PreF***
  - ***60 PreF versus 30 PreF***

This will be performed using an ANOVA model on the logarithm10 transformation of the concentrations including the vaccine group as covariates. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment.

In addition, the following immunogenicity analysis will be performed in the subset of subjects with IgG/IgG1data available:

- ***GMCs will be tabulated with 95% CI for anti-RSV A and anti-PCA***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI for anti-RSV A and anti-PCA.***

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

The analysis of safety will be performed on the ES.

6.3.1.1. Within group analysis

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 after vaccination will be tabulated with exact 95% CI. The same computations will be done for ≥ Grade 2 and Grade 3 AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for AEs resulting in medically attended visit.

The percentage of subjects reporting each individual **solicited local AE** (any grade, ≥ Grade 2, Grade 3, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each study vaccine for each group. The percentage of subjects reporting each individual **solicited general AE** (any grade, ≥ Grade 2, Grade 3, any related, ≥ Grade 2 related, Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each group.

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting fever will be reported by half degree (°C) cumulative increments. Similar tabulations will be performed for causally related fever, Grade 3 (> 39.5°C) causally related fever and fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination.

The percentage of subjects with any **unsolicited** symptoms within 30 days after vaccination 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 symptoms, for any causally related unsolicited symptoms, for Grade 3 causally related unsolicited symptoms and for unsolicited symptoms resulting in a medically attended visit (The verbatim reports of unsolicited symptoms 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).

SAEs reported throughout the study will be described in detail.

Pregnancy exposures throughout the study and pregnancy outcomes will be described in detail (if applicable).

The percentage of subjects using **concomitant medication** (any medication, any antipyretic and any antipyretic taken prophylactically) during the 7-day (Day 0 to Day 6) or 30-day (Day 0 to Day 29) follow-up period after vaccination will be summarised by group.

For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated for each timepoint.
- The maximum grading post-vaccination (from Day 7 to Day 90) versus baseline (Day 0) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 will be tabulated (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX D of the Protocol: FDA toxicity grading scale. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

Assessment of anti-NEO immune response at Day 30 post-vaccination for each group:

- GMCs pre-and post-vaccination will be tabulated with 95% CI and represented graphically.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody concentrations at Day 30 over pre-vaccination will be tabulated with 95% CI.
- Distribution of the antibody concentrations pre-and post-vaccination and of fold increase after vaccination will be tabulated.

6.3.1.2. Between group assessment

Exploratory comparisons between each investigational RSV vaccine group and (minus) the control group (*placebo*), and between the RSV vaccine groups will be done in terms of the percentage of subjects reporting any ≥ Grade 2, Grade 3 AE (solicited and unsolicited), and/or any fever > 38.5°C, and/or any vaccine-related SAE during the 7-day follow-up period after vaccination.

- PreF-30 *minus* placebo
- PreF-60 *minus* placebo
- PreF-120 *minus* placebo
- PreF-120 *minus* PreF-30
- PreF-120 *minus* PreF-60
- PreF-60 *minus* PreF-30

The standardised asymptotic 95% CI for the difference between the investigational RSV vaccine groups as well as between the investigational RSV groups and (minus) the control group will be computed.

6.4. Analysis for ranking RSV formulations

The totality of data and sum total of evidence for particular dose(s) in terms of safety and immunogenicity will be evaluated by study team in addition to the analyses described in section 6.1 and 6.3 on formulation selection. The desirability index approach described in the section below will be used as a descriptive tool to guide the formulation selection. In addition, any pertinent information from outside this study will be evaluated and may be used by the study team to help to make the final decision on a dose/formulation.

6.4.1. Definition of desirability in the context of Simulations

A desirability approach will be based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination.

This method is a multi-criteria decision making approach based on desirability functions. The main idea is to identify for each endpoint a desirability function that associates any value to another one between 0 and 1 depending on its desirability (‘0’ being considered as not desirable at all and ‘1’ as the most desirable). An index with values between 0 and 1 will be created for each endpoint. An overall desirability index can be calculated by computing a weighted geometric mean of the endpoint indexes. By definition, this overall index also takes values between 0 and 1 and characterises the level of desirability of any candidate formulation by a single value [Dewé, 2015].

The desirability index calculations will include reactogenicity and safety data up to Day7 post vaccination (on the TVC) and immunogenicity data at 30 days post-vaccination (on the ATP cohort for immunogenicity up to Day 30). The formulations will be ranked based on the values obtained with this overall desirability index.

6.4.2. Derived endpoints

The following endpoints will be computed and taken into account in the desirability analysis:

1. Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
2. Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
3. Geometric mean of neutralising antibody titres against RSV-A at Day 30 adjusted for pre-vaccination titres.
4. Geometric mean of PCA concentrations at Day 30 adjusted for pre-vaccination titres.

Each individual desirability index will be calculated based on data and tabulated by the treatment group and endpoints above. The details on how to calculate individual desirability index in terms of reactogenicity and immunogenicity and overall desirability index are elaborated in Annex 2.

6.5. Analysis of medically attended RTIs

The analysis will be performed on the ES by study group.

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

Viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be listed for any cases where this assay is performed.

Medically attended RSV-associated RTI co-infected or colonisation with another viral etiology identified by multiplex PCR will be described.

Medically attended RTI with any viral etiology identified by multiplex PCR will be described.

The proportion of subjects (with 95% CI) with at least one medically attended RTI (all causes) will be calculated by group.

7. ANALYSIS INTERPRETATION

All comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The statistical analyses will be performed in several steps:

- In preparation of the planned iSRC evaluation, analysis of safety and reactogenicity data up to at least 7 days post-vaccination of the first 25% of all subjects will be performed (see Section 8.10.2 of the Protocol for more information).
- ***In preparation of the planned IDMC evaluation, analysis of safety and reactogenicity data (including haematology/ biochemistry parameters) up to at least 30 days post-vaccination of all enrolled subjects will be performed.***

- The first main analysis on all subjects will be performed when all data up to 30 days post-vaccination are available (primary endpoints). In order to maintain the blind, this analysis by group will be performed by an independent statistician and the results which would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). No individual data listings will be provided.
- A second analysis will be performed when all data up to 90 days post-vaccination are available (secondary endpoints). At this point, the GSK statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided. Given that summary results may unblind some specific subjects, the study will be conducted in a single-blind manner from this point onwards, with subjects remaining blinded up to study conclusion and the investigators will not have access to the treatment allocation up to study conclusion.
- The final analysis will be performed when all data up to study conclusion are available. All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage.
- An integrated study report presenting all analyses will be written and made available to the investigators at the time of final analysis.
- If 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=web posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final Analysis	E1_01	Study report CTRS	N	Yes	All tables from TFL dated 13NOV2017
Analysis of Day 30	E1_04	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017
Analysis of Day 90	E1_05	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017

8.2. Statistical considerations for interim analyses

No interim analysis will be performed.

9. CHANGES FROM PLANNED ANALYSES

In order to align to ICH and CDISC terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

Changes in Amendment 1 mainly include the following.

For the sequence of analysis, the IDMC evaluation was newly added to review all available safety and reactogenicity data (including Day 30 haematology and biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo.

Since the document of criteria for eliminating subjects from analysis will not be used anymore, the table of Elimination codes has been modified for more clarity. Attribution of code 1070 to a subject requires CRDL confirmation. Attribution of these elimcodes including1040, 2040, 2050, 2060, 2070 and 2120 to subject need CRDL review of individual data listings.

In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A and RSV-B and concentrations against NEO have been added.

For the analysis of safety, the percentage of subjects reporting each individual solicited local AE (any, each grade, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be tabulated based on maximum intensity per subject for each study vaccine group; the percentage of subjects reporting each individual solicited general AE (any, each grade, any related, any Grade 2 related, any Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be based on maximum intensity per subject for each study vaccine group.

Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs.

The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). Hence the SAP does not need to define handling of data between the LOD and LLOQ anymore, as results will only be provided as of the LLOQ. It only needs to be defined that for results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.

Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV-A by considering the LOB for RSV-B is 6.

Additional analysis of the IgG total and IgG1 subclass and analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data have been added.

Changes of TFL/TOC

- ***In the analysis of safety section, figures of 'Individuals results of haematological (haemoglobin level, white blood cells and platelet count) and biochemical (ALT, AST and creatinine) parameters outside of the normal ranges in each group' has been added to replace the figures of 'Mean profile of haematological and biochemical parameters change from baseline (Day 0)';***
- ***In the analysis of safety section, the titles in all tables reporting 'Incidence and nature of symptoms (solicited and unsolicited) during the 7-day and 30-day post-vaccination period' have been changed from 'with causal relationship to' to 'considered related to vaccination';***
- ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will be summarized based on maximum intensity for each grade per subject for each group; therefore, analysis on 'incidence of solicited local/general symptoms reported during the 7-day post-vaccination period, including >=grade 2 category' will not be generated.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects with serious adverse events during the study period including number of events reported' and 'Number (%) of subjects with serious adverse events considered related to vaccination during the study period including number of events reported' by %UNSOL (EVENT=1) will not be reported because %CTR_SAE macro has been adapted to generate SAE, related SAE, fatal SAE and related fatal SAE.***
- ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30-day, 60-day or 90-day post-vaccination period and up to study end' will be reported; Therefore, 'Number and percentage of subjects reporting one medically attended RSV-associated RTI and medically attended RTI (all causes) within the 30-day post-vaccination period or throughout the study period' will not be generated;***
- ***In the analysis of medically attended RTIs, viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be only listed in the individual listings; therefore, analysis on 'Descriptive statistics of the viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases (All vaccinated subjects)' will not be reported;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added;***
- ***In the analysis of immunogenicity section, tables related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added.***

Changes in Amendment 2 mainly include the following.

- ***In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added for Day 90 and final analysis.***

Changes of TFL/TOC

- ***In the analysis of safety section, figures of "Individual results of hemoglobin levels beyond grade 2" will be reported for Day 90 and final analysis to replace the figures of "Individual results of hemoglobin levels outside of normal range";***
- ***In the analysis of safety section, figures of "Individual results of white blood cells counts levels lower than LL" and figures of "Individual results of white blood cells counts levels higher than UL" will be reported for Day 90 and final analysis to replace the figures of "Individual results of white blood cells counts levels outside of normal range".***
- ***In the analysis of immunogenicity section, one new template (Template 50) for "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)" has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, one new template (Template 51) for "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added for Day 90 and final analysis;***

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…).

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper:Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

Dewé W, Durand Ch, Marion S *et al*. A multi-criteria decision making approach to identify a vaccine formulation. *Journal of Biopharmaceutical Statistics*, 2015; epublication ahead of print: DOI: 10.1080/10543406.2015.1008517.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day and month are missing, 30 June is used.
- Onset day for an event (ae, medication, vaccination, …): The onset day is the number of days between the last study vaccination & the start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.
- Association of an event to the primary epoch: An adverse event belongs to the primary epoch, if the onset date is before and excluding Visit 5 or the last contact date, whichever is coming first.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose.

11.2.3. Demography

- Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 month when month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

- Conversion of weight to kg

  The following conversation rule is used:

  - Weight in Kilogram = weight in Pounds / 2.2
  - Weight in Kilogram = weight in ounces / 35.2

  The result is rounded to 2 decimals.

  The following conversion rule is used:

  - Weight in Kilogramm= weight in Pounds / 2.2
  - Weight in Kilogramm =weight in oncs / 35.2

  The result is rounded to 2 decimals.

- Conversion of height to cm

  The following conversation rule is used:

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (ie no decimal).

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (ie no decimal).

- Conversion of temperature to °C

  The following conversation rule is used:

  Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The following conversion rule is used:

  - Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

11.2.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- A seronegative subject is a subject whose antibody titre/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre/concentration is greater than or equal to the cut-off value of the assay
- The Geometric Mean Concentrations/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

- In order to compute fold increase of antibody titres/concentrations (ratio) between post-vaccination and pre-vaccination titres/concentrations and for GMC/GMT calculation, antibody titres/concentrations below the assay cut-off will be given an arbitrary value of half the cut-off.
- ***The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). For results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.***
- ***Considering cut-offs or neutralising antibody against RSV-A and RSV-B are below the assays' LLOQ, the following rules will be applied:***

Assay	***Raw result***	***Derivation for seropositivity status***	***Derivation for GMT calculation***	***Derivation for fold-increase between Post and Pre-vaccination titres***
Neutra RSV-A	***<8***	***NEG***	***4***	***LLOQ/2***
	[8-LLOQ[	***POS***	***8***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***
Neutra RSV-B	***<6***	***NEG***	***3***	***LLOQ/2***
	[6-LLOQ[	***POS***	***6***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***

- ***Vaccine response to the RSV neutralising antibodies (anti-RSV-A and anti-RSV-B) will be defined as:***
  - ***At least a 4-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre <7 log2 (<128).***
  - ***At least a 3-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in [7-8] log2 ([128-256]).***
  - ***At least a 2.5-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in >8-10 log2 (>256-1024).***
  - ***At least 1-fold from pre-vaccination if pre-vaccination neutralising antibody titre >10 log2 (>1024).***
- ***All CI computed will be two-sided 95% CI.***

11.2.5. Safety

- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.

- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- The preferred route for recording temperature in this study will be oral. For the analysis, temperatures will be coded as follows:

Grade	Temperature for oral, axillary or tympanic route	Temperature for rectal route
0	< 37.5°C	< 38.0°C
1	≥ 37.5°C - ≤ 38.5°C	≥ 38.0°C - ≤ 39.0°C
2	> 38.5°C - ≤ 39.5°C	> 39.0°C - ≤ 40.0°C
3	> 39.5°C	> 40.0°C

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

The intensity scale of the following solicited AEs will be assessed as described:

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults:

0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

The maximum intensity of fever will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults (via the preferred route for recording temperature in this study which is oral):

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

The investigator assessed the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment was based on the investigator's clinical judgement.

For clintrial.gov and EudraCT posting purposes, 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 name	Lower level term code	Corresponding Primary Term code
Pain	Pain	10033371	10033371
Redness	Erythema	10015150	10015150
Swelling	Swelling	10042674	10042674
Fatigue	Fatigue	10016256	10016256
Fever	Fever	10016558	10037660
Gastroinstestinal symptoms	Gastroinstestinal disorder	10017944	10017944
Headache	Headache	10019211	10019211

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age, SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
Immunogenicity	Ratio of GMT/GMC	2

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3 CALCULATION OF INDIVIDUAL AND OVERALL DESIRABILITY INDEX

The section below provide the details on how to calculate individual desirability index and overall desirability index score based on Annex E in the Protocol.

Reactogenicity

A logistic regression model will be fitted on each reactogenicity endpoint (any Grade 2/3 general AE and any related SAE, Grade 2/3 fever) reported during the 7-day follow-up period after vaccination, including all RSV formulations.

- The vaccine group as the fixed effect
- The age groups (18-32 years and 33-45 years) as the categorical covariant if deemed necessary.

The estimation of indication rate will be tabulated by treatment group. The SAS codes can be used as reference:

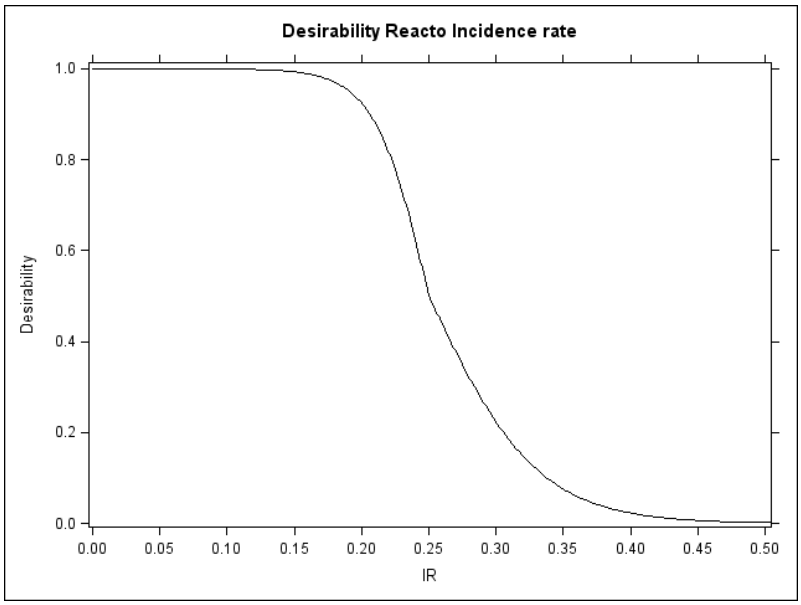
```
proc logistic data=React;
   class Treatment AgeGroup / param=glm;
   model response (event='AE')= Treatment| AgeGroup;
   lsmeans Treatment / ILINK e diff oddsratio adjust=bon cl;
run;
```

For any Grade 2/3 general AEs and any related SAEs, the incidence rate estimate (IR) will be transformed in a [0,1] desirability index using the following function:

$$DR1 = \begin{cases} \dfrac{1}{1+\exp(-50*(0.25-IR))}, & \text{if } IR \le 0.25 \\ \dfrac{1}{1+\exp(-25*(0.25-IR))}, & \text{if } IR \ge 0.25 \end{cases}$$

where IR is the incidence rate estimated by the model. This function will allocate a desirability value of 1, 0.5 and 0 to incidence rate equal to 0.1, 0.25 and 0.5 respectively (see Figure 2). But the calculation equally weights Grade 2/3 general AEs and any related SAEs.

Figure 2 Desirability function for the incidence rate of Grade 2/3 general AEs and related SAEs - for each investigational RSV vaccine formulation

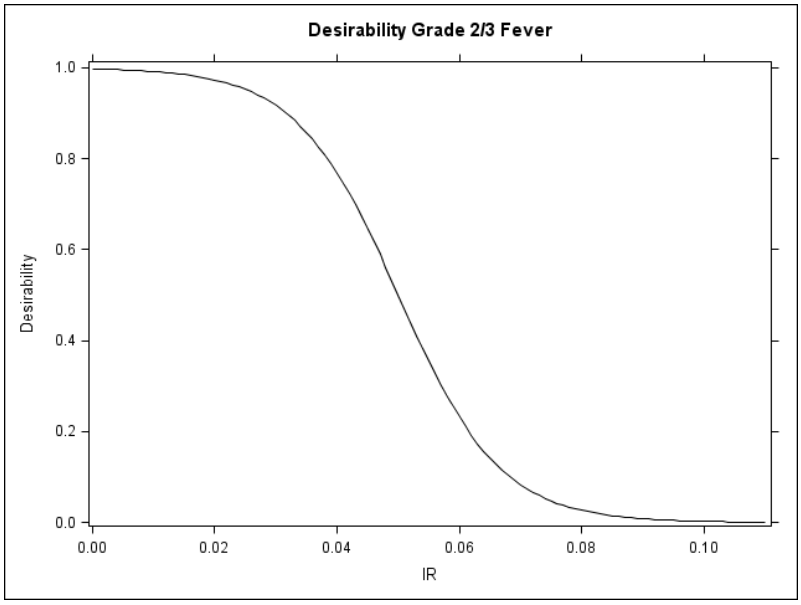


For Grade 2/3 fever, the incidence rate estimate (IR) will be transformed in a [0,1] desirability index using the following function:

$$DR2 = \frac{1}{1+\exp(-120*(0.05-IR))}$$

where IR is the incidence rate estimated by the model. As illustrated in Figure 3, the function will allocate desirability values of 1, 0.5 and 0 to incidence rate equal to 0, 0.05 and 0.1 respectively.

Figure 3 Desirability function for the incidence rate of Grade 2/3 fever - for each investigational RSV vaccine formulation



Finally, the reactogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DR = \sqrt{DR1 * DR2}$$

Immunogenicity

The ANCOVA model will be fitted on the log-transformed titre for each immune response of neutralising anti-RSV-A and PCA separately including

- The vaccine group as the fixed effect
- The pre-vaccination titre/concentration and age groups (18-32 years and 33-45 years) as the covariates if deemed necessary

The mean estimations of GMTs/GMCs for each treatment group at Day 30 and its 95% CI will be provided for immunogenicity desirability calculation. The estimated GMT and LL will be tabulated by treatment group.

As formulations inducing a high immune response will be considered suitable, the lower limit (LL) of the estimated GMT/C adjusted for pre-vaccination titres will be the statistical criterion considered for decision making.

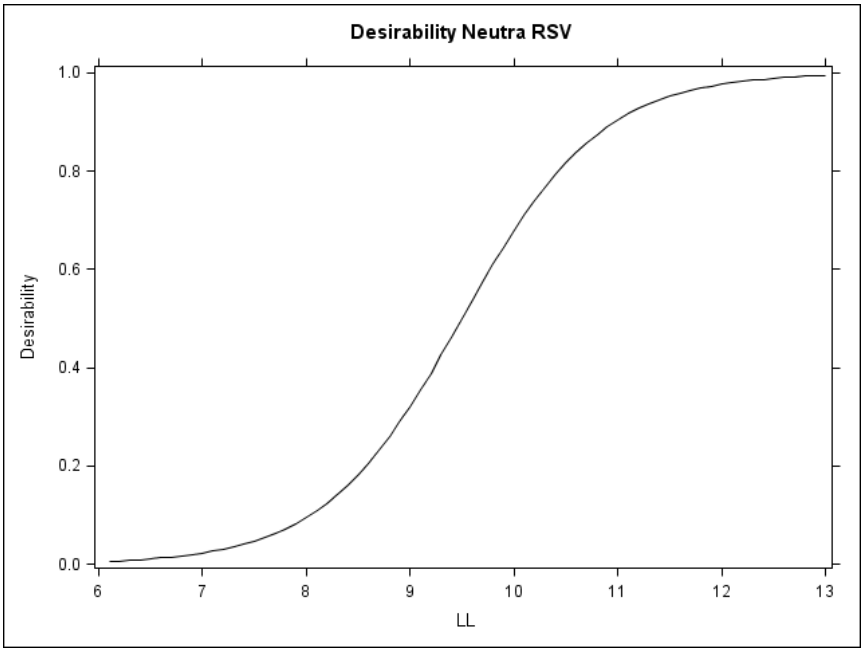
Neutralising anti-RSV-A titres

The LL of the GMT estimate will be transformed into a [0, 1] desirability index using the function:

$$\mathrm{DI1} = \frac{1}{1 + \exp(1.5 * (9.5 - \mathrm{LL}))}$$

where LL is the lower limit of the 95% confidence interval of the GMT adjusted for pre-vaccination titres in log base 2. The function was chosen to have a desirability of 0 at LL value ≤ 6 log2 (=128), and a desirability of 1 at LL value ≥ 13 log2. This function is illustrated in Figure 4.

Figure 4 Desirability function for neutralising anti-RSV-A GMTs - for each investigational RSV vaccine formulation



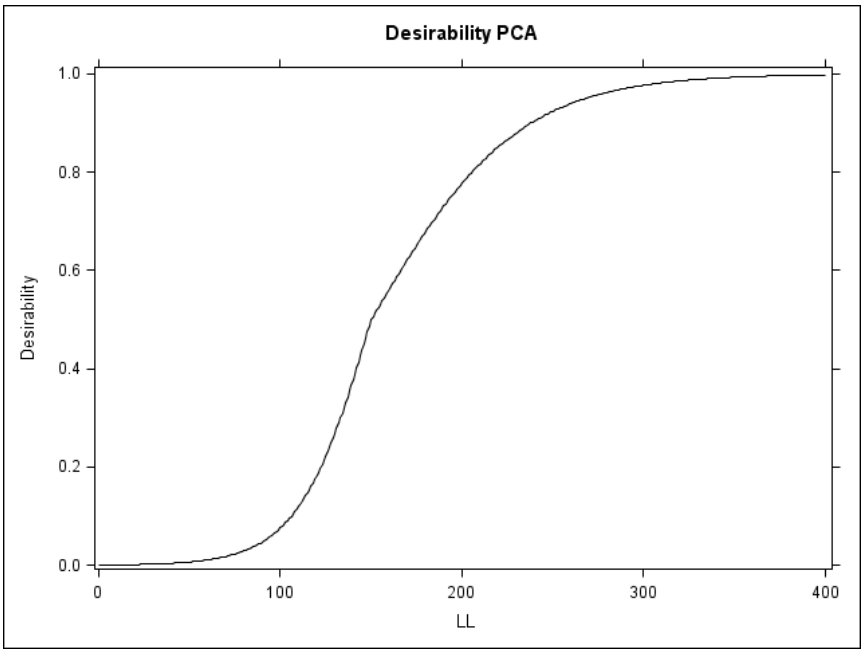
PCA concentrations

The LL of the GMC adjusted for pre-vaccination titres estimate will be transformed using the following function:

$$\mathrm{DI2} = \begin{cases} \dfrac{1}{1 + \exp(0.05 * (150 - \mathrm{LL}))}, & \text{if } \mathrm{LL} \leq 150 \\ \dfrac{1}{1 + \exp(0.025 * (150 - \mathrm{LL}))}, & \text{if } \mathrm{LL} \geq 150 \end{cases}$$

As illustrated in Figure 5, a PCA response of 25, 150 and 400 µg/mL will have a desirability value of 0, 0.5 and 1 respectively.

Figure 5 Desirability function for PCA concentrations - for each investigational RSV vaccine formulation



Finally, the immunogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DI = \sqrt{DI1 * DI2}$$

Overall desirability index

The overall desirability index for each formulation will be obtained by computing the following weighted geometric mean: $D = DR^{0.4} * DI^{0.6}$.

14. ANNEX 4: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used. The data display, title and footnote 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. These editorial/minor changes will not lead to a SAP amendment.

Template #	Table Title	Macro
Template 1	Number of subjects enrolled into the study as well as the number of subject excluded from ATP analysis with reasons for exclusion	%ELIMLIST
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=1)
Template 3	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=0)
Template 4	Number of subjects at each visit and list of withdrawn subjects (Exposed set)	%DROPOUT
Template 5	Summary of demographic characteristics (Exposed set)	%DEMOGRA
Template 6	Summary of demographic characteristics by age category (Exposed set)	%DEMOGRA
Template 7	Number of subjects by center (Exposed set)	%CENTER
Template 8	Number of subjects by center for each age category (Exposed set)	%CENTER
Template 9	Number of subjects by country and center (Exposed set)	%CENTER
Template 10	Deviations from specifications for age and intervals between study visits (Exposed set)	%INT_VAL
Template 11	Summary of vital signs characteristics (Exposed set)	%VITAL_SIGNS
Template 16	Study Population (Exposed set)	%CTR_DEMOG
Template 17	Number of enrolled subjects by country	%FREQ_DIS
Template 23	Number of enrolled subjects by age category	%FREQ_DIS
Template 24	Minimum and maximum activity dates (Exposed set)	%DATE
Template 25	Incidence and nature of symptoms (solicited and unsolicited) reported during the **7-day** (Days 0-6) post-vaccination period (Exposed set)	%LOCGEN
Template 26	Daily prevalence of **any fever** during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%SYMPLOT
Template 27	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ
Template 28	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period by **maximum intensity** (Exposed set)	%FREQ
Template 34	Incidence of solicited **general** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ
Template 35	Incidence of solicited **general** symptoms reported during the 7-	%FREQ

	day (Days 0-6) post-vaccination period **by maximum intensity** (Exposed set)	
Template 36	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **30-day** (Days 0-29) post-vaccination period (Exposed set)	%UNSOL
Template 37	Listing of **SAEs** reported up to study end (Exposed set)	%SAE
Template 38	Number (%) of subjects with serious adverse events up **Day 7** (Exposed set)	%CTR_SAE
Template 40	Compliance in returning symptom information (Exposed set)	% COMPLI
Template 41	Number and percentage of subjects taking a **concomitant medication** during the **7- day** (Days 0-6) post -vaccination period (Exposed set)	%CMED_INC
Template 42	Exploratory comparisons between groups in terms of percentage of subjects reported any **Grade 2/3 AE** and/or **any fever >38.5°C** and/or **any vaccine-related SAE** during the **7 day** (Days 0-6) Post- vaccination period (Exposed set)	%COMP_FQ_AE
Template 43	Solicited and unsolicited symptoms experienced by **at least 5 % of subjects**, classified by MedDRA Primary System Organ Class and Preferred Term within the **30-day** (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)	%UNSOL (NIH=5, EVENT=1)
Template 44	Distribution of change from baseline in **haematology and biochemistry** with respect to normal laboratory ranges (Exposed set)	%HAEMATO_BIOCH
Template 45	Summary of **haematology and biochemistry** results by maximum grade from **VISIT 2 (D7) up to VISIT 3 (D30)** versus baseline (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 46	Summary of **haematology** change from baseline by maximum grade from **VISIT2 (D7) up to VISIT 3 (D30)** (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 32	Individual results of **hemoglobin** levels **outside of the normal ranges** in <*group*> (Exposed set)	%HB_PROFIL
Template 48	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)	%GMT
Template 34	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)	%GMT
Template 35	Geometric mean of the individual ratio of **anti-RSV-A** neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)	%GMRACT
Template 36	GMTs and their 95% CIs for **anti-RSV-A** neutralising antibody at each timepoint (Per protocol set)	%GMTPLOT*
Template 37	Kinetics of GMTs for **anti-RSV-A** neutralising antibody on subjects with results available at all timepoints (Per protocol set)	%KIN_GM*
Template 38	Distribution of **anti-RSV-A** neutralising antibody titer (Per protocol set)	%DIS
Template 39	Distribution of **anti-neogenin** antibody concentration (Exposed set)	%DIS
Template 40	Distribution of fold of **anti-RSV-A** neutralising antibody titer by pre-vaccination titer category (Per protocol set)	%DIS
Template 41	Distribution of fold of anti-neogenin antibody concentration (Exposed set)	%DIS
Template 42	Reverse cumulative distribution curves for **anti-RSV-A**	%REVCUM

	neutralising antibody titers in each group at pre-vaccination (Per protocol set)	
Template 43	Individual results of **anti-RSV-A** neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)	%SCATTERPLOT*
Template 44	Vaccine response for **anti-RSV-A** neutralising antibody titer at each post-vaccination timepoint (Per protocol set)	%HUM_RESP*
Template 45	Estimated GMTs and 95% CIs for **anti-RSV-A** neutralising antibody titre (Per protocol set)	%GMT_ANOVA
Template 46	Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for **anti-RSV A** neutralizing antibody titre at **Day 30** (Per protocol set)	%GMT_RATIO
Template 47	Individual kinetics of **anti-neogenin** antibody concentrations by group (Exposed set)	%NEO_INDKIN*
Template 48	GM of individual ratios (fold increase post over pre) and their 95% CIs for **anti-RSV F IgG1 and IgG total** antibody assays and each group, at **Day 30** (Per protocol set)	%GMRPLOT*
Template 49	Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for **anti-RSV F IgG1** antibody concentrations at **Day 30** (Per protocol set)	%GMF_RATIO*
Template 50	***Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)***	***%GM_RATIO_PRE.SAS****
Template 51	***Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)***	***%GM_RATIO_FI.SAS****
Template 52	Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)	%Immuno_DI**
Template 53	Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%Reacto_DI**
Template 54	Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)	%Overall_DI**

* Name of specific macros created in study RSV F-001 (116969) and RSV F-020 (201510)

***** Name of specific macros newly created in study RSV F-021 (204812)***

Template 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the PPS analyses with reasons for exclusion

	Total			<*each group*>	
Title	**n**	**s**	**%**	**n**	**s**
Total enrolled cohort					
Study vaccine dose not administered at all but subject number allocated (code 1030)					
Exposed set					
<*Reason for elimination & elimination code*>					
<*Reason for elimination & elimination code*>					
Per protocol set for immunogenicity					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered Per protocol set relative to the Exposed set

Template 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<*each group*>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdraw:		
Serious Adverse Event		
Non-serious adverse event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Others		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
withdrawn = number of subjects who did not come for the last study visit

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<each group>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdrawal :		
Serious Adverse Event		
Non-Serious Adverse Event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Sponsor study termination		
Other - <reason>		
Other - <reason>		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last study visit

Template 4 Number of subjects at each visit and list of withdrawn subjects (Exposed set)

Group	Visit	N	Withdrawn Subject number	Reason for withdrawal
<each group>	VISIT 1 (D0)			
	VISIT 2 (D7)			
	VISIT 3 (D30)			
	VISIT 4 (D60)			
	VISIT 5 (D90)			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects who are still in the study up to the visit
Withdrawn = Subject who did not return after the visit

Template 5 Summary of demographic characteristics (Per Protocol Set)

		<each group> (N=)		Total (N=)	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Ethnicity	American Hispanic or Latino				
	Not American Hispanic or Latino				
Geographic Ancestry	African Heritage / African American				
	American Indian or Alaskan Native				
	Asian - Central/South Asian Heritage				
	Asian - East Asian Heritage				
	Asian - Japanese Heritage				
	Asian - South East Asian Heritage				
	Native Hawaiian or Other Pacific Islander				
	White - Arabic / North African Heritage				
	White - Caucasian / European Heritage				
	Other				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 6 Summary of demographic characteristics by age category (Exposed set)

		<each group> **(N=)**				**Total (N=)**			
		<subgroup>		***<subgroup>***		***<subgroup>***		***<subgroup>***	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean								
	SD								
	Median								
	Minimum								
	Maximum								
Ethnicity	American Hispanic or Latino								
	Not American Hispanic or Latino								
Geographic Ancestry	African Heritage / African American								
	American Indian or Alaskan Native								
	Asian - Central/South Asian Heritage								
	Asian - East Asian Heritage								
	Asian - Japanese Heritage								
	Asian - South East Asian Heritage								
	Native Hawaiian or Other Pacific Islander								
	White - Arabic / North African Heritage								
	White - Caucasian / European Heritage								
	Other								

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

<subgroup> by age category:
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects

Template 7 Number of subjects by center (Exposed set)

	<*each group*>	Total	
Center	**n**	**n**	**%**
PPD			
..			
All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 8 Number of subjects by center for each age category (Exposed set)

	30 PreF		60 PreF		120 PreF		Control		Total			
	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y		33-45Y	
Center	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**%**	**n**	**%**

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 9 Number of subjects by country and center (Exposed set)

		<*each group*>	Total	
Country	**Center**	**n**	**n**	**%**
	…			
	All			
	…			
All	All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 10 Deviations from specifications for age and intervals between study visits (Exposed set)

		Age	Dose:1-PI (D30)	Dose:1-PI (D60)	Dose:1-PI (D90)	Dose:1-CONCLUSION
Group		**Protocol**	**Protocol**	**Protocol**	**Protocol**	**Protocol**
		from 18 to 45 years	from 30 to 44 days	from 56 to 70 days	from 86 to 100 days	from 330 to 390 days
<each group>	n					
	N					
	%					
	range					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 11 Summary of vital signs characteristics at VISIT 1 (Day 0) (Exposed set)

		<each group> N =	Total N =
Characteristics	**Parameters**	**Value**	**Value**
Height (Cm)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Weight (Kg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Heart rate (Beats per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Respiratory rate (Breadth per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Systolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Diastolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation

Template 12 Study Population (Exposed set)

Number of subjects	**<each group>**	**Total**
Planned, N		
Randomised, N (Exposed set)		
Completed, n (%)		
Demographics	**<each group>**	**Total**
N (Exposed set)		
Females:Males		
Mean Age, years (SD)		
Median Age, years (minimum, maximum)		
White - caucasian / european heritage, n (%)		
Asian – South East Asian heritage, n (%)		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 13 Number of enrolled subjects by country

		<each group> **N =**	**Total N =**
Characteristics	**Categories**	**n**	**n**
Country	Czech Republic		
	Australia		
	...		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 (18-45 years)		
	Missing		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 dose 1 unknown

Template 15 Minimum and maximum activity dates (Exposed set)

Group	**Activity number**	**Activity Description**	**Minimum date**	**Maximum date**
<each group>	10	VISIT 1 (DAY 0)		
	20	VISIT 2 (M 1)		
	30	VISIT 3 (M 2)		
	40	VISIT 4 (M 3)		

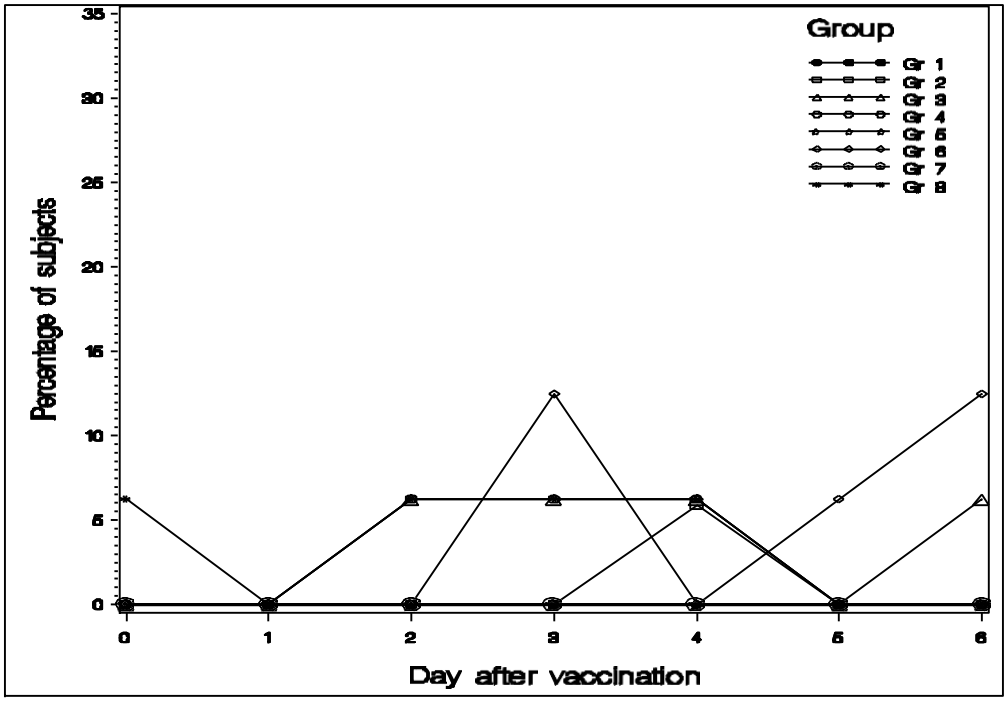
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 16 Incidence and nature of symptoms (solicited and unsolicited reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
<each group>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Note: the same table will be generated by group/sub-group, with sub-group= age category (see SAP).

Template 17 Daily prevalence of any fever during the 7-day (Days 0-6) post-vaccination period (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 18 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: $\leq$ 20 mm
1: > 20 mm to $\leq$ 50 mm
2: > 50 mm to $\leq$ 100 mm
3: > 100 mm

Template 19 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Type=Max grade & onset
All=any severity >Grade 0 for pain and any diameter >20mm for redness and swelling
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

Template 20 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Temperature (Oral) (°C)	All (≥37.5)					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related					
	>38.5 Related					
	>39.5 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:
0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 21 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Fever/(Oral) (°C)	All					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related*					
	>38.5 Related					
	>39.5 Related					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
All=any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral)
Related*= any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral) considered related to vaccination by the investigator
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 22 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Exposed set)

		<*each group*> N =			
				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**
At least one symptom					
<each SOC (code)>	<each PT (code)>				
...	..				
...	...				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 23 Listing of SAEs reported up to study end (Exposed set)

Group	**Sub. No.**	**Sex**	**Country**	**Race**	**Age at onset (Year)**	**Verbatim**	**Preferred term**	**Primary System Organ Class**	**MED type**	**Dose**	**Day of onset**	**Duration**	**Intensity**	**Causality**	**Outcome**
<*each group*>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 24 Number (%) of subjects with serious adverse events up to study end (Exposed set)

			<each group> N =		
Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**n***	**n**	**%**
SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related SAE	At least one symptom				
	<each SOC>	<each PT term>			
Fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 25 Compliance in returning symptom information (Exposed set)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
<each group>						

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 26 Number and percentage of subjects taking a concomitant medication during the 7- day (Days 0-6) post -vaccination period (Exposed set)

	<each group>				
				95% CI	
	N	**n**	**%**	**LL**	**UL**
Any					
Any antipyretics					
Prophylactic antipyretics					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N= number of administered doses
n/%= number/percentage of subjects who took the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 27 Exploratory comparisons between groups in terms of percentage of subjects reported any Grade 2/3 AE and/or any fever >38.5°C and/or any vaccine-related SAE during the 7-day (Days 0-6) post-vaccination period (Exposed set)

								Difference in percentage (Group 1 minus Group 2)			
										95 % CI	
Group 1	**N**	**n**	**%**	**Group 2**	**N**	**n**	**%**	**Difference**	**%**	**LL**	**UL**
30 PreF				Control				30 PreF - Control			
60 PreF				Control				60 PreF - Control			
120 PreF				Control				120 PreF - Control			
60 PreF				30 PreF				60 PreF - 30 PreF			
120 PreF				30 PreF				120 PreF - 30 PreF			
120 PreF				60 PreF				120 PreF - 60 PreF			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with the administered dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 28 Solicited and unsolicited symptoms experienced by at least 5 % of subjects, classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)

		<each group> **N =**		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**
At least one symptom				
<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 29 Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges (Exposed set)

			<each group >								
				Unknown		**Below**		**Within**		**Above**	
Laboratory parameter	**Timing**	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Aspartate Aminotransferase (AST)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Creatinine	…	…									
Eosinophils	…	…									
Haemoglobin	…	…									
Lymphocytes	…	…									
Neutrophils	…	…									
Platelet count	…	…									
White Blood Cells (WBC)	…	…									

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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
PI(D7) = Post-vaccination at Day 7
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 30 Summary of haematology and biochemistry results by maximum grade from VISIT 2 (D7) up to VISIT 3 (D30) versus baseline (Exposed set)

		VISIT2 (D7) up to VISIT5 (D90)												
		<each group >												
			Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT) increase by factor	Unknown													
	Grade 0													
	Grade 1													
	Grade 2													
	Grade 3													
	Grade 4													
	Total													
Aspartate Aminotransferase (AST) increase by factor	…													
Creatinine	…													
Eosinophils increase	…													
Hemoglobin decrease	…													
Lymphocytes decrease	…													
Neutrophils decrease	…													
Platelet count decrease	…													
White Blood Cells (WBC) decrease	…													
White Blood Cells (WBC) increase	…													

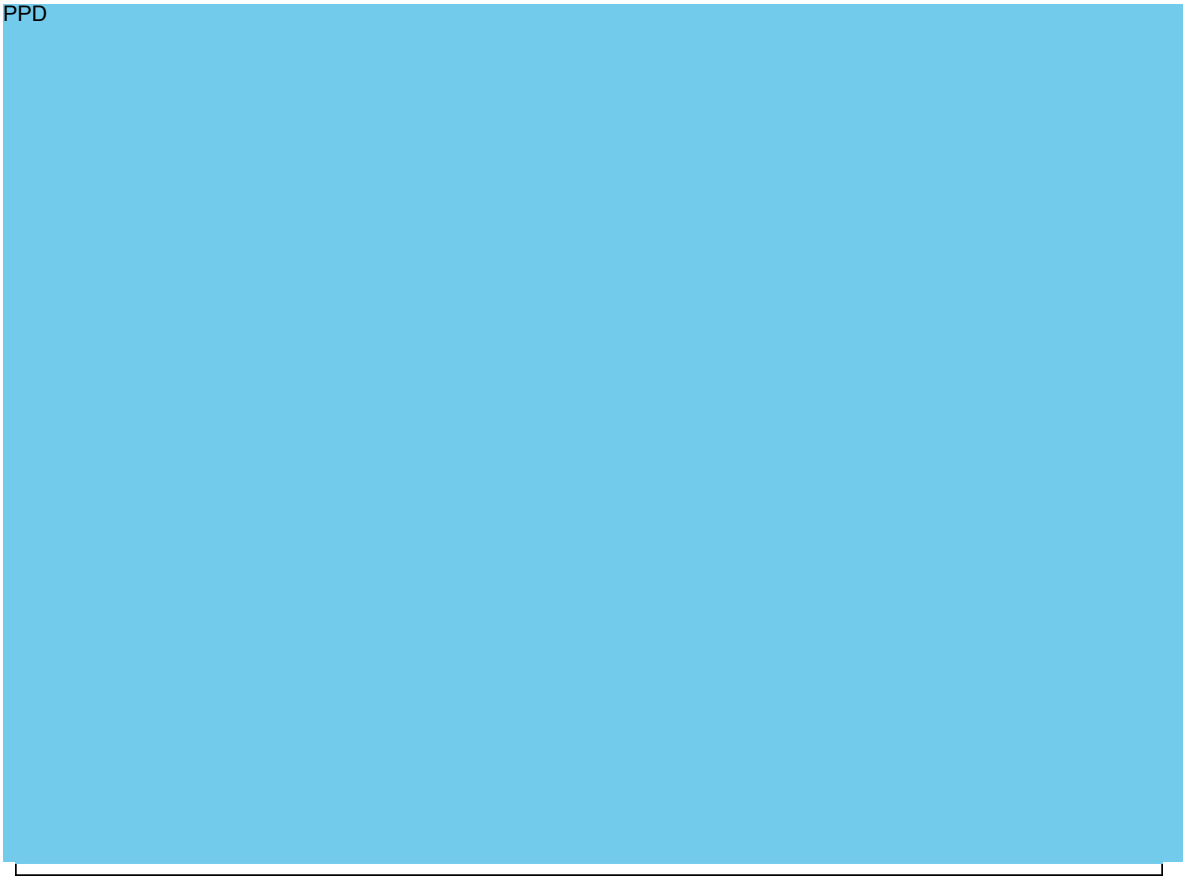
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of patients reporting at least once the laboratory event when the maximum grading over the follow-up period is considered

Template 31 Summary of haematology change from baseline by maximum grade from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)

	VISIT2 (D7) up to VISIT5 (D90)												
	<each group >												
		Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hemoglobin (Change from baseline)													

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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

Template 32 Individual results of hemoglobin levels outside of the normal ranges in < *group*> (Exposed set)



Note: This figure is shown as an example. For the unblinded report, one figure per group will be performed. For the blinded report, 4 graphs will be performed each of them presenting PPD subjects regardless of treatment (the first PPD subjects, from the PP_ th to the PPD th subject…). The X axis will include Day 0, Day 7 and Day 30. The Y axis will be adapted according to each parameter.

Template 33 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)

				≥cut-off				GMT				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE										
		PI(D30)										
		PI(D60)										
		PI(D90)										

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 34 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)

					≥cut-off				GMT				
							95% CI			95% CI			
Antibody	**Group**	**Sub-Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	18-32Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										
		33-45Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										

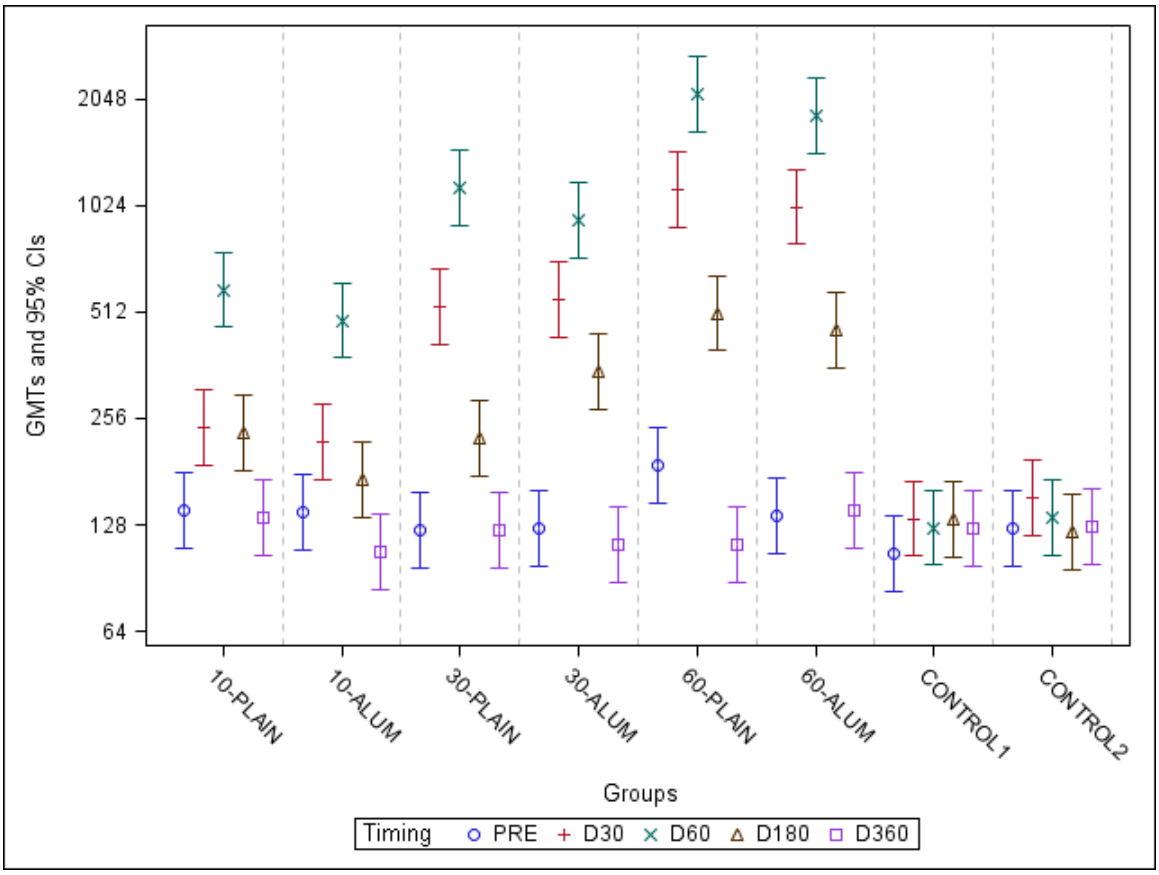
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 35 Geometric mean of the individual ratio of anti-RSV-A neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)

						GMT ratio			
								95% CI	
Group	**N**	**Time point description**	**GMT**	**Time point description**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
<*each group*>		PI(D30)		PRE		PI(D30) / PRE			
		PI(D60)		PRE		PI(D60) / PRE			
		PI(D90)		PRE		PI(D90) / PRE			

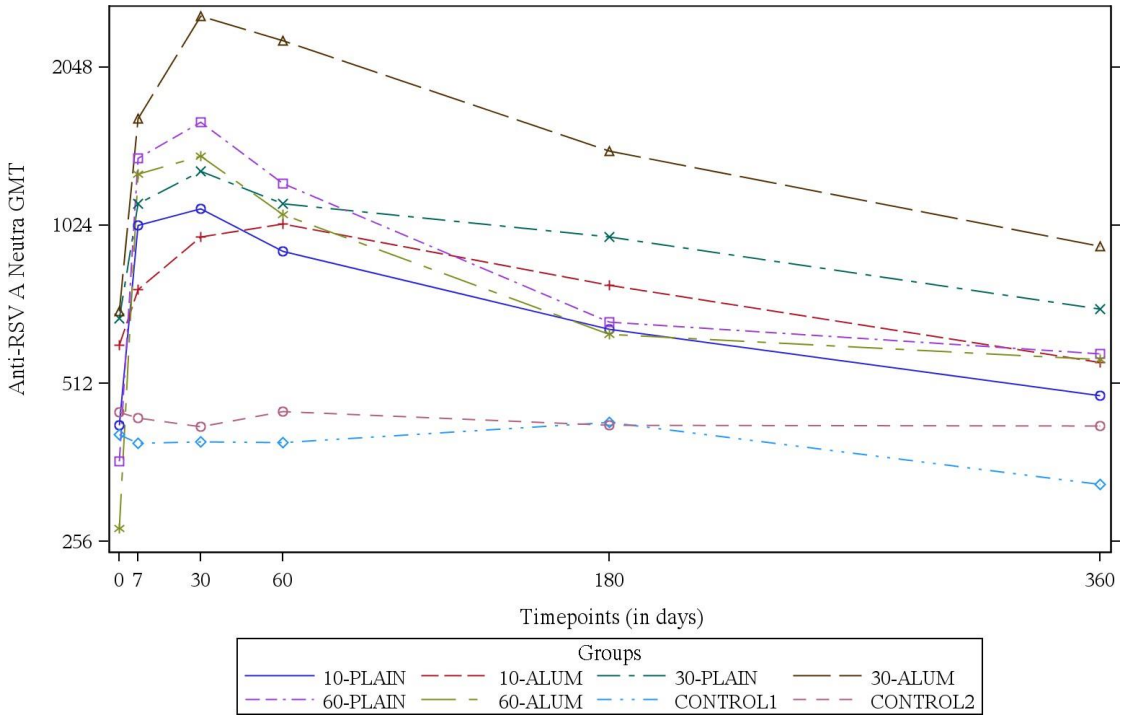
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 36 GMTs and their 95% CIs for anti-RSV-A neutralising antibody at each timepoint (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
95% CI = 95% confidence interval
Note: This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 37 Kinetics of GMTs for anti-RSV-A neutralising antibody on subjects with results available at all timepoints (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on subjects with results available at all timepoints
Note:

- This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints PRE, PI(D30), PI(D60) and PI(D90)
- For the kinetic of the estimated GMTs, footnote will be adapted as: GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures

Template 38 Distribution of anti-RSV-A neutralising antibody titer (Per protocol set)

				<7 Log2		≥7 Log2		≥8 Log2		≥9 Log2		≥10 Log2		≥11 Log2		≥12 Log2	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	*<each group>*	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 39 Distribution of anti-Neogenin antibody concentration (Exposed set)

				<55 ng/ml		≥55 ng/ml		≥100 ng/ml		≥150 ng/ml		≥200 ng/ml		≥250 ng/ml		≥300 ng/ml	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	*<each group>*	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 40 Distribution of fold of anti-RSV-A neutralising antibody titer by pre-vaccination titer category (Per protocol set)

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	30 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	60 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	120 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	Control	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

<each group>:

30 PreF = 30 µg PreF

60 PreF = 60 µg PreF

120 PreF = 120 µg PreF

Control = Placebo

N = number of subjects with available results

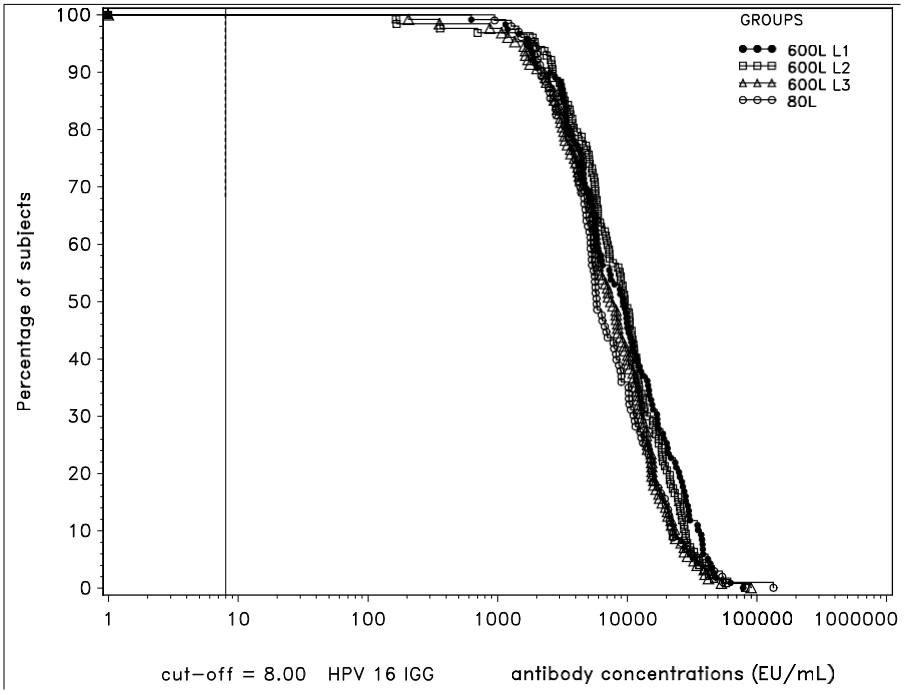
n/% = number/percentage of subjects with titer within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 41 Distribution of fold of anti-neogenin antibody concentration (Exposed set)

				<1		>=1		>=1.5		>=2		>=2.5		>=3		>=3.5		>=4		>=4.5		>=5	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	<*each group*>	PI(D30)																					
		PI(D60)																					
		PI(D90)																					

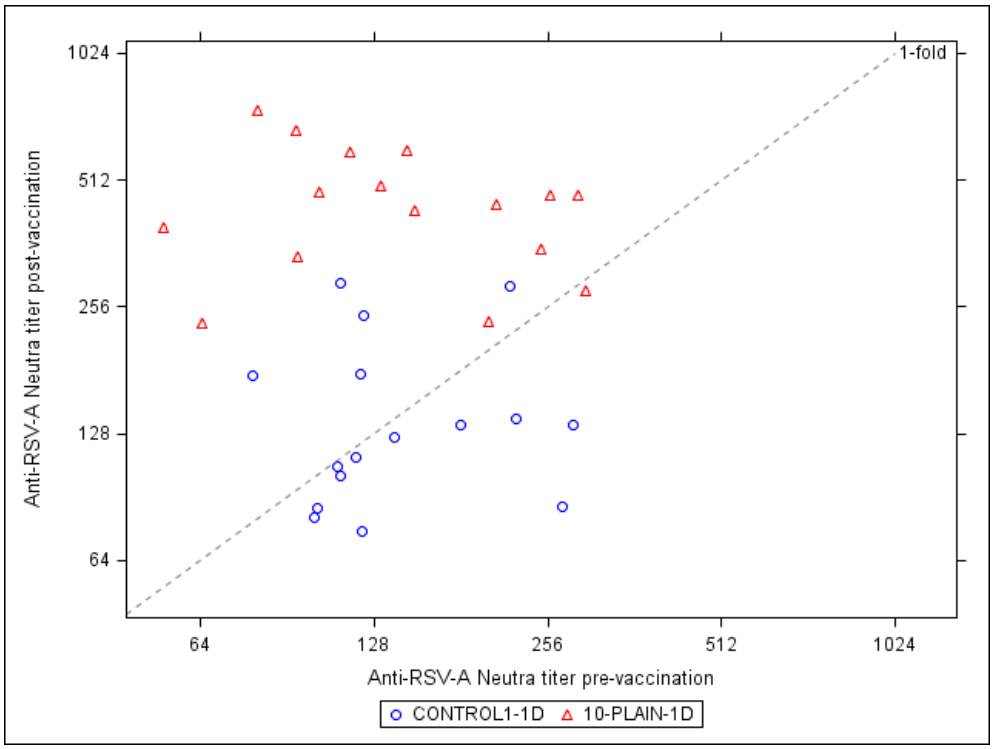
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 42 Reverse cumulative distribution curves for anti-RSV-A neutralising antibody titers in each group at <each time point> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be provided for each time point and each assay comparing the values of the groups:30 PreF, 60 PreF, 120 PreF and Control.

Template 43 Individual results of anti-RSV-A neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)



<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be generated for each assay and each timepoint separately (Day 30, 60, 90):

Template 44 Vaccine response for anti-RSV-A neutralising antibody titer at each post-vaccination timepoint (Per protocol set)

					Vaccine response*			
							95% CI	
Antibody	**Group**	**Post-vaccination timing**	**Pre-vaccination category (log2)**	**N**	**n**	**%**	**LL**	**UL**
<*each antibody*>	<*each group*>	PI(D30)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D60)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D90)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Total = all subjects with pre-vaccination result available
*Vaccine response defined as :
For subjects with pre-vaccination titer <7 log2: antibody titer at post-vaccination>= 4 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in [7-8] log2: antibody titer at post-vaccination >= 3 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in]8-10] log2 : antibody titer at post-vaccination >= 2.5 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer >10 log2: antibody titer at post-vaccination >= 1 fold the pre-vaccination antibody titer
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 45 Estimated GMTs and 95% CIs for anti-RSV-A neutralising antibody titre (Per protocol set)

				Estimated GMT		
					95% CI	
Antibody	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE				
		PI(D30)				
		PI(D60)				
		PI(D90)				

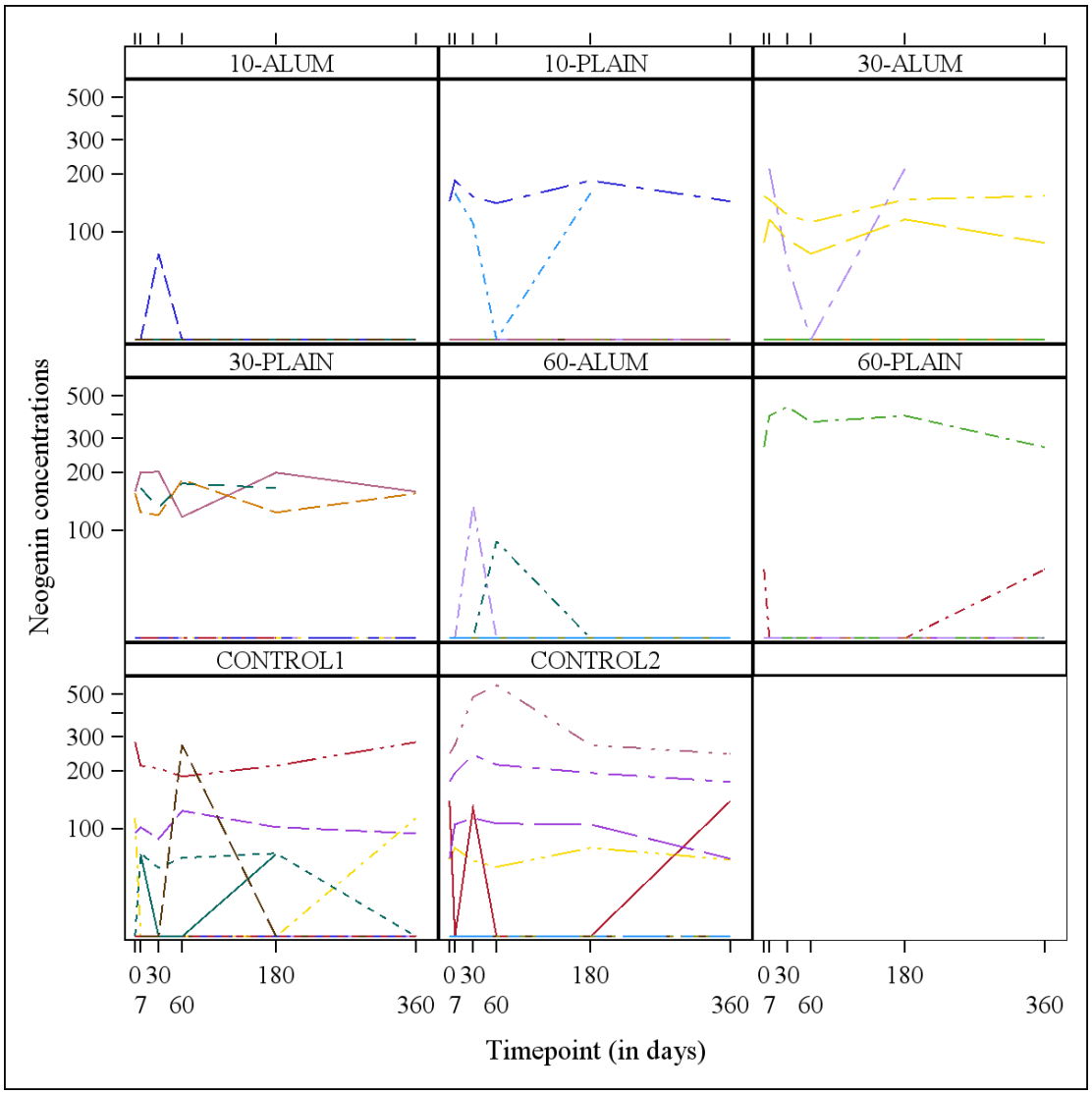
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures
N = Number of subjects with available results
95% CI = 95% confidence interval (ANOVA model); LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 46 Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for anti-RSV A neutralizing antibody titre at Day 30 (Per protocol set)

								GMT ratio			
										Tukey's 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMT**	**Group description**	**N**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
Anti-RSV A Neutralizing Antibody	PI(D30)	120 PreF			30 PreF			120 PreF/30 PreF			
		120 PreF			60 PreF			120 PreF/60 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

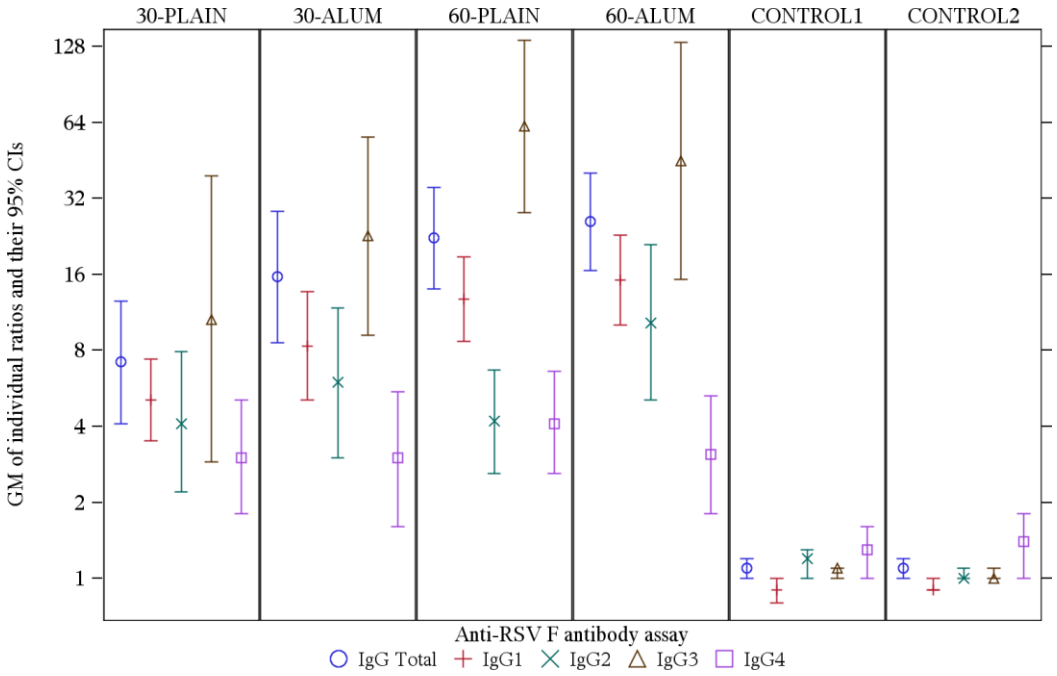
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
antibody titre estimated by the ANCOVA model
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMT ratio (ANCOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANCOVA model is xxxx
PI(D30) = Post-vaccination at Day 30

Template 47 Individual kinetics of anti-neogenin antibody concentrations by group (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. This graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 48 GM of individual ratios (fold increase post over pre) and their 95% CIs for anti-RSV F IgG1 and IgG total antibody assays and each group, at <Day xx> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: this graph is provided as an example. It will be adapted to display IgG total and Ig1 only, and the 4 groups: 30 PreF, 60 PreF, 120 PreF, Control.

Template 49 Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for anti-RSV F antibody concentrations (IgG Total) at Day 30 (Per protocol set)

								GMF ratio			
										Tukey s 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMF**	**Group description**	**N**	**GMF**	**Ratio order**	**Value**	**LL**	**UL**
anti-RSV F antibody (IgG Total)	PI(D30)	120 PreF			60 PreF			120 Pre/60 PreF			
		120 PreF			30 PreF			120 PreF/30 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Antibody concentration estimated by the ANOVA model
GMF = Geometric mean of fold increase
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMF ratio (ANOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANOVA model at PI(D30) is: xxxx
PI(D30) = Post-vaccination at Day 30

Template 50 Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)

									GM ratio		
				95% CI			**95% CI**			*95% CI*	
Timing	***Group description***	***N***	***IgG Total GMC***	***LL***	***UL***	***RSV-A neut GMT***	***LL***	***UL***	***Value***	***LL***	***UL***
PRE(D0)	***<each group>***										
PRE(D0)											
PRE(D0)											
PRE(D0)											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at Day30 and pre-vaccination for IgG Total and RSV-A neut
GMC = Geometric mean antibody concentration calculated on all subjects for IgG Total
GMT = Geometric mean antibody titre calculated on all subjects for RSV-A neut
GM Ratio=Geometric mean of individual ratio of IgG Total to RSV-A neut for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0

Template 51 Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)

									GMF Ratio		
										95% CI	
Timepoint	Group	N	IgG Total GMF	95% CI		RSV-A neut GMF	95%		Value	LL	UL
				LL	UL		LL	UL			
PI(D30)/PRE	<each group>										
PI(D30)/PRE											
PI(D30)/PRE											
PI(D30)/PRE											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at the two considered time points for IgG Total and anti-RSV-A
GMF = Geometric mean of fold increase
GMF Ratio= Geometric mean of individual ratio of fold increase for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30

Template 52 Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)

Group	GMT	LL1	DI1	GMC	LL2	DI2	DI
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = estimated log2-scale GMT adjusted for pre-vaccination titres for neutralising anti-RSV-A
GMC = estimated log10-scale GMC adjusted for pre-vaccination concentrations for PCA
LL1 = estimated log2-scale lower limit adjusted for pre-vaccination titres for neutralising anti-RSV-A
LL2 = estimated log10-scale lower limit adjusted for pre-vaccination concentrations for PCA
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 53 Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)

Group	*Incidence Rate (IR)*	*Incidence Rate (IR2)*	*DR1*	*DR2*	*DR*
<each group>					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µgPreF
120 PreF = 120 µg PreF
Control = Placebo
IR = incidence rate estimated by the model for any Grade 2/3 general AEs and any related SAEs
IR2 = incidence rate estimated by the model for Grade 2/3 fever
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index

Template 54 Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)

Group	*Reactogenicity Index*			*Immunogenicity Index*			*Overall Desirability Index*
	DR1	*DR2*	*DR*	*DI1*	*DI2*	*DI*	$DR^{0.4} * DI^{0.6}$
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 – 45 years.
eTrack study number and Abbreviated	204812 (RSV F-021)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	***Final: Amendment 3 (15-Mar-2018)*** ***Amendment 2 (09-Nov-2017)*** ***Amendment 1 (21-Jul-2017)*** ***Version 2.0 (10-Nov-2016)*** ***Version 1.0 (25-Aug-2016***
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 (Regulatory Affair) PPD (SERM physician) PPD (Public disclosure representative)
Approved by:	PPD ***(Clinical Research and Development Lead)*** PPD (Lead statistician) PPD (Lead stat analyst) PPD (Lead scientific writer)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	According-to-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
eCRF	Electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
MA-RTI	Medically Attended Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
NEO	Neogenin
PCA	Palivizumab Competing Antibodies
PCD	Primary completion Date
PCR	Polymerase Chain Reaction
PPS	Per Protocol Set
PreF	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
RSV	Respiratory syncytial virus

RTI	Respiratory Track Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	(GSK) Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
WBC	White Blood Cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25-AUG-2016	Version1: first version	RSV F-021 (204812) Protocol (20-Jul-2016)
10-NOV-2016	***Version2.0: Description of changes from Version 1.0 are as below*** ***1. The table of elimination code has been modified*** ***2 Algorithm for handling of data of PCA neutralising antibody concentrations between the LOB and LLOQ was added***	***RSV F-021 (204812) Protocol (20-Jul-2016)***
21-JUL-2017	***Amendment 1: Description of changes from Version 2.0 are as below:*** ***- Use of new template for SAP (Default-APP 9000058193 Statistical Analysis Plan_v1)*** ***- In section 6. Statistical Analyses, immunogenicity was moved before safety*** ***- For the sequence of analysis, IDMC analysis up to at least Day 30 including haematology and biochemistry parameters was newly-added*** ***- The table of elimination code has been modified for more clarity*** ***- In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A/B and concentrations against NEO have been added*** ***- In the analysis of safety section, the percentage of subjects reporting each individual solicited local/general AE during the 7-day follow-up period post vaccination based on maximum intensity per subject has been added*** ***- Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs*** ***- The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL).***	***RSV F-021 (204812) Protocol (20-Jul-2016)***

	- ***Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV A by considering the LOB for RSV-B is 6*** - ***Addition of analysis of the IgG total and IgG1 subclass*** - ***Addition of analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available*** - ***Changes of TFL/TOC*** • ***In the analysis of safety section, analysis on 'Individuals results of haematological and biochemical parameters outside of the normal ranges in each group' will be reported*** • ***In the analysis of safety section, the titles in all tables reporting 'incidence and nature of solicited and unsolicited symptoms' have been changed from 'with causal relationship to' to 'considered related to vaccination'*** • ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will also be reported based on maximum intensity per subject for each grade*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects with SAE or SAE considered related to vaccination during the study period' will not be reported*** • ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30/60/90-day post-vaccination period and up to study end' will be reported***	

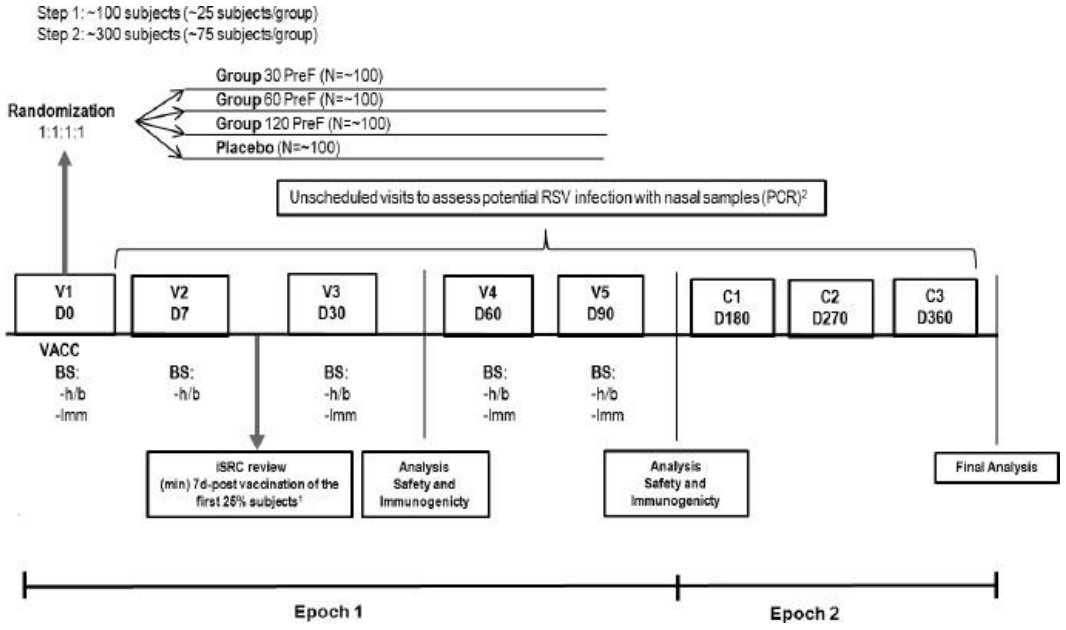
	• *In the analysis of medically attended RTIs, analysis on 'viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases' will be only listed in the individual listings* • *In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added* • *In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added* • *In the analysis of immunogenicity section, tables/figures related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added*	
09-NOV-2017	*Amendment 2: Description of changes from Amendment 1 are as below:* - PPD *(Clinical Research and Development Lead) was added* - *In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added* - *In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added* - *Changes of TFL/TOC* • *In the analysis of safety section, analysis on 'Individual results of hemoglobin levels beyond grade 2' have been added* • *In the analysis of safety section, analysis on 'Individual results of white blood cells counts levels lower than LL' and the figures of 'Individual results of white blood cells counts levels higher than UL' have been added*	*RSV F-021 (204812) Protocol Amendment 1 (21-Aug-2017)*

	• ***In the analysis of immunogenicity section, one new template of "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)"has been added*** • ***In the analysis of immunogenicity section, one new template of "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added***	

15-Mar-2018	***Amendment 3: Description of changes from Amendment 2 are as below:*** ***For final analysis,*** – ***Some tables have been updated including removing to Annex, creating new corresponding in-text table by deleting or collapsing some columns/rows;*** – ***Two figures of 'percentage of subjects reporting solicited local/general symptoms (any grade / grade 3) during the 7-day post-vaccination period' have been newly generated for the final analysis, respectively;*** – ***The table of 'Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges' has been splitted and modified into three in-text tables for Alanine Aminotransferase (ALT)/ Aspartate Aminotransferase (AST)/Eosinophils, Creatinine/Lymphocytes/ White Blood Cells (WBC), Haemoglobin/platelet count/Neutrophils, separately;*** – ***Two new in-text tables of 'Summary of haematology and biochemistry results by maximum grade in the specified category' and 'Summary of haematology change from baseline by maximum grade in the specified category' have been generated;*** – ***Some figures of Individual results for each parameter have been modified.***	***RSV F-021 (204812) Protocol Amendment 1 (21-Aug-2017)***

2. STUDY DESIGN

Figure 1. Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.

1 Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.

2 In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of an event related eCRF and the collection of a nasal swab within 72h after the medical attendance.

Vertical lines stand for analysis on all subjects.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
  - **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
  - Epoch 002: Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Primary Completion Date (PCD)**: Visit 3 (Day 30).
- **End of Study (EoS)**: Last testing results released of samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).
- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30 NaCl	X			
60 µg PreF	PreF-60 NaCl		X		
120 µg PreF	PreF-120 NaCl			X	
Placebo	Formulation buffer S9b				X

- **Control**: Placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.
- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.

The following group and sub-group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	30 PreF	30 µg PreF
2	60 PreF	60 µg PreF
3	120 PreF	120 µg PreF
4	Control	Placebo

Some tables might be presented by age category according to the following description:

Sub-group	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Age	1	18-32Y	18-32 years old subjects
	2	33-45Y	33-45 years old subjects

- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule:**
  - **Blood samples for haematology/biochemistry** will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Blood samples for humoral immune response evaluation** will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and at Visit 5 (Day 90).
  - **Nasal swabs** will be collected from subjects in case of a medically attended respiratory tract infection from enrolment (Visit 1) until study end (Contact 3).
- **Type of study**: self-contained
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring**:
  - When the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) have been vaccinated, enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC). Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' Safety Review Team (SRT) on a regular basis throughout the study. Analyses related to iSRC evaluation will be described in a separate document (SAP/TFL for iSRC).
  - ***When all subjects have been vaccinated, IDMC will review all available safety and reactogenicity data (including haematology/ biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo. The blinded safety data will be reviewed by the GSK Biologicals' SRT. Analyses related to IDMC evaluation will be described in a separate document (SAP/TFL for IDMC).***
- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

3. OBJECTIVES

3.1. Primary Objective

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

3.2. Secondary objectives

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30).
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

3.3. Tertiary objective

- If deemed necessary, to further characterize the immune response of a single intramuscular dose of the RSV investigational vaccines.

Refer to Section 5.7.3 Laboratory assays of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

4. ENDPOINTS

4.1. Primary

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);
  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of any vaccine-related SAE.
- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group

4.2. Secondary

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;
  - Occurrence of any SAE, for all subjects in all groups.
- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day 30) for all subjects in all groups.
  - Antibody concentrations against NEO
- Occurrence of medically attended RSV-associated RTIs up to study conclusion

4.3. Tertiary

See section 5.7.3 of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

5. ANALYSIS SETS

5.1. Definition

In order to align to ICH and CDISC terminology, the Total Vaccinated Cohort (TVC) and the According To Protocol cohort (ATP) have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively. Two cohorts will be defined for the purpose of the analysis: the Exposed Set (ES) and the Per-Protocol Set (PPS) for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

5.1.1. Exposed Set (ES)

The 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 the ES will include all vaccinated subjects for whom immunogenicity data are available.

5.1.2. Per-Protocol Set (PPS) for analysis of immunogenicity

The PPS for immunogenicity will be defined by time point and will include all vaccinated subjects.

- Meeting all eligibility criteria (i.e. no protocol violation linked to the inclusion/ exclusion criteria, including age).
- Who received the study vaccine according to protocol procedures.
- Who did not receive a concomitant vaccination/medication/product leading to exclusion from the PPS analysis up to the corresponding timepoint as described in Section 6.6.2 of the Protocol.
- Who did not present with an intercurrent medical condition leading to exclusion from the PPS analysis up to the corresponding timepoint, as described in Section 6.7 of the Protocol.
- Who complied with the post-vaccination blood sampling schedule at the corresponding timepoint, as specified in Table 5 of the Protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding timepoint.

When presenting different timepoints, the PPS for immunogenicity will be adapted for each timepoint (up to D30 and up to D90).

5.2. 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 sets.

5.2.1. Elimination from Exposed Set (ES)

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

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

5.2.2.1. Excluded subjects

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

Code	*Condition under which the code is used*	*Applicable Eli Type*	
		'M1' (Applicable up to Visit 3 - Day 30)	*'M2' (Applicable up to Visit 5 - Day 90)*
900	*Invalid informed consent or fraud data (Subjects receiving a code 900 should not receive any other elimination codes)*	*Applicable*	*Applicable*
1030	*Study vaccine not administered at all (Subjects receiving a code 1030 should not receive any other elimination codes)*	*Applicable*	*Applicable*
*1040**	*Administration of concomitant vaccine(s) forbidden in the protocol*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
1050	*Randomization failure (subject not randomized in the correct group)*	*Applicable*	*Applicable*
1060	*Randomization code was broken*	*Applicable*	*Applicable*
*1070***	*Subjects got vaccinated with the correct vaccine but containing a lower volume*	*Applicable*	*Applicable*
*1070***	*Administration not according to protocol for reason specified by the investigator other than site and route*	*Applicable*	*Applicable*
*1070***	*Site or route of study vaccine administration wrong or unknown*	*Applicable*	*Applicable*
*1070***	*Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)*	*Applicable*	*Applicable*

1070**	***Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number***	***Applicable***	***Applicable***
1080	***Vaccine temperature deviation***	***Applicable***	***Applicable***
1090	***Expired vaccine administered***	***Applicable***	***Applicable***
2010	***Protocol violation (inclusion/exclusion criteria)***	***Applicable*** ***DOB-VAC=18-45 years***	***Applicable*** ***DOB-VAC=18-45 years***
2040*	***Administration of any medication forbidden by the protocol***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2050*	***Underlying medical condition forbidden by the protocol***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2060*	***Concomitant infection related to the vaccine which may influence the immune response***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2070*	***Concomitant infection not related to the vaccine which may influence the immune response***	***Applicable (To check up to Visit 3 – Day 30)***	***Applicable (To check up to Visit 5 – Day 90)***
2090	***Subjects did not comply with blood sample schedule***	***Applicable*** ***VAC_1 to SER_2 = 30-44 (days)***	***Applicable*** ***VAC_1 to SER_3 = 56-70 (days)*** ***VAC_1 to SER_4 = 86-100 (days)***
2100	***Serological results not available post-vaccination***	***All assay for Day 30*** ***elimination code if ALL are missing*** ***v_ID for Neutra RSV-A=3240.001*** ***v_ID for Neutra RSV-B=3240.002*** ***v_ID for Neutra***	***All assay for Day60 and Day90*** ***elimination code if ALL are missing*** ***v_ID for Neutra RSV-A=3240.001*** ***v_ID for Neutra RSV-B=3240.002*** ***v_ID for Neutra***

		PCA=3241.009 ***v_ID for IgG total=3241.002*** ***v_ID for IgG 1=3241.005***	***PCA=3241.009*** ***v_ID for IgG total=3241.002*** ***v_ID for IgG 1=3241.005***
2120*	***Obvious incoherence or abnormality or error in data******	***All assay for Day 30***	***All assay for Day 60 and Day90***

**** Attribution of these elimcodes to subject need CRDL review of individual data listings***
***** Attribution of code 1070 to a subject requires CRDL confirmation***
****** Elimination criteria for implausible RSV serum immune responses (neut and/or ELISA): More than 4 fold decrease from pre-vaccination to Day 30; After Day 30, more than 4 fold increase or more than 8 fold decrease within a 30 day period***
Eli type is Internal GSK database code for type of elimination code
M1 for Visit 3 (Day30) analysis; M2 for Visit 5 (Day 90) analysis;

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

Manual randomization: In case of the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.

Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Annex 1 and will not be repeated below.

6.1. Demography

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

The analysis of demography will be performed on the ES and on the PPS for immunogenicity.

Demographic characteristics such as age at vaccination in years, race, ethnicity, vital signs and cohort description will be summarised 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 (18 - 32 years and 33 - 45 years).

Withdrawal status will be summarised by group using descriptive statistics:

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

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis will be performed on the applicable PPS cohort for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is ≥5%, a second analysis will be performed on the ES.

6.2.1.1. Within group analysis

Humoral Immune response to RSV vaccine

For each group, at each timepoint that blood samples are collected and for each assay (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI based on log-transformed values and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.

  Percentage of subjects above the seropositivity threshold and GMTs/GMCs will also be tabulated by group for each age category (18 - 32 years and 33 - 45 years).
- Pre- and post-vaccination antibody titres/concentrations will be displayed using reverse cumulative curves.
- The distributions of **neutralising** antibody titres will be tabulated in the tables with log2 scale (< 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 log2).
- Percentage of responders in terms of **neutralising** antibody titres will be tabulated with exact 95% CI.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- ***Distribution of the fold increase of the antibody titres/concentrations will be tabulated:***
  - ***For neutralising antibody titres against RSV-A and RSV-B: percentage of subjects with a fold increase equal to or above 1, 2, 2.5, 3, 4, 6, 8 10, 11 and 12 by pre-vaccination titre category: <7, 7-8,]8-9,]9-10,]10-11,]11-12, >12 log2, and cumulative: <7, ≥7, ≥8, ≥9, ≥10, ≥11, ≥12 log2.***
  - ***For antibody concentrations against NEO: percentage of subjects with a fold increase equal to or above 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5.***
- The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all timepoints.
- An analysis of variance model for repeated measures will be fitted to calculate GMTs/GMCs with treatment group, visit and their interaction as fixed effects if necessary.

If deemed necessary, the same analyses may be done by age category (18 - 32 years and 33 - 45 years).

6.2.1.2. Between group assessment

Exploratory comparisons will be performed for RSV neutralising antibody titres and PCA concentrations post-vaccination (Day 30, Day 60 and Day 90) between the different RSV vaccine groups.

- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment. This model includes:
  - The vaccine group as the fixed effect
  - The pre-vaccination titre/concentration as the covariate
  - Age groups (18-32 years and 33-45 years) and center as the categorical covariate if deemed necessary
- GMT/GMC ratios with corresponding 95% CI will be computed between the RSV vaccine groups
  - PreF-120 *minus* PreF-30
  - PreF-120 *minus* PreF-60
  - PreF-60 *minus* PreF-30

6.2.2. Additional considerations

In order to add the analysis of the anti-RSV F IgG Total and IgG1 subclass tested at Day 0 and Day 30 in a random subset of 50 subjects per group. The following analysis will be performed on the Per-Protocol Set (PPS) for analysis of immunogenicity for each group and for both assays:

- ***GMCs with 95% CI will be tabulated.***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.***
- ***Geometric mean of ratios of antibody concentrations at each post-vaccination timepoint over pre-vaccination (fold increase) will be tabulated with 95% CI, and represented graphically.***
- ***Individual ratios of antibody concentrations will be displayed using reverse cumulative curves.***
- ***Exploratory comparisons between groups: geometric mean ratios and 95% CIs of fold increase post/pre between the RSV groups:***
  - ***120 PreF versus 60 PreF***
  - ***120 PreF versus 30 PreF***
  - ***60 PreF versus 30 PreF***

This will be performed using an ANOVA model on the logarithm10 transformation of the concentrations including the vaccine group as covariates. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment.

In addition, the following immunogenicity analysis will be performed in the subset of subjects with IgG/IgG1data available:

- ***GMCs will be tabulated with 95% CI for anti-RSV A and anti-PCA***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI for anti-RSV A and anti-PCA.***

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

The analysis of safety will be performed on the ES.

6.3.1.1. Within group analysis

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 after vaccination will be tabulated with exact 95% CI. The same computations will be done for ≥ Grade 2 and Grade 3 AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for AEs resulting in medically attended visit.

The percentage of subjects reporting each individual **solicited local AE** (any grade, ≥ Grade 2, Grade 3, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each study vaccine for each group. The percentage of subjects reporting each individual **solicited general AE** (any grade, ≥ Grade 2, Grade 3, any related, ≥ Grade 2 related, Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each group.

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting fever will be reported by half degree (°C) cumulative increments. Similar tabulations will be performed for causally related fever, Grade 3 (> 39.5°C) causally related fever and fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination.

The percentage of subjects with any **unsolicited** symptoms within 30 days after vaccination 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 symptoms, for any causally related unsolicited symptoms, for Grade 3 causally related unsolicited symptoms and for unsolicited symptoms resulting in a medically attended visit (The verbatim reports of unsolicited symptoms 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).

SAEs reported throughout the study will be described in detail.

Pregnancy exposures throughout the study and pregnancy outcomes will be described in detail (if applicable).

The percentage of subjects using **concomitant medication** (any medication, any antipyretic and any antipyretic taken prophylactically) during the 7-day (Day 0 to Day 6) or 30-day (Day 0 to Day 29) follow-up period after vaccination will be summarised by group.

For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated for each timepoint.
- The maximum grading post-vaccination (from Day 7 to Day 90) versus baseline (Day 0) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 will be tabulated (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX D of the Protocol: FDA toxicity grading scale. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

Assessment of anti-NEO immune response at Day 30 post-vaccination for each group:

- GMCs pre-and post-vaccination will be tabulated with 95% CI and represented graphically.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody concentrations at Day 30 over pre-vaccination will be tabulated with 95% CI.
- Distribution of the antibody concentrations pre-and post-vaccination and of fold increase after vaccination will be tabulated.

6.3.1.2. Between group assessment

Exploratory comparisons between each investigational RSV vaccine group and (minus) the control group (*placebo*), and between the RSV vaccine groups will be done in terms of the percentage of subjects reporting any ≥ Grade 2, Grade 3 AE (solicited and unsolicited), and/or any fever > 38.5°C, and/or any vaccine-related SAE during the 7-day follow-up period after vaccination.

- PreF-30 *minus* placebo
- PreF-60 *minus* placebo
- PreF-120 *minus* placebo
- PreF-120 *minus* PreF-30
- PreF-120 *minus* PreF-60
- PreF-60 *minus* PreF-30

The standardised asymptotic 95% CI for the difference between the investigational RSV vaccine groups as well as between the investigational RSV groups and (minus) the control group will be computed.

6.4. Analysis for ranking RSV formulations

The totality of data and sum total of evidence for particular dose(s) in terms of safety and immunogenicity will be evaluated by study team in addition to the analyses described in section 6.1 and 6.3 on formulation selection. The desirability index approach described in the section below will be used as a descriptive tool to guide the formulation selection. In addition, any pertinent information from outside this study will be evaluated and may be used by the study team to help to make the final decision on a dose/formulation.

6.4.1. Definition of desirability in the context of Simulations

A desirability approach will be based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination.

This method is a multi-criteria decision making approach based on desirability functions. The main idea is to identify for each endpoint a desirability function that associates any value to another one between 0 and 1 depending on its desirability (‘0’ being considered as not desirable at all and ‘1’ as the most desirable). An index with values between 0 and 1 will be created for each endpoint. An overall desirability index can be calculated by computing a weighted geometric mean of the endpoint indexes. By definition, this overall index also takes values between 0 and 1 and characterises the level of desirability of any candidate formulation by a single value [Dewé, 2015].

The desirability index calculations will include reactogenicity and safety data up to Day 7 post vaccination (on the TVC) and immunogenicity data at 30 days post-vaccination (on the ATP cohort for immunogenicity up to Day 30). The formulations will be ranked based on the values obtained with this overall desirability index.

6.4.2. Derived endpoints

The following endpoints will be computed and taken into account in the desirability analysis:

1. Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
2. Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
3. Geometric mean of neutralising antibody titres against RSV-A at Day 30 adjusted for pre-vaccination titres.
4. Geometric mean of PCA concentrations at Day 30 adjusted for pre-vaccination titres.

Each individual desirability index will be calculated based on data and tabulated by the treatment group and endpoints above. The details on how to calculate individual desirability index in terms of reactogenicity and immunogenicity and overall desirability index are elaborated in Annex 2.

6.5. Analysis of medically attended RTIs

The analysis will be performed on the ES by study group.

The proportion of subjects (with 95% CI) with at least one medically attended RTI (all causes) will be calculated by group.

Viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be listed for any cases where this assay is performed.

Medically attended RSV-associated RTI co-infected or colonisation with another viral etiology identified by multiplex PCR will be described.

Medically attended RTI with any viral etiology identified by multiplex PCR will be described.

7. ANALYSIS INTERPRETATION

All comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The statistical analyses will be performed in several steps:

- In preparation of the planned iSRC evaluation, analysis of safety and reactogenicity data up to at least 7 days post-vaccination of the first 25% of all subjects will be performed (see Section 8.10.2 of the Protocol for more information).
- ***In preparation of the planned IDMC evaluation, analysis of safety and reactogenicity data (including haematology/ biochemistry parameters) up to at least 30 days post-vaccination of all enrolled subjects will be performed.***

- The first main analysis on all subjects will be performed when all data up to 30 days post-vaccination are available (primary endpoints). In order to maintain the blind, this analysis by group will be performed by an independent statistician and the results which would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). No individual data listings will be provided.
- A second analysis will be performed when all data up to 90 days post-vaccination are available (secondary endpoints). At this point, the GSK statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided. Given that summary results may unblind some specific subjects, the study will be conducted in a single-blind manner from this point onwards, with subjects remaining blinded up to study conclusion and the investigators will not have access to the treatment allocation up to study conclusion.
- The final analysis will be performed when all data up to study conclusion are available. All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage.
- An integrated study report presenting all analyses will be written and made available to the investigators at the time of final analysis.
- If 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=web posting, SR=study report, internal)**	**Dry run review needed (Y/N)**	***Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)**	**Reference for TFL**
Final Analysis	E1_01	Study report CTRS	N	Yes	All tables from TFL dated 15MAR2018
Analysis of Day 30	E1_04	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017
Analysis of Day 90	E1_05	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017

8.2. Statistical considerations for interim analyses

No interim analysis will be performed.

9. CHANGES FROM PLANNED ANALYSES

In order to align to ICH and CDISC terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

Changes in Amendment 1 mainly include the following.

For the sequence of analysis, the IDMC evaluation was newly added to review all available safety and reactogenicity data (including Day 30 haematology and biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo.

Since the document of criteria for eliminating subjects from analysis will not be used anymore, the table of Elimination codes has been modified for more clarity. Attribution of code 1070 to a subject requires CRDL confirmation. Attribution of these elimcodes including1040, 2040, 2050, 2060, 2070 and 2120 to subject need CRDL review of individual data listings.

In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A and RSV-B and concentrations against NEO have been added.

For the analysis of safety, the percentage of subjects reporting each individual solicited local AE (any, each grade, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be tabulated based on maximum intensity per subject for each study vaccine group; the percentage of subjects reporting each individual solicited general AE (any, each grade, any related, any Grade 2 related, any Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be based on maximum intensity per subject for each study vaccine group.

Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs.

The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). Hence the SAP does not need to define handling of data between the LOD and LLOQ anymore, as results will only be provided as of the LLOQ. It only needs to be defined that for results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.

Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV-A by considering the LOB for RSV-B is 6.

Additional analysis of the IgG total and IgG1 subclass and analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data have been added.

Changes of TFL/TOC

- ***In the analysis of safety section, figures of 'Individuals results of haematological (haemoglobin level, white blood cells and platelet count) and biochemical (ALT, AST and creatinine) parameters outside of the normal ranges in each group' has been added to replace the figures of 'Mean profile of haematological and biochemical parameters change from baseline (Day 0)';***
- ***In the analysis of safety section, the titles in all tables reporting 'Incidence and nature of symptoms (solicited and unsolicited) during the 7-day and 30-day post-vaccination period' have been changed from 'with causal relationship to' to 'considered related to vaccination';***
- ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will be summarized based on maximum intensity for each grade per subject for each group; therefore, analysis on 'incidence of solicited local/general symptoms reported during the 7-day post-vaccination period, including >=grade 2 category' will not be generated.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects with serious adverse events during the study period including number of events reported' and 'Number (%) of subjects with serious adverse events considered related to vaccination during the study period including number of events reported' by %UNSOL (EVENT=1) will not be reported because %CTR_SAE macro has been adapted to generate SAE, related SAE, fatal SAE and related fatal SAE.***
- ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30-day, 60-day or 90-day post-vaccination period and up to study end' will be reported; Therefore, 'Number and percentage of subjects reporting one medically attended RSV-associated RTI and medically attended RTI (all causes) within the 30-day post-vaccination period or throughout the study period' will not be generated;***
- ***In the analysis of medically attended RTIs, viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be only listed in the individual listings; therefore, analysis on 'Descriptive statistics of the viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases (All vaccinated subjects)' will not be reported;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added;***
- ***In the analysis of immunogenicity section, tables related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added.***

Changes in Amendment 2 mainly include the following.

- ***In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added for Day 90 and final analysis.***

Changes of TFL/TOC

- ***In the analysis of safety section, figures of "Individual results of hemoglobin levels beyond grade 2" will be reported for Day 90 and final analysis to replace the figures of "Individual results of hemoglobin levels outside of normal range";***
- ***In the analysis of safety section, figures of "Individual results of white blood cells counts levels lower than LL" and figures of "Individual results of white blood cells counts levels higher than UL" will be reported for Day 90 and final analysis to replace the figures of "Individual results of white blood cells counts levels outside of normal range".***
- ***In the analysis of immunogenicity section, one new template (Template 54) for "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)" has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, one new template (Template 55) for "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added for Day 90 and final analysis;***

Changes in Amendment 3 mainly include the following.

Changes of TFL/TOC for final analysis

- ***All tables concerned with 'Incidence and nature of symptoms (solicited and unsolicited)' have been moved to Annex; such tables for Grade 3 are kept as in-text tables;***
- ***Tables of 'Incidence of solicited local/general symptoms reported during the 7-day (Days 0-6) post-vaccination period' have been moved to Annex; such tables by maximum intensity are kept as in-text tables and corresponding figures have been newly generated for the final analysis, that is, 'Percentage of subjects reporting solicited local/general symptoms (any grade / grade 3) during the 7-day post-vaccination period';***
- ***All tables concerned with 'Percentage of subjects reporting the occurrence of unsolicited symptoms' have been moved to Annex; Such tables for Grade 3 and/or considered related to vaccination are kept as in-text tables with the simplification by removing the columns of LL and UL;***

- ***Tables of 'Percentage of subjects reporting the occurrence of SAE within the 30-day (Days 0-29) post-vaccination period/throughout the study period' are kept as in-text tables with the simplification by removing the columns of LL and UL;***
- ***All tables concerned with 'Number (%) of subjects reporting the occurrence of adverse events' have been moved to Annex;***
- ***All tables of 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs)' have been moved to Annex; MA-RTIs reported up to DBF of final analysis is kept as one in-text table with the simplification by removing the columns of LL and UL;***
- ***The table of 'Compliance in returning symptom information' and all tables concerned with 'Number and percentage of subjects taking a concomitant medication' have been moved to Annex;***
- ***The table of 'Exploratory comparisons between groups in terms of percentage of subjects reported any Grade 2/3 AE and/or any fever >38.5°C and/or any vaccine-related SAE during the 7 day (Days 0-6) Post- vaccination period' will not be reported in the final analysis;***
- ***The table of 'Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges' has been moved to Annex; Three splitted in-text tables for ALT/AST /Eosinophils, Creatinine/Lymphocytes/White Blood Cells and Haemoglobin/ platelet count/ Neutrophils have been generated, separately;***
- ***The table of 'Summary of haematology and biochemistry results by maximum grade' has been moved to Annex; One newly formatted in-text table of 'Summary of haematology and biochemistry results by maximum grade in the specified category' has been generated by collapsing the categories of unknown/grade 0 and grade 1 then renaming the new category of 'other', keeping grade 2, 3 and 4 column, and removing the column of n;***
- ***The table of 'Summary of haematology change from baseline by maximum grade' has been moved to Annex; One newly formatted in-text table of 'Summary of haematology change from baseline by maximum grade in the specified category' has been generated by collapsing the categories of unknown/grade 0 and grade 1 then renaming the new category of 'other', keeping grade 2, 3 and 4 column, and removing the column of n;***

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…).

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper:Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

Dewé W, Durand Ch, Marion S *et al*. A multi-criteria decision making approach to identify a vaccine formulation. *Journal of Biopharmaceutical Statistics*, 2015; epublication ahead of print: DOI: 10.1080/10543406.2015.1008517.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day and month are missing, 30 June is used.
- Onset day for an event (ae, medication, vaccination, …): The onset day is the number of days between the last study vaccination & the start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.
- Association of an event to the primary epoch: An adverse event belongs to the primary epoch, if the onset date is before and excluding Visit 5 or the last contact date, whichever is coming first.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins

on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose.

11.2.3. Demography

- Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 month when month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.
- Conversion of weight to kg

  The following conversation rule is used:

  - Weight in Kilogram = weight in Pounds / 2.2
  - Weight in Kilogram = weight in ounces / 35.2

  The result is rounded to 2 decimals.

- Conversion of height to cm

  The following conversation rule is used:

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (ie no decimal).

- Conversion of temperature to °C

  The following conversion rule is used:

  - Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

11.2.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- A seronegative subject is a subject whose antibody titre/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre/concentration is greater than or equal to the cut-off value of the assay
- The Geometric Mean Concentrations/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

- In order to compute fold increase of antibody titres/concentrations (ratio) between post-vaccination and pre-vaccination titres/concentrations and for GMC/GMT calculation, antibody titres/concentrations below the assay cut-off will be given an arbitrary value of half the cut-off.
- ***The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). For results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.***
- ***Considering cut-offs or neutralising antibody against RSV-A and RSV-B are below the assays' LLOQ, the following rules will be applied:***

Assay	***Raw result***	***Derivation for seropositivity status***	***Derivation for GMT calculation***	***Derivation for fold-increase between Post and Pre-vaccination titres***
Neutra RSV-A	***<8***	***NEG***	***4***	***LLOQ/2***
	[8-LLOQ[	***POS***	***8***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***
Neutra RSV-B	***<6***	***NEG***	***3***	***LLOQ/2***
	[6-LLOQ[	***POS***	***6***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***

- ***Vaccine response to the RSV neutralising antibodies (anti-RSV-A and anti-RSV-B) will be defined as:***
  - ***At least a 4-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre <7 log2 (<128).***
  - ***At least a 3-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in [7-8] log2 ([128-256]).***
  - ***At least a 2.5-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in >8-10 log2 (>256-1024).***
  - ***At least 1-fold from pre-vaccination if pre-vaccination neutralising antibody titre >10 log2 (>1024).***
- ***All CI computed will be two-sided 95% CI.***

11.2.5. Safety

- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.

- Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
- Doses without symptom sheets documented will be excluded.

- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- The preferred route for recording temperature in this study will be oral. For the analysis, temperatures will be coded as follows:

Grade	Temperature for oral, axillary or tympanic route	Temperature for rectal route
0	< 37.5°C	< 38.0°C
1	≥ 37.5°C - ≤ 38.5°C	≥ 38.0°C - ≤ 39.0°C
2	> 38.5°C - ≤ 39.5°C	> 39.0°C - ≤ 40.0°C
3	> 39.5°C	> 40.0°C

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

The intensity scale of the following solicited AEs will be assessed as described:

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults:

0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

The maximum intensity of fever will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults (via the preferred route for recording temperature in this study which is oral):

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

The investigator assessed the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment was based on the investigator's clinical judgement.

For clintrial.gov and EudraCT posting purposes, 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 name	Lower level term code	Corresponding Primary Term code
Pain	Pain	10033371	10033371
Redness	Erythema	10015150	10015150
Swelling	Swelling	10042674	10042674
Fatigue	Fatigue	10016256	10016256
Fever	Fever	10016558	10037660
Gastroinstestinal symptoms	Gastroinstestinal disorder	10017944	10017944
Headache	Headache	10019211	10019211

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age, SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
Immunogenicity	Ratio of GMT/GMC	2

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3 CALCULATION OF INDIVIDUAL AND OVERALL DESIRABILITY INDEX

The section below provide the details on how to calculate individual desirability index and overall desirability index score based on Annex E in the Protocol.

Reactogenicity

A logistic regression model will be fitted on each reactogenicity endpoint (any Grade 2/3 general AE and any related SAE, Grade 2/3 fever) reported during the 7-day follow-up period after vaccination, including all RSV formulations.

- The vaccine group as the fixed effect
- The age groups (18-32 years and 33-45 years) as the categorical covariant if deemed necessary.

The estimation of indication rate will be tabulated by treatment group. The SAS codes can be used as reference:

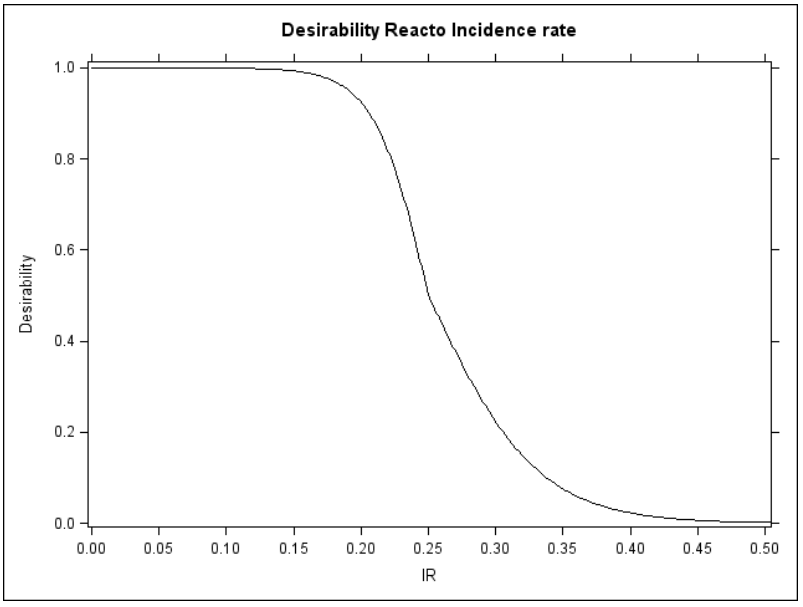
```
proc logistic data=React;
   class Treatment AgeGroup / param=glm;
   model response (event='AE')= Treatment| AgeGroup;
   lsmeans Treatment / ILINK e diff oddsratio adjust=bon cl;
run;
```

For any Grade 2/3 general AEs and any related SAEs, the incidence rate estimate ($\hat{I}R$) will be transformed in a [0,1] desirability index using the following function:

$$DR1 = \begin{cases} \dfrac{1}{1+\exp\left(-50 * \left(0.25 - \hat{I}R\right)\right)}, & if\ \hat{I}R \leq 0.25 \\ \dfrac{1}{1+\exp\left(-25 * 0.25 - \hat{I}R\right)}, & if\ \hat{I}R \geq 0.25 \end{cases}$$

where $\hat{I}R$ is the incidence rate estimated by the model. This function will allocate a desirability value of 1, 0.5 and 0 to incidence rate equal to 0.1, 0.25 and 0.5 respectively (see Figure 2). But the calculation equally weights Grade 2/3 general AEs and any related SAEs.

Figure 2 Desirability function for the incidence rate of Grade 2/3 general AEs and related SAEs - for each investigational RSV vaccine formulation

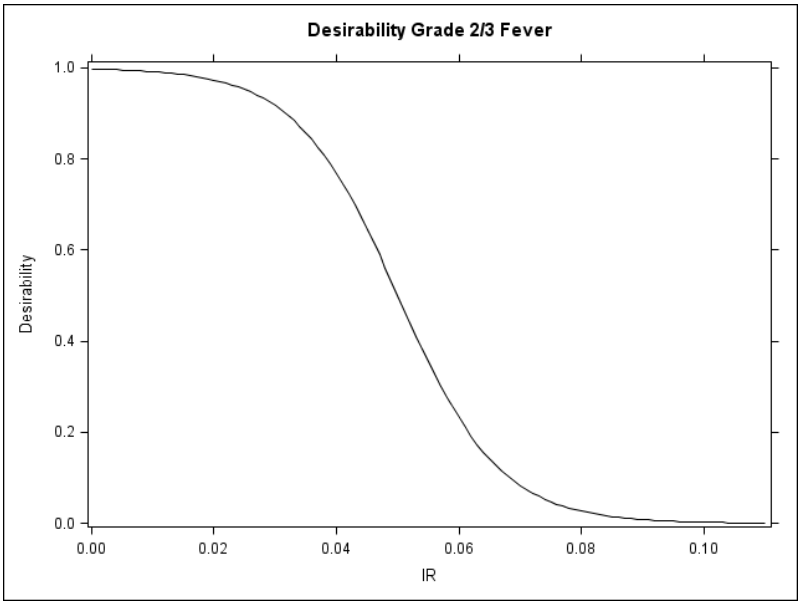


For Grade 2/3 fever, the incidence rate estimate ($\hat{I}R$) will be transformed in a [0,1] desirability index using the following function:

$$DR2 = \frac{1}{1+\exp(-120 * (0.05 - \hat{R}))}$$

where IR is the incidence rate estimated by the model. As illustrated in Figure 3, the function will allocate desirability values of 1, 0.5 and 0 to incidence rate equal to 0, 0.05 and 0.1 respectively.

Figure 3 Desirability function for the incidence rate of Grade 2/3 fever - for each investigational RSV vaccine formulation



Finally, the reactogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DR = \sqrt{DR1 * DR2}$$

Immunogenicity

The ANCOVA model will be fitted on the log-transformed titre for each immune response of neutralising anti-RSV-A and PCA separately including

- The vaccine group as the fixed effect
- The pre-vaccination titre/concentration and age groups (18-32 years and 33-45 years) as the covariates if deemed necessary

The mean estimations of GMTs/GMCs for each treatment group at Day 30 and its 95% CI will be provided for immunogenicity desirability calculation. The estimated GMT and LL will be tabulated by treatment group.

As formulations inducing a high immune response will be considered suitable, the lower limit (LL) of the estimated GMT/C adjusted for pre-vaccination titres will be the statistical criterion considered for decision making.

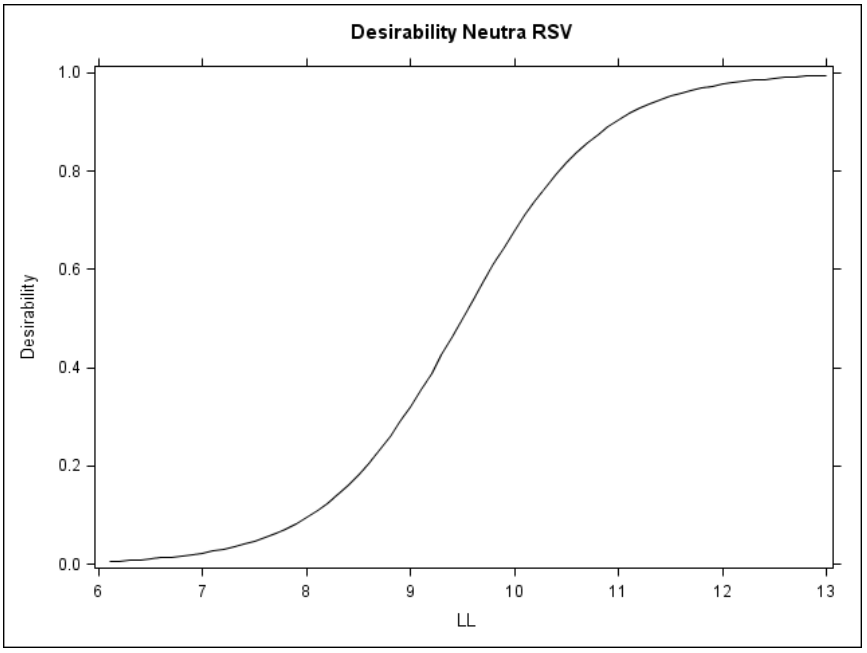
Neutralising anti-RSV-A titres

The LL of the GMT estimate will be transformed into a [0, 1] desirability index using the function:

$$DI1 = \frac{1}{1 + \exp(1.5 * (9.5 - LL))}$$

where LL is the lower limit of the 95% confidence interval of the GMT adjusted for pre-vaccination titres in log base 2. The function was chosen to have a desirability of 0 at LL value ≤ 6 log2 (=128), and a desirability of 1 at LL value ≥ 13 log2. This function is illustrated in Figure 4.

Figure 4 Desirability function for neutralising anti-RSV-A GMTs - for each investigational RSV vaccine formulation



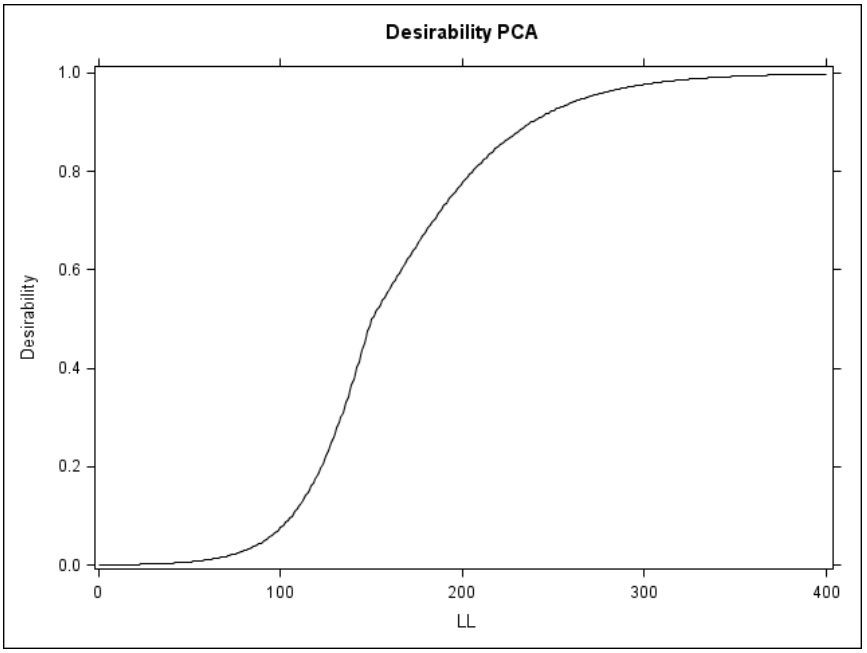
PCA concentrations

The LL of the GMC adjusted for pre-vaccination titres estimate will be transformed using the following function:

$$DI2 = \begin{cases} \frac{1}{1 + \exp 0.05 * 150 - LL}, & if\ LL \leq 150 \\ \frac{1}{1 + \exp 0.025 * 150 - LL}, & if\ LL \geq 150 \end{cases}$$

As illustrated in Figure 5, a PCA response of 25, 150 and 400 µg/mL will have a desirability value of 0, 0.5 and 1 respectively.

Figure 5 Desirability function for PCA concentrations - for each investigational RSV vaccine formulation



Finally, the immunogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DI = \overline{DI1 * DI2}$$

Overall desirability index

The overall desirability index for each formulation will be obtained by computing the following weighted geometric mean: $D = DR^{0.4} * DI^{0.6}$.

14. ANNEX 4: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used. The data display, title and footnote 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. These editorial/minor changes will not lead to a SAP amendment.

Template #	Table Title	Macro
Template 1	Number of subjects enrolled into the study as well as the number of subject excluded from PPS analysis with reasons for exclusion	%ELIMLIST
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=1)
Template 3	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=0)
Template 4	Number of subjects at each visit and list of withdrawn subjects (Exposed set)	%DROPOUT
Template 5	Summary of demographic characteristics (Exposed set)	%DEMOGRA
Template 6	Summary of demographic characteristics by age category (Exposed set)	%DEMOGRA
Template 7	Number of subjects by center (Exposed set)	%CENTER
Template 8	Number of subjects by center for each age category (Exposed set)	%CENTER
Template 9	Number of subjects by country and center (Exposed set)	%CENTER
Template 10	Deviations from specifications for age and intervals between study visits (Exposed set)	%INT_VAL
Template 11	Summary of vital signs characteristics (Exposed set)	%VITAL_SIGNS
Template 16	Study Population (Exposed set)	%CTR_DEMOG
Template 17	Number of enrolled subjects by country	%FREQ_DIS
Error! Not a valid result for table.	Number of enrolled subjects by age category	%FREQ_DIS
Error! Not a valid result for table.	Minimum and maximum activity dates (Exposed set)	%DATE
Template 26	Incidence and nature of symptoms (solicited and unsolicited) reported during the **7-day** (Days 0-6) post-vaccination period (Exposed set)	%LOCGEN
Template 27	Daily prevalence of **any fever** during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%SYMPLOT
Template 28	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ
Template 29	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period by **maximum intensity** (Exposed set)	%FREQ
Template 37	Incidence of solicited **general** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ

Template 38	Incidence of solicited **general** symptoms reported during the 7-day (Days 0-6) post-vaccination period **by maximum intensity** (Exposed set)	%FREQ
Template 39	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the **30-day** (Days 0-29) post-vaccination period (Exposed set)	%UNSOL
Template 39 ***	***Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the 30-day (Days 0-29) post-vaccination period (Exposed set)***	***%UNSOL***
Template 40	Listing of **SAEs** reported up to study end (Exposed set)	%SAE
Template 41 Distribution of anti-Neogenin antibody concentration (Exposed set) **Antibody** Anti-neogenin antibody ***<each group>:*** 30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo N = number of subjects with available results n/% = number/percentage of subjects with concentration within the specified range PRE = Pre-vaccination at	Number (%) of subjects with serious adverse events up **Day 7** (Exposed set)	%CTR_SAE

Day 0 PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 **Template**		

		< 1	>= 1	>= 1.5	>= 2	>= 2.5	>= 3
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ne t i - n e o g e n n antibody | l *a*(*c* *h*3 0 *g*) *r* *o* *u* *p* i | I (60) | I (90) ***<each group>:*** 30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo N = number of subjects with available results n/% = number/percentage of subjects with concentr		

ation within the specified range PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 Template 43		
Template 44	Compliance in returning symptom information (Exposed set)	% COMPLI
Error! Reference source not found.	Number and percentage of subjects taking a **concomitant medication** during the **7- day** (Days 0-6) post -vaccination period (Exposed set)	%CMED_INC
Template 45 Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set) **Antibody** Anti-RSV A Neu Antibody	Exploratory comparisons between groups in terms of percentage of subjects reported any **Grade 2/3 AE** and/or **any fever >38.5°C** and/or **any vaccine-related SAE** during the **7 day** (Days 0-6) Post- vaccination period (Exposed set)	%COMP_FQ_AE

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				≥8	PI(D30)																							
					PI(D60)																							
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30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo <7 = Log2 results are less than 7 at pre-vaccination ≥7 = Log2 results are ≥7 at pre-vaccination ≥8 = Log2 results are ≥8 at pre-vaccination ≥9 = Log2 results are ≥9 at pre-vaccination ≥10 = Log2 results are ≥10 at pre-vaccination ≥11 = Log2 results are ≥11 at pre-vaccination Total = all subjects with pre-vaccination result available																												

N = number of subjects with available results n/% = number/percentage of subjects with titre within the specified range PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 Template 46		
Template 47	Solicited and unsolicited symptoms experienced by **at least 5 % of subjects**, classified by MedDRA Primary System Organ Class and Preferred Term within the **30-day** (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)	%UNSOL (NIH=5, EVENT=1)
Template 48	Distribution of change from baseline in **haematology and biochemistry** with respect to normal laboratory ranges (Exposed set)	%HAEMATO_BIOCH
Template 49	Summary of **haematology and biochemistry** results by maximum grade from **VISIT 2 (D7) up to VISIT 3 (D30)** versus baseline (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 32	***Summary of haematology and biochemistry results by maximum grade in the specified category from VISIT 2 (D7) up to VISIT 3 (D30) versus baseline (Exposed set)***	***%freq_dis***
Template 50	Summary of **haematology** change from baseline by maximum grade from **VISIT2 (D7) up to VISIT 3 (D30)** (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 34	***Summary of haematology change from baseline by maximum grade in the specified category from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)***	***%freq_dis***
Template 35	Individual results of **hemoglobin** levels **outside of the normal ranges** in <*group*> (Exposed set)	%HB_PROFIL
Template 52	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)	%GMT
Template 7	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)	%GMT

Template	Geometric mean of the individual ratio of **anti-RSV-A** neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)	%GMRACT
Template	GMTs and their 95% CIs for **anti-RSV-A** neutralising antibody at each timepoint (Per protocol set)	%GMTPLOT*
Template	Kinetics of GMTs for **anti-RSV-A** neutralising antibody on subjects with results available at all timepoints (Per protocol set)	%KIN_GM*
Error! Reference source not found.1	Distribution of **anti-neogenin** antibody concentration (Exposed set)	%DIS
Error! Reference source not found.	Distribution of fold of **anti-neogenin** antibody concentration (Exposed set)	%DIS
Template 41 Distribution of anti-Neogenin antibody concentration (Exposed set) **Antibody** Anti-neogenin antibody ***<each group>:*** 30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo N = number of subjects with available results n/% = number/percentage of subjects with concentration within the specified	Distribution of **anti-RSV-A** neutralising antibody titer (Per protocol set)	%DIS

range PRE = Pre-vaccination at Day 0 PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 **Template**		

		< 1	>= 1	>= 1.5	>= 2	>= 2.5	>= 3		

ri **t** **i i** **y** nel t *a(* i *c* - *h*3 n 0 e*g)* o*r* g*o* e*u* n*p* i n a n t i b o d y l (6 0) i (9 0) **<each group>:** 30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo N = number of subjects with available		

results n/% = number/percentage of subjects with concentration within the specified range PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 Template		
Template	Distribution of fold of **anti-RSV-A** neutralising antibody titer by pre-vaccination titer category (Per protocol set)	%DIS
Template 45	Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set)	%DIS
Template 45 Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set) **Antibody** Anti-RSV A Neu Antibody	Reverse cumulative distribution curves for **anti-RSV-A** neutralising antibody titers in each group at pre-vaccination (Per protocol set)	%REVCUM

					PI(D60)																							
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30 PreF = 30 µg PreF 60 PreF = 60 µg PreF 120 PreF = 120 µg PreF Control = Placebo <7 = Log2 results are less than 7 at pre-vaccination ≥7 = Log2 results are ≥7 at pre-vaccination ≥8 = Log2 results are ≥8 at pre-vaccination ≥9 = Log2 results are ≥9 at pre-vaccination ≥10 = Log2 results are ≥10 at pre-vaccination ≥11 = Log2 results are ≥11 at pre-vaccination Total = all subjects with																												

pre-vaccination result available N = number of subjects with available results n/% = number/percentage of subjects with titre within the specified range PI(D30) = Post-vaccination at Day 30 PI(D60) = Post-vaccination at Day 60 PI(D90) = Post-vaccination at Day 90 Template		
Template	Individual results of **anti-RSV-A** neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)	%SCATTERPLOT*
Template	Vaccine response for **anti-RSV-A** neutralising antibody titer at each post-vaccination timepoint (Per protocol set)	%HUM_RESP*
Template 49	Estimated GMTs and 95% CIs for **anti-RSV-A** neutralising antibody titre (Per protocol set)	%GMT_ANOVA
Template	Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for **anti-RSV A** neutralizing antibody titre at **Day 30** (Per protocol set)	%GMT_RATIO
Template	Individual kinetics of **anti-neogenin** antibody concentrations by group (Exposed set)	%NEO_INDKIN*
Template	GM of individual ratios (fold increase post over pre) and their 95% CIs for **anti-RSV F IgG1 and IgG total** antibody assays and each group, at **Day 30** (Per protocol set)	%GMRPLOT*
Template	Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for **anti-RSV F IgG1** antibody concentrations at **Day 30** (Per protocol set)	%GMF_RATIO*
Template	***Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)***	***%GM_RATIO_PRE.SAS****
Template	***Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per***	***%GM_RATIO_FI.SAS****

	protocol set)	
Template	***Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)***	***%Immuno_DI*****
Error! Reference source not found.	***Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)***	***%Reacto_DI*****
Template	***Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)***	***%Overall_DI*****
Template 59	***Percentage of subjects reporting solicited local symptoms (any grade / grade 3) during the 7-day post-vaccination period (Exposed set)***	***%GFREQ***

* Name of specific macros created in study RSV F-001 (116969), RSV F-020 (201510)

***** Name of specific macros created in study RSV F-021 (204812)***

****** It is the simplified version of Template 22 added in in-text tables for the final analysis***

Template 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the PPS analyses with reasons for exclusion

	Total			<*each group*>	
Title	**n**	**s**	**%**	**n**	**s**
Total enrolled cohort					
Study vaccine dose not administered at all but subject number allocated (code 1030)					
Exposed set					
<*Reason for elimination & elimination code*>					
<*Reason for elimination & elimination code*>					
Per protocol set for immunogenicity					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered Per protocol set relative to the Exposed set

Template 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<*each group*>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdraw:		
Serious Adverse Event		
Non-serious adverse event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Others		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
withdrawn = number of subjects who did not come for the last study visit

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<each group>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdrawal :		
Serious Adverse Event		
Non-Serious Adverse Event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Sponsor study termination		
Other - <reason>		
Other - <reason>		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last study visit

Template 4 Number of subjects at each visit and list of withdrawn subjects (Exposed set)

Group	Visit	N	Withdrawn Subject number	Reason for withdrawal
<each group>	VISIT 1 (D0)			
	VISIT 2 (D7)			
	VISIT 3 (D30)			
	VISIT 4 (D60)			
	VISIT 5 (D90)			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects who are still in the study up to the visit
Withdrawn = Subject who did not return after the visit

Template 5 Summary of demographic characteristics (Per Protocol Set)

		<each group> (N=)		Total (N=)	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Ethnicity	American Hispanic or Latino				
	Not American Hispanic or Latino				
Geographic Ancestry	African Heritage / African American				
	American Indian or Alaskan Native				
	Asian - Central/South Asian Heritage				
	Asian - East Asian Heritage				
	Asian - Japanese Heritage				
	Asian - South East Asian Heritage				
	Native Hawaiian or Other Pacific Islander				
	White - Arabic / North African Heritage				
	White - Caucasian / European Heritage				
	Other				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 6 Summary of demographic characteristics by age category (Exposed set)

		<*each group*> (N=)				Total (N=)			
		<*subgroup*>		<*subgroup*>		<*subgroup*>		<*subgroup*>	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean								
	SD								
	Median								
	Minimum								
	Maximum								
Ethnicity	American Hispanic or Latino								
	Not American Hispanic or Latino								
Geographic Ancestry	African Heritage / African American								
	American Indian or Alaskan Native								
	Asian - Central/South Asian Heritage								
	Asian - East Asian Heritage								
	Asian - Japanese Heritage								
	Asian - South East Asian Heritage								
	Native Hawaiian or Other Pacific Islander								
	White - Arabic / North African Heritage								
	White - Caucasian / European Heritage								
	Other								

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

<subgroup> by age category:
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects

Template 7 Number of subjects by center (Exposed set)

	<each group>	Total	
Center	**n**	**n**	**%**
PPD			
PPD			
..			
All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 8 Number of subjects by center for each age category (Exposed set)

	30 PreF		60 PreF		120 PreF		Control		Total			
	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y		33-45Y	
Center	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**%**	**n**	**%**

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 9 Number of subjects by country and center (Exposed set)

		<each group>	Total	
Country	**Center**	**n**	**n**	**%**
	…			
	All			
	…			
All	All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 10 Deviations from specifications for age and intervals between study visits (Exposed set)

		Age	Dose:1-PI (D30)	Dose:1-PI (D60)	Dose:1-PI (D90)	Dose:1-CONCLUSION
Group		**Protocol**	**Protocol**	**Protocol**	**Protocol**	**Protocol**
		from 18 to 45 years	from 30 to 44 days	from 56 to 70 days	from 86 to 100 days	from 330 to 390 days
<each group>	n					
	N					
	%					
	range					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 11 Summary of vital signs characteristics at VISIT 1 (Day 0) (Exposed set)

		<each group> N =	Total N =
Characteristics	**Parameters**	**Value**	**Value**
Height (Cm)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Weight (Kg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Heart rate (Beats per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Respiratory rate (Breadth per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Systolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Diastolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation

Template 12 Study Population (Exposed set)

Number of subjects	**<each group>**	**Total**
Planned, N		
Randomised, N (Exposed set)		
Completed, n (%)		
Demographics	**<each group>**	**Total**
N (Exposed set)		
Females:Males		
Mean Age, years (SD)		
Median Age, years (minimum, maximum)		
White - caucasian / european heritage, n (%)		
Asian – South East Asian heritage, n (%)		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 13 Number of enrolled subjects by country

		<*each group*> N =	Total N =
Characteristics	**Categories**	**n**	**n**
Country	Czech Republic		
	Australia		
	...		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 (18-45 years)		
	Missing		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 dose 1 unknown

Template 15 Minimum and maximum activity dates (Exposed set)

Group	Activity number	Activity Description	Minimum date	Maximum date
<*each group*>	10	VISIT 1 (DAY 0)		
	20	VISIT 2 (M 1)		
	30	VISIT 3 (M 2)		
	40	VISIT 4 (M 3)		

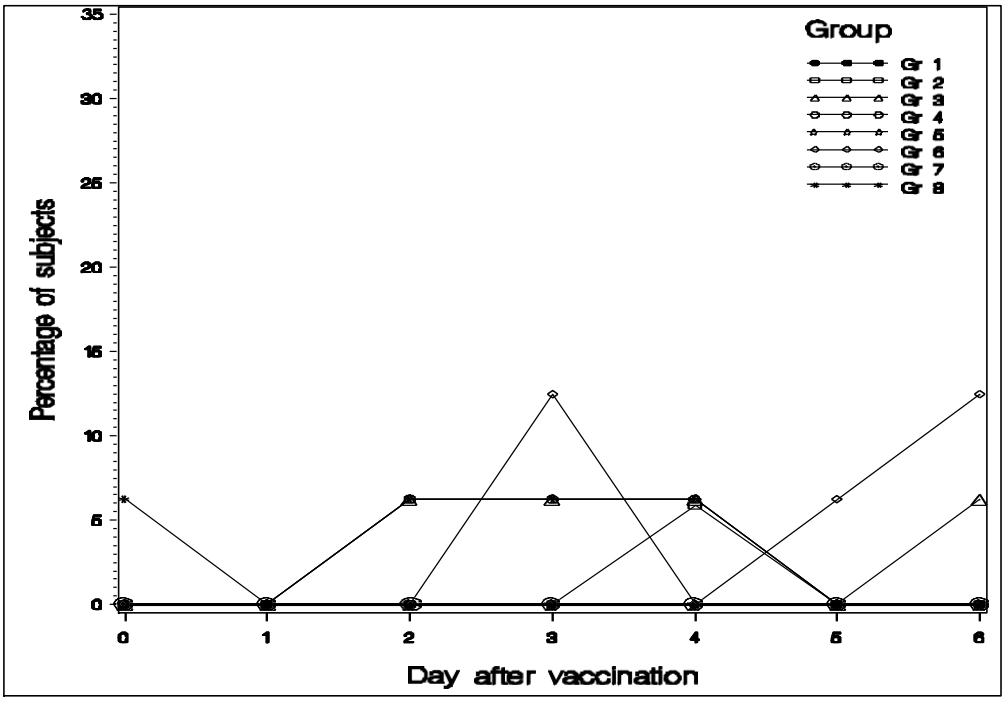
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 16 Incidence and nature of symptoms (solicited and unsolicited reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
<*each group*>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Note: the same table will be generated by group/sub-group, with sub-group= age category (see SAP).

Template 17 Daily prevalence of any fever during the 7-day (Days 0-6) post-vaccination period (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 18 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: $\leq$ 20 mm
1: > 20 mm to $\leq$ 50 mm
2: > 50 mm to $\leq$ 100 mm
3: > 100 mm

Template 19 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Type=Max grade & onset
All=any severity >Grade 0 for pain and any diameter >20mm for redness and swelling
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

Template 20 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Temperature (Oral) (°C)	All (≥37.5)					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related					
	>38.5 Related					
	>39.5 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:
0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 21 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Fever/(Oral) (°C)	All					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related*					
	>38.5 Related					
	>39.5 Related					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
All=any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral)
Related*= any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral) considered related to vaccination by the investigator
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 22 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Exposed set)

		<each group> N =			
				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**
At least one symptom					
<each SOC (code)>	<each PT (code)>				
...	..				
...	...				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 23 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Exposed set)

		<each group> N =	
Primary System Organ Class (CODE)	***Preferred Term (CODE)***	***n***	*%*
At least one symptom			
<each SOC (code)>	*<each PT (code)>*		
...	*..*		
...	*...*		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom

Note: It is the simplified version of Template 22 added as one in-text tables for final analysis

Template 24 Listing of SAEs reported up to study end (Exposed set)

Group	Sub. No.	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<*each group*>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 25 Number (%) of subjects with serious adverse events up to study end (Exposed set)

			<each group> N =		
Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**n***	**n**	**%**
SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related SAE	At least one symptom				
	<each SOC>	<each PT term>			
Fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 26 Compliance in returning symptom information (Exposed set)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
<each group>						

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 27 Number and percentage of subjects taking a concomitant medication during the 7- day (Days 0-6) post -vaccination period (Exposed set)

	<*each group*>				
				95% CI	
	N	**n**	**%**	**LL**	**UL**
Any					
Any antipyretics					
Prophylactic antipyretics					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N= number of administered doses
n/%= number/percentage of subjects who took the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 28 Exploratory comparisons between groups in terms of percentage of subjects reported any Grade 2/3 AE and/or any fever >38.5°C and/or any vaccine-related SAE during the 7-day (Days 0-6) post-vaccination period (Exposed set)

								Difference in percentage (Group 1 minus Group 2)			
										95 % CI	
Group 1	**N**	**n**	**%**	**Group 2**	**N**	**n**	**%**	**Difference**	**%**	**LL**	**UL**
30 PreF				Control				30 PreF - Control			
60 PreF				Control				60 PreF - Control			
120 PreF				Control				120 PreF - Control			
60 PreF				30 PreF				60 PreF - 30 PreF			
120 PreF				30 PreF				120 PreF - 30 PreF			
120 PreF				60 PreF				120 PreF - 60 PreF			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with the administered dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 29 Solicited and unsolicited symptoms experienced by at least 5 % of subjects, classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)

		<each group> **N =**		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**
At least one symptom				
<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 30 Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges (Exposed set)

			<each group >								
				Unknown		**Below**		**Within**		**Above**	
Laboratory parameter	**Timing**	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Aspartate Aminotransferase (AST)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Creatinine	…	…									
Eosinophils	…	…									
Haemoglobin	…	…									
Lymphocytes	…	…									
Neutrophils	…	…									
Platelet count	…	…									
White Blood Cells (WBC)	…	…									

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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
PI(D7) = Post-vaccination at Day 7
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Note: For the final analysis, three newly added in-text tables of 'Distribution of change from baseline in ALT, AST and Eosinophil's with respect to normal laboratory ranges (Exposed set)', 'Distribution of change from baseline in Creatinine, Lymphocytes and White Blood Cells (WBC) with respect to normal laboratory ranges (Exposed set)' and 'Distribution of change from baseline in Hemoglobin, Neutrophils and Platelet count with respect to normal laboratory ranges (Exposed set)' will use Template 30.

Template 24 Summary of haematology and biochemistry results by maximum grade from VISIT 2 (D7) up to VISIT 3 (D30) versus baseline (Exposed set)

		VISIT2 (D7) up to VISIT3 (D30)												
		<each group >												
			Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT) increase by factor	Unknown													
	Grade 0													
	Grade 1													
	Grade 2													
	Grade 3													
	Grade 4													
	Total													
Aspartate Aminotransferase (AST) increase by factor	…													
Creatinine	…													
Eosinophils increase	…													
Hemoglobin decrease	…													
Lymphocytes decrease	…													
Neutrophils decrease	…													
Platelet count decrease	…													
White Blood Cells (WBC) decrease	…													
White Blood Cells (WBC) increase	…													

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of patients reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
ALT/AST increase by factor: Grade 1 is 1.1-2.5xULN, Grade 2 is 2.6-5.0xULN, Grade 3 is 5.1-10xULN, Grade 4 is >10ULN; ULN is upper limit of the normal range.

Template 25 Summary of haematology and biochemistry results by maximum grade in the specified category from VISIT 2 (D7) up to VISIT 3 (D30) (Exposed set)

		<each group > N =	
Laboratory parameter	*Maximum grade*	*n*	*%*
Alanine Aminotransferase(ALT) increase by factor	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Aspartate Aminotransferase(AST) increase by factor	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Creatinine	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Eosinophils increase	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Hemoglobin decrease	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Lymphocytes decrease	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Neutrophils decrease	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
Platelet count decrease	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
White Blood Cells (WBC) decrease	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		
White Blood Cells (WBC) increase	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n = number of subjects in the specified category
% = n / Number of subjects with available results x 100
Other=all Unknown, Grade 0 and Grade 1

ALT/AST increase by factor: Grade 1 is 1.1-2.5xULN, Grade 2 is 2.6-5.0xULN, Grade 3 is 5.1-10xULN, Grade 4 is >10ULN; ULN is upper limit of the normal range.

Template 26 Summary of haematology change from baseline by maximum grade from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)

	VISIT2 (D7) up to VISIT3 (D30)												
	<each group >												
		Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hemoglobin (Change from baseline)													

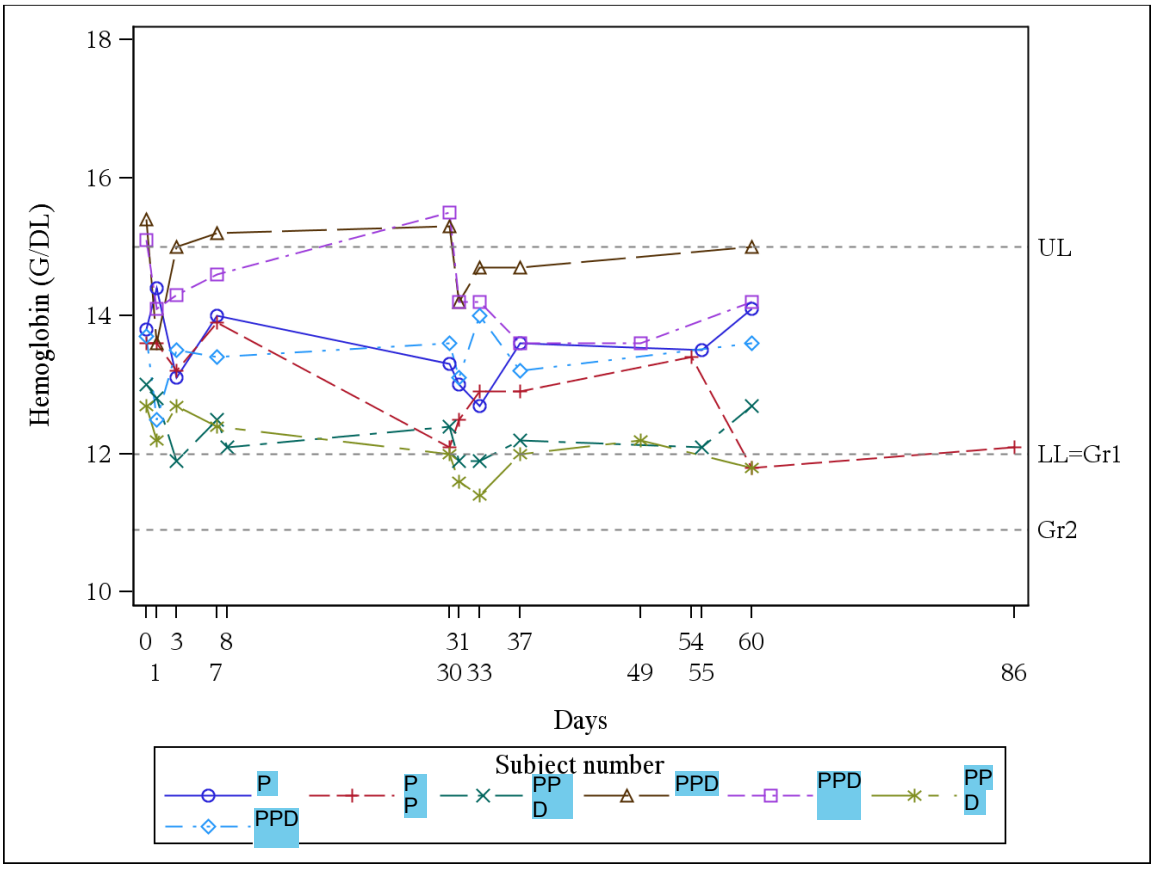
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of subjects reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
Hemoglobin (Female) change from baseline value (gm/dL): Grade 1 is any decrease-1.5, Grade 2 is 1.6-2.0, Grade 3 is 2.1-5.0 and Grade 4 is >5.0.

Template 34 Summary of haematology change from baseline by maximum grade in the specified category from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)

		<each group > N =	
Laboratory parameter	*Maximum grade*	*n*	*%*
Hemoglobin (Change from baseline)	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n= number of subjects in the specified category
% = n / Number of subjects with available results x 100
Other=all Unknown, Grade 0 and Grade 1
Hemoglobin (Female) change from baseline value (gm/dL): Grade 1 is any decrease-1.5, Grade 2 is 1.6-2.0, Grade 3 is 2.1-5.0 and Grade 4 is >5.0.

Template 35 Individual results of hemoglobin levels outside of the normal ranges in < *group*> (Exposed set)



Note: This figure is shown as an example. For the unblinded report, one figure per group will be performed. For the blinded report, 4 graphs will be performed each of them presenting 25 subjects regardless of treatment (the first 25 subjects, from the 26th to the 50th subject…). The X axis will include Day 0, Day 7 and Day 30. The Y axis will be adapted according to each parameter.

Template 36 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)

				≥cut-off				GMT				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE										
		PI(D30)										
		PI(D60)										
		PI(D90)										

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 37 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)

					≥cut-off				GMT				
							95% CI			95% CI			
Antibody	**Group**	**Sub-Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	18-32Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										
		33-45Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										

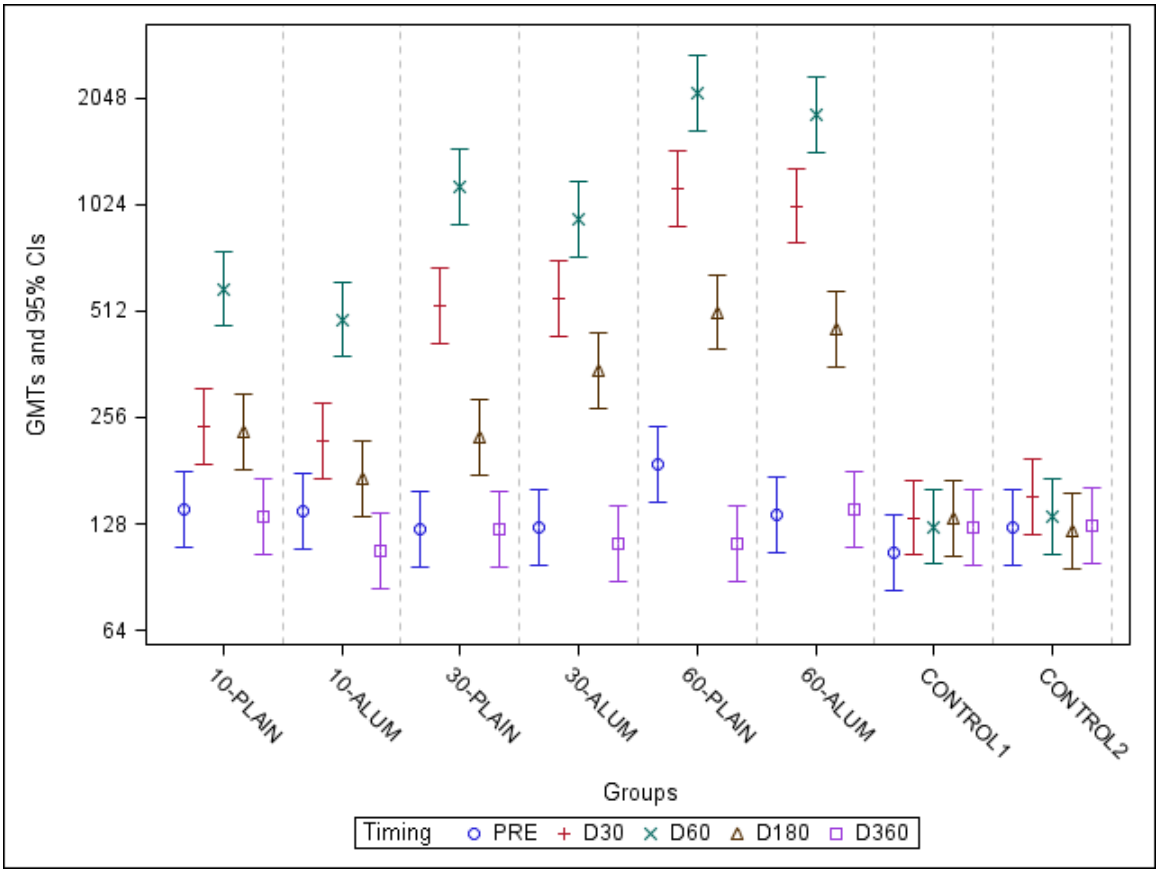
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 38 Geometric mean of the individual ratio of anti-RSV-A neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)

						GMT ratio			
								95% CI	
Group	**N**	**Time point description**	**GMT**	**Time point description**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
<*each group*>		PI(D30)		PRE		PI(D30) / PRE			
		PI(D60)		PRE		PI(D60) / PRE			
		PI(D90)		PRE		PI(D90) / PRE			

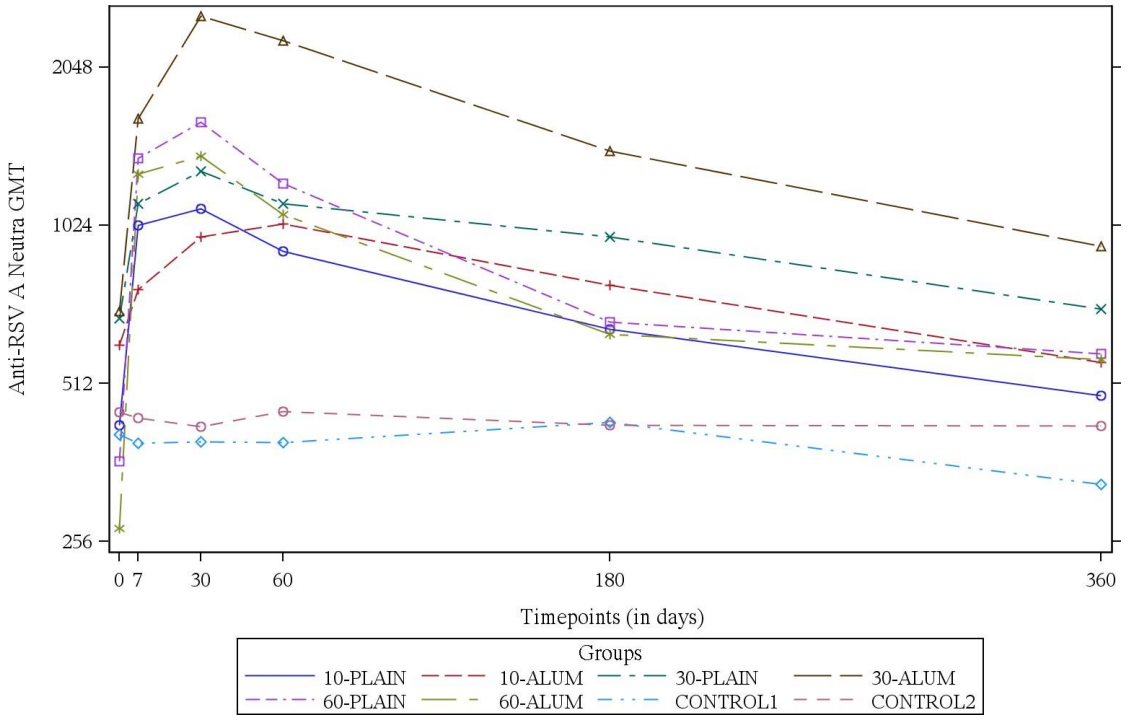
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 39 GMTs and their 95% CIs for anti-RSV-A neutralising antibody at each timepoint (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
95% CI = 95% confidence interval
Note: This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 40 Kinetics of GMTs for anti-RSV-A neutralising antibody on subjects with results available at all timepoints (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on subjects with results available at all timepoints

Note:

- This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints PRE, PI(D30), PI(D60) and PI(D90)
- For the kinetic of the estimated GMTs, footnote will be adapted as: GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures

Template 41 Distribution of anti-Neogenin antibody concentration (Exposed set)

				<55 ng/ml		≥55 ng/ml		≥100 ng/ml		≥150 ng/ml		≥200 ng/ml		≥250 ng/ml		≥300 ng/ml	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	*<each group>*	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 42 Distribution of fold of anti-neogenin antibody concentration (Exposed set)

				<1		>=1		>=1.5		>=2		>=2.5		>=3		>=3.5		>=4		>=4.5		>=5	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	*<each group>*	PI(D30)																					
		PI(D60)																					
		PI(D90)																					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 43 Distribution of anti-RSV-A neutralising antibody titer (Per protocol set)

				<7 Log2		≥7 Log2		≥8 Log2		≥9 Log2		≥10 Log2		≥11 Log2		≥12 Log2	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	<*each group*>	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 44 Distribution of fold of anti-RSV-A neutralising antibody titer by pre-vaccination titer category (Per protocol set)

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	30 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	60 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	120 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	Control	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

<each group>:

30 PreF = 30 µg PreF

60 PreF = 60 µg PreF

120 PreF = 120 µg PreF

Control = Placebo

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

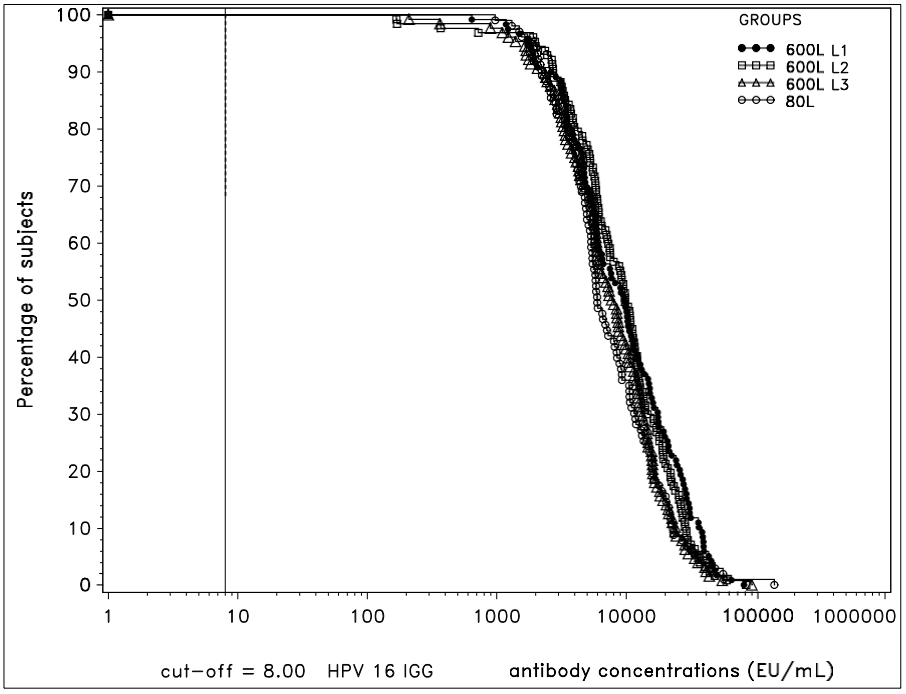
Template 45 Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set)

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	30 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥11	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	60 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	120 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥11	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	Control	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							

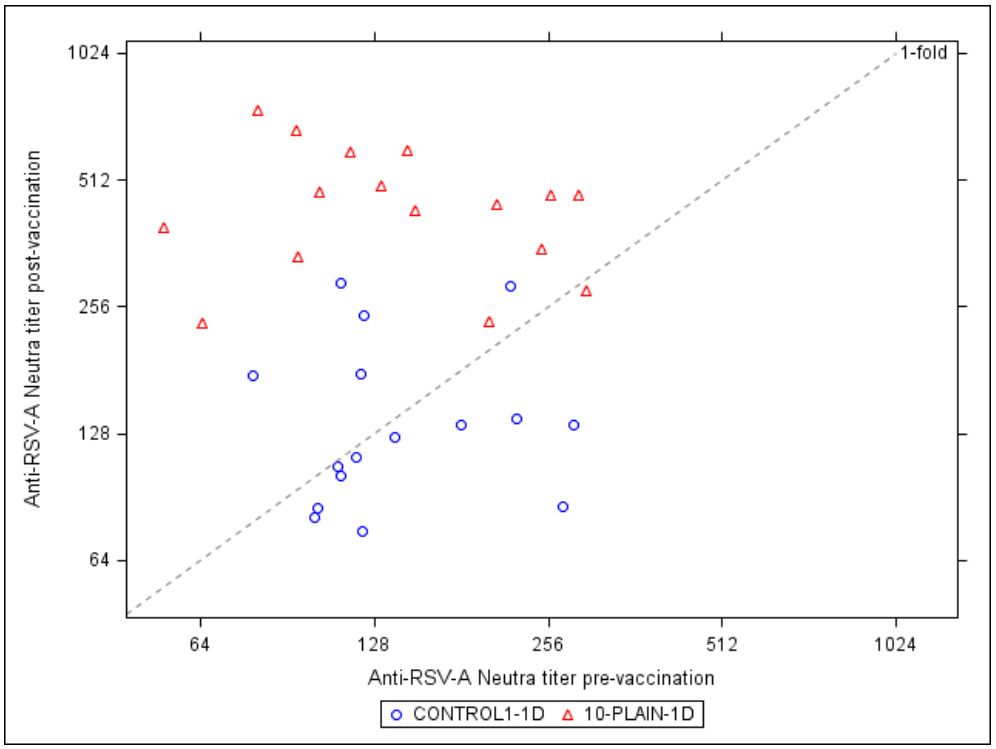
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
<7 = Log2 results are less than 7 at pre-vaccination
≥7 = Log2 results are ≥7 at pre-vaccination
≥8 = Log2 results are ≥8 at pre-vaccination
≥9 = Log2 results are ≥9 at pre-vaccination
≥10 = Log2 results are ≥10 at pre-vaccination
≥11 = Log2 results are ≥11 at pre-vaccination
Total = all subjects with pre-vaccination result available
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 46 Reverse cumulative distribution curves for anti-RSV-A neutralising antibody titers in each group at <each time point> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be provided for each time point and each assay comparing the values of the groups:30 PreF, 60 PreF, 120 PreF and Control.

Template 47 Individual results of anti-RSV-A neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)



<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be generated for each assay and each timepoint separately (Day 30, 60, 90):

Template 48 Vaccine response for anti-RSV-A neutralising antibody titer at each post-vaccination timepoint (Per protocol set)

					Vaccine response*			
							95% CI	
Antibody	**Group**	**Post-vaccination timing**	**Pre-vaccination category (log2)**	**N**	**n**	**%**	**LL**	**UL**
<*each antibody*>	<*each group*>	PI(D30)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D60)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D90)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Total = all subjects with pre-vaccination result available
*Vaccine response defined as :
For subjects with pre-vaccination titer <7 log2: antibody titer at post-vaccination>= 4 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in [7-8] log2: antibody titer at post-vaccination >= 3 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in]8-10] log2 : antibody titer at post-vaccination >= 2.5 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer >10 log2: antibody titer at post-vaccination >= 1 fold the pre-vaccination antibody titer
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 49 Estimated GMTs and 95% CIs for anti-RSV-A neutralising antibody titre (Per protocol set)

				Estimated GMT		
					95% CI	
Antibody	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE				
		PI(D30)				
		PI(D60)				
		PI(D90)				

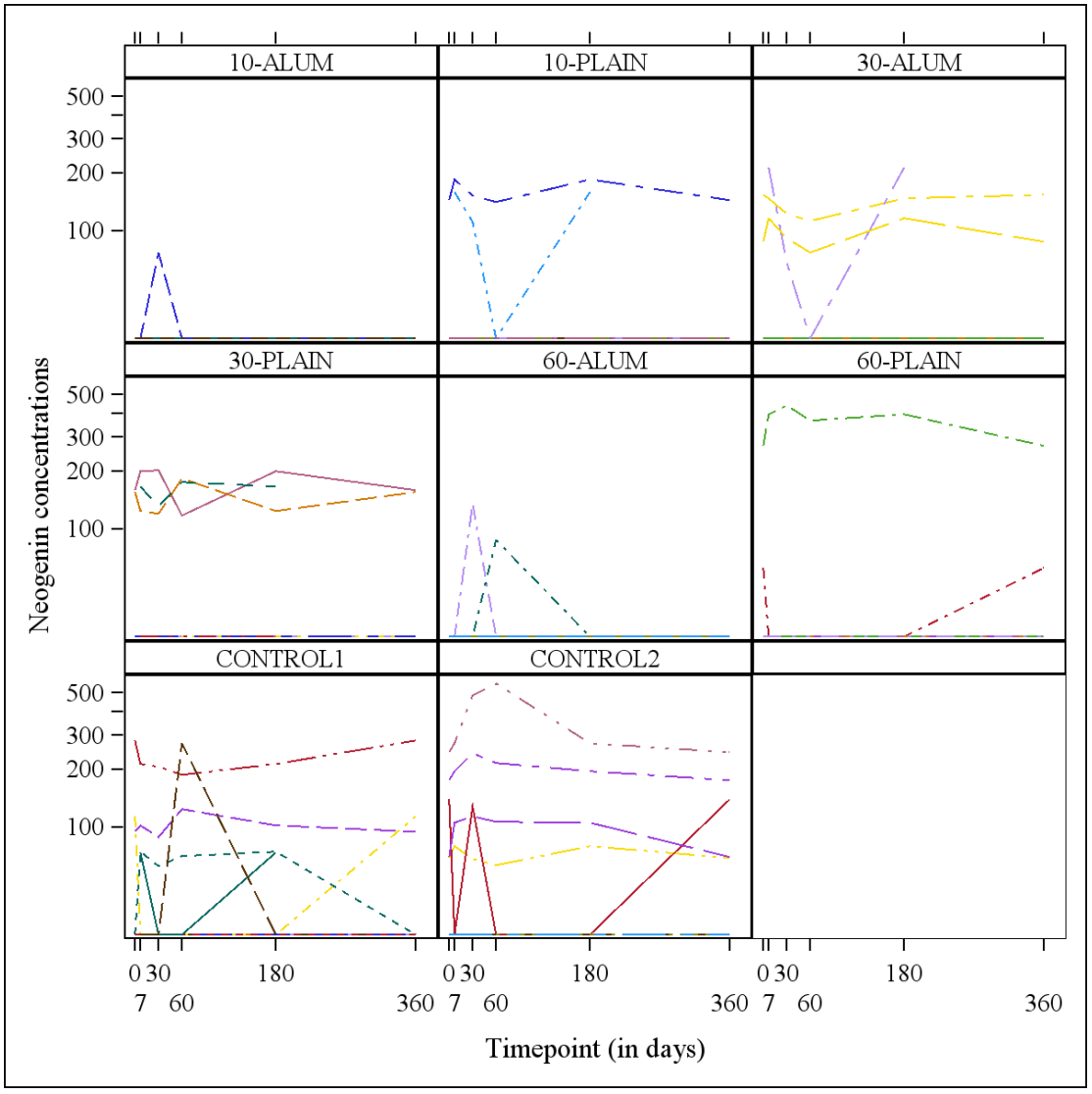
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures
N = Number of subjects with available results
95% CI = 95% confidence interval (ANOVA model); LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 50 Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for anti-RSV A neutralizing antibody titre at Day 30 (Per protocol set)

								GMT ratio			
										Tukey's 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMT**	**Group description**	**N**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
Anti-RSV A Neutralizing Antibody	PI(D30)	120 PreF			30 PreF			120 PreF/30 PreF			
		120 PreF			60 PreF			120 PreF/60 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

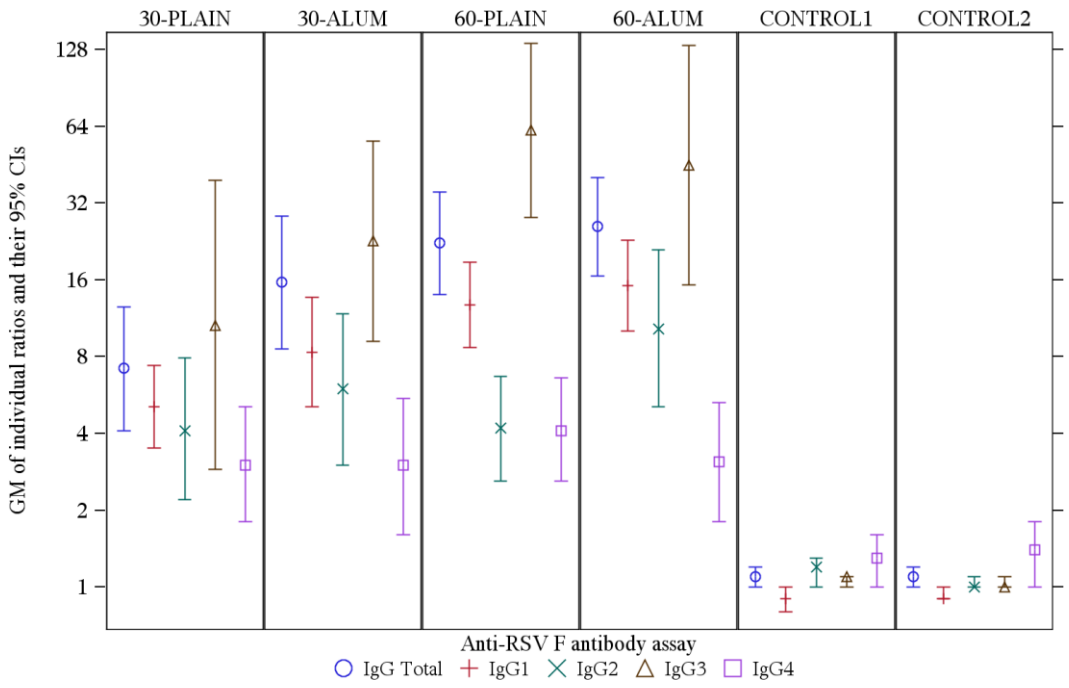
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
antibody titre estimated by the ANCOVA model
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMT ratio (ANCOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANCOVA model is xxxx
PI(D30) = Post-vaccination at Day 30

Template 51 Individual kinetics of anti-neogenin antibody concentrations by group (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. This graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 52 GM of individual ratios (fold increase post over pre) and their 95% CIs for anti-RSV F IgG1 and IgG total antibody assays and each group, at <Day xx> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: this graph is provided as an example. It will be adapted to display IgG total and Ig1 only, and the 4 groups: 30 PreF, 60 PreF, 120 PreF, Control.

Template 53 Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for anti-RSV F antibody concentrations (IgG Total) at Day 30 (Per protocol set)

								GMF ratio			
										Tukey s 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMF**	**Group description**	**N**	**GMF**	**Ratio order**	**Value**	**LL**	**UL**
anti-RSV F antibody (IgG Total)	PI(D30)	120 PreF			60 PreF			120 Pre/60 PreF			
		120 PreF			30 PreF			120 PreF/30 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Antibody concentration estimated by the ANOVA model
GMF = Geometric mean of fold increase
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMF ratio (ANOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANOVA model at PI(D30) is: xxxx
PI(D30) = Post-vaccination at Day 30

Template 54 Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)

									GM ratio		
				95% CI			95% CI			*95% CI*	
Timing	*Group description*	*N*	*IgG Total GMC*	*LL*	*UL*	*RSV-A neut GMT*	*LL*	*UL*	*Value*	*LL*	*UL*
PRE(D0)	*<each group>*										
PRE(D0)											
PRE(D0)											
PRE(D0)											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at Day30 and pre-vaccination for IgG Total and RSV-A neut
GMC = Geometric mean antibody concentration calculated on all subjects for IgG Total
GMT = Geometric mean antibody titre calculated on all subjects for RSV-A neut
GM Ratio=Geometric mean of individual ratio of IgG Total to RSV-A neut for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0

Template 55 Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)

									GMF Ratio		
										95% CI	
Timepoint	Group	N	IgG Total GMF	95% CI LL	95% CI UL	RSV-A neut GMF	95% LL	95% UL	Value	LL	UL
PI(D30)/PRE	<each group>										
PI(D30)/PRE											
PI(D30)/PRE											
PI(D30)/PRE											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at the two considered time points for IgG Total and anti-RSV-A
GMF = Geometric mean of fold increase
GMF Ratio= Geometric mean of individual ratio of fold increase for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30

Template 56 Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)

Group	*GMT*	*LL1*	*DI1*	*GMC*	*LL2*	*DI2*	*DI*
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = estimated log2-scale GMT adjusted for pre-vaccination titres for neutralising anti-RSV-A
GMC = estimated log10-scale GMC adjusted for pre-vaccination concentrations for PCA
LL1 = estimated log2-scale lower limit adjusted for pre-vaccination titres for neutralising anti-RSV-A
LL2 = estimated log10-scale lower limit adjusted for pre-vaccination concentrations for PCA
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 57 Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)

Group	*Incidence Rate* $(IR1)$	*Incidence Rate* $(IR2)$	*DR1*	*DR2*	*DR*
<each group>					

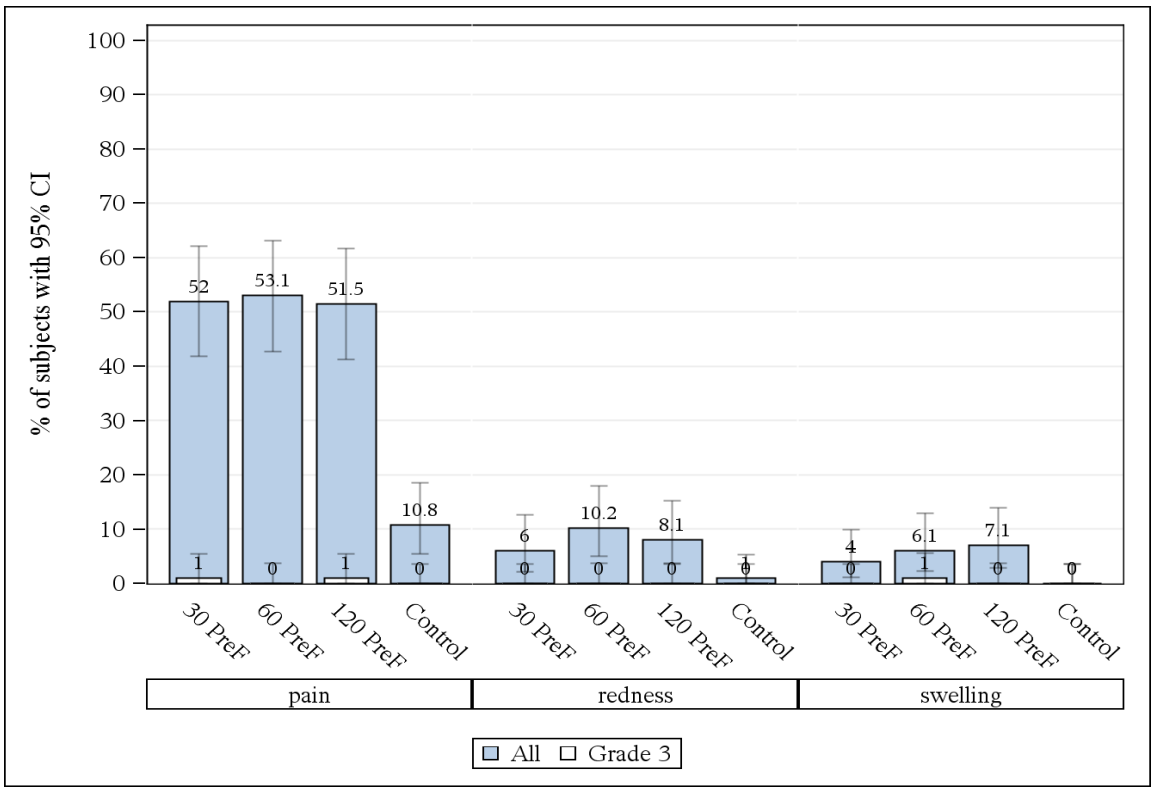
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µgPreF
120 PreF = 120 µg PreF
Control = Placebo
$IR1$ ***= incidence rate estimated by the model for any Grade 2/3 general AEs and any related SAEs***
$IR2$ ***= incidence rate estimated by the model for Grade 2/3 fever***
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index

Template 58 Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)

Group	*Reactogenicity Index*			*Immunogenicity Index*			*Overall Desirability Index*
	DR1	*DR2*	*DR*	*DI1*	*DI2*	*DI*	$DR^{0.4} * DI^{0.6}$
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 59 Percentage of subjects reporting solicited local symptoms (any grade / grade 3) during the 7-day post-vaccination period (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 – 45 years.
eTrack study number and Abbreviated	204812 (RSV F-021)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	***Final: Amendment 4 (01-Jun-2018)*** ***Amendment 3 (15-Mar-2018)*** ***Amendment 2 (09-Nov-2017)*** ***Amendment 1 (21-Jul-2017)*** ***Version 2.0 (10-Nov-2016)*** ***Version 1.0 (25-Aug-2016***
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 (Regulatory Affair) PPD (SERM physician) PPD (Public disclosure representative)
Approved by:	PPD ***(Clinical Research and Development Lead)*** PPD (Lead statistician) PPD (Lead stat analyst) PPD (Lead scientific writer)
APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)	

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	According-to-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
eCRF	Electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
MA-RTI	Medically Attended Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
NEO	Neogenin
PCA	Palivizumab Competing Antibodies
PCD	Primary completion Date
PCR	Polymerase Chain Reaction
PPS	Per Protocol Set
PreF	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
RSV	Respiratory syncytial virus

RTI	Respiratory Track Infection
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	(GSK) Biological's Internet Randomization System
SD	Standard Deviation
SRT	Safety Review Team
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
WBC	White Blood Cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25-AUG-2016	Version1: first version	RSV F-021 (204812) Protocol (20-Jul-2016)
10-NOV-2016	***Version2.0: Description of changes from Version 1.0 are as below*** ***1. The table of elimination code has been modified*** ***2 Algorithm for handling of data of PCA neutralising antibody concentrations between the LOB and LLOQ was added***	***Final - 20-Jul-2016***
21-JUL-2017	***Amendment 1: Description of changes from Version 2.0 are as below:*** ***- Use of new template for SAP (Default-APP 9000058193 Statistical Analysis Plan_v1)*** ***- In section 6. Statistical Analyses, immunogenicity was moved before safety*** ***- For the sequence of analysis, IDMC analysis up to at least Day 30 including haematology and biochemistry parameters was newly-added*** ***- The table of elimination code has been modified for more clarity*** ***- In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A/B and concentrations against NEO have been added*** ***- In the analysis of safety section, the percentage of subjects reporting each individual solicited local/general AE during the 7-day follow-up period post vaccination based on maximum intensity per subject has been added*** ***- Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs*** ***- The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL).***	***Final - 20-Jul-2016***

	- ***Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV A by considering the LOB for RSV-B is 6*** - ***Addition of analysis of the IgG total and IgG1 subclass*** - ***Addition of analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available*** - ***Changes of TFL/TOC*** • ***In the analysis of safety section, analysis on 'Individuals results of haematological and biochemical parameters outside of the normal ranges in each group' will be reported*** • ***In the analysis of safety section, the titles in all tables reporting 'incidence and nature of solicited and unsolicited symptoms' have been changed from 'with causal relationship to' to 'considered related to vaccination'*** • ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will also be reported based on maximum intensity per subject for each grade*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added*** • ***In the analysis of safety section, analysis on 'Number (%) of subjects with SAE or SAE considered related to vaccination during the study period' will not be reported*** • ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30/60/90-day post-vaccination period and up to study end' will be reported***	

	• *In the analysis of medically attended RTIs, analysis on 'viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases' will be only listed in the individual listings* • *In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added* • *In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added* • *In the analysis of immunogenicity section, tables/figures related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added*	
09-NOV-2017	***Amendment 2: Description of changes from Amendment 1 are as below:*** - PPD ***(Clinical Research and Development Lead) was added*** - ***In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added*** - ***In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added*** - ***Changes of TFL/TOC*** • ***In the analysis of safety section, analysis on 'Individual results of hemoglobin levels beyond grade 2' have been added*** • ***In the analysis of safety section, analysis on 'Individual results of white blood cells counts levels lower than LL' and the figures of 'Individual results of white blood cells counts levels higher than UL' have been added***	***Amendment 1 - 21-Aug-2017***

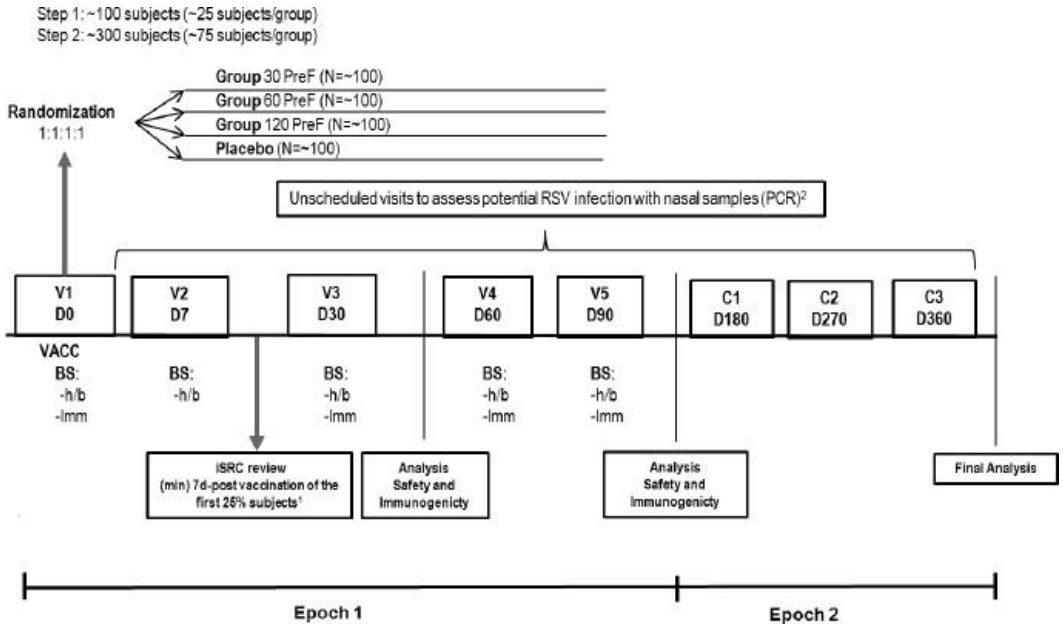
	• ***In the analysis of immunogenicity section, one new template of "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)"has been added*** • ***In the analysis of immunogenicity section, one new template of "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added***	

15-Mar-2018	***Amendment 3: Description of changes from Amendment 2 are as below:*** ***For final analysis,*** – ***Some tables have been updated including removing to Annex, creating new corresponding in-text table by deleting or collapsing some columns/rows;*** – ***Two figures of 'percentage of subjects reporting solicited local/general symptoms (any grade / grade 3) during the 7-day post-vaccination period' have been newly generated for the final analysis, respectively;*** – ***The table of 'Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges' has been splitted and modified into three in-text tables for Alanine Aminotransferase (ALT)/ Aspartate Aminotransferase (AST)/Eosinophils, Creatinine/Lymphocytes/ White Blood Cells (WBC), Haemoglobin/platelet count/Neutrophils, separately;*** – ***Two new in-text tables of 'Summary of haematology and biochemistry results by maximum grade in the specified category' and 'Summary of haematology change from baseline by maximum grade in the specified category' have been generated;*** – ***Some figures of Individual results for each parameter have been modified.***	***Amendment 1 - 21-Aug-2017***

01-Jun-2018	***Amendment 4: Description of changes from Amendment 3 are as below:*** ***For final analysis*** – ***Many tables and figures have been moved between in-text and post-text;*** – ***Two figures of 'percentage of subjects reporting solicited local/general symptoms (any grade / grade 3) during the 7-day post-vaccination period' will be updated to include grade 2, respectively;*** – ***The parameter of BMI has been added in the table of 'Summary of vital signs characteristics (Exposed set)' and report at VISIT 1 (D0), MA-RTI VISIT 1 and MA-RTI VISIT 2;*** – ***This table of 'Summary of haematology and biochemistry results by maximum grade in the specified category from VISIT 1 (D0) up to VISIT 2 (D7) (Exposed set)' will be newly added for the final analysis in in-text;*** – ***Please check the dry run meeting minutes for the details***	***Amendment 1 - 21-Aug-2017***

2. STUDY DESIGN

Figure 1. Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.

1 Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.

2 In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of an event related eCRF and the collection of a nasal swab within 72h after the medical attendance.

Vertical lines stand for analysis on all subjects.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
    - **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
    - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
    - Epoch 002: Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Primary Completion Date (PCD)**: Visit 3 (Day 30).
- **End of Study (EoS)**: Last testing results released of samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).
- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epochs	
			Epoch 001	Epoch 002
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30 NaCl	X			
60 µg PreF	PreF-60 NaCl		X		
120 µg PreF	PreF-120 NaCl			X	
Placebo	Formulation buffer S9b				X

- **Control**: Placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.
- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.

The following group and sub-group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	30 PreF	30 µg PreF
2	60 PreF	60 µg PreF
3	120 PreF	120 µg PreF
4	Control	Placebo

Some tables might be presented by age category according to the following description:

Sub-group	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Age	1	18-32Y	18-32 years old subjects
	2	33-45Y	33-45 years old subjects

- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule:**
  - **Blood samples for haematology/biochemistry** will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Blood samples for humoral immune response evaluation** will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and at Visit 5 (Day 90).
  - **Nasal swabs** will be collected from subjects in case of a medically attended respiratory tract infection from enrolment (Visit 1) until study end (Contact 3).
- **Type of study**: self-contained
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring**:
  - When the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) have been vaccinated, enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC). Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' Safety Review Team (SRT) on a regular basis throughout the study. Analyses related to iSRC evaluation will be described in a separate document (SAP/TFL for iSRC).
  - ***When all subjects have been vaccinated, IDMC will review all available safety and reactogenicity data (including haematology/ biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo. The blinded safety data will be reviewed by the GSK Biologicals' SRT. Analyses related to IDMC evaluation will be described in a separate document (SAP/TFL for IDMC).***
- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

3. OBJECTIVES

3.1. Primary Objective

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

3.2. Secondary objectives

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30).
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

3.3. Tertiary objective

- If deemed necessary, to further characterize the immune response of a single intramuscular dose of the RSV investigational vaccines.

Refer to Section 5.7.3 Laboratory assays of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

4. ENDPOINTS

4.1. Primary

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);
  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of any vaccine-related SAE.
- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group

4.2. Secondary

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;
  - Occurrence of any SAE, for all subjects in all groups.
- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day 30) for all subjects in all groups.
  - Antibody concentrations against NEO
- Occurrence of medically attended RSV-associated RTIs up to study conclusion

4.3. Tertiary

See section 5.7.3 of the Protocol for additional testing proposed to further characterize the immune response to the investigational RSV vaccine.

5. ANALYSIS SETS

5.1. Definition

In order to align to ICH and CDISC terminology, the Total Vaccinated Cohort (TVC) and the According To Protocol cohort (ATP) have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively. Two cohorts will be defined for the purpose of the analysis: the Exposed Set (ES) and the Per-Protocol Set (PPS) for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

5.1.1. Exposed Set (ES)

The 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 the ES will include all vaccinated subjects for whom immunogenicity data are available.

5.1.2. Per-Protocol Set (PPS) for analysis of immunogenicity

The PPS for immunogenicity will be defined by time point and will include all vaccinated subjects.

- Meeting all eligibility criteria (i.e. no protocol violation linked to the inclusion/ exclusion criteria, including age).
- Who received the study vaccine according to protocol procedures.
- Who did not receive a concomitant vaccination/medication/product leading to exclusion from the PPS analysis up to the corresponding timepoint as described in Section 6.6.2 of the Protocol.
- Who did not present with an intercurrent medical condition leading to exclusion from the PPS analysis up to the corresponding timepoint, as described in Section 6.7 of the Protocol.
- Who complied with the post-vaccination blood sampling schedule at the corresponding timepoint, as specified in Table 5 of the Protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding timepoint.

When presenting different timepoints, the PPS for immunogenicity will be adapted for each timepoint (up to D30 and up to D90).

5.2. 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 sets.

5.2.1. Elimination from Exposed Set (ES)

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

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

5.2.2.1. Excluded subjects

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

Code	*Condition under which the code is used*	*Applicable Eli Type*	
		'M1' (Applicable up to Visit 3 - Day 30)	*'M2' (Applicable up to Visit 5 - Day 90)*
900	*Invalid informed consent or fraud data (Subjects receiving a code 900 should not receive any other elimination codes)*	*Applicable*	*Applicable*
1030	*Study vaccine not administered at all (Subjects receiving a code 1030 should not receive any other elimination codes)*	*Applicable*	*Applicable*
*1040**	*Administration of concomitant vaccine(s) forbidden in the protocol*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
1050	*Randomization failure (subject not randomized in the correct group)*	*Applicable*	*Applicable*
1060	*Randomization code was broken*	*Applicable*	*Applicable*
*1070***	*Subjects got vaccinated with the correct vaccine but containing a lower volume*	*Applicable*	*Applicable*
*1070***	*Administration not according to protocol for reason specified by the investigator other than site and route*	*Applicable*	*Applicable*
*1070***	*Site or route of study vaccine administration wrong or unknown*	*Applicable*	*Applicable*
*1070***	*Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)*	*Applicable*	*Applicable*

Code	*Condition under which the code is used*	*Applicable Eli Type*	
		'M1' (Applicable up to Visit 3 - Day 30)	*'M2' (Applicable up to Visit 5 - Day 90)*
*1070***	*Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number*	*Applicable*	*Applicable*
1080	*Vaccine temperature deviation*	*Applicable*	*Applicable*
1090	*Expired vaccine administered*	*Applicable*	*Applicable*
2010	*Protocol violation (inclusion/exclusion criteria)*	*Applicable* *DOB-VAC=18-45 years*	*Applicable* *DOB-VAC=18-45 years*
*2040**	*Administration of any medication forbidden by the protocol*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
*2050**	*Underlying medical condition forbidden by the protocol*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
*2060**	*Concomitant infection related to the vaccine which may influence the immune response*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
*2070**	*Concomitant infection not related to the vaccine which may influence the immune response*	*Applicable (To check up to Visit 3 – Day 30)*	*Applicable (To check up to Visit 5 – Day 90)*
2090	*Subjects did not comply with blood sample schedule*	*Applicable* *VAC_1 to SER_2 = 30-44 (days)*	*Applicable* *VAC_1 to SER_3 = 56-70 (days)* *VAC_1 to SER_4 = 86-100 (days)*
2100	*Serological results not available post-vaccination*	*All assay for Day 30* *elimination code if ALL are missing*	*All assay for Day60 and Day90* *elimination code if ALL are missing*

Code	*Condition under which the code is used*	*Applicable Eli Type*	
		'M1' (Applicable up to Visit 3 - Day 30)	*'M2' (Applicable up to Visit 5 - Day 90)*
		v_ID for Neutra RSV-A=3240.001 *v_ID for Neutra RSV-B=3240.002* *v_ID for Neutra PCA=3241.009* *v_ID for IgG total=3241.002* *v_ID for IgG 1=3241.005*	*v_ID for Neutra RSV-A=3240.001* *v_ID for Neutra RSV-B=3240.002* *v_ID for Neutra PCA=3241.009* *v_ID for IgG total=3241.002* *v_ID for IgG 1=3241.005*
*2120**	*Obvious incoherence or abnormality or error in data****	*All assay for Day 30*	*All assay for Day 60 and Day90*

**** Attribution of these elimcodes to subject need CRDL review of individual data listings***
***** Attribution of code 1070 to a subject requires CRDL confirmation***
****** Elimination criteria for implausible RSV serum immune responses (neut and/or ELISA): More than 4 fold decrease from pre-vaccination to Day 30; After Day 30, more than 4 fold increase or more than 8 fold decrease within a 30 day period***
Eli type is Internal GSK database code for type of elimination code
M1 for Visit 3 (Day30) analysis; M2 for Visit 5 (Day 90) analysis;

5.2.2.2. Right censored Data

Not applicable

5.2.2.3. Visit-specific censored Data

Not applicable

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

The following important protocol deviations will be reported by groups:

Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

Manual randomization: In case of the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule.

Short follow-up: subjects who completed the last study contact before the minimum length of follow-up requirement.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Annex 1 standard data derivation rule and statistical methods and will not be repeated below.

6.1. Demography

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

The analysis of demography will be performed on the ES and on the PPS for immunogenicity.

Demographic characteristics such as age at vaccination in years, race, ethnicity, vital signs and cohort description will be summarised 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 (18 - 32 years and 33 - 45 years).

Withdrawal status will be summarised by group using descriptive statistics:

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

6.2. Immunogenicity

6.2.1. Analysis of immunogenicity planned in the protocol

The analysis will be performed on the applicable PPS cohort for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is ≥5%, a second analysis will be performed on the ES.

6.2.1.1. Within group analysis

Humoral Immune response to RSV vaccine

For each group, at each timepoint that blood samples are collected and for each assay (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI based on log-transformed values and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.

  Percentage of subjects above the seropositivity threshold and GMTs/GMCs will also be tabulated by group for each age category (18 - 32 years and 33 - 45 years).
- Pre- and post-vaccination antibody titres/concentrations will be displayed using reverse cumulative curves.
- The distributions of **neutralising** antibody titres will be tabulated in the tables with log2 scale (< 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 log2).
- Percentage of responders in terms of **neutralising** antibody titres will be tabulated with exact 95% CI.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- ***Distribution of the fold increase of the antibody titres/concentrations will be tabulated:***
  - ***For neutralising antibody titres against RSV-A and RSV-B: percentage of subjects with a fold increase equal to or above 1, 2, 2.5, 3, 4, 6, 8 10, 11 and 12 by pre-vaccination titre category: <7, 7-8,]8-9,]9-10,]10-11,]11-12, >12 log2, and cumulative: <7, ≥7, ≥8, ≥9, ≥10, ≥11, ≥12 log2.***
  - ***For antibody concentrations against NEO: percentage of subjects with a fold increase equal to or above 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5.***

The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all timepoints.

- An analysis of variance model for repeated measures will be fitted to calculate GMTs/GMCs with treatment group, visit and their interaction as fixed effects if necessary.

If deemed necessary, the same analyses may be done by age category (18 - 32 years and 33 - 45 years).

6.2.1.2. Between group assessment

Exploratory comparisons will be performed for RSV neutralising antibody titres and PCA concentrations post-vaccination (Day 30, Day 60 and Day 90) between the different RSV vaccine groups.

- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment. This model includes:
  - The vaccine group as the fixed effect
  - The pre-vaccination titre/concentration as the covariate
  - Age groups (18-32 years and 33-45 years) and center as the categorical covariate if deemed necessary
- GMT/GMC ratios with corresponding 95% CI will be computed between the RSV vaccine groups
  - PreF-120 *minus* PreF-30
  - PreF-120 *minus* PreF-60
  - PreF-60 *minus* PreF-30

6.2.2. Additional considerations

In order to add the analysis of the <u>anti-RSV F IgG Total and IgG1 subclass</u> tested at Day 0 and Day 30 in a random subset of 50 subjects per group. The following analysis will be performed on the Per-Protocol Set (PPS) for analysis of immunogenicity for each group and for both assays:

- ***GMCs with 95% CI will be tabulated.***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.***
- ***Geometric mean of ratios of antibody concentrations at each post-vaccination timepoint over pre-vaccination (fold increase) will be tabulated with 95% CI, and represented graphically.***
- ***Individual ratios of antibody concentrations will be displayed using reverse cumulative curves.***
- ***Exploratory comparisons between groups: geometric mean ratios and 95% CIs of fold increase post/pre between the RSV groups:***
  - ***120 PreF versus 60 PreF***
  - ***120 PreF versus 30 PreF***
  - ***60 PreF versus 30 PreF***

This will be performed using an ANOVA model on the logarithm10 transformation of the concentrations including the vaccine group as covariates. If a statistically significant difference is found (p <0.05), pairwise comparisons will be made using Tukey's multiple comparison adjustment.

In addition, the following immunogenicity analysis will be performed in the subset of subjects with IgG/IgG1data available:

- ***GMCs will be tabulated with 95% CI for anti-RSV A and anti-PCA***
- ***Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI for anti-RSV A and anti-PCA.***

6.3. Analysis of safety

6.3.1. Analysis of safety planned in the protocol

The analysis of safety will be performed on the ES.

6.3.1.1. Within group analysis

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 after vaccination will be tabulated with exact 95% CI. The same computations will be done for ≥ Grade 2 and Grade 3 AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for AEs resulting in medically attended visit.

The percentage of subjects reporting each individual **solicited local AE** (any grade, ≥ Grade 2, Grade 3, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each study vaccine for each group. The percentage of subjects reporting each individual **solicited general AE** (any grade, ≥ Grade 2, Grade 3, any related, ≥ Grade 2 related, Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated for each group.

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting fever will be reported by half degree (°C) cumulative increments. Similar tabulations will be performed for causally related fever, Grade 3 (> 39.5°C) causally related fever and fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination.

The percentage of subjects with any **unsolicited** symptoms within 30 days after vaccination 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 symptoms, for any causally related unsolicited symptoms, for Grade 3 causally related unsolicited symptoms and for unsolicited symptoms resulting in a medically attended visit (The verbatim reports of unsolicited symptoms 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).

SAEs reported throughout the study will be described in detail.

Pregnancy exposures throughout the study and pregnancy outcomes will be described in detail (if applicable).

The percentage of subjects using **concomitant medication** (any medication, any antipyretic and any antipyretic taken prophylactically) during the 7-day (Day 0 to Day 6) or 30-day (Day 0 to Day 29) follow-up period after vaccination will be summarised by group.

For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated for each timepoint.
- The maximum grading post-vaccination (from Day 7 to Day 90) versus baseline (Day 0) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 will be tabulated (Grades will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see APPENDIX D of the Protocol: FDA toxicity grading scale. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

Assessment of anti-NEO immune response at Day 30 post-vaccination for each group:

- GMCs pre-and post-vaccination will be tabulated with 95% CI and represented graphically.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody concentrations at Day 30 over pre-vaccination will be tabulated with 95% CI.
- Distribution of the antibody concentrations pre-and post-vaccination and of fold increase after vaccination will be tabulated.

6.3.1.2. Between group assessment

Exploratory comparisons between each investigational RSV vaccine group and (minus) the control group (*placebo*), and between the RSV vaccine groups will be done in terms of the percentage of subjects reporting any ≥ Grade 2, Grade 3 AE (solicited and unsolicited), and/or any fever > 38.5°C, and/or any vaccine-related SAE during the 7-day follow-up period after vaccination.

- PreF-30 *minus* placebo
- PreF-60 *minus* placebo
- PreF-120 *minus* placebo

- PreF-120 minus PreF-30
- PreF-120 minus PreF-60
- PreF-60 minus PreF-30

The standardised asymptotic 95% CI for the difference between the investigational RSV vaccine groups as well as between the investigational RSV groups and (minus) the control group will be computed.

6.4. Analysis for ranking RSV formulations

The totality of data and sum total of evidence for particular dose(s) in terms of safety and immunogenicity will be evaluated by study team in addition to the analyses described in section 6.1 and 6.3 on formulation selection. The desirability index approach described in the section below will be used as a descriptive tool to guide the formulation selection. In addition, any pertinent information from outside this study will be evaluated and may be used by the study team to help to make the final decision on a dose/formulation.

6.4.1. Definition of desirability in the context of Simulations

A desirability approach will be based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination.

This method is a multi-criteria decision making approach based on desirability functions. The main idea is to identify for each endpoint a desirability function that associates any value to another one between 0 and 1 depending on its desirability (‘0’ being considered as not desirable at all and ‘1’ as the most desirable). An index with values between 0 and 1 will be created for each endpoint. An overall desirability index can be calculated by computing a weighted geometric mean of the endpoint indexes. By definition, this overall index also takes values between 0 and 1 and characterises the level of desirability of any candidate formulation by a single value [Dewé, 2015].

The desirability index calculations will include reactogenicity and safety data up to Day 7 post vaccination (on the TVC) and immunogenicity data at 30 days post-vaccination (on the ATP cohort for immunogenicity up to Day 30). The formulations will be ranked based on the values obtained with this overall desirability index.

6.4.2. Derived endpoints

The following endpoints will be computed and taken into account in the desirability analysis:

1. Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
2. Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.

3. Geometric mean of neutralising antibody titres against RSV-A at Day 30 adjusted for pre-vaccination titres.
4. Geometric mean of PCA concentrations at Day 30 adjusted for pre-vaccination titres.

Each individual desirability index will be calculated based on data and tabulated by the treatment group and endpoints above. The details on how to calculate individual desirability index in terms of reactogenicity and immunogenicity and overall desirability index are elaborated in Annex 2.

6.5. Analysis of medically attended RTIs

The analysis will be performed on the ES by study group.

The proportion of subjects (with 95% CI) with at least one medically attended RTI (all causes) will be calculated by group.

Viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be listed for any cases where this assay is performed.

Medically attended RSV-associated RTI co-infected or colonisation with another viral etiology identified by multiplex PCR will be described.

Medically attended RTI with any viral etiology identified by multiplex PCR will be described.

7. ANALYSIS INTERPRETATION

All comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The statistical analyses will be performed in several steps:

- In preparation of the planned iSRC evaluation, analysis of safety and reactogenicity data up to at least 7 days post-vaccination of the first 25% of all subjects will be performed (see Section 8.10.2 of the Protocol for more information).
- ***In preparation of the planned IDMC evaluation, analysis of safety and reactogenicity data (including haematology/ biochemistry parameters) up to at least 30 days post-vaccination of all enrolled subjects will be performed.***

- The first main analysis on all subjects will be performed when all data up to 30 days post-vaccination are available (primary endpoints). In order to maintain the blind, this analysis by group will be performed by an independent statistician and the results which would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). No individual data listings will be provided.
- A second analysis will be performed when all data up to 90 days post-vaccination are available (secondary endpoints). At this point, the GSK statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided. Given that summary results may unblind some specific subjects, the study will be conducted in a single-blind manner from this point onwards, with subjects remaining blinded up to study conclusion and the investigators will not have access to the treatment allocation up to study conclusion.
- The final analysis will be performed when all data up to study conclusion are available. All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage.
- An integrated study report presenting all analyses will be written and made available to the investigators at the time of final analysis.
- If 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=web posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final Analysis	E1_01	Study report CTRS	N	Yes	All tables from TFL dated 01JUN2018
Analysis of Day 30	E1_04	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017
Analysis of Day 90	E1_05	Internal CTRS	N	Yes	All tables from TFL dated 13NOV2017

8.2. Statistical considerations for interim analyses

No interim analysis will be performed.

9. CHANGES FROM PLANNED ANALYSES

In order to align to ICH and CDISC terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

Changes in Amendment 1 mainly include the following.

For the sequence of analysis, the IDMC evaluation was newly added to review all available safety and reactogenicity data (including Day 30 haematology and biochemistry parameters) of all enrolled subjects up to at least 30 days post administration of the study vaccine or placebo.

Since the document of criteria for eliminating subjects from analysis will not be used anymore, the table of Elimination codes has been modified for more clarity. Attribution of code 1070 to a subject requires CRDL confirmation. Attribution of these elimcodes including1040, 2040, 2050, 2060, 2070 and 2120 to subject need CRDL review of individual data listings.

In the analysis of immunogenicity section, the distribution of fold increase of the antibody titres against RSV-A and RSV-B and concentrations against NEO have been added.

For the analysis of safety, the percentage of subjects reporting each individual solicited local AE (any, each grade, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be tabulated based on maximum intensity per subject for each study vaccine group; the percentage of subjects reporting each individual solicited general AE (any, each grade, any related, any Grade 2 related, any Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will also be based on maximum intensity per subject for each study vaccine group.

Evaluation of last secondary objective 'To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion' will be performed based on MA-RTIs rather than MA-RSV associated RTIs.

The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). Hence the SAP does not need to define handling of data between the LOD and LLOQ anymore, as results will only be provided as of the LLOQ. It only needs to be defined that for results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.

Algorithm for handling of data of RSV-B neutralising antibody tires between the LOB and LLOQ is defined as similar as for RSV-A by considering the LOB for RSV-B is 6.

Additional analysis of the IgG total and IgG1 subclass and analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data have been added.

Changes of TFL/TOC

- ***In the analysis of safety section, figures of 'Individuals results of haematological (haemoglobin level, white blood cells and platelet count) and biochemical (ALT, AST and creatinine) parameters outside of the normal ranges in each group' has been added to replace the figures of 'Mean profile of haematological and biochemical parameters change from baseline (Day 0)';***
- ***In the analysis of safety section, the titles in all tables reporting 'Incidence and nature of symptoms (solicited and unsolicited) during the 7-day and 30-day post-vaccination period' have been changed from 'with causal relationship to' to 'considered related to vaccination';***
- ***In the analysis of safety section, analysis on 'Incidence of solicited local/general symptoms reported during the 7-day post-vaccination period' will be summarized based on maximum intensity for each grade per subject for each group; therefore, analysis on 'incidence of solicited local/general symptoms reported during the 7-day post-vaccination period, including >=grade 2 category' will not be generated.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects reporting the occurrence of adverse events within the 7-day and 30-day post-vaccination period' will be added.***
- ***In the analysis of safety section, analysis on 'Number (%) of subjects with serious adverse events during the study period including number of events reported' and 'Number (%) of subjects with serious adverse events considered related to vaccination during the study period including number of events reported' by %UNSOL (EVENT=1) will not be reported because %CTR_SAE macro has been adapted to generate SAE, related SAE, fatal SAE and related fatal SAE.***
- ***In the analysis of safety section, analysis on 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs), during the 30-day, 60-day or 90-day post-vaccination period and up to study end' will be reported; Therefore, 'Number and percentage of subjects reporting one medically attended RSV-associated RTI and medically attended RTI (all causes) within the 30-day post-vaccination period or throughout the study period' will not be generated;***
- ***In the analysis of medically attended RTIs, viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be only listed in the individual listings; therefore, analysis on 'Descriptive statistics of the viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases (All vaccinated subjects)' will not be reported;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of RSV-B will be added;***
- ***In the analysis of immunogenicity section, tables/figures related to the analysis of the IgG total and IgG1 subclass will be added;***
- ***In the analysis of immunogenicity section, tables related to the analysis of anti-RSV A and anti-PCA in the subset of subjects with IgG/IgG1 data available will be added.***

Changes in Amendment 2 mainly include the following.

- ***In the analysis of immunogenicity section, the analysis on GM ratios between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, the analysis on GM ratios of fold increase post/pre (Day 30/Day 0) between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers has been added for Day 90 and final analysis.***

Changes of TFL/TOC

- ***In the analysis of safety section, figures of "Individual results of hemoglobin levels beyond grade 2" will be reported for Day 90 and final analysis to replace the figures of "Individual results of hemoglobin levels outside of normal range";***
- ***In the analysis of safety section, figures of "Individual results of white blood cells counts levels lower than LL" and figures of "Individual results of white blood cells counts levels higher than UL" will be reported for Day 90 and final analysis to replace the figures of "Individual results of white blood cells counts levels outside of normal range".***
- ***In the analysis of immunogenicity section, one new template (Template 54) for "Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)" has been added for Day 90 and final analysis;***
- ***In the analysis of immunogenicity section, one new template (Template 55) for "Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)" has been added for Day 90 and final analysis;***

Changes in Amendment 3 mainly include the following.

Changes of TFL/TOC for final analysis

- ***All tables concerned with 'Incidence and nature of symptoms (solicited and unsolicited)' have been moved to Annex; such tables for Grade 3 are kept as in-text tables;***
- ***Tables of 'Incidence of solicited local/general symptoms reported during the 7-day (Days 0-6) post-vaccination period' have been moved to Annex; such tables by maximum intensity are kept as in-text tables and corresponding figures have been newly generated for the final analysis, that is, 'Percentage of subjects reporting solicited local/general symptoms (any grade / grade 3) during the 7-day post-vaccination period';***
- ***All tables concerned with 'Percentage of subjects reporting the occurrence of unsolicited symptoms' have been moved to Annex; Such tables for Grade 3 and/or considered related to vaccination are kept as in-text tables with the simplification by removing the columns of LL and UL;***

- ***Tables of 'Percentage of subjects reporting the occurrence of SAE within the 30-day (Days 0-29) post-vaccination period/throughout the study period' are kept as in-text tables with the simplification by removing the columns of LL and UL;***
- ***All tables concerned with 'Number (%) of subjects reporting the occurrence of adverse events' have been moved to Annex;***
- ***All tables of 'Number and percentage of subjects reporting the occurrence of medically attended respiration tract infections (MA-RTIs)' have been moved to Annex; MA-RTIs reported up to DBF of final analysis is kept as one in-text table with the simplification by removing the columns of LL and UL;***
- ***The table of 'Compliance in returning symptom information' and all tables concerned with 'Number and percentage of subjects taking a concomitant medication' have been moved to Annex;***
- ***The table of 'Exploratory comparisons between groups in terms of percentage of subjects reported any Grade 2/3 AE and/or any fever >38.5°C and/or any vaccine-related SAE during the 7 day (Days 0-6) Post- vaccination period' will not be reported in the final analysis;***
- ***The table of 'Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges' has been moved to Annex; Three splitted in-text tables for ALT/AST /Eosinophils, Creatinine/Lymphocytes/White Blood Cells and Haemoglobin/ platelet count/ Neutrophils have been generated, separately;***
- ***The table of 'Summary of haematology and biochemistry results by maximum grade' has been moved to Annex; One newly formatted in-text table of 'Summary of haematology and biochemistry results by maximum grade in the specified category' has been generated by collapsing the categories of unknown/grade 0 and grade 1 then renaming the new category of 'other', keeping grade 2, 3 and 4 column, and removing the column of n;***
- ***The table of 'Summary of haematology change from baseline by maximum grade' has been moved to Annex; One newly formatted in-text table of 'Summary of haematology change from baseline by maximum grade in the specified category' has been generated by collapsing the categories of unknown/grade 0 and grade 1 then renaming the new category of 'other', keeping grade 2, 3 and 4 column, and removing the column of n;***

Changes in Amendment 4 mainly include the following.

Please check the dry run meeting minutes for details.

C.A.R.S./Clinical R&D/RSV F/Studies/021 (204812)/11 Statistics/11.05 General/11.05.03 Meeting Material/Analysis E01_01/RSV F-021 (204812) Dry Run Minutes E01_01.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…).

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper:Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

Dewé W, Durand Ch, Marion S *et al*. A multi-criteria decision making approach to identify a vaccine formulation. *Journal of Biopharmaceutical Statistics*, 2015; epublication ahead of print: DOI: 10.1080/10543406.2015.1008517.

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day and month are missing, 30 June is used.
- Onset day for an event (ae, medication, vaccination, …): The onset day is the number of days between the last study vaccination & the start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.
- Association of an event to the primary epoch: An adverse event belongs to the primary epoch, if the onset date is before and excluding Visit 5 or the last contact date, whichever is coming first.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose.

11.2.3. Demography

- Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 month when month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.
- Conversion of weight to kg

The following conversation rule is used:

  - Weight in Kilogram = weight in Pounds / 2.2
  - Weight in Kilogram = weight in ounces / 35.2

  The result is rounded to 2 decimals.

- Conversion of height to cm

The following conversation rule is used:

  - Height in Centimetres = Height in Feet * 30.48
  - Height in Centimetres = Height in Inch * 2.54

  The result is rounded to the unit (ie no decimal).

- Conversion of temperature to °C

The following conversion rule is used:

  - Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

11.2.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- A seronegative subject is a subject whose antibody titre/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre/concentration is greater than or equal to the cut-off value of the assay.
- The Geometric Mean Concentrations/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres 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 calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.
- In order to compute fold increase of antibody titres/concentrations (ratio) between post-vaccination and pre-vaccination titres/concentrations and for GMC/GMT calculation, antibody titres/concentrations below the assay cut-off will be given an arbitrary value of half the cut-off.
- ***The cut-off for the updated (qualified) version of the PCA assay will be set at the level of the assay LLOQ (9.60 µg/mL). For results below the cut-off (LLOQ), an arbitrary value of half of the cut-off will be considered for calculation of GMC and fold increase.***
- ***Considering cut-offs or neutralising antibody against RSV-A and RSV-B are below the assays' LLOQ, the following rules will be applied:***

Assay	***Raw result***	***Derivation for seropositivity status***	***Derivation for GMT calculation***	***Derivation for fold-increase between Post and Pre-vaccination titres***
Neutra RSV-A	***<8***	***NEG***	***4***	***LLOQ/2***
	[8-LLOQ[	***POS***	***8***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***
Neutra RSV-B	***<6***	***NEG***	***3***	***LLOQ/2***
	[6-LLOQ[	***POS***	***6***	***LLOQ/2***
	≥LLOQ	***POS***	***Exact value***	***Exact value***

- ***Vaccine response to the RSV neutralising antibodies (anti-RSV-A and anti-RSV-B) will be defined as:***
  - ***At least a 4-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre <7 log2 (<128).***
  - ***At least a 3-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in [7-8] log2 ([128-256]).***
  - ***At least a 2.5-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in >8-10 log2 (>256-1024).***

- ***At least 1-fold from pre-vaccination if pre-vaccination neutralising antibody titre >10 log2 (>1024).***

- ***All CI computed will be two-sided 95% CI.***

11.2.5. Safety

- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
  - Doses without symptom sheets documented will be excluded.
- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- The preferred route for recording temperature in this study will be oral. For the analysis, temperatures will be coded as follows:

Grade	Temperature for oral, axillary or tympanic route	Temperature for rectal route
0	< 37.5°C	< 38.0°C
1	≥ 37.5°C - ≤ 38.5°C	≥ 38.0°C - ≤ 39.0°C
2	> 38.5°C - ≤ 39.5°C	> 39.0°C - ≤ 40.0°C
3	> 39.5°C	> 40.0°C

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered
Concomitant medication	All subjects with study vaccine administered

The intensity scale of the following solicited AEs will be assessed as described:

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults:

0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

The maximum intensity of fever will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults (via the preferred route for recording temperature in this study which is oral):

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

The investigator assessed the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment was based on the investigator's clinical judgement.

For clintrial.gov and EudraCT posting purposes, 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 name	Lower level term code	Corresponding Primary Term code
Pain	Pain	10033371	10033371
Redness	Erythema	10015150	10015150
Swelling	Swelling	10042674	10042674
Fatigue	Fatigue	10016256	10016256
Fever	Fever	10016558	10037660
Gastroinstestinal symptoms	Gastroinstestinal disorder	10017944	10017944
Headache	Headache	10019211	10019211

11.2.6. Number of decimals displayed

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age, SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
Immunogenicity	Ratio of GMT/GMC	2

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3 CALCULATION OF INDIVIDUAL AND OVERALL DESIRABILITY INDEX

The section below provide the details on how to calculate individual desirability index and overall desirability index score based on Annex E in the Protocol.

Reactogenicity

A logistic regression model will be fitted on each reactogenicity endpoint (any Grade 2/3 general AE and any related SAE, Grade 2/3 fever) reported during the 7-day follow-up period after vaccination, including all RSV formulations.

- The vaccine group as the fixed effect
- The age groups (18-32 years and 33-45 years) as the categorical covariant if deemed necessary.

The estimation of indication rate will be tabulated by treatment group. The SAS codes can be used as reference:

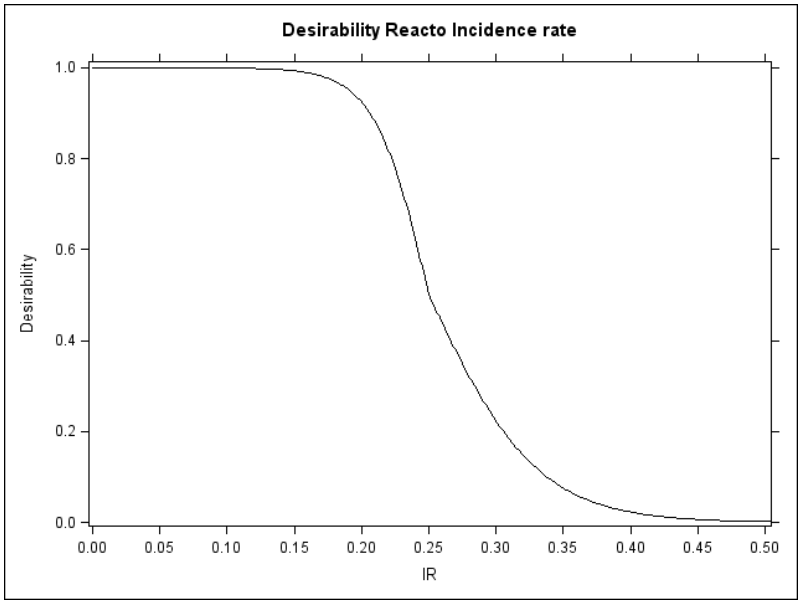
```
proc logistic data=React;
  class Treatment AgeGroup / param=glm;
  model response (event='AE')= Treatment| AgeGroup;
  lsmeans Treatment / ILINK e diff oddsratio adjust=bon cl;
run;
```

For any Grade 2/3 general AEs and any related SAEs, the incidence rate estimate (IR) will be transformed in a [0,1] desirability index using the following function:

$$DR1 = \begin{cases} \dfrac{1}{1+\exp(-50*(0.25-IR))}, & \text{if } IR \le 0.25 \\ \dfrac{1}{1+\exp(-25*(0.25-IR))}, & \text{if } IR \ge 0.25 \end{cases}$$

where IR is the incidence rate estimated by the model. This function will allocate a desirability value of 1, 0.5 and 0 to incidence rate equal to 0.1, 0.25 and 0.5 respectively (see Figure 2). But the calculation equally weights Grade 2/3 general AEs and any related SAEs.

Figure 2 Desirability function for the incidence rate of Grade 2/3 general AEs and related SAEs - for each investigational RSV vaccine formulation

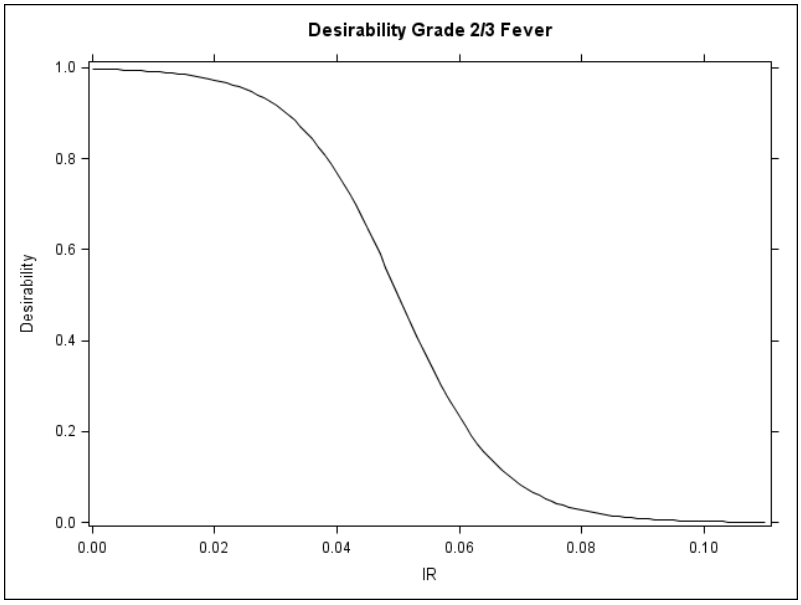


For Grade 2/3 fever, the incidence rate estimate (IR) will be transformed in a [0,1] desirability index using the following function:

$$DR2 = \frac{1}{1+\exp(-120*(0.05-IR))}$$

where IR is the incidence rate estimated by the model. As illustrated in Figure 3, the function will allocate desirability values of 1, 0.5 and 0 to incidence rate equal to 0, 0.05 and 0.1 respectively.

Figure 3 Desirability function for the incidence rate of Grade 2/3 fever - for each investigational RSV vaccine formulation



Finally, the reactogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DR = \sqrt{DR1 * DR2}$$

Immunogenicity

The ANCOVA model will be fitted on the log-transformed titre for each immune response of neutralising anti-RSV-A and PCA separately including

- The vaccine group as the fixed effect
- The pre-vaccination titre/concentration and age groups (18-32 years and 33-45 years) as the covariates if deemed necessary

The mean estimations of GMTs/GMCs for each treatment group at Day 30 and its 95% CI will be provided for immunogenicity desirability calculation. The estimated GMT and LL will be tabulated by treatment group.

As formulations inducing a high immune response will be considered suitable, the lower limit (LL) of the estimated GMT/C adjusted for pre-vaccination titres will be the statistical criterion considered for decision making.

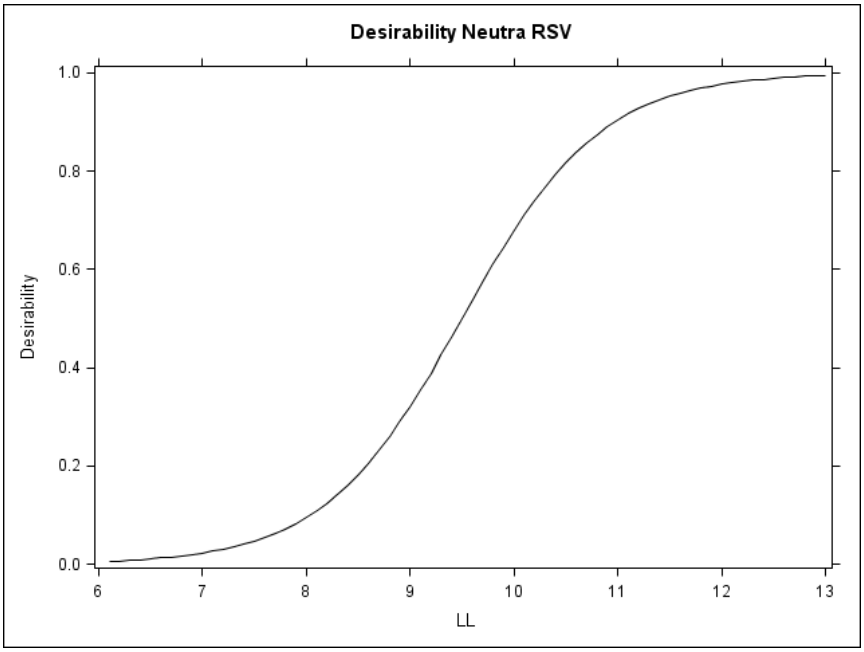
Neutralising anti-RSV-A titres

The LL of the GMT estimate will be transformed into a [0, 1] desirability index using the function:

$$\mathrm{DI1} = \frac{1}{1 + \exp(1.5 * (9.5 - \mathrm{LL}))}$$

where LL is the lower limit of the 95% confidence interval of the GMT adjusted for pre-vaccination titres in log base 2. The function was chosen to have a desirability of 0 at LL value ≤ 6 log2 (=128), and a desirability of 1 at LL value ≥ 13 log2. This function is illustrated in Figure 4.

Figure 4 Desirability function for neutralising anti-RSV-A GMTs - for each investigational RSV vaccine formulation



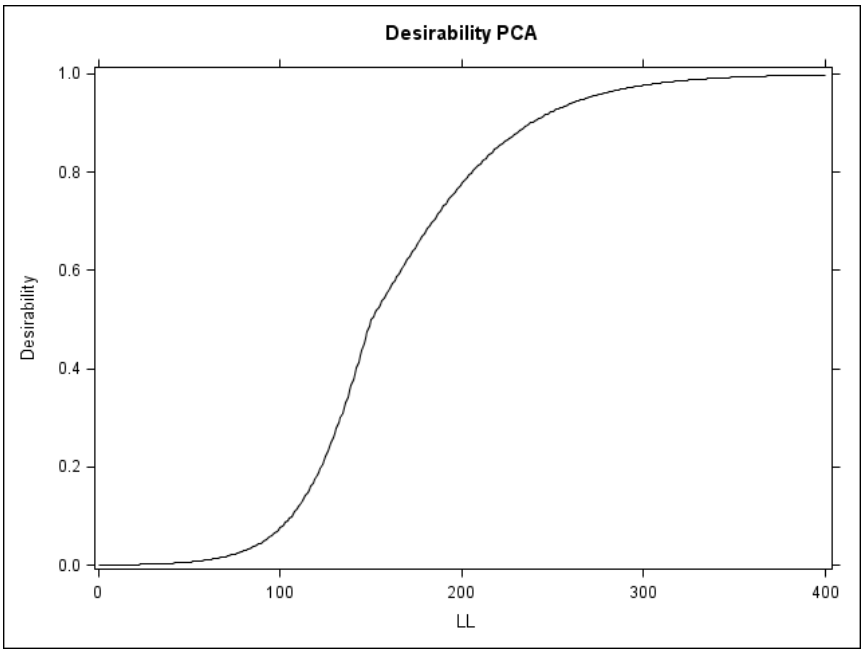
PCA concentrations

The LL of the GMC adjusted for pre-vaccination titres estimate will be transformed using the following function:

$$\mathrm{DI2} = \begin{cases} \dfrac{1}{1 + \exp(0.05 * (150 - \mathrm{LL}))}, & \text{if } \mathrm{LL} \leq 150 \\ \dfrac{1}{1 + \exp(0.025 * (150 - \mathrm{LL}))}, & \text{if } \mathrm{LL} \geq 150 \end{cases}$$

As illustrated in Figure 5, a PCA response of 25, 150 and 400 µg/mL will have a desirability value of 0, 0.5 and 1 respectively.

Figure 5 Desirability function for PCA concentrations - for each investigational RSV vaccine formulation



Finally, the immunogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DI = \sqrt{DI1 * DI2}$$

Overall desirability index

The overall desirability index for each formulation will be obtained by computing the following weighted geometric mean: $D = DR^{0.4} * DI^{0.6}$.

14. ANNEX 4: STUDY SPECIFIC MOCK TFL

The following draft study specific mock TFLs will be used. The data display, title and footnote 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. These editorial/minor changes will not lead to a SAP amendment.

Template #	Table Title	Macro
Template 1	Number of subjects enrolled into the study as well as the number of subject excluded from PPS analysis with reasons for exclusion	%ELIMLIST
Template 2	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=1)
Template 3	Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)	%DROP_SUM (OTH=0)
Template 4	Number of subjects at each visit and list of withdrawn subjects (Exposed set)	%DROPOUT
Template 5	Summary of demographic characteristics (Exposed set)	%DEMOGRA
Template 6	Summary of demographic characteristics by age category (Exposed set)	%DEMOGRA
Template 7	Number of subjects by center (Exposed set)	%CENTER
Template 8	Number of subjects by center for each age category (Exposed set)	%CENTER
Template 9	Number of subjects by country and center (Exposed set)	%CENTER
Template 10	Deviations from specifications for age and intervals between study visits (Exposed set)	%INT_VAL
Template 11	Summary of vital signs characteristics (Exposed set)	%VITAL_SIGNS
Template 12	Study Population (Exposed set)	%CTR_DEMOG
Template 13	Number of enrolled subjects by country	%FREQ_DIS
Template 14	Number of enrolled subjects by age category	%FREQ_DIS
Template 15	Minimum and maximum activity dates (Exposed set)	%DATE
Template 16	Incidence and nature of symptoms (solicited and unsolicited) reported during the **7-day** (Days 0-6) post-vaccination period (Exposed set)	%LOCGEN
Template 17	Daily prevalence of **any fever** during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%SYMPLOT
Template 18	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ
Template 19	Incidence of solicited **local** symptoms reported during the 7-day (Days 0-6) post-vaccination period by **maximum intensity** (Exposed set)	%FREQ
Template 20	Incidence of solicited **general** symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)	%FREQ
Template 21	Incidence of solicited **general** symptoms reported during the 7-day (Days 0-6) post-vaccination period **by maximum intensity** (Exposed set)	%FREQ
Template 22	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class	%UNSOL

	and Preferred Term, during the **30-day** (Days 0-29) post-vaccination period (Exposed set)	
Template 23	***Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, during the 30-day (Days 0-29) post-vaccination period (Exposed set)***	***%UNSOL***
Template 24	Listing of **SAEs** reported up to study end (Exposed set)	%SAE
Template 25	Number (%) of subjects with serious adverse events up **Day 7** (Exposed set)	%CTR_SAE
Template 26	Compliance in returning symptom information (Exposed set)	% COMPLI
Template 27	Number and percentage of subjects taking a **concomitant medication** during the **7- day** (Days 0-6) post -vaccination period (Exposed set)	%CMED_INC
Template 28	Exploratory comparisons between groups in terms of percentage of subjects reported any **Grade 2/3 AE** and/or **any fever >38.5°C** and/or **any vaccine-related SAE** during the **7 day** (Days 0-6) Post- vaccination period (Exposed set)	%COMP_FQ_AE
Template 29	Solicited and unsolicited symptoms experienced by **at least 5 % of subjects**, classified by MedDRA Primary System Organ Class and Preferred Term within the **30-day** (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)	%UNSOL (NIH=5, EVENT=1)
Template 30	Distribution of change from baseline in **haematology and biochemistry** with respect to normal laboratory ranges (Exposed set)	%HAEMATO_BIOCH
Template 31	Summary of **haematology and biochemistry** results by maximum grade from **VISIT 2 (D7) up to VISIT 3 (D30)** versus baseline (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 32	***Summary of haematology and biochemistry results by maximum grade in the specified category from VISIT 2 (D7) up to VISIT 3 (D30) versus baseline (Exposed set)***	***%freq_dis***
Template 33	Summary of **haematology** change from baseline by maximum grade from **VISIT2 (D7) up to VISIT 3 (D30)** (Exposed set)	%HAEMATO_BIOCH_GR_CHANGE
Template 34	***Summary of haematology change from baseline by maximum grade in the specified category from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)***	***%freq_dis***
Template 35	Individual results of **hemoglobin** levels **outside of the normal ranges** in <*group*> (Exposed set)	%HB_PROFIL
Template 36	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)	%GMT
Template 37	Number and percentage of subjects with **anti-RSV-A** neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)	%GMT
Template 38	Geometric mean of the individual ratio of **anti-RSV-A** neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)	%GMRACT
Template 39	GMTs and their 95% CIs for **anti-RSV-A** neutralising antibody at each timepoint (Per protocol set)	%GMTPLOT*
Template 40	Kinetics of GMTs for **anti-RSV-A** neutralising antibody on subjects with results available at all timepoints (Per protocol set)	%KIN_GM*
Template 41	Distribution of **anti-neogenin** antibody concentration (Exposed set)	%DIS
Template 42	Distribution of fold of **anti-neogenin** antibody concentration (Exposed set)	%DIS
Template 43	Distribution of **anti-RSV-A** neutralising antibody titer (Per	%DIS

	protocol set)	
Template 45	Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set)	%DIS
Template 46	Reverse cumulative distribution curves for **anti-RSV-A** neutralising antibody titers in each group at pre-vaccination (Per protocol set)	%REVCUM
Template 47	Individual results of **anti-RSV-A** neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)	%SCATTERPLOT*
Template 48	Vaccine response for **anti-RSV-A** neutralising antibody titer at each post-vaccination timepoint (Per protocol set)	%HUM_RESP*
Template 49	Estimated GMTs and 95% CIs for **anti-RSV-A** neutralising antibody titre (Per protocol set)	%GMT_ANOVA
Template 50	Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for **anti-RSV A** neutralizing antibody titre at **Day 30** (Per protocol set)	%GMT_RATIO
Template 51	Individual kinetics of **anti-neogenin** antibody concentrations by group (Exposed set)	%NEO_INDKIN*
Template 52	GM of individual ratios (fold increase post over pre) and their 95% CIs for **anti-RSV F IgG1 and IgG total** antibody assays and each group, at **Day 30** (Per protocol set)	%GMRPLOT*
Template 53	Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for **anti-RSV F IgG1** antibody concentrations at **Day 30** (Per protocol set)	%GMF_RATIO*
Template 54	***Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)***	***%GM_RATIO_PRE.SAS****
Template 55	***Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)***	***%GM_RATIO_FI.SAS****
Template 56	***Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)***	***%Immuno_DI****
Template 57	***Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)***	***%Reacto_DI****
Template 58	***Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)***	***%Overall_DI****
Template 59	***Percentage of subjects reporting solicited local symptoms (any grade / grade 3) during the 7-day post-vaccination period (Exposed set)***	***%GFREQ***

* Name of specific macros created in study RSV F-001 (116969), RSV F-020 (201510)

***** *Name of specific macros created in study RSV F-021 (204812)*

****** *It is the simplified version of Template 22 without UL and LL added for the final analysis*

Template 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the PPS analyses with reasons for exclusion

	Total			*<each group>*	
Title	**n**	**s**	**%**	**n**	**s**
Total enrolled cohort					
Study vaccine dose not administered at all but subject number allocated (code 1030)					
Exposed set					
<*Reason for elimination & elimination code*>					
<*Reason for elimination & elimination code*>					
Per protocol set for immunogenicity					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered Per protocol set relative to the Exposed set

Template 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<each group>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdraw:		
Serious Adverse Event		
Non-serious adverse event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Others		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
withdrawn = number of subjects who did not come for the last study visit

Template 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Exposed set)

	<each group>	Total
Number of subjects vaccinated		
Number of subjects completed		
Number of subjects withdrawn		
Reasons for withdrawal :		
Serious Adverse Event		
Non-Serious Adverse Event		
Protocol violation		
Consent withdrawal (not due to an adverse event)		
Migrated/moved from study area		
Lost to follow-up (subjects with incomplete vaccination course)		
Lost to follow-up (subjects with complete vaccination course)		
Sponsor study termination		
Other - <reason>		
Other - <reason>		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last study visit

Template 4 Number of subjects at each visit and list of withdrawn subjects (Exposed set)

Group	Visit	N	Withdrawn Subject number	Reason for withdrawal
<each group>	VISIT 1 (D0)			
	VISIT 2 (D7)			
	VISIT 3 (D30)			
	VISIT 4 (D60)			
	VISIT 5 (D90)			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects who are still in the study up to the visit
Withdrawn = Subject who did not return after the visit

Template 5 Summary of demographic characteristics (Per Protocol Set)

		<each group> (N=)		Total (N=)	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Ethnicity	American Hispanic or Latino				
	Not American Hispanic or Latino				
Geographic Ancestry	African Heritage / African American				
	American Indian or Alaskan Native				
	Asian - Central/South Asian Heritage				
	Asian - East Asian Heritage				
	Asian - Japanese Heritage				
	Asian - South East Asian Heritage				
	Native Hawaiian or Other Pacific Islander				
	White - Arabic / North African Heritage				
	White - Caucasian / European Heritage				
	Other				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Template 6 Summary of demographic characteristics by age category (Exposed set)

		<*each group*> (N=)				Total (N=)			
		<*subgroup*>		<*subgroup*>		<*subgroup*>		<*subgroup*>	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination	Mean								
	SD								
	Median								
	Minimum								
	Maximum								
Ethnicity	American Hispanic or Latino								
	Not American Hispanic or Latino								
Geographic Ancestry	African Heritage / African American								
	American Indian or Alaskan Native								
	Asian - Central/South Asian Heritage								
	Asian - East Asian Heritage								
	Asian - Japanese Heritage								
	Asian - South East Asian Heritage								
	Native Hawaiian or Other Pacific Islander								
	White - Arabic / North African Heritage								
	White - Caucasian / European Heritage								
	Other								

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

<subgroup> by age category:
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects

Template 7 Number of subjects by center (Exposed set)

	<each group>	Total	
Center	**n**	**n**	**%**
PPD			
PPD			
..			
All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 8 Number of subjects by center for each age category (Exposed set)

	30 PreF		60 PreF		120 PreF		Control		Total			
	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y	33-45Y	18-32Y		33-45Y	
Center	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**%**	**n**	**%**

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 9 Number of subjects by country and center (Exposed set)

		<each group>	Total	
Country	**Center**	**n**	**n**	**%**
	…			
	All			
	…			
All	All			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Template 10 Deviations from specifications for age and intervals between study visits (Exposed set)

		Age	Dose:1-PI (D30)	Dose:1-PI (D60)	Dose:1-PI (D90)	Dose:1-CONCLUSION
Group		**Protocol**	**Protocol**	**Protocol**	**Protocol**	**Protocol**
		from 18 to 45 years	from 30 to 44 days	from 56 to 70 days	from 86 to 100 days	from 330 to 390 days
<each group>	n					
	N					
	%					
	range					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 11 Summary of vital signs characteristics at VISIT 1 (Day 0) (Exposed set)

		<each group> N =	Total N =
Characteristics	**Parameters**	**Value**	**Value**
Height (Cm)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Weight (Kg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Heart rate (Beats per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Respiratory rate (Breadth per minute)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Systolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		
Diastolic blood pressure (Mmhg)	Mean		
	SD		
	Median		
	Minimum		
	Maximum		
	Unknown		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = total number of subjects
Value = value of the considered parameter
SD = standard deviation

Template 12 Study Population (Exposed set)

Number of subjects	<each group>	Total
Planned, N		
Randomised, N (Exposed set)		
Completed, n (%)		
Demographics	**<each group>**	**Total**
N (Exposed set)		
Females:Males		
Mean Age, years (SD)		
Median Age, years (minimum, maximum)		
White - caucasian / european heritage, n (%)		
Asian – South East Asian heritage, n (%)		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 13 Number of enrolled subjects by country

		<each group> **N =**	**Total N =**
Characteristics	**Categories**	**n**	**n**
Country	Czech Republic		
	Australia		
	...		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 (18-45 years)		
	Missing		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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 dose 1 unknown

Template 15 Minimum and maximum activity dates (Exposed set)

Group	**Activity number**	**Activity Description**	**Minimum date**	**Maximum date**
<each group>	10	VISIT 1 (DAY 0)		
	20	VISIT 2 (M 1)		
	30	VISIT 3 (M 2)		
	40	VISIT 4 (M 3)		

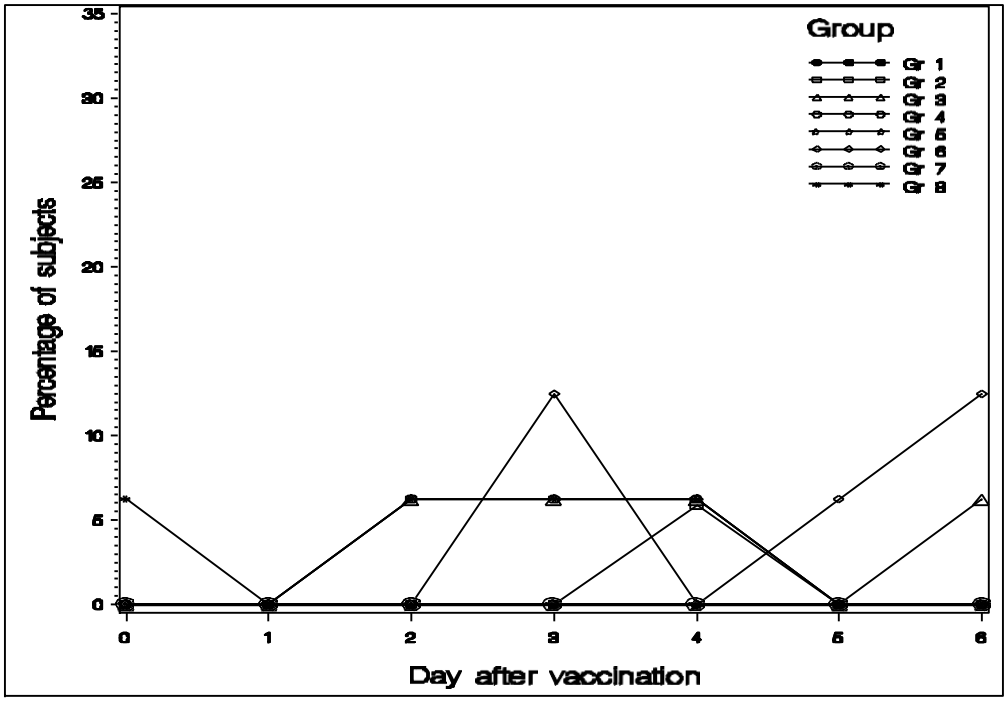
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 16 Incidence and nature of symptoms (solicited and unsolicited reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
<*each group*>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Note: the same table will be generated by group/sub-group, with sub-group= age category (see SAP).

Template 17 Daily prevalence of any fever during the 7-day (Days 0-6) post-vaccination period (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 18 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤ 50					
	>50 and ≤ 100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: $\leq$ 20 mm
1: > 20 mm to $\leq$ 50 mm
2: > 50 mm to $\leq$ 100 mm
3: > 100 mm

Template 19 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Onset ≤48h					
	Medical advice					
Redness (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					
Swelling (mm)	All					
	>20 and ≤50					
	>50 and ≤100					
	>100					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Type=Max grade & onset
All=any severity >Grade 0 for pain and any diameter >20mm for redness and swelling
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
The maximum intensity of local injection site redness/swelling was coded as follows for adults:
0: ≤ 20 mm
1: > 20 mm to ≤ 50 mm
2: > 50 mm to ≤ 100 mm
3: > 100 mm

Template 20 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Temperature (Oral) (°C)	All (≥37.5)					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related					
	>38.5 Related					
	>39.5 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF =120 µg PreF
Control = Placebo
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:
0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 21 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period by maximum intensity (Exposed set)

		<each group>				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Gastrointestinal symptoms	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Headache	All					
	Grade 1					
	Grade 2					
	Grade 3					
	Related*					
	Grade 2 Related					
	Grade 3 Related					
	Onset ≤48h					
	Medical advice					
Fever/(Oral) (°C)	All					
	>38.0					
	>38.5					
	>39.0					
	>39.5					
	Related*					
	>38.5 Related					
	>39.5 Related					
	Medical advice					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
All=any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral)
Related*= any grade>0 for Fatigue, Gastrointestinal symptoms, Headache and any >37.5°C for Temperature/(Oral) considered related to vaccination by the investigator
N=number of vaccinated subjects who returned the diary card
n/% = number/percentage of subjects reporting the AE at least once. Maximum intensity only
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Temperatures were coded as follows for adults:

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

Template 22 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Exposed set)

		<each group> N =			
				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**
At least one symptom					
<each SOC (code)>	<each PT (code)>				
...	..				
...	...				

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 23 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Exposed set)

		<each group> N =	
Primary System Organ Class (CODE)	***Preferred Term (CODE)***	***n***	*%*
At least one symptom			
<each SOC (code)>	*<each PT (code)>*		
...	*..*		
...	*...*		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom

Note: It is the simplified version of Template 22 without UL and LL added for final analysis

Template 24 Listing of SAEs reported up to study end (Exposed set)

Group	Sub. No.	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
<each group>															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

Template 25 Number (%) of subjects with serious adverse events up to study end (Exposed set)

			<each group> N =		
Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**n***	**n**	**%**
SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related SAE	At least one symptom				
	<each SOC>	<each PT term>			
Fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			
Related fatal SAE	At least one symptom				
	<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 26 Compliance in returning symptom information (Exposed set)

Group	**Number of doses**	**Doses NOT according to protocol**	**Number of general SS**	**Compliance % general SS**	**Number of local SS**	**Compliance % local SS**
<each group>						

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Template 27 Number and percentage of subjects taking a concomitant medication during the 7- day (Days 0-6) post -vaccination period (Exposed set)

	<*each group*>				
				95% CI	
	N	n	%	LL	UL
Any					
Any antipyretics					
Prophylactic antipyretics					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N= number of administered doses
n/%= number/percentage of subjects who took the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 28 Exploratory comparisons between groups in terms of percentage of subjects reported any Grade 2/3 AE and/or any fever >38.5°C and/or any vaccine-related SAE during the 7-day (Days 0-6) post-vaccination period (Exposed set)

								Difference in percentage (Group 1 minus Group 2)			
										95 % CI	
Group 1	N	n	%	Group 2	N	n	%	Difference	%	LL	UL
30 PreF				Control				30 PreF - Control			
60 PreF				Control				60 PreF - Control			
120 PreF				Control				120 PreF - Control			
60 PreF				30 PreF				60 PreF - 30 PreF			
120 PreF				30 PreF				120 PreF - 30 PreF			
120 PreF				60 PreF				120 PreF - 60 PreF			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with the administered dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 29 Solicited and unsolicited symptoms experienced by at least 5 % of subjects, classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period including number of events - SAE excluded (Exposed set)

		<each group> N =		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n***	**n**	**%**
At least one symptom				
<each SOC>	<each PT term>			

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 30 Distribution of change from baseline in haematology and biochemistry with respect to normal laboratory ranges (Exposed set)

			<each group >								
				Unknown		**Below**		**Within**		**Above**	
Laboratory parameter	**Timing**	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Aspartate Aminotransferase (AST)	PI(D7)	Unknown									
		Below									
		Within									
		Above									
	PI(D30)	…									
	PI(D60)	…									
	PI(D90)	…									
Creatinine	…	…									
Eosinophils	…	…									
Haemoglobin	…	…									
Lymphocytes	…	…									
Neutrophils	…	…									
Platelet count	…	…									
White Blood Cells (WBC)	…	…									

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo

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
PI(D7) = Post-vaccination at Day 7
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Note: For the final analysis, three newly added in-text tables of 'Distribution of change from baseline in ALT, AST and Eosinophil's with respect to normal laboratory ranges (Exposed set)', 'Distribution of change from baseline in Creatinine, Lymphocytes and White Blood Cells (WBC) with respect to normal laboratory ranges (Exposed set)' and 'Distribution of change from baseline in Hemoglobin, Neutrophils and Platelet count with respect to normal laboratory ranges (Exposed set)' will use Template 30.

Template 31 Summary of haematology and biochemistry results by maximum grade from VISIT 2 (D7) up to VISIT 3 (D30) versus baseline (Exposed set)

		VISIT2 (D7) up to VISIT3 (D30)												
		<each group >												
			Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**Baseline PRE(D0)**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alanine Aminotransferase (ALT) increase by factor	Unknown													
	Grade 0													
	Grade 1													
	Grade 2													
	Grade 3													
	Grade 4													
	Total													
Aspartate Aminotransferase (AST) increase by factor	…													
Creatinine	…													
Eosinophils increase	…													
Hemoglobin decrease	…													
Lymphocytes decrease	…													
Neutrophils decrease	…													
Platelet count decrease	…													
White Blood Cells (WBC) decrease	…													
White Blood Cells (WBC) increase	…													

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with at least one available result for the specified laboratory parameter and follow-up period
n/% = number/percentage of patients reporting at least once the laboratory event when the maximum grading over the follow-up period is considered
ALT/AST increase by factor: Grade 1 is 1.1-2.5xULN, Grade 2 is 2.6-5.0xULN, Grade 3 is 5.1-10xULN, Grade 4 is >10ULN; ULN is upper limit of the normal range.

Template 32 ***Summary of haematology and biochemistry results by maximum grade in the specified category from VISIT 2 (D7) up to VISIT 3 (D30) (Exposed set)***

		<each group > N =	
Laboratory parameter	***Maximum grade***	***n***	***%***
Alanine Aminotransferase(ALT) increase by factor	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Aspartate Aminotransferase(AST) increase by factor	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Creatinine	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Eosinophils increase	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Hemoglobin decrease	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Lymphocytes decrease	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Neutrophils decrease	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
Platelet count decrease	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
White Blood Cells (WBC) decrease	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		
White Blood Cells (WBC) increase	***Other***		
	Grade 2		
	Grade 3		
	Grade 4		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n = number of subjects in the specified category
% = n / Number of subjects with available results x 100
Other=all Unknown, Grade 0 and Grade 1

ALT/AST increase by factor: Grade 1 is 1.1-2.5xULN, Grade 2 is 2.6-5.0xULN, Grade 3 is 5.1-10xULN, Grade 4 is >10ULN; ULN is upper limit of the normal range.

Template 33 Summary of haematology change from baseline by maximum grade from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)

	VISIT2 (D7) up to VISIT3 (D30)												
	<each group >												
		Unknown		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
Laboratory parameter	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hemoglobin (Change from baseline)													

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
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
Hemoglobin (Female) change from baseline value (gm/dL): Grade 1 is any decrease-1.5, Grade 2 is 1.6-2.0, Grade 3 is 2.1-5.0 and Grade 4 is >5.0.

Template 34 ***Summary of haematology change from baseline by maximum grade in the specified category from VISIT2 (D7) up to VISIT3 (D30) (Exposed set)***

		<each group > N =	
Laboratory parameter	*Maximum grade*	*n*	*%*
Hemoglobin (Change from baseline)	*Other*		
	Grade 2		
	Grade 3		
	Grade 4		

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with the administered dose
n= number of subjects in the specified category
% = n / Number of subjects with available results x 100
Other=all Unknown, Grade 0 and Grade 1
Hemoglobin (Female) change from baseline value (gm/dL): Grade 1 is any decrease-1.5, Grade 2 is 1.6-2.0, Grade 3 is 2.1-5.0 and Grade 4 is >5.0.

Template 35 Individual results of hemoglobin levels outside of the normal ranges in < *group*> (Exposed set)

Note: This figure is shown as an example. For the unblinded report, one figure per group will be performed. For the blinded report, 4 graphs will be performed each of them presenting PPD subjects regardless of treatment (the first PPD subjects, from the PPD th to the PPD th subject…). The X axis will include Day 0, Day 7 and Day 30. The Y axis will be adapted according to each parameter.

Template 36 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs (Per protocol set)

				≥cut-off				GMT				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE										
		PI(D30)										
		PI(D60)										
		PI(D90)										

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 37 Number and percentage of subjects with anti-RSV-A neutralising antibody titer equal to or above <cut-off> and GMTs - by age category (Per protocol set)

					≥cut-off				GMT				
							95% CI			95% CI			
Antibody	**Group**	**Sub-Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Anti-RSV-A Neutralizing Antibody	<each group>	18-32Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										
		33-45Y	PRE										
			PI(D30)										
			PI(D60)										
			PI(D90)										

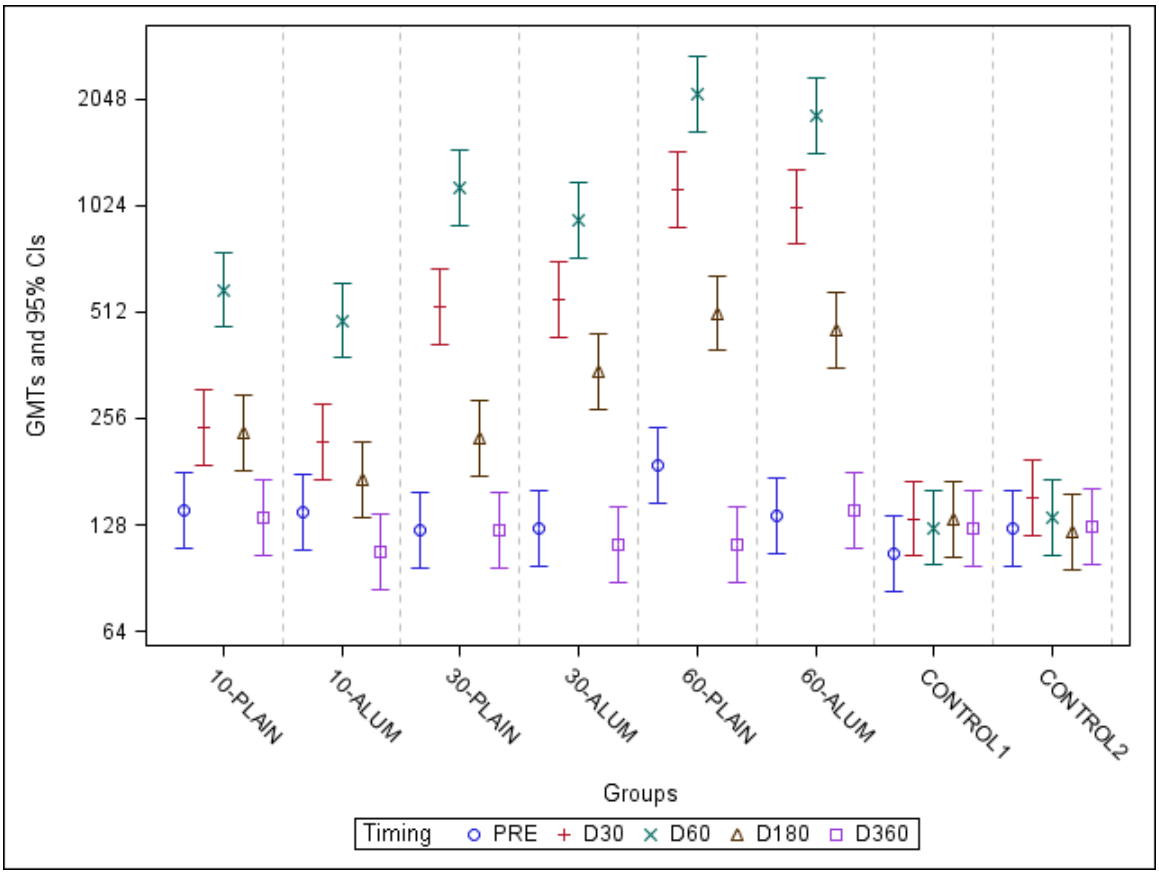
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
18-32Y = 18-32 years old subjects
33-45Y = 33-45 years old subjects
GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with available results
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
n/% = number/percentage of subjects with titer equal to or above specified value
MIN/MAX = Minimum/Maximum
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 38 Geometric mean of the individual ratio of anti-RSV-A neutralising antibody titers at each post-vaccination timepoint compared to pre-vaccination with 95% CI (Per protocol set)

						GMT ratio			
								95% CI	
Group	**N**	**Time point description**	**GMT**	**Time point description**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
<*each group*>		PI(D30)		PRE		PI(D30) / PRE			
		PI(D60)		PRE		PI(D60) / PRE			
		PI(D90)		PRE		PI(D90) / PRE			

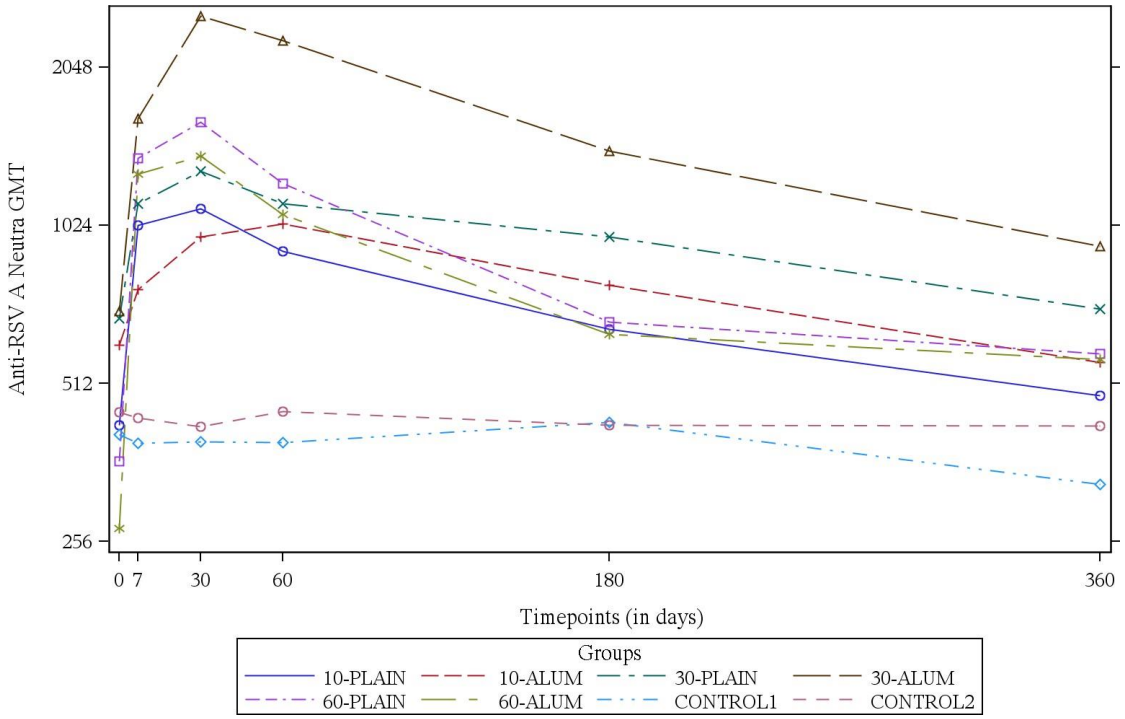
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 39 GMTs and their 95% CIs for anti-RSV-A neutralising antibody at each timepoint (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on all subjects
95% CI = 95% confidence interval
Note: This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 40 Kinetics of GMTs for anti-RSV-A neutralising antibody on subjects with results available at all timepoints (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer calculated on subjects with results available at all timepoints
Note:

- This graph is provided as an example. For each assay separately, this graph will display the 4 groups and the 4 immuno timepoints PRE, PI(D30), PI(D60) and PI(D90)
- For the kinetic of the estimated GMTs, footnote will be adapted as: GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures

Template 41 Distribution of anti-Neogenin antibody concentration (Exposed set)

				<55 ng/ml		≥55 ng/ml		≥100 ng/ml		≥150 ng/ml		≥200 ng/ml		≥250 ng/ml		≥300 ng/ml	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	<*each group*>	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 42 Distribution of fold of anti-neogenin antibody concentration (Exposed set)

				<1		>=1		>=1.5		>=2		>=2.5		>=3		>=3.5		>=4		>=4.5		>=5	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-neogenin antibody	<*each group*>	PI(D30)																					
		PI(D60)																					
		PI(D90)																					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 43 Distribution of anti-RSV-A neutralising antibody titer (Per protocol set)

				<7 Log2		≥7 Log2		≥8 Log2		≥9 Log2		≥10 Log2		≥11 Log2		≥12 Log2	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	*<each group>*	PRE															
		PI(D30)															
		PI(D60)															
		PI(D90)															

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PRE = Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 44 Distribution of fold of anti-RSV-A neutralising antibody titer by pre-vaccination titer category (Per protocol set)

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	30 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	60 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	120 PreF	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
	Control	<7	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		[7-8]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]8-9]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]9-10]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]10-11]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		]11-12]	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		> 12	PI (D30)																							
			PI (D60)																							
			PI (D90)																							
		Total	PI (D30)																							
			PI (D60)																							
			PI (D90)																							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

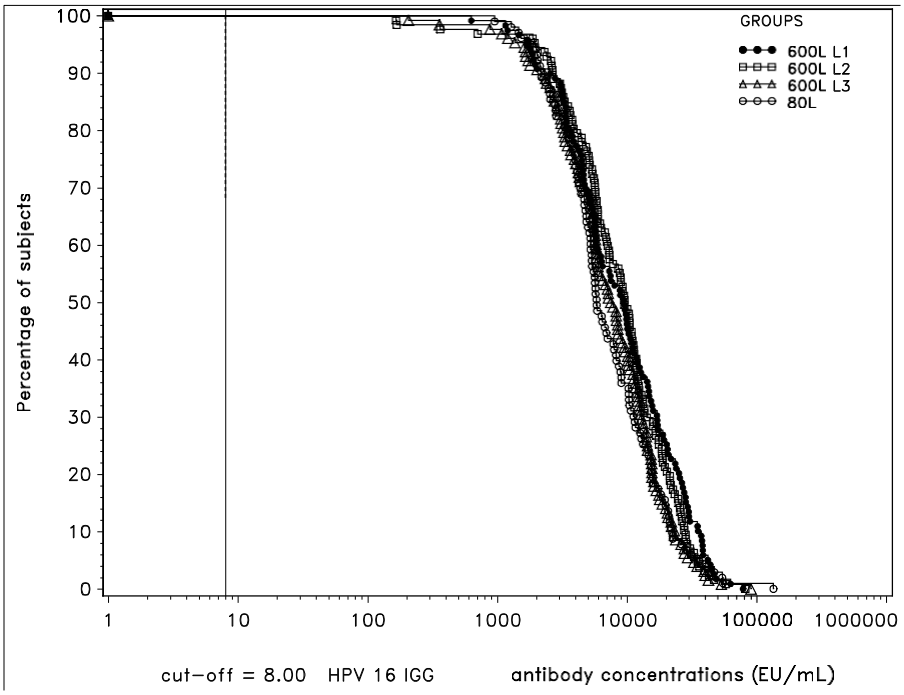
Template 45 Distribution of fold of anti-RSV-A neutralising antibody titer by cumulative pre-vaccination titer category (Per protocol set)

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anti-RSV A Neutralizing Antibody	30 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥11	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	60 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	120 PreF	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							

					<1		≥1		≥2		≥2.5		≥3		≥4		≥6		≥8		≥10		≥11		≥12	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥11	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
	Control	<7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥7	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥8	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥9	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		≥10	PI(D30)																							
			PI(D60)																							
			PI(D90)																							
		Total	PI(D30)																							
			PI(D60)																							
			PI(D90)																							

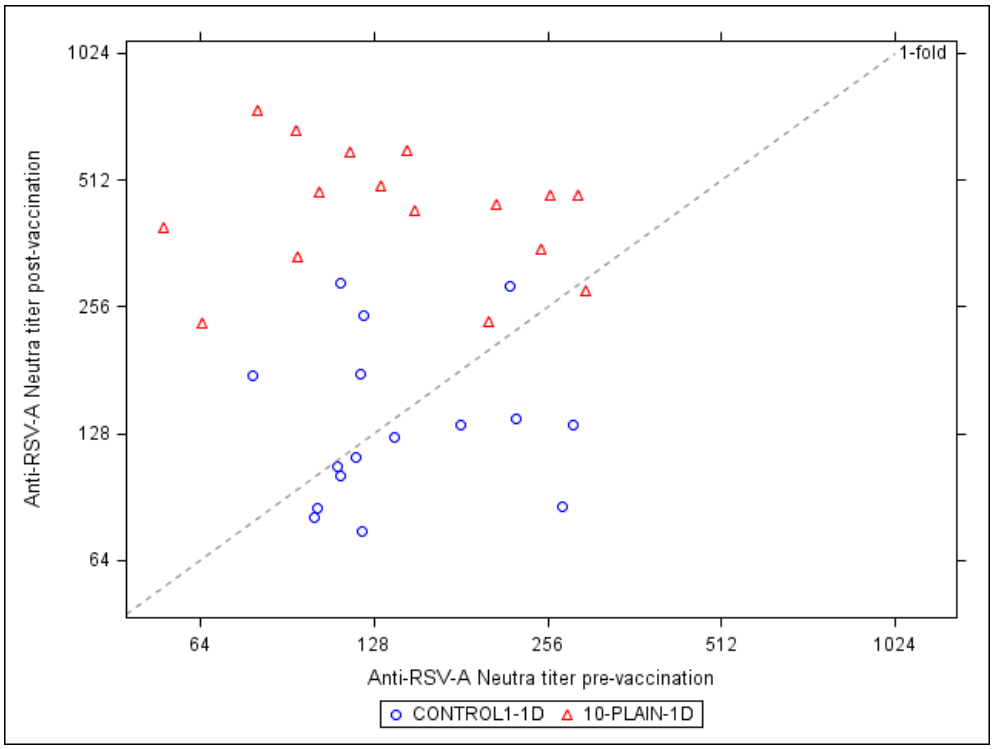
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
<7 = Log2 results are less than 7 at pre-vaccination
≥7 = Log2 results are ≥7 at pre-vaccination
≥8 = Log2 results are ≥8 at pre-vaccination
≥9 = Log2 results are ≥9 at pre-vaccination
≥10 = Log2 results are ≥10 at pre-vaccination
≥11 = Log2 results are ≥11 at pre-vaccination
Total = all subjects with pre-vaccination result available
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 46 Reverse cumulative distribution curves for anti-RSV-A neutralising antibody titers in each group at <each time point> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be provided for each time point and each assay comparing the values of the groups:30 PreF, 60 PreF, 120 PreF and Control.

Template 47 Individual results of anti-RSV-A neutralising antibody titer at Day <30/60/90> versus pre-vaccination in <each group> and Control (Per protocol set)



<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. The same graph will be generated for each assay and each timepoint separately (Day 30, 60, 90):

Template 48 Vaccine response for anti-RSV-A neutralising antibody titer at each post-vaccination timepoint (Per protocol set)

					Vaccine response*			
							95% CI	
Antibody	**Group**	**Post-vaccination timing**	**Pre-vaccination category (log2)**	**N**	**n**	**%**	**LL**	**UL**
<*each antibody*>	<*each group*>	PI(D30)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D60)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					
		PI(D90)	<7					
			[7-8]					
			]8-10]					
			>10					
			Total					

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Total = all subjects with pre-vaccination result available
*Vaccine response defined as :
For subjects with pre-vaccination titer <7 log2: antibody titer at post-vaccination>= 4 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in [7-8] log2: antibody titer at post-vaccination >= 3 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer in]8-10] log2 : antibody titer at post-vaccination >= 2.5 fold the pre-vaccination antibody titer
For subjects with pre-vaccination titer >10 log2: antibody titer at post-vaccination >= 1 fold the pre-vaccination antibody titer
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 49 Estimated GMTs and 95% CIs for anti-RSV-A neutralising antibody titre (Per protocol set)

				Estimated GMT		
					95% CI	
Antibody	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
Anti-RSV-A Neutralizing Antibody	<each group>	PRE				
		PI(D30)				
		PI(D60)				
		PI(D90)				

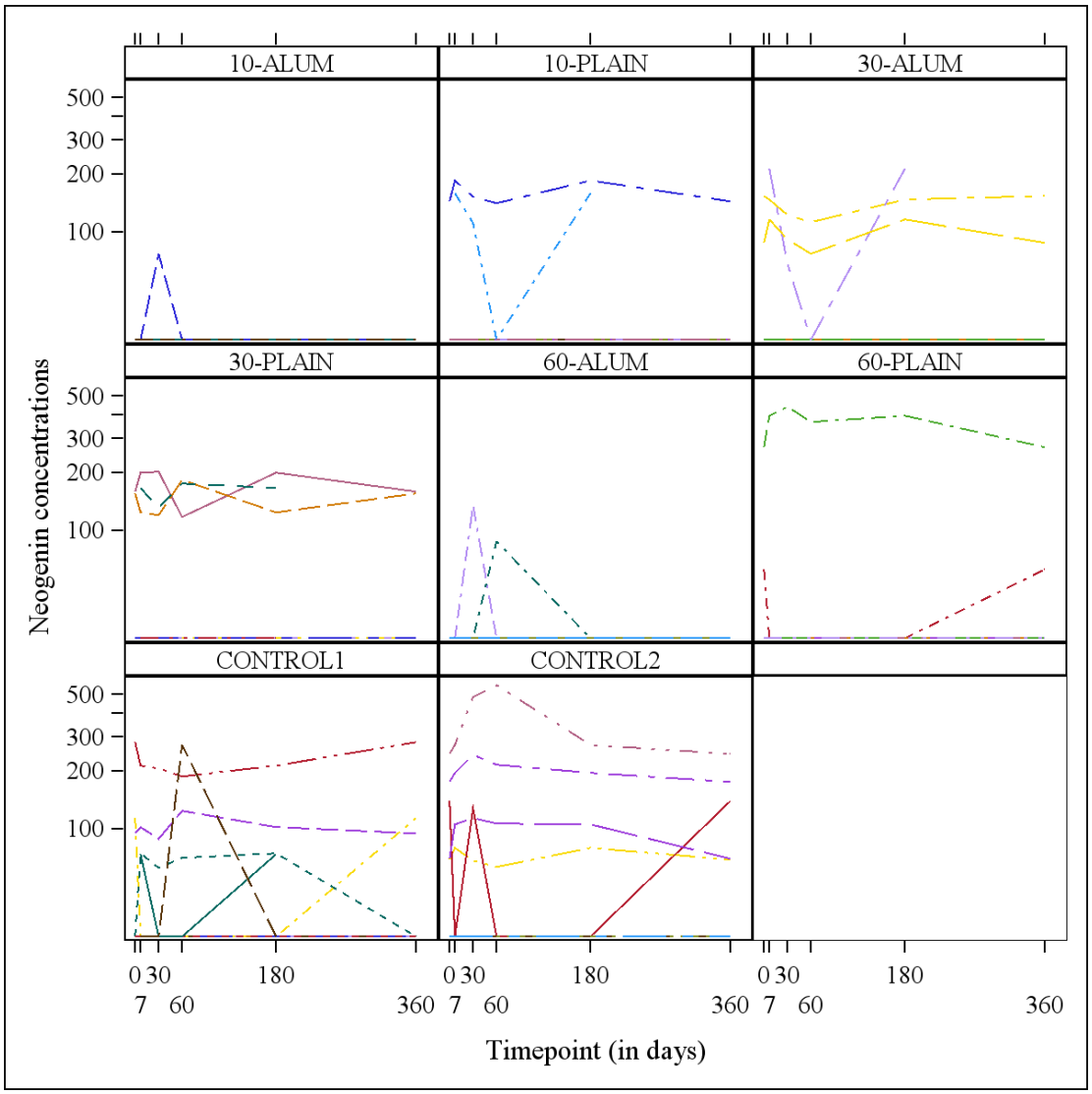
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = geometric mean antibody titer estimated by the ANOVA model for repeated measures
N = Number of subjects with available results
95% CI = 95% confidence interval (ANOVA model); LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30
PI(D60) = Post-vaccination at Day 60
PI(D90) = Post-vaccination at Day 90

Template 50 Exploratory comparisons (GMT ratios) between RSV groups with corresponding 95% confidence interval for anti-RSV A neutralizing antibody titre at Day 30 (Per protocol set)

								GMT ratio			
										Tukey's 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMT**	**Group description**	**N**	**GMT**	**Ratio order**	**Value**	**LL**	**UL**
Anti-RSV A Neutralizing Antibody	PI(D30)	120 PreF			30 PreF			120 PreF/30 PreF			
		120 PreF			60 PreF			120 PreF/60 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

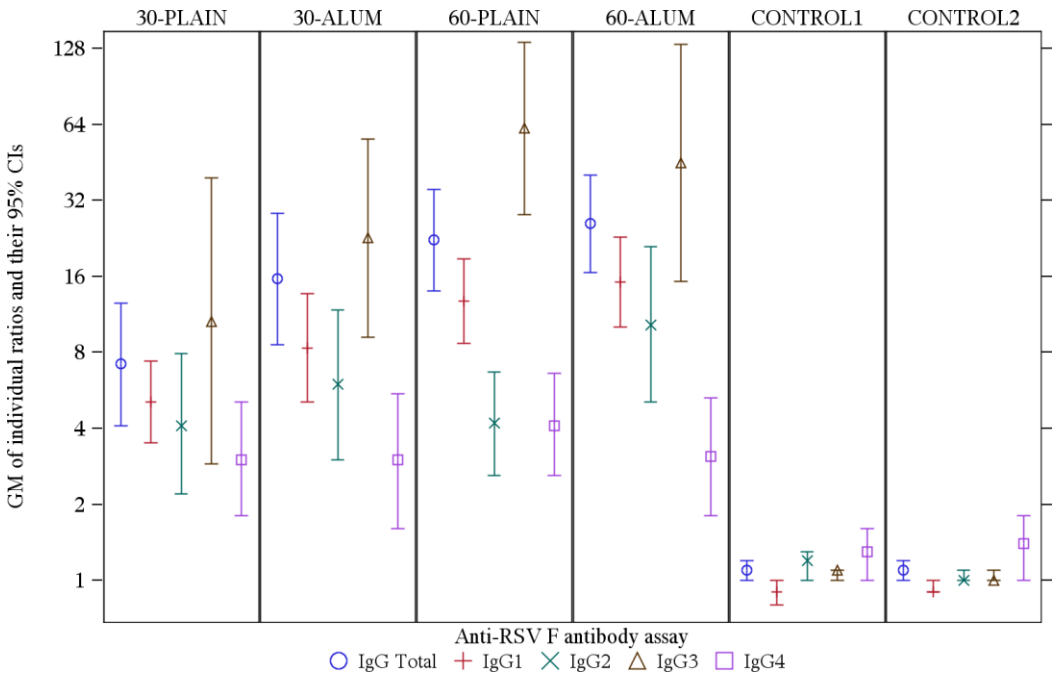
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
antibody titre estimated by the ANCOVA model
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMT ratio (ANCOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANCOVA model is xxxx
PI(D30) = Post-vaccination at Day 30

Template 51 Individual kinetics of anti-neogenin antibody concentrations by group (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: This graph is provided as an example. This graph will display the 4 groups and the 4 immuno timepoints: PRE, PI(D30), PI(D60) and PI(D90)

Template 52 GM of individual ratios (fold increase post over pre) and their 95% CIs for anti-RSV F IgG1 and IgG total antibody assays and each group, at <Day xx> (Per protocol set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
Note: this graph is provided as an example. It will be adapted to display IgG total and Ig1 only, and the 4 groups: 30 PreF, 60 PreF, 120 PreF, Control.

Template 53 Exploratory comparisons (GM ratios of fold increase post/pre) between RSV groups with corresponding 95% confidence interval for anti-RSV F antibody concentrations (IgG Total) at Day 30 (Per protocol set)

								GMF ratio			
										Tukey s 95% CI	
Antibody	**Timepoint**	**Group description**	**N**	**GMF**	**Group description**	**N**	**GMF**	**Ratio order**	**Value**	**LL**	**UL**
anti-RSV F antibody (IgG Total)	PI(D30)	120 PreF			60 PreF			120 Pre/60 PreF			
		120 PreF			30 PreF			120 PreF/30 PreF			
		60 PreF			30 PreF			60 PreF/30 PreF			

30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Antibody concentration estimated by the ANOVA model
GMF = Geometric mean of fold increase
N = Number of subjects with pre-vaccination results available
Tukey's 95% CI = 95% confidence interval for the GMF ratio (ANOVA model, Tukey's adjustment), LL = lower limit, UL = upper limit
Pvalue of ANOVA model at PI(D30) is: xxxx
PI(D30) = Post-vaccination at Day 30

Template 54 ***Comparisons of GM ratios with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at pre-vaccination (Per protocol set)***

									GM ratio		
				95% CI			95% CI			*95% CI*	
Timing	*Group description*	*N*	*IgG Total GMC*	*LL*	*UL*	*RSV-A neut GMT*	*LL*	*UL*	*Value*	*LL*	*UL*
PRE(D0)	*<each group>*										
PRE(D0)											
PRE(D0)											
PRE(D0)											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at Day30 and pre-vaccination for IgG Total and RSV-A neut
GMC = Geometric mean antibody concentration calculated on all subjects for IgG Total
GMT = Geometric mean antibody titre calculated on all subjects for RSV-A neut
GM Ratio=Geometric mean of individual ratio of IgG Total to RSV-A neut for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0

Template 55 ***Exploratory comparisons (GM ratios of fold increase post/pre) with corresponding 95% confidence interval between anti-RSV F antibody concentrations (IgG Total) and anti-RSV-A neutralising antibody titers at Day 30 (Per protocol set)***

									GMF Ratio		
										95% CI	
Timepoint	*Group*	*N*	*IgG Total GMF*	*95% CI*		*RSV-A neut GMF*	*95%*		*Value*	*LL*	*UL*
				LL	*UL*		*LL*	*UL*			
PI(D30)/PRE	*<each group>*										
PI(D30)/PRE											
PI(D30)/PRE											
PI(D30)/PRE											

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
N = Number of subjects with available results at the two considered time points for IgG Total and anti-RSV-A
GMF = Geometric mean of fold increase
GMF Ratio= Geometric mean of individual ratio of fold increase for each group
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
PRE= Pre-vaccination at Day 0
PI(D30) = Post-vaccination at Day 30

Template 56 *Desirability index of immunogenicity during the 30-day (Days 0-29) post-vaccination period (Per protocol set)*

Group	*GMT*	*LL1*	*DI1*	*GMC*	*LL2*	*DI2*	*DI*
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
GMT = estimated log2-scale GMT adjusted for pre-vaccination titres for neutralising anti-RSV-A
GMC = estimated log10-scale GMC adjusted for pre-vaccination concentrations for PCA
LL1 = estimated log2-scale lower limit adjusted for pre-vaccination titres for neutralising anti-RSV-A
LL2 = estimated log10-scale lower limit adjusted for pre-vaccination concentrations for PCA
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 57 *Desirability index of reactogenicity during the 7-day (Days 0-6) post-vaccination period (Exposed set)*

Group	*Incidence Rate (IR)*	*Incidence Rate (IR2)*	*DR1*	*DR2*	*DR*
<each group>					

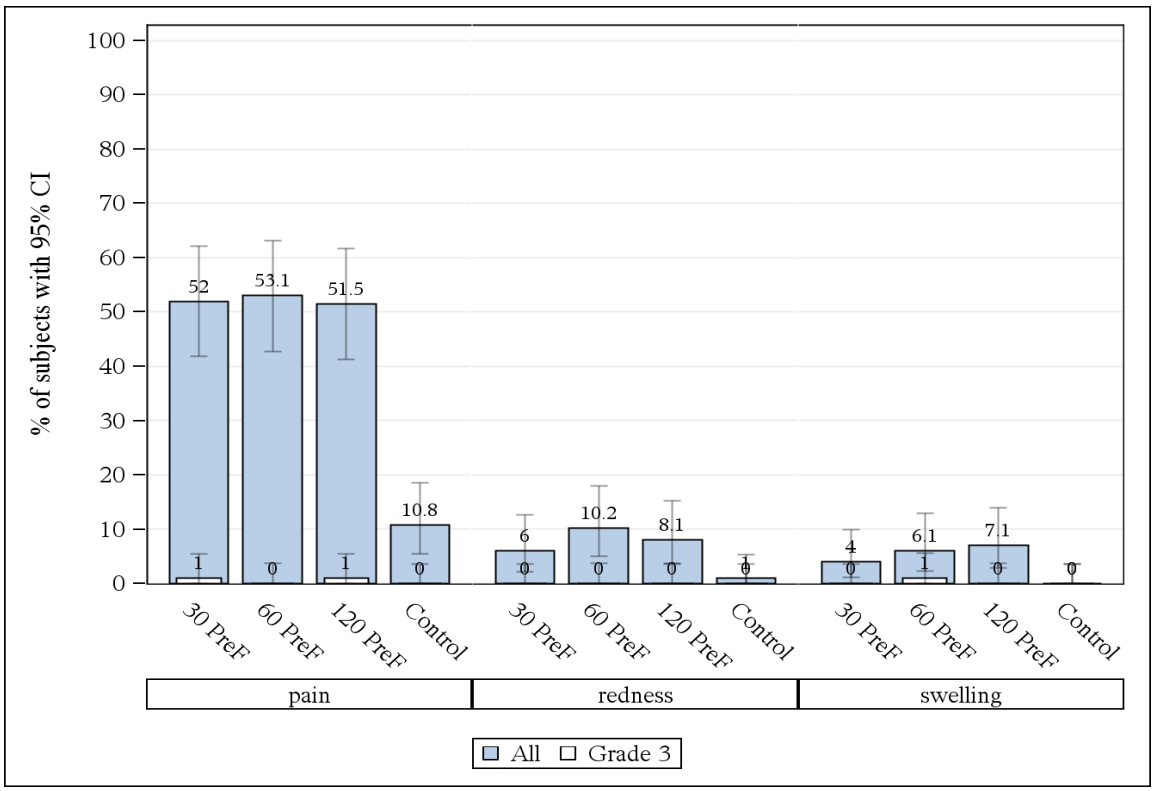
<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µgPreF
120 PreF = 120 µg PreF
Control = Placebo
IR = *incidence rate estimated by the model for any Grade 2/3 general AEs and any related SAEs*
IR2 = *incidence rate estimated by the model for Grade 2/3 fever*
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index

Template 58 *Desirability index based on reactogenicity and safety (Exposed set up to Day 7) and immunogenicity (Per protocol set up to Day 30)*

Group	*Reactogenicity Index*			*Immunogenicity Index*			*Overall Desirability Index*
	DR1	*DR2*	*DR*	*DI1*	*DI2*	*DI*	$DR^{0.4} * DI^{0.6}$
<each group>							

<each group>:
30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo
DR1 = desirability index for any Grade 2/3 general AEs and any related SAEs
DR2 = desirability index for Grade 2/3 fever
DR = reactogenicity index
DI1 = desirability index for neutralising anti-RSV-A
DI2 = desirability index for PCA concentrations
DI = immunogenicity index

Template 59 Percentage of subjects reporting solicited local symptoms (any grade / grade 3) during the 7-day post-vaccination period (Exposed set)



30 PreF = 30 µg PreF
60 PreF = 60 µg PreF
120 PreF = 120 µg PreF
Control = Placebo