GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase I, randomized, placebo-controlled, observer-blind study to evaluate the safety, reactogenicity and immunogenicity of GSK's investigational respiratory syncytial virus (RSV) vaccine (adjuvanted with $AS01_B$) when administered intramuscularly according to a 0, 2-month schedule in Japanese adults 60-80 years of age.
eTrack study number and Abbreviated Title	209699 (RSV OA=ADJ-003)
Scope:	All data pertaining to the above study (except iSRC analysis).
Date of Statistical Analysis Plan	Final 23 September 2019

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
$AS01_B$:	MPL, QS-21, liposome based Adjuvant System (50µg MPL and 50µg QS-21)
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
eDiary	electronic Diary
ELU/mL	ELISA unit per milliliter
Eli Type	Internal database code for type of elimination code
EoS	End of Study
ES	Exposed Set
eTMF	Electronic Trial Master File
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titer
GSK	GlaxoSmithKline
HR	Hazard Ratio
IU/mL	International Units per milliLiter
LL	Lower Limit of the confidence interval

Mcg or µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
ToC	Table of Content
UL	Upper Limit of the confidence interval
WBR	Web-based Randomization

1. DOCUMENT HISTORY

Date	Description	Protocol Version
23 SEP 2019	First version	Final: 30 APR 2019

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

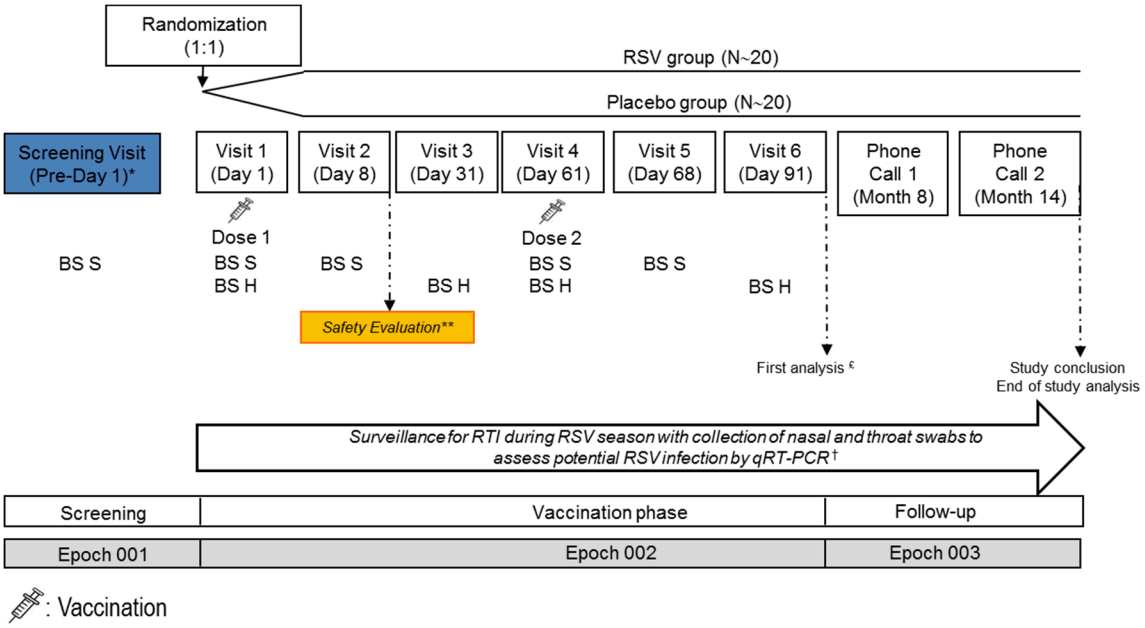
Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2-month schedule, up to one month after the last dose (Day 91, Visit 6).	• Occurrence of AEs from first vaccination up to 30 days after the second vaccination (Day 91): – Occurrence of each solicited local and general AE during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after each vaccination. – Occurrence of any unsolicited AE during a 30-day follow up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination. – Occurrence of any hematological (erythrocytes, WBC and differential count, platelets count and hemoglobin level) and biochemical (ALT, AST, creatinine, BUN and uric acid) laboratory abnormalities at Days 1, 8, 61 and 68. – Occurrence of all Grade 3 non-serious AEs (solicited and unsolicited) during the 30-day follow-up period after each vaccination. – Occurrence of SAEs from Dose 1 up to 30 days after the second vaccine dose (Day 91). – Occurrence of pIMDs from Dose 1 up to 30 days after the second vaccine dose (Day 91).
Secondary	
• To evaluate the humoral immune responses of the investigational RSV vaccine administered IM according to a 0, 2-month schedule, up to one month after the last dose (Day 91, Visit 6).	• Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), on the day of second vaccination (Day 61) and 30 days post-Dose 2 (Day 91): – Neutralizing antibody titers against RSV-A. – RSVPreF3-specific IgG antibody concentrations.
• To evaluate the safety of 2 doses of the investigational RSV vaccine administered IM according to a 0, 2 -month schedule, up to the end of follow-up (Month 14, Phone call 2).	• Occurrence of SAEs from Dose 1 up to the end of follow-up. • Occurrence of pIMDs from Dose 1 up to the end of follow-up.
• To evaluate the occurrence of RSV-associated respiratory tract infections (RTI) during the RSV seasons in combined nasal and throat swab samples collected during the assessment visit for potential RSV-RTI.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in the combined nasal and throat swabs collected during the assessment visit for potential RSV-RTI during the RSV seasons, up to the end of follow-up.

Objectives	Endpoints
Tertiary	
• To further characterize immune responses to investigational RSV vaccine formulation.	• Humoral immune response with respect to components of the investigational vaccine at pre-vaccination (Day 1) and 30 days post-Dose 2 (Day 91): – Neutralizing antibody titers against RSV serotype B. • Any further exploratory immunology to detect RSV-related immune responses, such as but not limited to: – Antibodies against specific protein F epitopes. – Potential new immunological markers for protection. – Cross-reactive neutralizing antibody titers against hMPV.
• To evaluate the occurrence of RSV-associated RTI during the RSV seasons using self-collected nasal swabs.	• Occurrence of qRT-PCR confirmed RSV-associated RTI in self-collected nasal swab samples during the RSV seasons, up to the end of follow-up.

IM: intramuscular; RSV: respiratory syncytial virus; AE: adverse event; WBC: white blood cells; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; SAE: serious adverse event; pIMD: potential immune-mediated disease; RTI: respiratory tract infection; qRT-PCR: quantitative reverse transcription polymerase chain reaction, hMPV: Human metapneumovirus

3. STUDY DESIGN

Figure 1 Study design overview



BS S: Blood sample for safety evaluation (hematology/biochemistry)
BS H: Blood sample for humoral immune responses
qRT-PCR: quantitative reverse transcription polymerase chain reaction
* Visit 1 should take place no longer than 30 days after the Screening Visit. In case Visit 1 occurs more than 30 days after the Screening Visit, a re-screening visit should be scheduled before Visit 1 during which blood sample collection for safety laboratory assessment must be repeated (maximum one re-screening per subject is allowed). Only

laboratory results from the re-screening visit, if it occurs, will be taken into consideration and recorded in the eCRF. Medical history, physical examination and review of inclusion/exclusion criteria must be repeated if a re-screening visit occurs. The subject can only be randomized once the investigator receives the results and confirms the eligibility criteria.

** An internal Safety Review Committee (iSRC) evaluation of safety data up to Day 8 from all subjects will be performed before proceeding with administration of Dose 2. Additional iSRC evaluations will happen during the conduct of the study.

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

£ A first analysis will be performed on all data collected up to Day 91 for at least primary and secondary endpoints (except for the occurrence of RSV RTI). The analysis will be based on data as clean as possible.

- **Type of study**: self-contained.
- **Experimental design**: A phase I, observer-blind, randomized, placebo-controlled, single-country study with 2 parallel groups (see Figure 1):
- **Duration of the study:** approximately 14 months per subject.
  - Epoch 001: Screening Visit (Day -30 to -3)
  - Epoch 002: Primary (vaccination phase) starting at Visit 1 (Day 1) and ending at Visit 6 (Day 91)
  - Epoch 003: Follow-up starting after Visit 6 (Day 91) and ending at Phone Call 2 (Month 14)
- **Primary Completion Date (PCD):** last visit of the vaccination phase (Visit 6 [Day 91]).
- **End of Study (EoS):** Last testing results released of samples collected up to Phone call 2 (Month 14) (for assays related to secondary endpoints only), or Last subject last Phone Call, whichever comes last.

  While no samples will be collected at Phone calls 1 and 2, nasal and throat swabs may be collected in case of RTI symptoms up to the Phone call 2 (Month 14) timepoint, if this timepoint falls within the RSV season.
- **Study groups:**
  - **RSV Group:** subjects receiving 2 doses of the investigational RSV vaccine containing 120 µg RSVPreF3 adjuvanted with $AS01_B$.
  - **Placebo:** subjects receiving 2 doses of placebo as control.
- **Vaccination schedule:** Two vaccine doses administered intramuscularly at Day 1 and Day 61.
- **Treatment allocation:** Subjects will be randomized using a centralized randomization system on internet (SBIR) on Day 1.

A total of approximately 40 participants are planned to be enrolled in this study in a 1:1 ratio. The target is to enrol approximately 28 eligible participants aged 60-69 years (approximately 14 per group) and approximately 12 (and minimum 10) eligible participants aged 70-80 years (approximately 6 per group). The randomization algorithm will use a minimization procedure accounting for age, center and gender.

- **Blinding:** observer-blind.

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

- **RTI surveillance:** Active and passive surveillance will only be carried out during RSV seasons (from August until end of February) throughout the entire study:

  - Active surveillance: study participants will be contacted by the investigator/study staff every 2 weeks to identify if they experienced an RTI.
  - Passive surveillance: study participants are instructed to contact the investigator/study staff as soon as they experience an RTI.

  At the beginning of the RSV season, study participants will be reminded of the start of the RTI surveillance.

- **Safety monitoring:** The study will be conducted with oversight by an internal Safety Review Committee (iSRC). An iSRC evaluation of safety data up to Day 8 from all subjects will be performed before proceeding with administration of Dose 2. The investigator is not permitted to start the administration of the next dose until receipt of the favourable outcome of the safety evaluation by the iSRC. A second data review iSRC meeting will be held to review all available safety data up to 30 days post-Dose 2. During the follow-up phase, 2 iSRC meetings will be planned with an interval of approximately 6 months.

- **Group description for analysis**

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

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

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	All subjects who sign informed consent.
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Per Protocol	All subjects who received at least 1 dose of the study treatment to which they are randomized and have post-vaccination data minus subjects with protocol deviations that lead to exclusion.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all), 800 (Fraudulent data) and code 900 (invalid informed consent or other GCP noncompliance) will be used for identifying subjects eliminated from ES.

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

4.2.2.1. Excluded subjects

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

- For codes 800, 900, 1030, 1050 and 1060: subjects will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2010, 2040, 2060, 2080: subjects will be eliminated from a specific visit (at which the condition is met) onwards.
- For codes 2090, 2100, 2120: subjects will be eliminated for the specific visit at which the condition is met.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	ES and PPS for analysis of immunogenicity
900	Invalid informed consent or other GCP non-compliance	All	ES and PPS for analysis of immunogenicity
1030	Study vaccine not administered at all	All	ES and PPS for analysis of immunogenicity
1040	Administration of concomitant vaccine(s) forbidden in the protocol Any investigational or non-registered vaccine other than the study vaccine used during the study period	All	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last vaccine dose, except for inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 30 days after each vaccination.		
1050	Randomization failure	All	PPS for analysis of immunogenicity
1060	Randomization code was broken	All	PPS for analysis of immunogenicity
1070	Vaccination not according to protocol Incomplete vaccination course Subject was vaccinated with the correct vaccine but containing a lower volume Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) Route of the study vaccine is not intramuscular Wrong reconstitution of administered vaccine	Vaccination visits 1 and 4	PPS for analysis of immunogenicity
1080	Vaccine temperature deviation Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visits 1 and 4	PPS for analysis of immunogenicity
1090	Expired vaccine administered	Vaccination visits 1 and 4	PPS for analysis of immunogenicity
2010	Protocol violation (inclusion/exclusion criteria)	All	PPS for analysis of immunogenicity
2040	Administration of any medication forbidden by the protocol Any investigational or non-registered medication used during the study period Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the study period Long-acting immune-modifying drugs administered at any time during the study period Immunoglobulins and/or any blood products administered during the study period	All	PPS for analysis of immunogenicity
2060	Intercurrent medical condition Subjects may be eliminated from the PPS if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status (other than RSV infection).	All	PPS for analysis of immunogenicity
2080	Subjects did not comply with vaccination schedule number of days between dose 1 and dose 2 is outside [55-65 days]	Visit 4	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2090	Subjects did not comply with blood sample schedule Number of days between dose 1 and visit 3 blood sample is outside [30-37 days] Number of days between dose 2 and visit 6 blood sample is outside [30-37 days]	Visits 3 and 6	PPS for analysis of immunogenicity
2100	Serological results not available post-vaccination No immunological result at visit x for all 2 following tests: RSV A Neutralising antibody titer and RSVPreF3-specific IgG antibody concentration	Visits 3, 4, 6	PPS for analysis of immunogenicity
2120	Obvious incoherence or abnormality or error in data Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at lab	Visits 1, 3, 4, 6	PPS for analysis of immunogenicity

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in Section 10.1 while the study specific data derivation rules and statistical methods are described in Section 9.

5.1. Demography

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

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

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

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

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

Withdrawal status will be summarized by group using descriptive statistics:

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

5.1.2. Additional considerations

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure, pulse oximetry) reported at visit 1 will be summarized by study group using descriptive statistics.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

NA

5.2.2. Additional considerations

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

5.3. Immunogenicity

The primary analysis will be based on the Per Protocol set for analysis of immunogenicity. If in any study group and at any timepoint, the percentage of vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 10% or more, a second analysis based on the Exposed set will be performed to complement the Per Protocol analysis.

5.3.1. Analysis of immunogenicity planned in the protocol

5.3.1.1. Humoral immune response

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

- Percentage of subjects above pre-defined threshold and their exact 95% CI will be tabulated.
- Geometric mean concentrations (GMCs)/ geometric mean titers (GMTs) and their 95% CI will be tabulated and represented graphically.
- Antibody titer/concentration will be displayed using reverse cumulative curves.
- The distributions of antibody titers/concentrations will be tabulated.
- Geometric mean of ratios of antibody titer/concentrations at each post-vaccination time point over pre-vaccination (Day 1) will be tabulated with 95% CI.
- Individual post-vaccination results (at Days 31, 61 and 91) versus pre-vaccination results (Day 1) will be plotted using scatter plots. Results of the placebo group will be used as a reference.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers) will be tabulated.

- The ratio of fold increase (post over pre-vaccination) of RSVPreF3 ELISA antibody concentrations over the fold increase (post over pre-vaccination) of RSV-A and RSVB neutralizing antibody titers will be computed and tabulated using descriptive statistics.
- The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points.

The immunogenicity analysis might also be performed by age category (60-69 years and 70-80 years).

5.4. Analysis of safety and reactogenicity

The primary analysis will be performed on the Exposed Set.

5.4.1. Analysis of safety and reactogenicity planned in the protocol

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 30-day follow-up period will be tabulated with exact 95% confidence interval (CI) after each dose and overall. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination, for Grade 3 AEs considered related to vaccination and for Grade 3 non-serious AEs.
- The percentage of subjects with any AE (solicited and unsolicited) resulting in a medically attended visit during the 30-day follow-up period will also be tabulated after each dose and overall.
- The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall.
- For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) will be tabulated for each group after each dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for Grade 3 (> 39.0°C) causally related fever. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after each vaccination.
- For each group and for each hematology and biochemistry parameter:
    i. The percentage of subjects having hematology and biochemistry results below or above the laboratory normal ranges will be tabulated by time point.
    ii. The summary of grading post-vaccination will be tabulated versus baseline. Grades will be based on the FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”, see Protocol Section 12.7 The laboratory parameters not included on FDA Toxicity Grading Scale will not be graded.

- The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported from Dose 1 up to 30 days after the second vaccine dose (Day 91) will be tabulated with exact 95% CI.
- The percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported from Dose 1 up to 30 days after the second vaccine dose (Day 91) will be tabulated with exact 95% CI.
- The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. SAEs will also be described in detail.
- The percentage of subjects with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. pIMDs will also be described in detail.

The analysis of safety might also be performed by age category (60-69 years and 70-80 years).

5.4.2. Additional considerations

- Compliance in completing solicited adverse events information will be tabulated after each dose and overall.
- The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group after each vaccine dose and overall.
- The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after each dose and overall.
- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the 7-day and 4-day follow-up period will be tabulated with exact 95% confidence interval (CI) after each dose and overall. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination, and for Grade 3 AEs considered related to vaccination.

- The number of days with solicited symptoms reported during the 7-day follow-up period will be tabulated for each solicited adverse event, after each dose using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same tabulation will be done for Grade 3 symptoms, and also during the whole post-vaccination period (to include the total number of days for symptoms ongoing beyond the follow-up period).
- The incidence of each solicited symptom (any grade and grade 3) will also be represented graphically per group and per dose.

5.4.2.1. Solicited Adverse Events

Solicited adverse events will be reported daily during the 7-day follow up period after each vaccination by the subject in the eDiaries. Missing or non-evaluable measurements will not be replaced. The data will be made available for site follow-up on the eDiary web-portal.

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

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

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

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

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

5.4.2.2. Unsolicited Adverse Events

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

The analysis of unsolicited adverse events includes the following categories:

- Any unsolicited adverse event
- Possibly related unsolicited adverse events
- Grade 3 unsolicited adverse events
- Grade 3 possibly related unsolicited adverse events
- Serious adverse events (SAEs)
- Possibly related SAEs
- Potential immune-mediated disease (pIMD)
- Medically attended adverse events

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

In addition, the following time periods will be considered to report SAEs/pIMDs at the first and end of study analyses (E1_02 and E1_01, see section 7.1):

- from Dose 1 up to 30 days post-dose 2 (or up to 90 days post-dose 1 for subjects who did not received the second dose)

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

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

5.4.2.3. Combined Solicited and Unsolicited Adverse Events

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

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

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

5.4.2.4. Clinical Safety Laboratory Investigations

In case of invalid or missing results or clinically significant grade 3 and above abnormal laboratory findings, a repeat testing may be done to confirm the first result (see Protocol section 12.5.6). For the analysis, the following rules will be applied:

- In general, the first result will be considered, except if this result is missing.
- In case of retesting for a grade 3 and above at pre-vaccination, the retesting will be considered if the result is < grade 3.

5.4.2.5. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.5. Analysis of RTI

5.5.1. Analysis of RTI planned in the protocol

The analysis will be performed on the ES.

Any RTI episode for which a visit for the assessment of potential RSV-RTI has been performed (with nasal/throat swab sampling) will be described in detail in a listing. This will present the results of the qRT-PCR performed on the nasal swab collected by the subject and on the nasal/throat swab collected by an appropriately qualified person (i.e., medical or nursing) at the assessment visit.

5.5.2. Additional considerations

Information collected at assessment visit will be further described for RSV RTI episodes versus Non-RSV RTI episodes. An RTI episode will be considered as associated to RSV when the qRT-PCR test performed on nasal/throat swabs collected at assessment visit is positive. It will include: vital signs, clinical signs and symptoms, self-collected nasal swab result, medically attended visit and SAE related to the episode.

6. ANALYSIS INTERPRETATION

The analyses will be descriptive with the aim to characterize the safety/reactogenicity and immunogenicity of the RSV group with respect to the placebo.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The following analyses will be performed stepwise:

- A first analysis will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints up to Day 91 are available (except for the occurrence of RSV RTI). This analysis will be considered as final for those endpoints. A statistical report will be written.

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

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

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

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Reference for TFL TOC
End of study analysis	E1_01	CTRS, SR	See column 5 in TFL TOC
Analysis up to Day 91	E1_02	Internal	See column 5 in TFL TOC

7.2. Statistical considerations for interim analyses

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

8. CHANGES FROM PLANNED ANALYSES

NA

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Handling of missing data

9.1.1. Dates

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

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month.

  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.

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

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

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

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

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

See also exceptions in section 9.1.

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

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

10.1.2.4. Unsolicited adverse events

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

DOB = SEP1983, Date of vaccination = 14SEP2018

-> Derived DOB=15SEP1983 and derived Age = 34 years

DOB = SEP1983, Date of vaccination = 15SEP2018

-> Derived DOB=15SEP1983 and derived Age = 35 years

10.1.3.2. Numerical serology results

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

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

10.1.3.3. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titeror concentration transformations. Antibody titeror concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.4. Onset day

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

10.1.3.5. Duration of events

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

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

10.1.3.6. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.7. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a subject following multiple vaccines will be counted as only one occurrence.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

10.1.4.3. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

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