Statistical Analysis Plan

209141

Phase II randomized, observer-blind, placebo-controlled, multi-country study in healthy non-pregnant women 18-45 years of age to evaluate the safety, reactogenicity and immunogenicity of a 1st intramuscular dose of GSK Biologicals' investigational RSV maternal vaccine (GSK388550A) when given alone and given in co-administration with a single intramuscular dose of Boostrix (US formulation SB776423 or ex-US formulation SB263855) and to evaluate the safety, reactogenicity and immunogenicity of a 2nd dose of the RSV maternal vaccine.

EudraCT number: 2019-002258-22

Date of Document: 03 DECEMBER 2020

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Phase II randomized, observer-blind, placebo-controlled, multi-country study in healthy non-pregnant women 18-45 years of age to evaluate the safety, reactogenicity and immunogenicity of a 1st intramuscular dose of GSK Biologicals' investigational RSV maternal vaccine (GSK388550A) when given alone and given in co-administration with a single intramuscular dose of Boostrix (US formulation SB776423 or ex-US formulation SB263855) and to evaluate the safety, reactogenicity and immunogenicity of a 2nd dose of the RSV maternal vaccine.
eTrack study number and Abbreviated Title	209141 (RSV MAT-011)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 21 October 2019
Date of Statistical Analysis plan amendment	Amendment 2 Final: 28 February 2020 Amendment 3 Final: 03 April 2020 Amendment 4 Final: 03 December 2020

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

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LIST OF ABBREVIATIONS

Ab	Antibody
AE(s)	Adverse Event(s)
AE	Adverse Event
Anti-	Antibodies against
BS H	Blood Sample Humoral
CDC	Centers for Disease Control
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CoP	Correlate of Protection
D	Diphtheria
dTpa	Diphtheria, Tetanus and acellular Pertussis
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EoS	End of Study
eTDF	Electronic Temperature excursion Decision Form
Ex-US	Outside the US
FDA	Food and Drug Administration, United States of America
FHA	Filamentous Hemagglutinin
FU	Follow-up
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
IAF	Informed Assent Form

IB	Investigator Brochure
ICF	Informed Consent Form
ICH:	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LSLV	Last Subject Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibody
PCD	Primary Completion Date
PP	Per protocol
PRN	Pertactin
PRO	Patient Related Outcomes
PT	Pertussis Toxoid
RRA	Recruitment/Randomisation Agreement
RSV	Respiratory Syncytial Virus
RSVPreF3	RSV maternal vaccine
SAE:	Serious Adverse Event
SBIR	Source data Base for Internet Randomisation
SD	Standard Deviation

SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRT	Safety Review Team
T	Tetanus
UP	Urine Pregnancy Test

1. DOCUMENT HISTORY

Date	Description	Protocol Version
03 DEC 2020	Amendment 4	Amendment 4: 30-AUG-2020
03 APR 2020	Amendment 3	Amendment 3: 03-APR-2020
28 FEB 2020	Amendment 2	Amendment 2: 28-FEB-2020
21 OCT 2019	first version	Final: 28 JUN 2019

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints (*Amended 03-DEC-2020*)

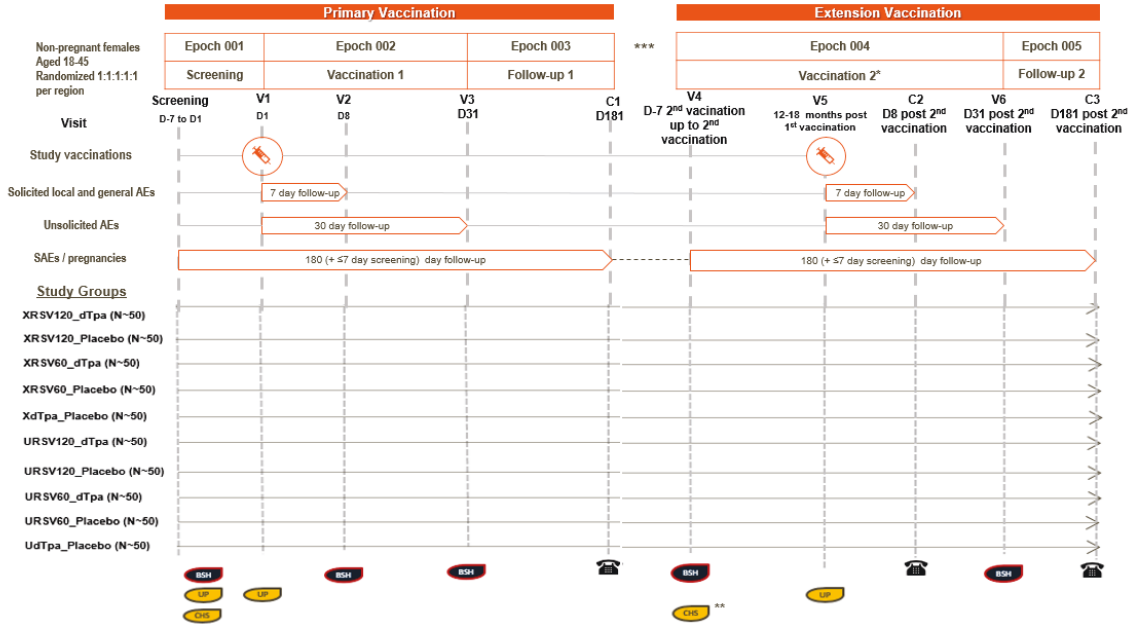
Objectives	Endpoints
Primary *(US + ex-US data to be pooled)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone or co-administered with dTpa from Vaccination up to Day 31.	*Safety* • Occurrence of any Adverse Events (AEs) from Vaccination to Day 31: – Occurrence of each solicited local AEs at the site of injection in both limbs from Vaccination to Day 8; – Occurrence of solicited general AEs from Vaccination to Day 8; – Occurrence of any unsolicited AEs from Vaccination to Day 31; – Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
• To evaluate the safety of a 2nd dose of RSVPreF3 given from 12 up to18 months post 1st Dose up to Day 31 days post 2nd dose vaccination	• Occurrence of any AEs from 2nd dose to Day 31 post-2nd dose vaccination, for all subjects: • Occurrence of each solicited local AE at the site of injection in both deltoids from 2nd dose vaccination to Day 8 post-2nd dose vaccination • Occurrence of solicited general AEs from 2nd dose vaccination to Day 8 post 2nd dose vaccination • Occurrence of any unsolicited AEs from 2nd dose to Day 31 post- 2nd dose vaccination • Occurrence of Serious Adverse Events (SAEs) from 2nd dose vaccination to Day 31 post 2nd dose vaccination.
Immunogenicity • To evaluate the humoral immune response to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa, at Screening, Day 8 and Day 31 post 1st dose vaccination	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8 and Day 31 in all groups • RSV IgG antibody concentrations at Screening, Day 8 and Day 31.
Secondary *(US and ex-US data to be considered pooled, then separately)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given	*Safety* • Occurrence of any AEs from Vaccination to Day 31, for all subjects:

Objectives	Endpoints
alone or co-administered with dTpa from 1st dose vaccination up to Day 31 by formulation.	– Occurrence of each solicited local AE at the site of injection in both limbs from Vaccination to Day 8 – Occurrence of solicited general AEs from Vaccination to Day 8 – Occurrence of any unsolicited AEs from Vaccination to Day 31 – Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa compared to dTpa-Placebo groups from 1st dose vaccination up to Day 181.	• Occurrence of SAEs from Vaccination up to Day 181.
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered from Vaccination up to Day 181 by formulation.	• Occurrence of SAEs from Vaccination up to Day 181.
• To evaluate the safety of RSVPreF3 (pooled for all groups receiving RSVPreF3) for the 1st dose vaccination.	• Occurrence of SAEs from Vaccination up to Day 181.
• To evaluate the safety of 2nd dose of RSVPreF3 given from 12 to up to 18 months post 1st dose vaccination up to Day 181 post 2nd dose vaccination.	• Occurrence of SAEs from 2nd dose vaccination up to Day 181 post-2nd dose vaccination.
Immunogenicity • To evaluate the humoral immune response and persistence to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa at Screening, Day 8, and Day 31 post 1st dose vaccination, and at 12 to 18 months by formulation.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8, Day 31, and a single timepoint between 12 to 18 months post 1st vaccination. • RSV IgG antibody concentrations at Screening, Day 8, Day 31, and a single timepoint between 12 to 18 months post 1st vaccination.
• To evaluate the humoral immune response to the pertussis component of the dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post 1st dose vaccination by formulation.	• Antibody concentrations against pertussis toxoid (anti-PT), filamentous hemagglutinin (anti-FHA), and pertactin (anti-PRN) concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the diphtheria (D) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post 1st dose vaccination by formulation.	• Anti-D concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the tetanus (T) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post 1st dose vaccination by formulation.	• Anti-T concentrations at Screening and Day 31.
• To evaluate the humoral immune response of a 2nd dose vaccination of RSVPreF3 (120 µg), following a first dose vaccination of either 60 µg or 120 µg.	• RSV A neutralizing antibody titers concentrations 31 days post 2nd dose vaccination. • RSV IgG antibody concentrations 31 days post 2nd dose vaccination.

Objectives	Endpoints
Tertiary	
If necessary, additional testing to further characterize the response to the RSV maternal investigational vaccine will be performed.	

3. STUDY DESIGN

Figure 1 Study design overview *(Amended 03-DEC-2020)*



Note: study groups labeled X = ex-US; study groups labeled U = US. V = visit, C = phone contact
= Vaccination; N = number of subjects; V = Visit; D = Day; AE = adverse event; UP = Urine pregnancy test; CHS = Chemical/Hematological Screening, FU = follow-up
BSH = blood sample (5 mL) for humoral immune responses (RSV-A neutralization and RSV IgG antibody concentrations at Screening, Visit 2, [Day 8] Visit 3, [Day 31], Visit 4, [up to D7 prior to 2nd vaccination], and Visit 6 [D31 post 2nd vaccination]
dTpa ELISAs at Screening and Visit 3 [Day 31])
* All subject groups will be given RSV 120mcg and subjects will be followed in an open labeled study
** Hematological and biochemical laboratory testing at Visit 4 (D -7 up to and including 2nd dose vaccination) at the investigator's discretion
***There will be no follow-up between C1 and V4. New medical history and relevant new safety events during this period will be recorded at visit 4 for subjects who agree to the study extension and sign the informed consent addendum.

The study will be conducted with 2 formulations of dTpa, dTpa_300 (in the US) and dTpa_500 (ex-US) [Christy, 1995].

Approximately 500 eligible subjects (250 in the US and 250 ex-US) will be enrolled. Of these, approximately 250 subjects will be randomized to 5 US study groups in a 1:1:1:1:1 ratio using SBIR, and the remaining approximately 250 will be randomized to 5 ex-US study groups in a 1:1:1:1:1 ratio using SBIR. The randomization algorithm will use a minimization procedure by treating study formulation (US and ex-US) as a stratification factor, and age at the time of vaccination (18-32 or 33-45 years of age) and center as minimization factors.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities, are essential and required for study conduct.

- Type of study: self-contained
- Experimental design:
  - Primary Vaccination: multi-centric study, multi-country Phase II, observer-blind, randomized, with 5 parallel groups in each formulation (US, ex-US).

Study Extension: multi-centric study, multi-country Phase II, open label, with all 5 parallel groups in each formulation (US, ex-US) receiving the experimental RSV maternal (120µg) vaccine.

- Duration of the study: The primary study will be approximately 6 months for each enrolled subject, the duration of the study extension will be 18 up to 24 months.
  - Primary Vaccination
    - Epoch 001: Screening
    - Epoch 002: Primary vaccination starting at Visit 1 (Day 1) and ending just before the Visit 3 (Day 31)
    - Epoch 003: Follow-up after Visit 3 (Day 31) to Phone Contact 1 on (Day 181)
  - End of Primary Study: Subjects must sign the ICF addendum to join the study extension.
  - Study Extension: 6-month period starting at the beginning of 12 months up to the beginning of 18th month after Visit 1 (≥12 to <18 months)
    - Epoch 004: 2nd dose vaccination starting from Visit 4 (up -7 days prior to vaccination) to Visit 6 (Day 31 post 2nd dose vaccination)
    - Epoch 005: 2nd dose vaccination Study Follow-up 2 starting after Visit 6 (Day 31 post 2nd dose vaccination) and ending at Phone Contact 3 (Day 181 post 2nd vaccination).
- Primary completion Date (PCD): Visit 3 (Day 31) or last visit of Primary Epoch 002

Refer to list of abbreviations for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 6, to occur no later than 8 months after last subject last visit (LSLV), which occurs with phone contact 3 on Day 181 post 2nd vaccination.

Refer to list of abbreviations for the definition of EoS.

- **Study groups:**

Table 2 Study groups, pooled study groups (*Amended 03-DEC-2020*)

Pooled Groups label in tables	Pooled definition for footnote	Group label in tables	Group definition for footnote
RSV120_dTpa	Subjects who received RSV120 and dTpa	XRSV120_dTpa	Subject who received RSV MAT 120 and *Boostrix*-ex-US (dTpa_500)
		URSV120_dTpa	Subjects who received RSV MAT 120 and *Boostrix*-US (dTpa_300)
RSV120_Placebo	Subjects who received RSV120 and placebo	XPlacebo_RSV120	Subject who received RSV MAT 120 and Placebo
		UPlacebo_RSV120	Subject who received RSV MAT 120 and Placebo
RSV60_ dTpa	Subjects who received RSV60 and dTpa	XRSV60_dTpa	Subjects who received RSV MAT 60 and *Boostrix*-ex-US (dTpa_500)
		URSV60_dTpa	Subjects who received RSV MAT 60 and *Boostrix*-US (dTpa_300)
RSV60_Placebo	Subjects who received RSV60 and placebo	XPlacebo_RSV60	Subjects who received RSV MAT 60 and Placebo
		UPlacebo_RSV60	Subject who received RSV MAT 60 and Placebo
dTpa_Placebo	Subjects who received *Boostrix*(dTpa) and Placebo	XPlacebo_dTpa	Subject who received *Boostrix*-ex-US (dTpa_500) and Placebo
		UPlacebo_dTpa	Subject who received *Boostrix*-US (dTpa_300) and Placebo
RSV_placebo	Subjects who received RSV60 and placebo combined with subjects who received RSV120 and placebo		
RSV_dTpa	Subjects who received RSV60 and dTpa combined with subjects who received RSV 120 and dTpa		

Table 3 Study groups, treatment and epochs foreseen in the study (Amended 03-DEC-2020)

Study Groups	Number of subjects	Age (Min-Max)	Treatment name 1	Treatment name 2	Epochs (Blinding)				
					Epoch 001 (Screening)	Epoch 002 (observer-blind)	Epoch 003 (single-blind)	Epoch 004 (open Label)	Epoch 005 (open study)
XRSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-ex-US (dTpa_500)	*RSV MAT 120*	x	x	x	x	x
Xplacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	*RSV MAT 120*	x	x	x	x	x
XRSV60_dTpa	50	18 – 45 years	*RSV MAT 60 Boostrix-ex-US (dTpa_500)*	*RSV MAT 120*	x	x	x	x	x
Xplacebo_RSV60	50	18 – 45 years	*RSV MAT 60* Placebo	*RSV MAT 120*	x	x	x	x	x
Xplacebo_dTpa	50	18 – 45 years	*Boostrix-ex-US (dTpa_500)* Placebo	*RSV MAT 120*	x	x	x	x	x
URSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-US (dTpa_300)	*RSV MAT 120*	x	x	x	x	x
Uplacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	*RSV MAT 120*	x	x	x	x	x
URSV60_dTpa	50	18 – 45 years	*RSV MAT 60 Boostrix-US*	*RSV MAT 120*	x	x	x	x	x
Uplacebo_RSV60	50	18 – 45 years	*RSV MAT 60* Placebo	*RSV MAT 120*	x	x	x	x	x
Uplacebo_dTpa	50	18 – 45 years	*Boostrix*-US (dTpa_300) Placebo	*RSV MAT 120*	x	x	x	x	x

- **Control:** (active comparator).
- **Treatment allocation**: (randomised stratified).
- **Blinding:** As described in Table 3**.**
- **Data collection**: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject paper Diary (pDiary).
- **Safety monitoring:**

If the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately.

4. ANALYSIS SETS *(Amended 03-DEC-2020)*

4.1. Definition

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

Analysis Set	Description
Enrolled	Subjects who agreed to participate in a clinical study after completion of the informed consent process. And subject is not a screen failure.
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 randomised and have post-vaccination data minus subjects with protocol deviations that lead to exclusion
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data

4.1.1. Exposed Set

The ES will include all subjects who received at least 1 dose of the study treatment.

- A **safety** analysis based on the ES will include all subjects who received at least 1 dose of the study treatment.

4.1.2. Per Protocol Analysis Set

Per protocol analysis set will be defined by time points. It will include all subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data minus subjects with protocol deviations that lead to exclusion at Screening, Day 8 and Day 31 post 1st dose, Visit 4 and Visit 6 post 2nd dose.

- An **immunogenicity** analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available, if, in any study group and at any timepoint, the percentage of enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more.

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 fraudulent data) will be used for identifying subjects eliminated from ES

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

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

4.2.2.1. Excluded subjects from Per-protocol analysis set

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

Table 4 Elimination code and condition (*Amended 03-DEC-2020*)

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	All	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-45 years	All	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2150	Failure to report safety events per protocol	All	Safety
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 2/Day 8 Visit 3/Day 31 Visit 6	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 8 Visit 3/Day 31 Visit 6	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 8, check the interval from vaccination to day 8 BS = 7 – 10 days; • For PPS at Day 31, check the interval from vaccination to day 31 BS = 30 – 45 days; • For PPS at Visit 6, check the interval from Visit to Visit 5 • BS = 365 – 548 days;	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2120.Vx*	Obvious incoherence or abnormality or error in data	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 2/Day 8 Visit 3/Day 31 Visit 4 Visit 6	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
** Attribution of code 1070 to a subject requires CRDL confirmation
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
DOB-Date of Birth, VAC-Vaccination, BS- Blood Sample

4.2.3. Elimination from solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

5.1. Demography

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

These analyses will be performed on the Exposed set and on the Per protocol set for immunogenicity.

For all subjects, demographic characteristics (e.g., age at vaccination (18–32; 33-45 years), race and ethnicity, vaccination history will be summarized by overall and vaccine group using descriptive statistics.

- Frequency tables will be generated for categorical variables such as age
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height, weight and body mass index (BMI).

5.1.2. Additional considerations

Demographic characteristics will also be summarized on Enrolled Set for web public disclosure.

Subject disposition will be summarized by group using descriptive statistics:

- Number of subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set.

Summary of important protocol deviations leading to elimination will be tabulated by group. An individual listing will also be provided.

Summary of medical history will be performed on Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) and preferred term.

Summary of vaccination history will be performed on Exposed Set by using GSKDRUG dictionary.

Additional analyses by country and/or by site may be performed if deemed necessary

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol (*Amended 03-DEC-2020)*

The primary analysis on immunogenicity will be based on the Per Protocol set. If, in any study group and at any timepoint, the percentage of enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Exposed Analysis Set will be performed to complement the Per Protocol analysis.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled for the first vaccination)* For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically pooled. • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI pooled. • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentrations may be calculated at Screening, and/or Day 8, and/or Day 31 post 1st vaccination pooled for all subjects. • A further exploratory between-groups analysis will be performed at Day 8 or Day 31 using an ANCOVA model by including study groups, study formulation (US and ex-US), age category, and level of antibodies at Screening as covariates.
Secondary	*(US and ex-US data to be considered pooled, then separately* for the first vaccination) For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically by formulation (US and ex-US) Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI by formulation (US and ex-US). • Antibody titer/concentration will be displayed using reverse cumulative curves by formulation (US and ex-US). • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points by formulation (US and ex-US). • Booster response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). For the data collected for the second vaccination, the humoral immune response of RSV PreF3 will be summarized based on 2 dose level (60 and 120 µg) from the first vaccination.

Endpoint	Statistical Analysis Methods
	• GMCs/GMTs and their 95% CI will be tabulated and represented graphically for prior and post 2nd dose vaccination • Geometric mean of ratios of antibody titer/concentrations at individual post- 2nd dose vaccination time point (visit 6) over prior 2nd dose vaccination time point (visit 4) will be tabulated with 95% CI • Antibody titer/concentration will be displayed using reverse cumulative curves on prior and post 2nd vaccination • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points including the visits from the first vaccination. Booster responses to PT, FHA and PRN antigens are defined as: • For subjects with pre-vaccination antibody concentration below the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the assay cut-offs, • For subjects with pre-vaccination antibody concentration between the assay cut-offs and below 4 times the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration, and • For subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-offs: post-vaccination antibody concentration ≥2 times the pre-vaccination antibody concentration. – The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). – The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN, anti-D, anti-T will be calculated at Screening and Day 31 pooled for all subjects and by formulation (US and ex-US). – A further exploratory between-groups analysis will be performed at Day 31 using an ANCOVA model by including study groups, study formulation (US and ex-US), age category, and level of antibodies at Screening as covariates. – For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group on Day 31 post vaccination will be calculated for each formulation. – For *Boostrix* seroprotection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for each formulation.
Tertiary	Will be described in a Statistical Analysis Plan finalised before database unblinding/freezing.

*The statistical method will not be applied to primary endpoint. For detailed rationale, refer to Section 8.
**pooled group definition is detailed in Table 2

5.2.2. Additional considerations

5.2.2.1. Between group analysis

The Non-inferiority on RSV-A neutralizing antibody titers at 31 days post 1st vaccination in the co-administration of RSVPreF3 vaccine + *Boostrix* compared to RSV+ Placebo will be evaluated based on the criterion below:

- The criterion to evaluate non-inferiority with respect to RSV-A neutralizing antibody titers is that the upper limits of the 95% CI on the GMT ratio (RSVPreF3 +*Placebo* divided by RSVPre3 + Boostrix) is less than or equal to 1.5 at 31 days post vaccination.

Following model will be applied to RSVPreF3 IgG antibody concentrations and RSV-A neutralizing antibody titers.

For the analysis of subjects at visit 3 (Day 31), the model will be explored and fitted via the proc glm procedure according to the following code:

```
PROC glm data=sero;
    CLASS group;
    MODEL log_val = baseline group age_cat country_US country_BE
    Output out= pred;
    LSMEANS group/pdiff cl alpha=0.1;
RUN;
```

where **log_val** represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint (Day 8) or (Day 31), **baseline** is pre-vaccination logarithm10 transformation of the concentrations/titers, **group** indicates the study group, pooled groups (US and ex-US) will considered in model then separate by formulation. **age_cat** is indicator variable (0/1) and will be treated as continuous in the model, age_cat equals 0 if the age category at vaccination between 18 - 32 years, otherwise age_cat equals 1 if age category is between 33 - 45 years at vaccination. **Country_US** is indicator variable (0/1) and will treated as continuous in the model, if subject from US, then variable will equal to 1, otherwise equals to 0, **Country_BE** is indicator variable (0/1) and will treated as continuous in model, if subject from BE, then variable equals to 1, otherwise equals to 0, if subject is from Canada, above two indicators equal to 0. The inclusion of age category at vaccination, in the model depends on the availability of the variable and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

When considering group as separated by Boostrix formulation, remove Country_US and Country_BE from model._

GMT/GMC ratios between vaccine groups obtained using above model will be calculated by exponentiating mean difference of logarithm- transformed titres. The 90% CI and 95% CI for GMT/GMC ratio will be obtained by exponential-transformation of the CI for the group least square mean of the log-transformed titres/concentration from the above model.

5.2.2.2. Percentage difference between two groups

The percentage difference of response rate in terms of antigen PT, FHA and PRN [Camargo, 1984; Melville, 1983], together with the two-sided standardized asymptotic 95% CI in the RSVPreF3 dTpa group (minus) the dTpa Placebo group on Day 31 will be provided.

The percentage difference of seroprotection rate in terms of antigen D and antigen T [Vidor, 2008] with the two-sided standardized asymptotic 95% CI for RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group by formulation at Day 31 will be calculated.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol (*Amended 03-DEC-2020*)

The following safety analyses will be performed based on the Solicited Safety or Exposed Sets. The following safety analysis will be performed on the pooled data then the US and ex-US separately.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled)* *For each group with 1st dose vaccination of RSVPreF3 (two dose levels) when given alone or co-ad with dTpa; the following points will be analysed for 1st and 2nd dose vaccination.* The percentage of subjects with at least one local AE on left or right arm with at least one general AE and with any ("solicited or unsolicited") AE during the 7-day follow up period (the day of vaccination + 6 subsequent days) or 30 -day follow up period (the day of vaccination + 29 subsequent days) post 1st and 2nd vaccination period will be tabulated with exact 95% CI by study group. 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 AEs resulting in medically attended visits. The percentage of subjects reporting each individual solicited local AE (any grade, Grade 3 and those resulting in a medically attended visit) and solicited general AE (any grade, Grade 3, any related, Grade 3 related and those resulting in a medically attended visit) during the 7-day follow-up period (the day of vaccination + 6 subsequent days) will be tabulated based on maximum intensity for each group. For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (the day of vaccination + 6 subsequent days) will be tabulated for each group. Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) causally related fever, and

Endpoint	Statistical Analysis Methods
	fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after each vaccination. The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (the day of vaccination + 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOC) and 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 and leading to withdrawal from study. The verbatim term of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of SAE classified by the MedDRA SOC and Preferred Terms and reported during the 30-day follow-up period (the day of vaccination + 29 subsequent days) will be tabulated with exact 95% CI. SAEs will also be described in detail. The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period and during the 30-day follow-up period will be summarized by each group and pooled.
Secondary	*(US and ex-US data to be considered pooled, then separately)* *For each group with 1st dose vaccination of RSVPreF3 (two dose level) when given alone or co-administered with dTpa; the following points will be analysed for 1st and 2nd dose vaccination.* The percentage of subjects with at least one local AE with at least one general AE and with any ("solicited or unsolicited") AE during the 7-day or 30 -day follow-up as well any SAE up period to 180 days post 1st and 2nd vaccination time points will be tabulated with exact 95% CI by study group. 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 AEs resulting in medically attended visits and AEs leading to withdrawal from study. The percentage of subjects with at least one report of SAE classified by the MedDRA SOC and Preferred Terms and reported during the 30-day or 180-day follow-up period will be tabulated with exact 95% CI for each formulation (US and ex-US). The percentage of subjects reporting each individual solicited local AE on left or Right arms (any grade, Grade 3 and those resulting in a medically attended visit) and solicited general AE (any grade, Grade 3, any related, Grade 3 related and those resulting in a medically attended visit) during the 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) will be tabulated based on maximum intensity for each group for each formulation (US and ex-US). For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period will be tabulated for each group for each formulation (US and ex-US). Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) 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 each vaccination. For each formulation (US and ex-US), 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) SOC and 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 term of unsolicited AEs will

Endpoint	Statistical Analysis Methods
	be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology.
Tertiary	Will be described in a Statistical Analysis Plan finalised before database unblinding/freezing.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

The analysis of solicited events will be performed on Solicited Safety Set. The intensity of the following solicited events will be assessed as described:

Table 5 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	
Redness at injection site		
Swelling at injection site		
Temperature*		
Headache		
Fatigue		
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)		

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

The maximum intensity of solicited administration site redness/swelling will be scored at GSK Biological as follows:

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

Duration in days of solicited local and general adverse events within 7 days after vaccination will be tabulated by study group and overall, and if needed by age group. The derivation rule of duration in days for solicited events is detailed in section 10.1.3.9.

5.3.2.2. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set.

5.3.2.3. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited 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	Injection site pain	10022086
Redness	Injection site redness	10022098
Swelling	Injection site swelling	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Headache	Headache	10019211
Gastrointestinal symptoms†	Gastrointestinal disorder	10017944

Please note – to check for AE term in CDISC during dry run

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

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

5.3.2.4. Other analysis

Other safety analysis will be performed on Exposed Set.

Concomitant medications/products will be coded using the GSKDRUG dictionary. The number and percentage of subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination and 12 months following vaccination will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

7.1.1. First and final study

Analyses to evaluate objectives and endpoints will be performed in steps.

- A **first analysis** will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints pertaining to safety and immunogenicity up to Day 31 are available. 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, subjects and investigators will be unblinded after Day 181 post 1st vaccination. The investigators will be provided with the individual data listings or with the randomization listings after Day 181.
- The **second analysis** will evaluate safety data and will be performed when **all subjects** have completed visits up to (and including) C1 (Day 181) and the data are available. From this point the study is unblinded and will continue as an open label study.
- The **third analysis** will evaluate safety and immunogenicity data and will be performed when **all subjects** have completed visits up to (and including) Visit 6 (Day 31 post 2nd dose vaccination) and the data are available. At this time, any available safety data will also be provided.
- The final end-of-study will be performed when all data for at least primary and secondary endpoints up to study conclusion at Day 181 post 2nd dose vaccination (C3) are available. 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. these analyses will be documented in in an amended study report. If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed.

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
First Analysis (E1_02)	Internal, Public disclosure
Second Analysis (E1_03)	Internal
Third Analysis (E1_04)	Internal
Final Analysis (E1_01)	Public disclosure, Study report

7.2. Statistical considerations for interim analyses

NA

8. CHANGES FROM PLANNED ANALYSES *(AMENDED 03-DEC-2020)*

The calculation of GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3_Placebo in terms of RSV-A Nab titers and RSV IgG antibody concentrations at Screening, Day 8 and Day 31 pooled for all subjects will be removed from analyses plan. We will report adjusted GMT/GMC ratio and their 95% CI which is generated from ANCOVA model.

Adjusted GMT/GMC ratio with both 90% CI and 95% CI which are generated from ANCOVA model will be reported in terms of RSV-A Nab titers and RSV IgG antibody concentrations.

The calculation of GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa_Placebo groups in terms of antigens PT, FHA, PRN, D and T will be added at Day 31 pooled for all RSV formulation.

Lab assay cut-off of RSV-A Nab titers for humoral immunity will be reported by using both IU/ml (International units/millilitre) and ED60.

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. Data derivation

9.1.1. Immunogenicity (*Amended 03-DEC-2020*)

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, analysis will exclude subjects with missing or non-evaluable measurements.

- 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, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

Following table shows all antigens will be analysed at considered time point for different treatment groups

	Immunogenicity Endpoints	**Statistical Analysis Methods**
RSVPreF3	• RSVPreF3 IgG antibody concentration, and • Neutralizing antibody titers against RSV-A	(US and ex-US data to be considered pooled, then separately for the first vaccination, US and ex-US data to be pooled for second vaccination) For the data collected for the second vaccination, the humoral immune response of RSV PreF3 will be summarized based on 2 dose levels (60 and 120 µg) from the first vaccination. • GMCs/GMTs and their 95% CI will be tabulated and represented graphically • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • A further exploratory between-groups of RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentration, analysis will be performed at Day 8 and Day 31 post 1st dose using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates

	Immunogenicity Endpoints	Statistical Analysis Methods
Boostrix (dTpa)	• Booster response to PT • Booster response to FHA • Booster response to PRN	For the subjects received RSVPreF3 dTpa and subjects received dTpa placebo (US and ex-US data to be considered pooled, then separately for the first vaccination) (US and ex-US data to be considered pooled for the second vaccination) • Booster response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for US and ex-US pooled formulation and separately. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN will be calculated between Day 31 post vaccination over Screening for US and ex-US pooled data and separately. • For 1st vaccination, a further exploratory between-groups analysis will be performed at Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates • For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately
	• Anti-D concentration • Anti-T concentration	• The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for US and ex-US pooled data and separately • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-D, anti-Twill be calculated at Screening and Day 31 post vaccination for US and ex-US pooled data and separately. • Protection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately.

9.1.1.1. Laboratory assays cut-offs for humoral immunity (Antibody determination) *(Amended 03-DEC-2020)*

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay. The cut-off tests for immunogenicity evaluation will be as per following:

Sample	Component	Method	Unit	Cut-off*	ULOQ
Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	ED60 and/or IU (international unit)	18 for ED60 56 for IU	ED60 : 123535 IU : 217400
Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	ELU/mL	25	251 769
Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	IU/mL	2.046	3182.397
Serum	Bordetella pertussis.Pertactin Ab.IgG	ELI	IU/mL	2.187	6313.300
Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	IU/mL	2.693	883.559
Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	IU/mL	0.030	59.545
Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	IU/mL	0.037	116.428

Ab = antibody; ELI = Enzyme-linked immunosorbent assay (ELISA); IgG = immunoglobulin G; RSV = respiratory syncytial virus; ED60 = serum dilution inducing 60% inhibition in plaque forming units; IU/ml = International units/milliliter, IU= International units

Assay cut-off and unit might be subject to change before starting of testing (e.g. in case of requalification, revalidation or standardisation). In this case, this will be documented in the clinical report.

9.2. Statistical Method

NA

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.

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.

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

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

10.1.2.3. Solicited adverse events *(Amended 03-DEC-2020)*

- 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 Exposed
- Set 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 vaccination will be considered not having that symptom after vaccination.
  - When a specific solicited adverse event is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the adverse event in question), all daily measurements will be imputed as Grade 0.
  - When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.
  - When a specific solicited adverse event is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the adverse event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows, also counting this AE as "unknow" row of the solicited adverse event summary tables.Dose without symptom sheets documented will be excluded.

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

10.1.3.8. 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).

10.1.3.9. 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.

10.1.3.10. 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.

10.1.3.11. 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 by as only one occurrence. However specific tables or figures could be conducted to report solicited local events by 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. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

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

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

10.1.4.4. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

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

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Phase II randomized, observer-blind, placebo-controlled, multi-country study in healthy non-pregnant women 18-45 years of age to evaluate the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV maternal vaccine (GSK388550A) when given alone and given in co-administration with a single intramuscular dose of Boostrix (US formulation SB776423 or ex-US formulation SB263855).
eTrack study number and Abbreviated Title	209141 (RSV MAT-011)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 21 October 2019
Date of Statistical Analysis plan amendment	Amendment 2 Final: 28 FEB 2020 Amendment 3 Final: 03 April 2020

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

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LIST OF ABBREVIATIONS

Ab	Antibody
AE(s)	Adverse Event(s)
AE	Adverse Event
Anti-	Antibodies against
BS H	Blood Sample Humoral
CDC	Centers for Disease Control
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CoP	Correlate of Protection
D	Diphtheria
dTpa	Diphtheria, Tetanus and acellular Pertussis
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EoS	End of Study
eTDF	Electronic Temperature excursion Decision Form
Ex-US	Outside the US
FDA	Food and Drug Administration, United States of America
FHA	Filamentous Hemagglutinin
FU	Follow-up
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
IAF	Informed Assent Form

IB	Investigator Brochure
ICF	Informed Consent Form
ICH:	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LSLV	Last Subject Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibody
PCD	Primary Completion Date
PP	Per protocol
PRN	Pertactin
PRO	Patient Related Outcomes
PT	Pertussis Toxoid
RRA	Recruitment/Randomisation Agreement
RSV	Respiratory Syncytial Virus
RSVPreF3	RSV maternal vaccine
SAE:	Serious Adverse Event
SBIR	Source data Base for Internet Randomisation
SD	Standard Deviation

SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRT	Safety Review Team
T	Tetanus
UP	Urine Pregnancy Test

1. DOCUMENT HISTORY

Date	Description	Protocol Version
03 APR 2020	Amendment 3	Amendment 3: 03-APR-2020
28 FEB 2020	Amendment 2	Amendment 2: 28-FEB-2020
21 Oct 2019	first version	Final: 28 JUN 2019

2. OBJECTIVES/ENDPOINTS

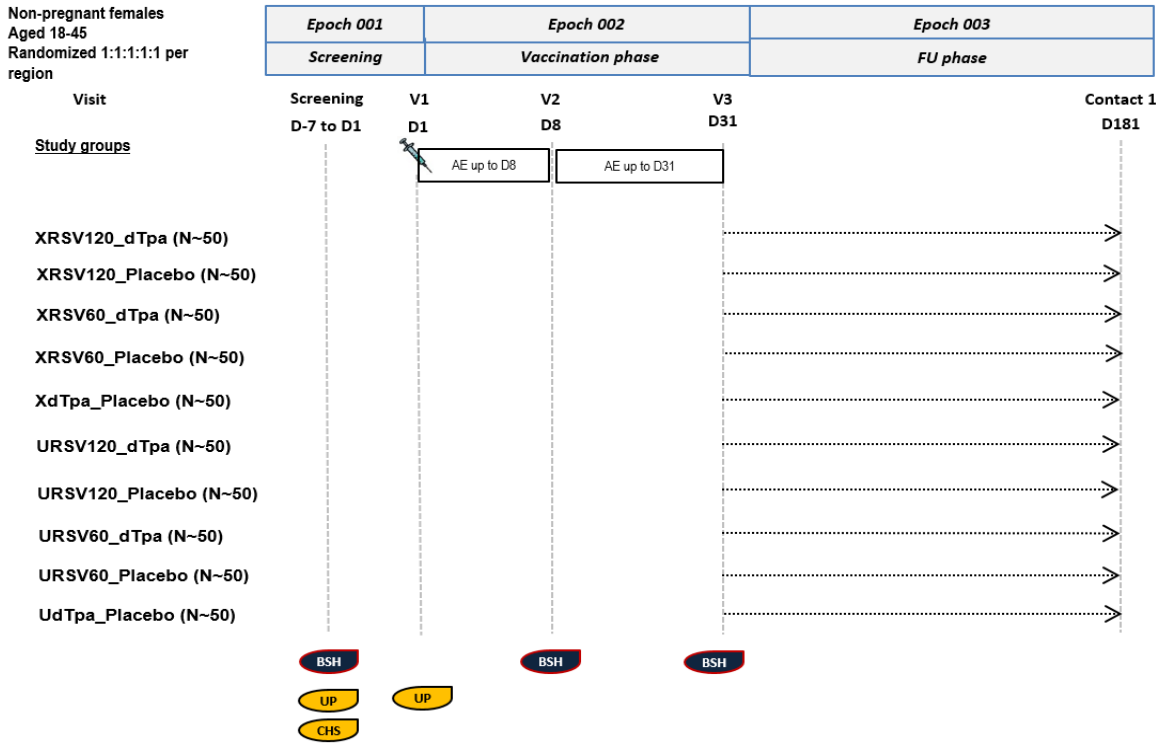
Table 1 Study objectives and endpoints (*Amended 03-APR-2020*)

Objectives	Endpoints
Primary *(US + ex-US data to be pooled)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone or co-administered with dTpa from Vaccination up to Day 31.	*Safety* • Occurrence of any Adverse Events (AEs) from Vaccination to Day 31: – Occurrence of each solicited local AEs at the site of injection in both limbs from Vaccination to Day 8; – Occurrence of solicited general AEs from Vaccination to Day 8; – Occurrence of any unsolicited AEs from Vaccination to Day 31; – Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
Immunogenicity • To evaluate the humoral immune response to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa, at Screening, Day 8 and Day 31.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8 and Day 31 in all groups • RSV IgG antibody concentrations at Screening, Day 8 and Day 31.
Secondary *(US and ex-US data to be considered pooled, then separately)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone or co-administered with dTpa from Vaccination up to Day 31 by formulation.	*Safety* • Occurrence of any AEs from Vaccination to Day 31, for all subjects: – Occurrence of each solicited local AE at the site of injection in both limbs from Vaccination to Day 8 – Occurrence of solicited general AEs from Vaccination to Day 8 – Occurrence of any unsolicited AEs from Vaccination to Day 31 – Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa compared to dTpa-Placebo groups from Vaccination up to Day 181.	• Occurrence of SAEs from Vaccination up to Day 181..
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered from Vaccination up to Day 181. by formulation.	• Occurrence of SAEs from Vaccination up to Day 181..

Objectives	Endpoints
• To evaluate the safety of RSVPreF3 (pooled for all groups receiving RSVPreF3).	• Occurrence of SAEs from Vaccination up to Day 181..
Immunogenicity • To evaluate the humoral immune response to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa at Screening, Day 8, Day 31, post vaccination by formulation.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8, Day 31,. • RSV IgG antibody concentrations at Screening, Day 8, Day 31.
• To evaluate the humoral immune response to the pertussis component of the dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 by formulation.	• Antibody concentrations against pertussis toxoid (anti-PT), filamentous hemagglutinin (anti-FHA), and pertactin (anti-PRN) concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the diphtheria (D) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post vaccination by formulation.	• Anti-D concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the tetanus (T) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post vaccination by formulation.	• Anti-T concentrations at Screening and Day 31.
Tertiary	
If necessary, additional testing to further characterize the response to the RSV maternal investigational vaccine will be performed.	

3. STUDY DESIGN

Figure 1 Study design overview *(Amended 07-APR-2020)*



Note: study groups labeled X = ex-US; study groups labeled U = US. V = visit, C = phone contact
= Vaccination; N = number of subjects; V = Visit; D = Day; AE = adverse event; UP = Urine pregnancy test; CHS = Chemical/Hematological Screening, FU = follow-up
BSH = blood sample (5 mL) for humoral immune responses (RSV-A neutralization and RSV IgG antibody concentrations at Screening, Visit 2 [Day 8] and Visit 3 [Day 31], and dTpa ELISAs at Screening and Visit 3 [Day 31])

The study will be conducted with 2 formulations of dTpa, dTpa_300 (in the US) and dTpa_500 (ex-US) [Christy, 1995].

Approximately 500 eligible subjects (250 in the US and 250 ex-US) will be enrolled. Of these, approximately 250 subjects will be randomized to 5 US study groups in a 1:1:1:1:1 ratio using SBIR, and the remaining approximately 250 will be randomized to 5 ex-US study groups in a 1:1:1:1:1 ratio using SBIR. The randomization algorithm will use a minimization procedure by treating study formulation (US and ex-US) as a stratification factor, and age at the time of vaccination (18-32 or 33-45 years of age) and center as minimization factors.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements,

including those specified in the schedule of activities, are essential and required for study conduct.

- **Type of study:** self-contained
- **Experimental design:** multi-centric study, multi-country Phase II, observer-blind, randomized, with 5 parallel groups in each formulation (US, ex-US).
- **Duration of the study:** Approximately 6 months for each enrolled subject
  - Epoch 001: Screening
  - Epoch 002: Primary (i.e., vaccination phase) starting at Visit 1 (Day 1) and ending just before the Visit 3 (Day 31)
  - Epoch 003: Follow-up contact on Day 181
- **Primary completion Date (PCD):** Visit 3 (Day 31) or last visit of Primary Epoch
- **End of Study (EoS):** Last testing results released of samples collected at Visit 3, to occur no later than 8 months after last subject last visit (LSLV), which occurs with Contact 1 on Day 181 .
- **Study groups:**

Table2 Study groups, pooled study groups (*Amended 03-APR-2020*)

Pooled Groups label in tables	Pooled definition for footnote	Group label in tables	Group definition for footnote
RSV120_dTpa	Subjects who received RSV120 and dTpa	XRSV120_dTpa	Subject who received RSV MAT 120 and *Boostrix*-ex-US (dTpa_500)
		URSV120_dTpa	Subjects who received RSV MAT 120 and *Boostrix*-US (dTpa_300)
RSV120_Placebo	Subjects who received RSV120 and placebo	XPlacebo_RSV120	Subject who received RSV MAT 120 and Placebo
		UPlacebo_RSV120	Subject who received RSV MAT 120 and Placebo
RSV60_ dTpa	Subjects who received RSV60 and dTpa	XRSV60_dTpa	Subjects who received RSV MAT 60 and *Boostrix*-ex-US (dTpa_500)
		URSV60_dTpa	Subjects who received RSV MAT 60 and *Boostrix*-US (dTpa_300)
RSV60_Placebo	Subjects who received RSV60 and placebo	XPlacebo_RSV60	Subjects who received RSV MAT 60 and Placebo
		UPlacebo_RSV60	Subject who received RSV MAT 60 and Placebo
dTpa_Placebo	Subjects who received *Boostrix*(dTpa) and Placebo	XPlacebo_dTpa	Subject who received *Boostrix*-ex-US (dTpa_500) and Placebo
		UPlacebo_dTpa	Subject who received *Boostrix*-US (dTpa_300) and Placebo

RSV_placebo	Subjects who received RSV60 and placebo combined with subjects who received RSV120 and placebo		
RSV_dTpa	Subjects who received RSV60 and dTpa combined with subjects who received RSV 120 and dTpa		

Table 3 Study groups, treatment and epochs foreseen in the study (*Amended 03-APR-2020*)

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)			
				Epoch 001 (Screening)	Epoch 002 (observer-blind)	Epoch 003 (single-blind)	
XRSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-ex-US (dTpa_500)	x	x	x	
Xplacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	x	x	x	
XRSV60_dTpa	50	18 – 45 years	*RSV MAT 60 Boostrix-ex-US (dTpa_500)*	x	x	x	
Xplacebo_RSV60	50	18 – 45 years	*RSV MAT 60* Placebo	x	x	x	
Xplacebo_dTpa	50	18 – 45 years	*Boostrix-ex-US (dTpa_500)* Placebo	x	x	x	
URSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-US (dTpa_300)	x	x	x	
Uplacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	x	x	x	
URSV60_dTpa	50	18 – 45 years	*RSV MAT 60 Boostrix-US*	x	x	x	
Uplacebo_RSV60	50	18 – 45 years	*RSV MAT 60* Placebo	x	x	x	
Uplacebo_dTpa	50	18 – 45 years	*Boostrix*-US (dTpa_300) Placebo	x	x	x	

- **Control:** (active comparator).
- **Treatment allocation**: (randomised stratified).
- **Blinding:** As described in Table 3**.**
- **Data collection**: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject paper Diary (pDiary).
- **Safety monitoring:**

If the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately.

4. ANALYSIS SETS *(Amended 03-APR-2020)*

4.1. Definition

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

Analysis Set	Description
Enrolled	Subjects who agreed to participate in a clinical study after completion of the informed consent process. And subject is not a screen failure.
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 randomised and have post-vaccination data minus subjects with protocol deviations that lead to exclusion
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data

4.1.1. Exposed Set

The ES will include all subjects with study vaccine administration documented.

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

4.1.2. Per Protocol Analysis Set

Per protocol analysis set will be defined by time points. It will include all of enrolled subjects who have immunogenicity data at Screening, Day 8 and Day 31.

- An **immunogenicity** analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available, If, in any study group and at any timepoint, the percentage of enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more.

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 fraudulent data) will be used for identifying subjects eliminated from ES

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

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

4.2.2.1. Excluded subjects from Per-protocol analysis set

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

Table 4 Elimination code and condition (*Amended 03-APR-2020*)

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-45 years	All	Immunogenicity
2150	Failure to report safety events per protocol	All	Safety
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181 Visit 4/Day 365	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 8, check the interval from vaccination to day 8 BS = 7 – 10 days; • For PPS at Day 31, check the interval from vaccination to day 31 BS = 30 – 45 days; • For PPS at Day 181, check the interval from phone contact to visit 4 BS=0-30 days	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 2/Day 8 Visit 3/Day 31 Visit 4/Day 181	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
** Attribution of code 1070 to a subject requires CRDL confirmation
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
DOB-Date of Birth, VAC-Vaccination, BS- Blood Sample

4.2.3. Elimination from solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

5.1. Demography

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

These analyses will be performed on the Exposed set and on the Per protocol set for immunogenicity.

For all subjects, demographic characteristics (e.g., age at vaccination (18–32; 33-45 years), race and ethnicity, vaccination history will be summarized by overall and vaccine group using descriptive statistics.

- Frequency tables will be generated for categorical variables such as centre.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height, weight and body mass index (BMI).

5.1.2. Additional considerations

Demographic characteristics will also be summarized on Enrolled Set for web public disclosure.

Subject disposition will be summarized by group using descriptive statistics:

- Number of subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set.

Summary of important protocol deviations leading to elimination will be tabulated by group. An individual listing will also be provided.

Summary of medical history will be performed on Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) and preferred term.

Summary of vaccination history will be performed on Exposed Set by using GSKDRUG dictionary.

Additional analyses by country and/or by site may be performed if deemed necessary

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol (*Amended 03-APR-2020)*

The primary analysis on immunogenicity will be based on the Per Protocol set. If, in any study group and at any timepoint, the percentage of enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Exposed Analysis Set will be performed to complement the Per Protocol analysis.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled)* For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically pooled. • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI pooled. • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentrations may be calculated at Screening, and/or Day 8, and/or Day 31 pooled for all subjects. • A further exploratory between-groups analysis will be performed at Day 8 or Day 31 using an ANCOVA model by including study groups, study formulation (US and ex-US), age category, and level of antibodies at Screening as covariates.

Endpoint	Statistical Analysis Methods
Secondary	*(US and ex-US data to be considered pooled, then separately* For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically by formulation (US and ex-US). • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI by formulation (US and ex-US). • Antibody titer/concentration will be displayed using reverse cumulative curves by formulation (US and ex-US). • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points by formulation (US and ex-US). • Response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). Booster responses to PT, FHA and PRN antigens are defined as: 1. For subjects with pre-vaccination antibody concentration below the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the assay cut-offs, 2. For subjects with pre-vaccination antibody concentration between the assay cut-offs and below 4 times the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration, and 3. For subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-offs: post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration. • The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN, anti-D, anti-T will be calculated at Screening and Day 31 pooled for all subjects and by formulation (US and ex-US). • A further exploratory between-groups analysis in terms of anti-PT, anti-FHA, anti-PRN, anti-D, anti-T will be performed at Day 31 using an ANCOVA model by including study groups, study formulation (US and ex-US), age category, and level of antibodies at Screening as covariates. • For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group on Day 31 post vaccination will be calculated for each formulation. • For Boostrix seroprotection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for each formulation.
Tertiary	Will be described in a Statistical Analysis Plan finalised before database unblinding/freezing.

*The statistical method will not be applied to primary endpoint. For detailed rationale, refer to Section 8.
**pooled group definition is detailed in Table 2

5.2.2. Additional considerations

At first analysis at Day 31 and final analysis at Day181, immunogenicity analysis will be performed on PPS.

5.2.2.1. Between group analysis

The Non-inferiority on RSV-A neutralizing antibody titers at 31 days post vaccination in the co-administration of RSVPre F3 vaccine + *Boostrix* compared to RSV+ Placebo will be evaluated based on the criterion below:

- The criterion to evaluate non-inferiority with respect to RSV-A neutralizing antibody titers is that the upper limits of the 95% CI on the GMT ratio (RSVPreF3 +*Placebo* divided by RSVPre3 + Boostrix) is less than or equal to 1.5 at 31 days post vaccination.

RSVPreF3 IgG antibody concentrations, RSV-A neutralizing antibody titers will applied to following model.

For the analysis of subjects at visit 3 (Day 31), the model will be explored and fitted via the proc glm procedure according to the following code:

```
PROC glm data=sero;
  CLASS group;
  MODEL log_val = baseline group age_cat country_US country_BE
  Output out= pred;
 LSMEANS group/pdiff cl alpha=0.1;
RUN;
```

where **log_val** represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint (Day 8) or (Day 31), **baseline** is pre-vaccination logarithm10 transformation of the concentrations/titers, **group** indicates the study group, pooled groups (US and ex-US) will considered in model then separate by formulation. **age_cat** is indicator variable (0/1) and will be treated as continuous in the model, age_cat equals 0 if the age category at vaccination between 18 - 32 years, otherwise age_cat equals 1 if age category is between 33 - 45 years at vaccination. **Country_US** is indicator variable (0/1) and will treated as continuous in the model, if subject from US, then variable will equal to 1, otherwise equals to 0, **Country_BE** is indicator variable (0/1) and will treated as continuous in model, if subject from BE, then variable equals to 1, otherwise equals to 0, if subject is from Canada, above two indicators equal to 0. The inclusion of age category at vaccination, in the model depends on the availability of the variable and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

When considering group as separated by Boostrix formulation, remove Country_US and Country_BE from model._

GMT/GMC ratios between vaccine groups obtained using above model will be calculated by exponentiating mean difference of logarithm- transformed titres. The 90% CI for GMT/GMC ratio will be obtained by exponential-transformation of the CI for the group least square mean of the log-transformed titres/concentration from the above model.

5.2.2.2. Percentage difference between two groups

We will conduct percentage difference of response rate in term of antigen PT, FHA and PRN [Camargo, 1984; Melville-Smith, 1983]. with the two-sided standardized asymptotic 95% CI in the RSVPreF3 dTpa group (minus) the dTpa Placebo group on Day 31.

Percentage difference of seroprotection rate in term of antigen D and antigen T [Vidor, 2008] with the two-sided standardized asymptotic 95% CI for RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group by formulation at Day 31 will be calculated.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol (Amended 03-APR-2020)

The following safety analyses will be performed based on the Exposed Set. The following safety analysis will be performed on the pooled data then the US and ex-US separately.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled)* 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 (solicited or unsolicited) AE during the 7-day or 30 day visit post vaccination period will be tabulated with exact 95% CI by study group. 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 AEs resulting in medically attended visits. The percentage of subjects reporting each individual solicited local AE (any related, any grade and grade 3 related AE and those resulting in medically attended visit) and solicited general AE (any related, any grade and grade 3 related AE and those resulting in medically attended visit) during the 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) will be tabulated based on maximum intensity for each group. For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period will be tabulated for each group. Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) 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 each vaccination. The percentage of subjects with any unsolicited AEs during the Day 1 to Day 30 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 and SOC. 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 CRDL and the signs

Endpoint	Statistical Analysis Methods
	and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of SAE classified by the MedDRA SOC and Preferred Terms and reported during the 30-day follow-up period will be tabulated with exact 95% CI. SAEs will also be described in detail. The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period and during the 30-day follow-up period will be summarized by each group and pooled.

Endpoint	Statistical Analysis Methods
Secondary	*(US and ex-US data to be considered pooled, then separately)* The percentage of subjects with at least one solicited AE(local and general), with at least one unsolicited AE and with any ("solicited or unsolicited") AE during the 7-day or 30 -day as well any SAE up to 180 days post vaccination will be tabulated with exact 95% CI by study group. 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 AEs resulting in medically attended visits. The percentage of subjects with at least one report of SAE classified by the MedDRA SOC and Preferred Terms and reported during the 30-day follow-up period will be tabulated with exact 95% CI for each formulation (US and ex-US). The percentage of subjects reporting each individual solicited local AE (any grade, Grade 3 and those resulting in a medically attended visit) and solicited general AE (any grade, Grade 3, any related, Grade 3 related and those resulting in a medically attended visit) during the 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) will be tabulated based on maximum intensity for each group for each formulation (US and ex-US). For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period will be tabulated for each group for each formulation (US and ex-US). Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) 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 each vaccination. For each formulation (US and ex-US), 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) SOC and preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) from vaccination up to day 30 will be summarized by each group for each formulation (US and ex-US).
Tertiary	Will be described in a Statistical Analysis Plan finalised before database unblinding/freezing.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

The analysis of solicited events will be performed on Solicited Safety Set. The intensity of the following solicited events will be assessed as described:

Table 5 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	
Redness at injection site		
Swelling at injection site		
Temperature*		
Headache		
Fatigue		
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)		

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

The maximum intensity of solicited administration site redness/swelling will be scored at GSK Biological as follows:

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

Duration in days of solicited local and general adverse events within 7 days after vaccination will be tabulated by study group and overall, and if needed by age group. The derivation rule of duration in days for solicited events is detailed in section 10.1.3.9.

5.3.2.2. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set.

5.3.2.3. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited 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	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Headache	Headache	10019211
Gastrointestinal symptoms†	Gastrointestinal disorder	10017944

Please note – to check for AE term in cDISC during dry run
†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

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

5.3.2.4. Other analysis

Other safety analysis will be performed on Exposed Set.

Concomitant medications/products will be coded using the GSKDRUG dictionary. The number and percentage of subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination and 12 months following vaccination will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

7.1.1. First and final study

Analyses to evaluate objectives and endpoints will be performed in steps.

A first analysis will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints pertaining to safety and immunogenicity up to Day 31 are available. 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 unblinded some specific subjects, the study will be considered as single-blind from this point onwards, with subjects and investigators remaining blinded up to study end. The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion are available. 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	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis (E1_01)	Public disclosure, Study report
First Analysis (E1_02)	Public disclosure

7.2. Statistical considerations for interim analyses

NA

8. CHANGES FROM PLANNED ANALYSES*(AMENDED 03-APR-2020)*

The calculation of GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3_Placebo in terms of RSV-A Nab titers and RSV IgG antibody concentrations at Screening, Day 8 and Day 31 pooled for all subjects will be removedfrom analyses plan. We will report adjusted GMT/GMC ratio and their 95% CI which is generated from ANCOVA model.

Adjusted GMT/GMC ratio with both 90% CI and 95% CI which are generated from ANCOVA model will be reported in terms of RSV-A Nab titers and RSV IgG antibody concentrations.

The calculation of GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa_Placebo groups in terms of antigens PT, FHA , PRN, D and T will be added at Day 31 pooled for all RSV formulation.

Lab assay cut-off of RSV-A Nab titer for humoral immunity to be reported by using both IU/ml (International units/millilitre) and ED60

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 **Error! Reference source not found.**

9.1. Data derivation

9.1.1. Immunogenicity (Amended 07-APR-2020)

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.

- 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, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

Following table will demonstrate all antigens will be analysed at considered time point for different treatment groups

	Immunogenicity Endpoints	Statistical Analysis Methods
RSVPreF3	• RSVPreF3 IgG antibody concentration, and • Neutralizing antibody titers against RSV-A	*(US and ex-US data to be considered pooled, then separately)* • GMCs/GMTs and their 95% CI will be tabulated and represented graphically • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • A further exploratory between-groups of RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentration, analysis will be performed at Day 8 and Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates
Boostrix (dTpa)	• Booster response to PT • Booster response to FHA • Booster response to PRN	*For the subjects received RSVPreF3 dTpa and subjects received dTpa placebo* • Booster response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for US and ex-US pooled formulation and separately. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN will be calculated between Day 31 over Screening for US and ex-US pooled data and separately. • A further exploratory between-groups analysis will be performed at Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates • For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately
	• Anti-D concentration • Anti-T concentration	For the subjects received RSVPreF3 dTpa and subjects received dTpa placebo • The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for US and ex-US pooled data and separately • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-D, anti-Twill be calculated at Screening and Day 31 for US and ex-US pooled data and separately. • Protection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately.

9.1.1.1. Laboratory assays cut-offs for humoral immunity (Antibody determination) *(Amended 03-APR-2020)*

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay. The cut-off tests for immunogenicity evaluation will be as per following:

Sample	Component	Method	Unit	Cut-off*	ULOQ
Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	ED60 and/or IU (international unit)	18 for ED60 56 for IU	ED60 : 123535 IU : 217400
Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	ELU/mL	25	251 769
Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	IU/mL	2.046	3182.397
Serum	Bordetella pertussis.Pertactin Ab.IgG	ELI	IU/mL	2.187	6313.300
Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	IU/mL	2.693	883.559
Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	IU/mL	0.030	59.545
Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	IU/mL	0.037	116.428

Ab = antibody; ELI = Enzyme-linked immunosorbent assay (ELISA); IgG = immunoglobulin G; RSV = respiratory syncytial virus; ED60 = serum dilution inducing 60% inhibition in plaque forming units; IU/ml = International units/milliliter, IU= International units

Assay cut-off and unit might be subject to change before starting of testing (e.g. in case of requalification, revalidation or standardisation). In this case, this will be documented in the clinical report.

9.2. Statistical Method

NA

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 **Error! Reference source not found.** (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.

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.

The following exceptions apply:

- Adverse event start dates with missing day:
    - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
    - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

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

10.1.2.3. Solicited adverse events

- 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 Exposed Set 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 vaccination will be considered not having that symptom after vaccination.
  - When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.
  - When a specific solicited adverse event is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the adverse event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited adverse event summary tables.
  - Dose without symptom sheets documented will be excluded.

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

10.1.3.8. 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).

10.1.3.9. 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.

10.1.3.10. 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.

10.1.3.11. 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 by as only one occurrence. However specific tables or figures could be conducted to report solicited local events by 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. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

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

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

10.1.4.4. 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 [**Error! Reference source not found.**, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [**Error! Reference source not f ound.**, 1985].

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

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Signature Page for 209141 TMF-1765379 v1.0

Reason for signing: Approved	Name: Feng Gao Role: Approver Date of signature: 30-Apr-2020 16:03:07 GMT+0000

Signature Page for TMF-1765379 v1.0

	Statistical Analysis Plan
Detailed Title:	Phase II randomized, observer-blind, placebo-controlled, multi-country study in healthy non-pregnant women 18-45 years of age to evaluate the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV maternal vaccine (GSK388550A) when given alone and given in co-administration with a single intramuscular dose of Boostrix (US formulation SB776423 or ex-US formulation SB263855).
eTrack study number and Abbreviated Title	209141 (RSV MAT-011)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 21 October 2019

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

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LIST OF ABBREVIATIONS

Ab	Antibody
AE(s)	Adverse Event(s)
AE	Adverse Event
Anti-	Antibodies against
BS H	Blood Sample Humoral
CDC	Centers for Disease Control
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CoP	Correlate of Protection
D	Diphtheria
dTpa	Diphtheria, Tetanus and acellular Pertussis
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EoS	End of Study
eTDF	Electronic Temperature excursion Decision Form
Ex-US	Outside the US
FDA	Food and Drug Administration, United States of America
FHA	Filamentous Hemagglutinin
FU	Follow-up
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
IAF	Informed Assent Form

IB	Investigator Brochure
ICF	Informed Consent Form
ICH:	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LSLV	Last Subject Last Visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibody
PCD	Primary Completion Date
PP	Per protocol
PRN	Pertactin
PRO	Patient Related Outcomes
PT	Pertussis Toxoid
RRA	Recruitment/Randomisation Agreement
RSV	Respiratory Syncytial Virus
RSVPreF3	RSV maternal vaccine
SAE:	Serious Adverse Event
SBIR	Source data Base for Internet Randomisation
SD	Standard Deviation

SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRT	Safety Review Team
T	Tetanus
UP	Urine Pregnancy Test

1. DOCUMENT HISTORY

Date	Description	Protocol Version
21 Oct 2019	first version	Final: 28 JUN 2019

2. OBJECTIVES/ENDPOINTS

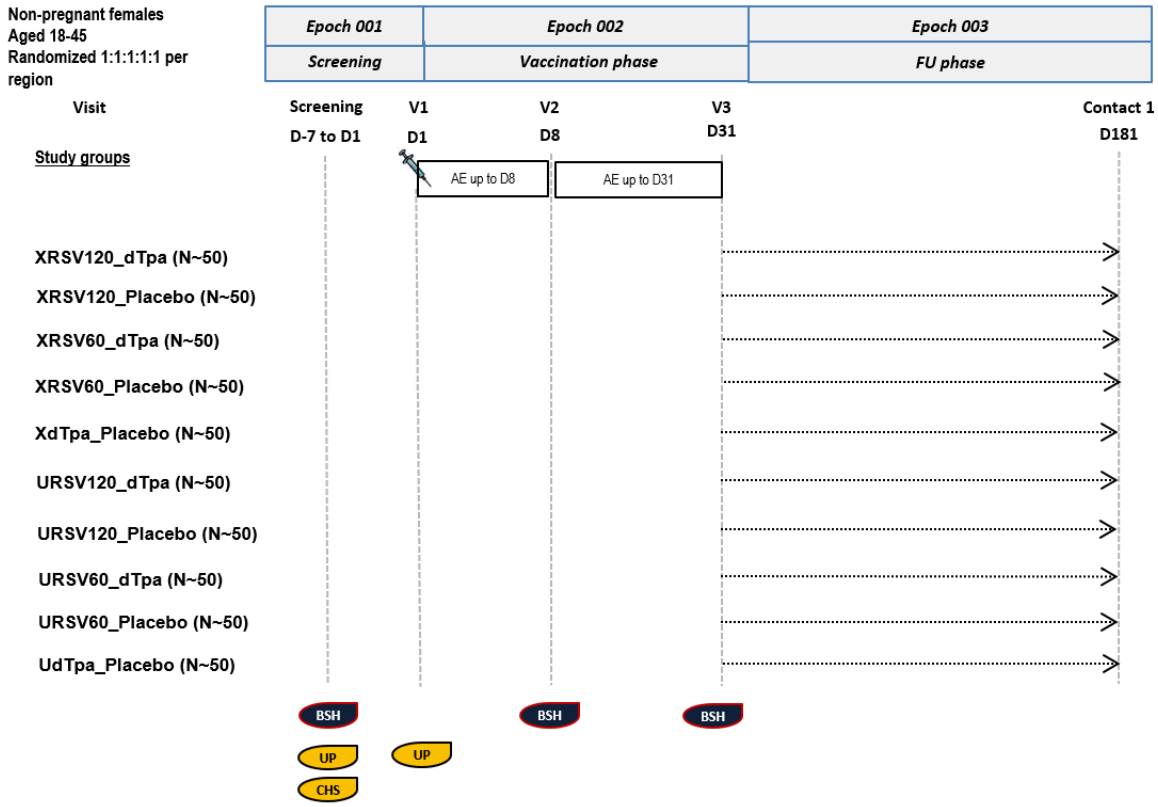
Table 1 Study objectives and endpoints

Objectives	Endpoints
Primary *(US + ex-US data to be pooled)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone or co-administered with dTpa from Vaccination up to Day 31.	*Safety* • Occurrence of any Adverse Events (AEs) from Vaccination to Day 31: — Occurrence of each solicited local AEs at the site of injection in both limbs from Vaccination to Day 8; — Occurrence of solicited general AEs from Vaccination to Day 8; — Occurrence of any unsolicited AEs from Vaccination to Day 31; — Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
Immunogenicity • To evaluate the humoral immune response to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa, at Screening, Day 8 and Day 31.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8 and Day 31 in all groups • RSV IgG antibody concentrations at Screening, Day 8 and Day 31.
Secondary *(US and ex-US data to be considered pooled, then separately)*	
Safety • To evaluate the safety and reactogenicity of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone or co-administered with dTpa from Vaccination up to Day 31 by formulation.	*Safety* • Occurrence of any AEs from Vaccination to Day 31, for all subjects: — Occurrence of each solicited local AE at the site of injection in both limbs from Vaccination to Day 8 — Occurrence of solicited general AEs from Vaccination to Day 8 — Occurrence of any unsolicited AEs from Vaccination to Day 31 — Occurrence of Serious Adverse Events (SAEs) from Vaccination to Day 31.
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa compared to dTpa-Placebo groups from Vaccination up to Day 181.	• Occurrence of SAEs from Vaccination up to Day 181.
• To evaluate the safety of 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered from Vaccination up to Day 181 by formulation.	• Occurrence of SAEs from Vaccination up to Day 181.
• To evaluate the safety of RSVPreF3 (pooled for all groups receiving RSVPreF3).	• Occurrence of SAEs from Vaccination up to Day 181.

Objectives	Endpoints
Immunogenicity • To evaluate the humoral immune response to 2 dose levels (60 and 120 µg) of RSVPreF3 when given alone and co-administered with dTpa at Screening, Day 8 and Day 31 post vaccination by formulation.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8 and Day 31. • RSV IgG antibody concentrations at Screening, Day 8 and Day 31.
• To evaluate the humoral immune response to the pertussis component of the dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 by formulation.	• Antibody concentrations against pertussis toxoid (anti-PT), filamentous hemagglutinin (anti-FHA), and pertactin (anti-PRN) concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the diphtheria (D) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post vaccination by formulation.	• Anti-D concentrations at Screening and Day 31.
• To evaluate the humoral immune response to the tetanus (T) component of dTpa vaccine when given alone and co-administered with 2 dose levels (60 and 120 µg) of RSVPreF3 at Screening and Day 31 post vaccination by formulation.	• Anti-T concentrations at Screening and Day 31.
Tertiary	
If necessary, additional testing to further characterize the response to the RSV maternal investigational vaccine will be performed.	

3. STUDY DESIGN

Figure 1 Study design overview



Note: study groups labeled X = ex-US; study groups labeled U = US.

= Vaccination; N = number of subjects; CHS= Chemical/Hematological Screening Visit; D = Day; AE = adverse event; UP = Urine pregnancy test; FU = follow-up; BSH = blood sample (5 mL) for humoral immune responses (RSV-A neutralization and RSV IgG antibody concentrations at Screening, Visit 2 [Day 8] and Visit 3 [Day 31], and dTpa ELISAs at Screening and Visit 3 [Day 31])

The study will be conducted with 2 formulations of dTpa, dTpa_300 (in the US) and dTpa_500 (ex-US) [Christy, 1995].

Approximately 500 eligible subjects (250 in the US and 250 ex-US) will be enrolled. Of these, approximately 250 subjects will be randomized to 5 US study groups in a 1:1:1:1:1 ratio using SBIR, and the remaining approximately 250 will be randomized to 5 ex-US study groups in a 1:1:1:1:1 ratio using SBIR. The randomization algorithm will use a minimization procedure by treating study formulation (US and ex-US) as a stratification factor, and age at the time of vaccination (18-32 or 33-45 years of age) and center as minimization factors.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities, are essential and required for study conduct.

- **Type of study:** self-contained
- **Experimental design:** multi-centric study, multi-country Phase II, observer-blind, randomized, with 5 parallel groups in each formulation (US, ex-US).
- **Duration of the study:** Approximately 6 months for each enrolled subject
  - Epoch 001: Screening
  - Epoch 002: Primary (i.e., vaccination phase) starting at Visit 1 (Day 1) and ending just before the Visit 3 (Day 31)
  - Epoch 003: Follow-up contact on Day 181
- **Primary completion Date (PCD):** Visit 3 (Day 31) or last visit of Primary Epoch
- **End of Study (EoS):** Last testing results released of samples collected at Visit 3, to occur no later than 8 months after last subject last visit (LSLV), which occurs with Contact 1 on Day 181.
- **Study groups:**

Table 2 Study groups, pooled study groups

Group order	Group label	Group definition	Pooled Group label	Pooled group definition
1	XRSV120_dTpa	Subject who received RSV MAT 120 Boostrix-ex-US (dTpa_500)	RSV120_dTpa	Subjects who received RSV120 and dTpa
2	URSV120_dTpa	Subjects who received RSV MAT 120 Boostrix-US (dTpa_300)	RSV120_dTpa	Subjects who received RSV120 and dTpa
3	XPlacebo_RSV120	Subject who received RSV MAT 120 Placebo	RSV120_Placebo	Subjects who received RSV120 and placebo
4	UPlacebo_RSV120	Subject who received *RSV MAT 120* Placebo	RSV120_Placebo	Subjects who received RSV120 and placebo
5	XRSV60_ dTpa	Subjects who received RSV MAT 60 Boostrix-ex-US (dTpa_500)	RSV60_ dTpa	Subjects who received RSV60 and dTpa
6	URSV60_ dTpa	*RSV MAT 60* Boostrix-US (dTpa_300)	RSV60_ dTpa	Subjects who received RSV60 and dTpa
7	XPlacebo_RSV60	Subjects who received RSV MAT 60 Placebo	RSV60_Placebo	Subjects who received RSV60 and placebo
8	UPlacebo_RSV60	Subject who received *RSV MAT 60* Placebo	RSV60_Placebo	Subjects who received RSV60 and placebo
9	XPlacebo_dTpa	Subject who received Boostrix-US (dTpa_500) Placebo	dTpa_Placebo	Subjects who received Boostrix(dTpa) and Placebo

Group order	Group label	Group definition	Pooled Group label	Pooled group definition
10	UPlacebo_dTpa	Subject who received *Boostrix*-US (dTpa_300) Placebo	dTpa_Placebo	Subjects who received Boostrix(dTpa) and Placebo

Table 3 Study groups, treatment and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)		
				Epoch 001 (Screening)	Epoch 002 (observer-blind)	Epoch 003 (single-blind)
XRSV120_dTpa	50	18 - 45 years	*RSV MAT 120 Boostrix*-ex-US (dTpa_500)	x	x	x
XPlacebo_RSV120	50	18 - 45 years	*RSV MAT 120* Placebo	x	x	x
XRSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-ex-US (dTpa_500)*	x	x	x
XPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x
XPlacebo_dTpa	50	18 - 45 years	*Boostrix-ex-US (dTpa_500)* Placebo	x	x	x
URSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-US (dTpa_300)	x	x	x
UPlacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	x	x	x
URSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-US*	x	x	x
UPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x
UPlacebo_dTpa	50	18 – 45 years	*Boostrix*-US (dTpa_300) Placebo	x	x	x

- **Control:** (active comparator).
- **Treatment allocation**: (randomised stratified).
- **Blinding:** As described in Table 3
- **Data collection**: standardised Electronic Case Report Form (eCRF). Solicited symptoms will be collected using a subject paper Diary (pDiary).
- **Safety monitoring:**

If the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately.

4. ANALYSIS SETS

4.1. Definition

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

Analysis Set	Description
Enrolled	All subjects who completed the informed consent process and signed the informed consent form
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 randomised and have post-vaccination data minus subjects with protocol deviations that lead to exclusion
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data

4.1.1. Exposed Set

The ES will include all subjects with study vaccine administration documented.

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

4.1.2. Per Protocol Analysis Set

Per protocol analysis set will be defined by time points. It will include all of enrolled subjects who have immunogenicity data at Screening, Day 8 and Day 31.

- An **immunogenicity** analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available, If, in any study group and at any timepoint, the percentage of enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more.

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 fraudulent data) will be used for identifying subjects eliminated from ES

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

4.2.2.1. Excluded subjects from Per-protocol analysis set

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

Table 4 Elimination code and condition

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-45 years	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 8, check the interval from vaccination to day 8 BS = 7 – 10 days; • For PPS at Day 31, check the interval from vaccination to day 31 BS = 30 – 45 days;	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 2/Day 8 Visit 3/Day 31	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
** Attribution of code 1070 to a subject requires CRDL confirmation
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
DOB-Date of Birth, VAC-Vaccination, BS- Blood Sample

4.2.3. Elimination from solicited safety set

4.2.3.1. Excluded subjects

4.2.3.1.1. Solicited safety set

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in section 10 while the study specific data derivation rules and stat methods are described in section 9

5.1. Demography

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

These analyses will be performed on the Exposed set and on the Per protocol set for immunogenicity.

For all subjects, demographic characteristics (e.g., age at vaccination (18 – 32; 33-45 years), race and ethnicity, vaccination history will be summarized by overall and vaccine group using descriptive statistics.

- Frequency tables will be generated for categorical variables such as centre.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height, weight and body mass index (BMI).

5.1.2. Additional considerations

Demographic characteristics will also be summarized on Enrolled Set for web public disclosure.

Subject disposition will be summarized by group using descriptive statistics:

- Number of subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set.

Summary of important protocol deviations leading to elimination will be tabulated by group. An individual listing will also be provided.

Summary of medical history will be performed on Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) and preferred term.

Additional analyses by country and/or by site may be performed if deemed necessary

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol

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 enrolled or vaccinated subjects with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Set will be performed to complement the Per Protocol analysis.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled)**** For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically pooled. • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI pooled. • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentrations will be calculated at Screening, Day 8 and Day 31 pooled for all subjects.* • A further exploratory between-groups analysis will be performed at Day 8 or Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates.
Secondary	*(US and ex-US data to be considered pooled, then separately*) For each group, at each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified): • GMCs/GMTs and their 95% CI will be tabulated and represented graphically by formulation (US and ex-US). • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI by formulation (US and ex-US). • Antibody titer/concentration will be displayed using reverse cumulative curves by formulation (US and ex-US). • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points by formulation (US and ex-US). • Booster response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). Booster responses to PT, FHA and PRN antigens are defined as: • For subjects with pre-vaccination antibody concentration below the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the assay cut-offs, • For subjects with pre-vaccination antibody concentration between the assay cut-offs and below 4 times the assay cut-offs: post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration, and

Endpoint	Statistical Analysis Methods
	• For subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-offs: post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration. – The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for each formulation (US and ex-US). – The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN, anti-D, anti-T will be calculated at Screening and Day 31 pooled for all subjects and by formulation (US and ex-US). – A further exploratory between-groups analysis will be performed at Day 31 using an ANCOVA model by including study groups, age category, country and level of antibodies at Screening as covariates . – For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group on Day 31 post vaccination will be calculated for each formulation. – For *Boostrix* seroprotection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for each formulation.
Will doTertiary	Will be described in a seperate Statistical Analysis .

*The statistical method will not be applied to primary endpoint. For detailed rationale, refer to Section 8.
**pooled group definition is detailed in Table 2

5.2.2. Additional considerations

At first analysis at Day 31 and final analysis at Day 181, immunogenicity analysis will be performed on PPS.

5.2.2.1. Between group analysis

This analysis is exploratory. RSVPreF3 IgG antibody concentrations, RSV-A neutralizing antibody titers will applied to following model.

For the analysis of subjects at visit 3 (Day 31), the model will be explored and fitted via the proc glm procedure according to the following code:

```
PROC glm data=sero;
  CLASS group;
  MODEL log_val = baseline group age_cat country_US
country_BE
  Output out= pred;
  LSMEANS group/pdiff cl alpha=0.1;
 RUN;
```

where **log_val** represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint (Day 31), **baseline** is pre-vaccination logarithm10 transformation of the concentrations/titers, **group** indicates the study group, pooled groups (US and ex-US) will considered in model then separate by formulation. **age_cat** is indicator variable (0/1) and will be treated as continuous in the model, if the age category at vaccination between 18 - 32 years, otherwise age_cat equals 1 if age category is between 33 - 45 years at vaccination. **Country_US** is indicator variable (0/1) and will treated as continuous in the model, if subject from US, then variable will equal to 1, otherwise equals to 0, **Country_BE** is indicator variable (0/1) and will treated as continuous in model, if subject from BE, then variable equals to 1, otherwise equals to 0, if subject is from Canada, above two indicators equal to 0. The inclusion of age category at vaccination, in the model depends on the availability of the variable and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

GMT/GMC ratios between vaccine groups obtained using above model will be calculated by exponentiating mean difference of logarithm- transformed titres. The 90% CI for GMT/GMC ratio will be obtained by exponential-transformation of the CI for the group least square mean of the log-transformed titres/concentration from the above model.

5.2.2.2. Percentage difference between two groups

We will conduct percentage difference of booster responses [Camargo, 1984; Melville -Smith, 1983]. with the two-sided standardized asymptotic 95% CI for dTpa vaccine group when given alone and co-administered with RSVPreF3 by formulation at Day 31.

Percentage difference of protection rate [Vidor, 2008] with the two-sided standardized asymptotic 95% CI for RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group by formulation at Day 31 will be calculated

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol

The following safety analyses will be performed based on the Exposed Set. The following safety analysis will be performed on the pooled data then the US and ex-US separately.

Endpoint	Statistical Analysis Methods
Primary	*(US + ex-US data to be pooled)* 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 as well as180-day follow up will be tabulated with exact 95% CI by study group. 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 AEs resulting in medically attended visits. The percentage of subjects reporting each individual solicited local AE (any grade, Grade 3 and those resulting in a medically attended visit) and solicited general AE (any grade, Grade 3, any

Endpoint	Statistical Analysis Methods
	related, Grade 3 related and those resulting in a medically attended visit) during the 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) will be tabulated based on maximum intensity for each group. For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period will be tabulated for each group. Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) 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 each vaccination. The percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e. on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the 30-day follow-up period will be tabulated with exact 95% CI. SAEs will also be described in detail. The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period and during the 30-day follow-up period will be summarized by each group and pooled.
Secondary	*(US and ex-US data to be considered pooled, then separately)* 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% CI by study group for each formulation (US and ex-US). 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 AEs resulting in medically attended visits. The percentage of subjects reporting each individual solicited local AE (any grade, Grade 3 and those resulting in a medically attended visit) and solicited general AE (any grade, Grade 3, any related, Grade 3 related and those resulting in a medically attended visit) during the 7-day follow-up period (i.e. on the day of vaccination and 6 subsequent days) will be tabulated based on maximum intensity for each group for each formulation (US and ex-US). For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period will be tabulated for each group for each formulation (US and ex-US). Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 or above (> 39.0°C/102.2°F) 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 each vaccination. For each formulation (US and ex-US), 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

Endpoint	Statistical Analysis Methods
	reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the 30-day follow-up period will be tabulated with exact 95% CI for each formulation (US and ex-US), reported during the entire study period (from vaccination up to day 181) will be tabulated with exact 95% CI for each formulation (US and ex-US), pooled formulations and pooled all groups receiving RSVPreF3 will also be described in detail. The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) from vaccination up to day 181 will be summarized by each group for each formulation (US and ex-US),
Tertiary	Will be described in a separate Statistical Analysis Plan

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

The analysis of solicited events will be performed on Solicited Safety Set. The intensity of the following solicited events will be assessed as described:

Table 5 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	
Redness at injection site		
Swelling at injection site		
Temperature*		
Headache		
Fatigue		
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)		

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

The maximum intensity of solicited administration site redness/swelling will be scored at GSK Biological as follows:

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

Duration in days of solicited local and general adverse events within 7 days after vaccination will be tabulated by study group and overall, and if needed by age group. The derivation rule of duration in days for solicited events is detailed in section 10.1.3.9.

5.3.2.2. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set.

5.3.2.3. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited 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	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Headache	Headache	10019211
Gastrointestinal symptoms†	Gastrointestinal disorder	10017944

Please note – to check for AE term in cDISC during dry run
†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

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

5.3.2.4. Other analysis

Other safety analysis will be performed on Exposed Set.

Concomitant medications/products will be coded using the GSKDRUG dictionary. The number and percentage of subjects taking concomitant medications (any medication, any

antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination and 6 months following vaccination will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

7.1.1. First and final study

Analyses to evaluate objectives and endpoints will be performed in steps.

A first analysis will be performed on all data available and as clean as possible, when data for at least primary and secondary endpoints pertaining to safety and immunogenicity up to Day 31 are available. 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 unblinded some specific subjects, the study will be considered as single-blind from this point onwards, with subjects and investigators remaining blinded up to study end. The investigators will not be provided with the individual data listings or with the randomization listings until the end of study analysis.

The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion are available. 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	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis (E1_01)	Public disclosure, Study report
First Analysis (E1_02)	Public disclosure

7.2. Statistical considerations for interim analyses

NA

8. CHANGES FROM PLANNED ANALYSES

The calculation of GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentrations will be calculated at Screening, Day 8 and Day 31 pooled for all subjects will remove from analyses plan, since we will report adjusted GMT/GMC ratio and their 90% CI which is generated from ANCOVA model.

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 **Error! Reference source not found.**

9.1. Data derivation

9.1.1. 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.

- 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, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

Following table will demonstrate all antigens will be analysed at considered time point for different treatment groups

	Immunogenicity Endpoints	Statistical Analysis Methods
RSVPreF3	• RSVPreF3 IgG antibody concentration, and • Neutralizing antibody titers against RSV-A	*(US and ex-US data to be considered pooled, then separately)* • GMCs/GMTs and their 95% CI will be tabulated and represented graphically • Geometric mean of ratios of antibody titer/concentrations at each individual post-vaccination time point over pre-vaccination (screening) will be tabulated with 95% CI • Antibody titer/concentration will be displayed using reverse cumulative curves pooled. • The kinetics of GMT/GMCs will be plotted as a function of time for subjects with results available at all time points pooled. • A further exploratory between-groups of RSVPreF3 dTpa and RSVPreF3 alone in terms of RSV-A Nab titers and RSV IgG antibody concentration, analysis will be performed at Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates

	Immunogenicity Endpoints	Statistical Analysis Methods
Boostrix (dTpa)	• Booster response to PT • Booster response to FHA • Booster response to PRN	*For the subjects received RSVPreF3 dTpa and subjects received dTpa placebo* • Booster response rates for PT, FHA and PRN (with exact 95% CI) will be calculated by group for US and ex-US pooled formulation and separately. • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-PT, anti-FHA, anti-PRN will be calculated between Day 31 over Screening for US and ex-US pooled data and separately. • A further exploratory between-groups analysis will be performed at Day 31 using an ANCOVA model by including study groups, country, age category, and level of antibodies at Screening as covariates • For Boostrix booster response to antigens PT, FHA and PRN, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with a booster response to each antigen in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately
	• Anti-D concentration • Anti-T concentration	For the subjects received RSVPreF3 dTpa and subjects received dTpa placebo • The percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL by ELISA and the percentage of subjects with anti-T antibody concentrations ≥1.0 IU/mL by ELISA (with exact 95% CI) will be calculated by group for US and ex-US pooled data and separately • The GMT/GMCs ratio and their 90% CI between RSVPreF3 dTpa and dTpa placebo in terms of anti-D, anti-Twill be calculated at Screening and Day 31 for US and ex-US pooled data and separately. • Protection rate (percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA) for antigens D and T, the two-sided standardized asymptotic 95% CI for the group differences in the percentage of subjects with antibody concentrations ≥0.1 IU/mL in the RSVPreF3 dTpa vaccine group and (minus) the dTpa Placebo vaccine group at Day 31 post vaccination will be calculated for US and ex-US pooled data and separately.

9.1.1.1. Laboratory assays cut-offs for humoral immunity (Antibody determination)

A seronegative subject is a subject whose antibody titre is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre is greater than or equal to the cut-off value of the assay. The cut-off tests for immunogenicity evaluation will be as per following:

System	Component	Method	Unit	Cut-off*	ULOQ
Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	ED60 and/or IU (international unit)	18 for ED60 TBD for IU	TBD
Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	ELU/mL	25	TBD
Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	IU/mL	2.046	TBD
Serum	Bordetella pertussis.Pertactin Ab.IgG	ELI	IU/mL	2.187	TBD
Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	IU/mL	2.693	TBD
Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	IU/mL	0.057	TBD
Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	IU/mL	0.043	TBD

Ab = antibody; ELI = Enzyme-linked immunosorbent assay (ELISA); IgG = immunoglobulin G; RSV = respiratory syncytial virus; ED60 = serum dilution inducing 60% inhibition in plaque forming units; IU/ml = International units/milliliter, IU= International units

Assay cut-off and unit might be subject to change before starting of testing (e.g. in case of requalification, revalidation or standardisation). In this case, this will be documented in the clinical report.

9.2. Statistical Method

NA

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 **Error! Reference source not found.** (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.

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.

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

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

10.1.2.3. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

10.1.3.8. 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).

10.1.3.9. 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.

10.1.3.10. 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.

10.1.3.11. 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. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

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

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

10.1.4.4. 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 [**Error! Reference source not found.**, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [**Error! Reference source not found.**, 1985].

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

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