Protocol

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: 14 APRIL 2021

CONFIDENTIAL

209141 (RSV MAT-011)
Protocol Amendment 6 Final

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89,
1330 Rixensart, Belgium

Primary Study vaccine(s) and number(s)	GlaxoSmithKline (GSK) Biological Respiratory Syncytial Virus (RSV) RSVPreF3 candidate vaccine (GSK3888550A)
Other Study vaccine(s)/product(s)	GSK Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine (*Boostrix* [US formulation SB776423]) GSK Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine (*Boostrix* [ex-US formulation SB263855]) Placebo (150 mM Sodium chloride [NaCl])
eTrack study number and abbreviated title	209141 (RSV MAT-011)
Investigational New Drug (IND) number	18434
EudraCT number	2019-002258-22
Date of protocol	Final Version 3: 23 August 2019
Date of protocol amendment	Amendment 1 Final: 21 October 2019 Amendment 2 Final: 23 January 2020 Amendment 3 Final: 3 April 2020 Amendment 4 Final: 28 August 2020 Amendment 5 Final: 2 November 2020 Amendment 6 Final: 9 April 2021
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.
Short title	A Phase II study of a primary dose of investigational RSV maternal vaccine, given alone or with Boostrix, with a 2nd dose investigational RSV maternal vaccine.

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Co-ordinating author(s)	PPD, Science Writer
Contributing authors (Cont.) ***(Amended 09-APR-2021)***	• Joon Hyung Kim, PPD PPD • PPD, PPD PPD • PPD, Lead Statistician • PPD, Study Statistician • PPD, Oversight Data Manager • PPD, Study Delivery Lead • PPD, Safety Physician • PPD, Safety Physician • PPD, Safety Product Leader • PPD, Safety Scientist • PPD, Regulatory Affairs Representative • PPD, Clinical Read-Out Team Leader • PPD, Clinical Trial Supply manager

GSK Protocol WS v 16.0.1

Protocol Amendment 6 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209141(RSV MAT-011)
IND number	18434
EudraCT number	2019-002258-22
Date of protocol amendment	***Amendment 6 Final: 9 April 2021***
Short Title	A Phase II study of a primary dose of investigational RSV maternal vaccine, given alone or with Boostrix, with a 2nd dose of investigational RSV maternal vaccine.
Sponsor signatory	Joon Hyung Kim, Clinical Epidemiology Project Lead
Signature	
Date	

Protocol Amendment 6 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine(s) and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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eTrack study number and Abbreviated Title	209141(RSV MAT-011)
IND number	18434
EudraCT number	2019-002258-22
Date of protocol amendment	***Amendment 6 Final: 9 April 2021***
Short Title	A Phase II study of a primary dose of investigational RSV maternal vaccine, given alone or with Boostrix, with a 2nd dose investigational RSV maternal vaccine.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'institut 89,
1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.8.3

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. GSK Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.5.5.1.

PROTOCOL AMENDMENT/ADMINISTRATIVE CHANGE SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 6	9-APR-2021
Amendment 5	2-NOV-2020
Amendment 4	28-AUG-2020
Amendment 3	3-APR-2020
Amendment 2	23-JAN-2020
Amendment 1	21-OCT-2019
Original Protocol	23-AUG-2019

Amendment 6: 9 April 2021

Overall Rationale for Amendment 6:

This study has been amended to include a clarification in the Exclusion criteria section to align with Protocol section 7.5.2 and reflect the flexibility of reducing the interval between administration of a coronavirus disease 2019 (COVID-19) vaccine and the RSV maternal vaccine. Also, several administrative changes in personnel and minor edits to the protocol are included.

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Contributing Authors	New SDL as added	New personnel replaced previous personnel
6.4.2 Prior/Concomitant therapy for extension	Note added describing flexibility of reducing vaccination window in case COVID-19 mass vaccination	To allow flexibility to allowed vaccination window in case of emergency mass vaccination on COVID-19 pandemic
8.3.2 Medical and vaccination history	Medical history and concomitant medications will both be reported	To align with rest of protocol
8.5.5.1 Contact information for reporting of serious adverse events (SAEs), pregnancies and study holding rules	New GSK Clinical Safety & Pharmacovigilance email address	The email address recently changed and is updated here
8.5.4 Reporting of serious adverse events, pregnancies, and other events	Changed Pregnancy Reporting from 2 weeks to 24 hrs	To align the protocol with the SOP for pregnancy reporting all new amendments should make this edit per the new templates
12.5.8.4 Completion and transmission of pregnancy reports to GSK		

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1. SYNOPSIS

Indication:

Active immunization of pregnant women during the third trimester of pregnancy to prevent respiratory syncytial virus (RSV) - associated lower respiratory tract illness (LRTI) in infants by placental transfer of maternal antibodies.

Rationale:

GSK is developing an investigational RSV maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization. In the RSV maternal program to date, a Phase 1/2 study (study RSV MAT-001; NCT 03674177) is ongoing in healthy non-pregnant women 18-45 years of age (YOA) to determine the safety and immunogenicity of 3 dose levels of RSVPreF3 (30, 60 and 120µg) vaccine compared to placebo. Preliminary safety and immunogenicity information is available in the investigator brochure.

In many countries, the use of acellular pertussis vaccination is recommended for women during pregnancy to protect young infants against pertussis before they can benefit from the infant vaccination series [Mazzilli, 2018]. *Boostrix*, a vaccine against diphtheria, tetanus and acellular pertussis is administered in the third trimester of pregnancy in many countries. Since RSVPreF3 is intended for administration in the third trimester of pregnancy, it will be important to evaluate any potential interference of co-administration with *Boostrix*.

This study (RSV MAT-011), in healthy non-pregnant women, will be the first to evaluate co-administration of 2 dose levels of RSVPreF3 with *Boostrix* (dTpa). Selection of the 60 and 120µg RSVPreF3 doses was based on preliminary results of the ongoing (RSV MAT 001) Phase 1 / 2 study.

Two formulations of dTpa vaccine, each containing either 300 micrograms or 500 micrograms of aluminum are licensed in the US and outside the US (ex-US), respectively. As such, the *Boostrix* (US formulation) (dTpa_300) will be administered to subjects in centers located in the US, while the *Boostrix* (ex-US formulation) (dTpa_500) will be administered to subjects in centers ex-US [Christy, 1995]. In previous studies both, Boostrix formulations have had a similar immunogenicity and safety profiles. Therefore, any potential differences in immune response to Boostrix in this study may be the result of population differences or immune response in the setting of RSVPreF3 co-administration [Theeten, 2005; Melville-Smith, 1983].

This will be a Phase II study to evaluate safety and reactogenicity of co-administration of RSVPreF3 and dTpa_300 or dTpa_500 in non-pregnant women 18-45 YOA. Additionally, this study will evaluate whether co-administration of dTpa affects the magnitude of the immune response to RSVPreF3 and whether RSVPreF3 affects the magnitude of the immune response to dTpa.

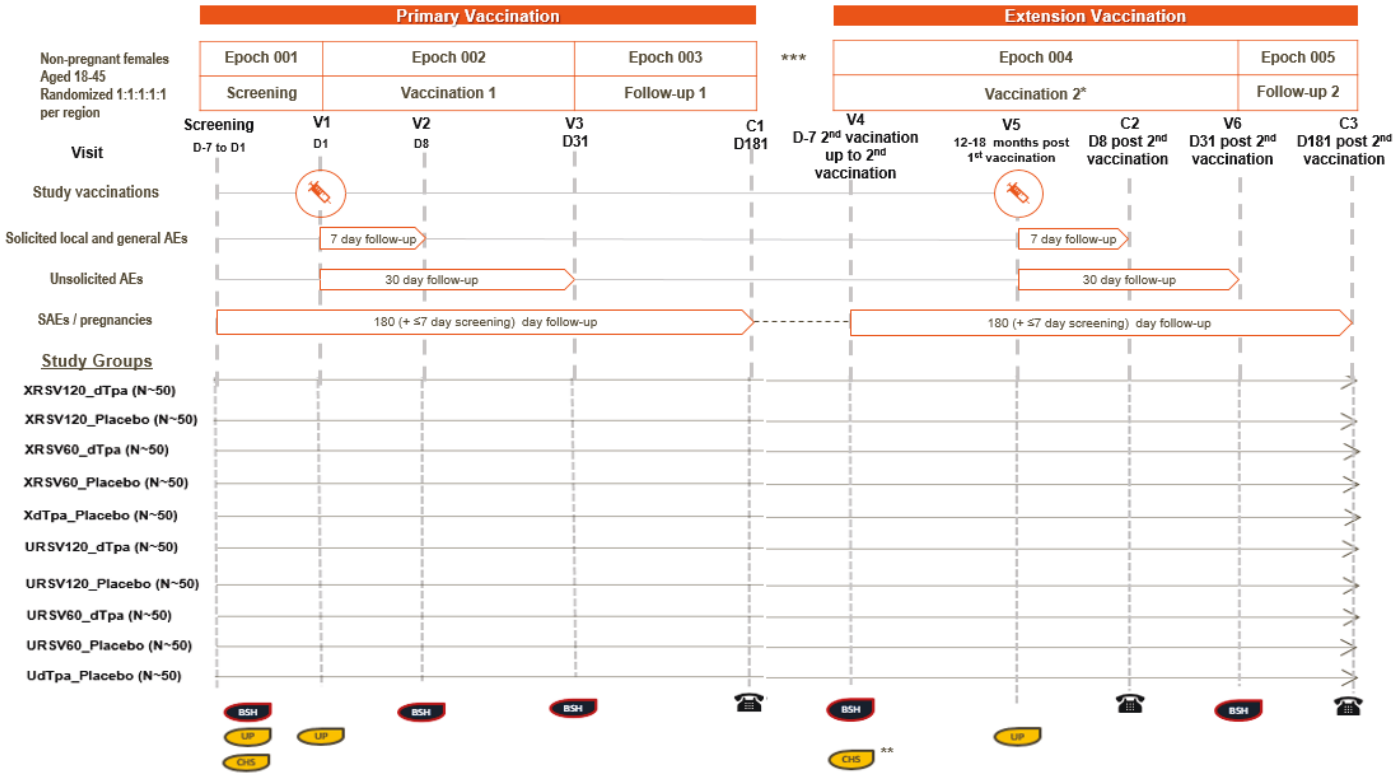
For those who provide consent, the durability of the response to RSVPreF3 will be measured from 12 to 18 months following initial vaccination. In addition, a second immunization with the RSV Maternal (120µg) vaccine will be administered from 12 months to 18 months after the first vaccination to evaluate the immunogenicity and safety profile of RSVPreF3 vaccine second dose.

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.
• 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 alone or co-administered with dTpa from 1st dose 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

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

Overall Design:



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.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 3 Schedule of Activities

Epoch	Epoch 001	Epoch 002 (Vaccination 1)			Epoch 003 (Follow-up 1)		Epoch 004 (Vaccination 2)				Epoch 005 (Follow-up 2)
Type of contact	Screening	Visit 1	Visit 2	Visit 3	Phone Contact 1		Visit 4	Visit 5	Phone Contact 2	Visit 6	Phone Contact 3
Time points	Day -7 to Day 1	Day 1	Day 8	Day 31	Day 181	Day 181 to -7 before 2nd vaccination	Day -7 to Day of 2nd vaccination	From 12 up to 18 months post 1st vaccination	Day 8 post 2nd vaccination	Day 31 post 2nd vaccination	Day 181 post 2nd vaccination
Sampling time points	Pre-Vacc 1	Vacc 1	Post-Vacc 1	Post-Vacc 1	Post-Vacc 1	Pre-Vacc 2	Pre-Vacc 2	Vacc 2	Post-Vacc 2	Post-Vacc 2	Post-Vacc 2
Informed consent	●						●				
Assign subject number	●										
Check inclusion/exclusion criteria	●	O					●				
Check contraindications to subsequent vaccine(s) administration							O	O			
Phone contact					●				●		●
Collect demographic data	●[1]										
Medical history	O	●					●				
Physical examination [2]	●	●	●	O			●			O	
Urine pregnancy test [3]	●	●						●			
Pre-vaccination body temperature and heart rate		●									
Pre-vaccination vital sign readings[4]								●			
Distribution of subject card		O						O			

Epoch	**Epoch 001**	**Epoch 002 (Vaccination 1)**			**Epoch 003 (Follow-up 1)**		**Epoch 004 (Vaccination 2)**				**Epoch 005 (Follow-up 2)**
Type of contact	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Phone Contact 1**		**Visit 4**	**Visit 5**	**Phone Contact 2**	**Visit 6**	**Phone Contact 3**
Time points	**Day -7 to Day 1**	**Day 1**	**Day 8**	**Day 31**	**Day 181**	**Day 181 to -7 before 2nd vaccination**	**Day -7 to Day of 2nd vaccination**	**From 12 up to 18 months post 1st vaccination**	**Day 8 post 2nd vaccination**	**Day 31 post 2nd vaccination**	**Day 181 post 2nd vaccination**
Sampling time points	**Pre-Vacc 1**	**Vacc 1**	**Post-Vacc 1**	**Post-Vacc 1**	**Post-Vacc 1**	**Pre-Vacc 2**	**Pre-Vacc 2**	**Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**
Hematological and biochemical laboratory testing (~5.5 mL)	O						O[9]				
Blood sampling for humoral immune response (~5 mL) [5]	●		●	●			●			●	
Study group and treatment number allocation (SBIR)		O									
Treatment number allocation (SBIR)								O			
Vaccine administration		●						●			
Recording of administered treatment number		●						●			
60 minutes post vaccination observation period		O						O			
Training on use of diary cards		O	O					O			
Distribution of diary cards[6]		O	O					O			
Collection of diary cards			O	O						O	
Diary card transcription by investigator or designate			●	●						●	
Recording of solicited adverse events		●	●					●	●		
Recording of unsolicited adverse events		●	●	●				●	●	●	

Epoch	**Epoch 001**	**Epoch 002 (Vaccination 1)**			**Epoch 003 (Follow-up 1)**		**Epoch 004 (Vaccination 2)**				**Epoch 005 (Follow-up 2)**
Type of contact	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Phone Contact 1**		**Visit 4**	**Visit 5**	**Phone Contact 2**	**Visit 6**	**Phone Contact 3**
Time points	**Day -7 to Day 1**	**Day 1**	**Day 8**	**Day 31**	**Day 181**	**Day 181 to -7 before 2nd vaccination**	**Day -7 to Day of 2nd vaccination**	**From 12 up to 18 months post 1st vaccination**	**Day 8 post 2nd vaccination**	**Day 31 post 2nd vaccination**	**Day 181 post 2nd vaccination**
Sampling time points	**Pre-Vacc 1**	**Vacc 1**	**Post-Vacc 1**	**Post-Vacc 1**	**Post-Vacc 1**	**Pre-Vacc 2**	**Pre-Vacc 2**	**Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**
Recording of AE leading to withdrawal		●	●	●	●			●	●	●	●
Recording of serious AE[7]	●	●	●	●	●		●	●	●	●	●
Recording of pregnancies		●	●	●	●		●	●	●	●	●
Recording of concomitant medications/vaccinations[8]		●	●	●	●		●	●	●	●	●
Record any intercurrent medical conditions			●	●	●		●	●	●	●	●
Screening conclusion	●										
Investigator sign-off on eCRF before analysis	●			●	●					●	●
COVID-19 eCRFs log page							●	●	●	●	●
Study conclusion primary study					●						
Study conclusion extension											●

Vacc: vaccination

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF

1 Date of birth (month and year or year only, as per local regulations), race, ethnicity and childbearing potential (if subject not of childbearing potential, the specific reason should be documented in the eCRF) (see Section 12.6.1.1.1 for more detail).

2 Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) measured after at least 10 minutes of rest.

Screening: Physical exam, vital signs (blood pressure, heart rate and respiratory rate, temperature), and weight, height and BMI will be recorded in the eCRF.

Visit 1: History directed physical exam will be performed and the vital signs will be recorded in the eCRF

Visit 2 Physical examination will be performed only if deemed necessary by the investigator. If performed, only vital signs (blood pressure, heart rate and respiratory rate) will be required recorded in the eCRF
Visit 3: Physical examination will be performed only if deemed necessary by the investigator.
Visit 4: Perform history directed physical exam will be performed and vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF. Weight, height and BMI should also be recorded in the eCRF.
Visit 6: Physical examination will be performed only if deemed necessary by the investigator.
3 Only for women of childbearing potential. Urine pregnancy test is sufficient to determine the eligibility to enter the study. Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.
4Pre-vaccination vital signs: At Visit 5, the pre-vaccination vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF
5 Sub-groups, Method, cut-off, and laboratory locations will be defined in Section 8.4.3.
6 Primary Vaccination: The diary card will be distributed at the day of vaccination and will be used for recording solicited and unsolicited AEs, and concomitant medications/products on the day of vaccination and for 6 subsequent days and for recording unsolicited AEs and concomitant medications/products and vaccinations from Day 8 to Day 31.
Second Vaccination: The diary card will be distributed at the day of vaccination and will be used for recording solicited and unsolicited AEs, and concomitant medications/products on the day of vaccination and for 6 subsequent days and for recording unsolicited AEs and concomitant medications/products and vaccinations from Day 8 to Day 31.
7. For Screening and Visit 1 (prior to study vaccine administration), only those SAEs that are considered related to study participation need to be recorded.
8 Recording of Concomitant medications/vaccinations/products will be described in Section 7.5
9 Hematological and biochemical laboratory testing at Visit 4 (D -7 up to and including 2nd dose vaccination) at the investigator's discretion

Whenever possible, the investigator should arrange study visits within the intervals described in Table 4.

Table 4 Intervals between study visits

Interval	Optimal timing	Allowed interval
Screening Visit→ Visit 1	≤7 days	-7 - 1 days*
Visit 1 → Visit 2	8 days	7 - 10 days
Visit 1 → Visit 3	31 days	30 - 45 days
Visit 1 → Phone Contact 1	181 days	165 - 195 days
Visit 4 →Visit 5	≤7 days	-7 to 1 days*
Visit 1 → Visit 5	365 days	365 - 548 days**
Visit 5 → Phone Contact 2	8 days	7 - 10 days
Visit 5 → Visit 6	31 days	30 - 45 days
Visit 5 → Phone Contact 3	181 days	165 - 195 days

*From 7 days prior to vaccination up to and including the day of vaccination.
** For a 6-month period ≥12 to <18 months post 1st vaccination

3. INTRODUCTION

3.1. Study rationale

GSK is developing an investigational RSV maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization. In the RSV maternal program to date, a Phase 1/2 study (study RSV MAT-001; NCT 03674177) is ongoing in healthy non-pregnant women 18-45 years of age (YOA) to determine the safety and immunogenicity of 3 dose levels of RSVPreF3 (30, 60 and 120 µg) compared to placebo. Preliminary safety information is available in the investigator brochure.

In many countries, the use of acellular pertussis vaccination is recommended for women during pregnancy to protect young infants against pertussis before they can benefit from the infant vaccination series [Mazzilli, 2018]. *Boostrix*, a vaccine against diphtheria, tetanus and acellular pertussis is administered in the third trimester of pregnancy in many countries. Since RSVPreF3 is intended for administration in the third trimester of pregnancy, it will be important to evaluate any potential interference of co-administration with *Boostrix*.

This study (RSV MAT-011), in healthy non-pregnant women, will be the first to evaluate co-administration of RSVPreF3 with *Boostrix* (dTpa). Selection of the 60 and 120µg RSVPreF3 doses was based on preliminary results of the ongoing (RSV MAT 001) Phase 1/2 study.

Two formulations of dTpa vaccine, one containing 300 micrograms and the other containing 500 micrograms of aluminum are licensed in the US and outside the US (ex-US), respectively. As such, the *Boostrix* (US formulation) (dTpa_300) will be administered to subjects in centers located in the US, while the *Boostrix* (ex-US formulation) (dTpa_500) will be administered to subjects in centers ex-US. In previous studies both, *Boostrix* formulations have had a similar immunogenicity and safety profiles. Therefore, any potential differences in immune response to *Boostrix* in this study

may be the result of population differences or immune response in the setting of RSVPreF3 co-administration [Theeten, 2005].

This will be a Phase II study to evaluate safety and reactogenicity of co-administration of RSVPreF3 and dTpa_300 or dTpa_500 in non-pregnant women 18-45 YOA. Additionally, this study will evaluate whether co-administration of dTpa affects the magnitude of the immune response to RSVPreF3 and whether RSVPreF3 affects the magnitude of the immune response to dTpa.

Finally, a second dose vaccination of RSVPreF3 (120 µg) will be administered to the consenting subjects from 12 to 18 months following initial vaccination to evaluate the immunogenicity and safety profile of RSVPreF3. This extension of the study will recruit the same non-pregnant women as a proxy for women who may require additional dosing in successive pregnancies.

3.2. Background

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies of the RSV maternal (RSVPreF3) vaccine and background information pertaining to maternal immunization and RSV infection**.**

3.3. Benefit/Risk assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the RSV maternal (RSVPreF3) vaccine**.**

Please refer to the local Prescribing Information for information regarding the summary of potential risks and benefits of *Boostrix***.**

3.3.1. Risk assessment

The investigational RSV maternal (RSVPreF3) vaccine is in an early stage of clinical development. This is the first time that the RSV maternal (RSVPreF3) and *Boostrix* vaccines will be co-administered.

Based on the following data, there are currently no known important risks associated with the investigational RSV maternal (RSVPreF3) vaccine or its co-administration with *Boostrix* that preclude further development:

- Extensive prior experience with *Boostrix* administered alone.
- Results of non-clinical studies of the RSV maternal (RSVPreF3) vaccine given alone and co-administered with *Boostrix*.
- Available safety data from an ongoing Phase I/II study of the RSV maternal (RSVPreF3) vaccine administered alone.

All 500 enrolled subjects will remain under observation at the vaccination center for at least 60 minutes after vaccination.

3.3.2. Benefit assessment

Subjects may or may not benefit from receiving the investigational RSV maternal vaccine and / or *Boostrix*. The efficacy of the RSV maternal vaccine has not yet been evaluated. Subjects who receive *Boostrix* may have the benefit of being protected against diphtheria, tetanus and pertussis diseases [Mazzilli, 2018]. However, the effects of administering *Boostrix* together with the RSV maternal vaccine are unknown.

At the time of screening, the investigator will review the potential participant dTpa vaccination history. All women who are not up-to-date with dTpa vaccine based on local recommendations will be informed of their options:

1. to participate in the trial and potentially be randomized to receive a dose of *Boostrix* or
2. to opt out of the study.

Of these women, those who chose to participate and did not receive *Boostrix* as part of the trial, will counselled on their options to receive the vaccine at the time of unblinding.

3.3.3. Overall Benefit: Risk conclusion

The balance of anticipated benefits and apparent risks associated with the RSV maternal (RSVPreF3) vaccine, with *Boostrix*, and with co-administration of the RSV maternal (RSVPreF3) vaccine and *Boostrix* continues to be acceptable following the ongoing systematic review of safety data.

4. OBJECTIVE(S) AND ENDPOINT(S)

Table 5 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.
• 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 alone or co-administered with dTpa from 1st dose 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.

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

5. STUDY DESIGN

5.1. Scientific rationale for study design

This study is part of a clinical development plan of the RSVPreF3 vaccine for the protection of infants from RSV LRTI through maternal immunisation. This study will evaluate the safety and immunogenicity of the RSVPreF3 vaccine when it is co-administered with *Boostrix* in healthy non-pregnant women aged 18 to 45 years old. Two dose levels of RSVPreF3 will be evaluated in order to optimally select the dose level for further development. Two formulations of *Boostrix*, one containing 300 micrograms (dTpa_300) and the other containing 500 micrograms (dTpa_500) of aluminum are licensed in the US and outside the US (ex-US), respectively. The difference between the two formulations being the level of aluminium adjuvant. Both formulations will be studied.

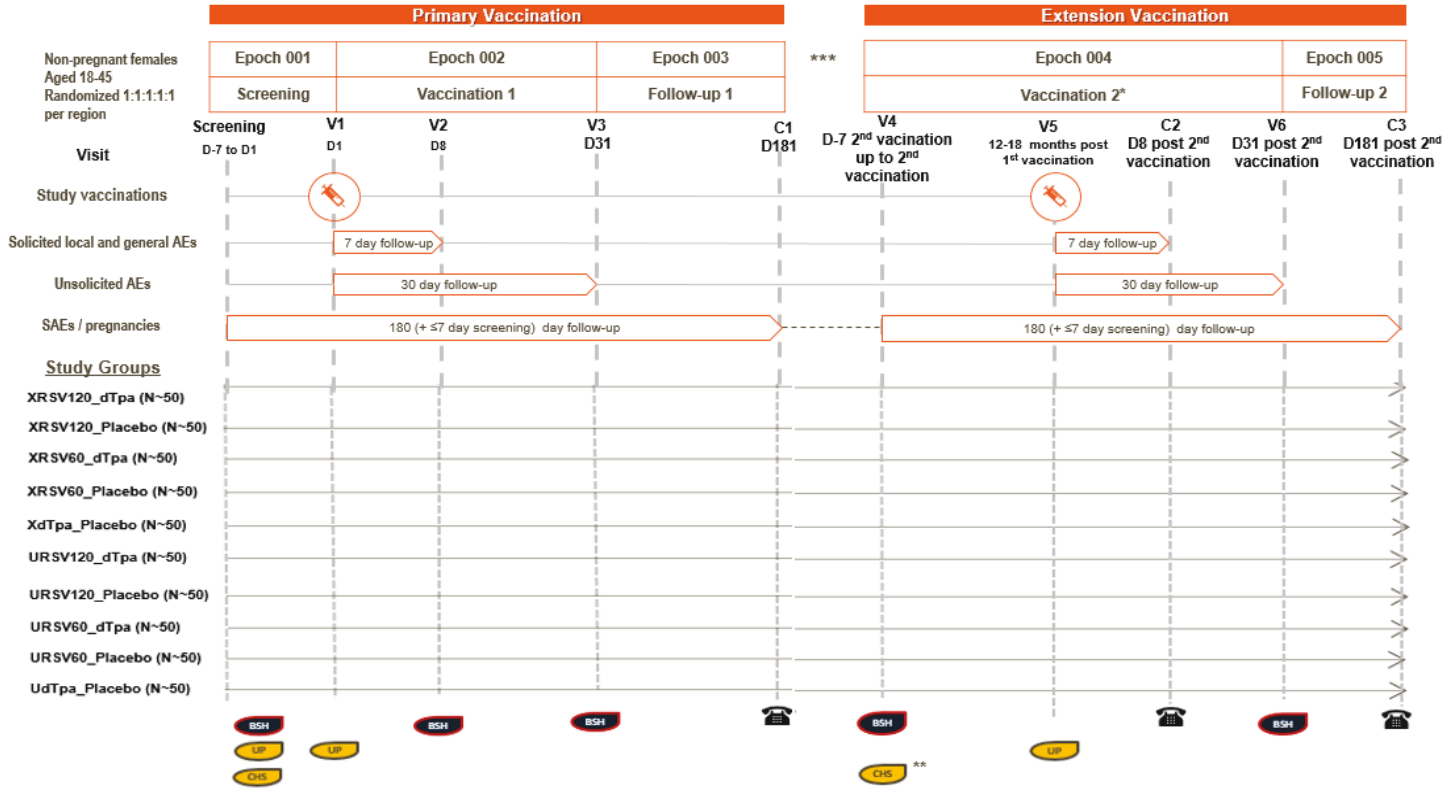
Approximately 500 women will be randomised to 5 equal study groups corresponding to the two dose levels of RSVPreF3 given with and without co-administration of *Boostrix* and a comparator group receiving *Boostrix* plus a placebo. To facilitate decision making in the clinical development plan the primary analysis will take place at day 31. The primary objectives compare the safety and the immune response to RSVPreF3, 31 days after vaccination in the five pooled study groups. The sample size of 100 subjects per group in the combined formulations is planned to provide reasonable confidence to evaluate the AE rate and quantify immunogenicity interference. If an AE is not observed in a given treatment group, then this sample size provides at least 95% confidence to rule out an AE rate greater than 3.6% and there will be at least 90% power to claim non-inferiority with a margin of 1.5 between RSVPreF3 alone and RSVPreF3 in co-administration with *Boostrix*.

By enrolling approximately half the subjects in the US and half outside the US, as secondary objectives the effect of co-administration of RSVPreF3 data will be collected on both commercial *Boostrix* formulations. While secondary analyses will be described by formulation, differences between the US and ex-US formulations could be explained by ethnic and environmental differences. Specified secondary endpoints will be described pooled across all subjects or by formulation.

Finally, a second dose vaccination of RSVPreF3 will be administered to consenting subjects from 12 months to 18 months following 1st vaccination to evaluate the immunogenicity and safety profile of RSVPreF3. The intention of this study extension is to assess the durability of the immune response after the first dose vaccination, and to assess the safety and immunogenicity following a second dose vaccination of the RSVPreF3 maternal vaccine. This extension of the study will recruit the same non-pregnant women as a proxy for women who may require additional dosing in successive pregnancies.

5.2. Overall design

Figure 1 Study design overview



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 unblinded open label manner
** 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).

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 (Section 2), 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 unblinded, 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 and from 18 up to 24 months for subjects that agree to participate in the study extension.
  - 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^{th} month up to the beginning of 18^{th} 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

Refer to glossary of terms 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 glossary of terms for the definition of EoS.

- Study groups:

Table 6 Study groups, treatment and epochs foreseen in the study

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 study)	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 6**.**
- 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.

Refer to section 8.6 for detailed description of holding rules and safety monitoring.

5.3. Number of subjects

Approximately 500 subjects will be randomised such that approximately 475 (based on 5% drop out rate) evaluable subjects complete the study.

Withdrawals will not be replaced.

5.4. Subject and study completion

A subject is considered to have completed the study if she is available for the concluding phone contact 3 (Day 181 post second vaccination) as described in the protocol.

For those subjects that do not agree to participate in the study extension, the concluding contact will be the Day 181 phone contact as described in previous version of protocol (RSV MAT-011 (209141) Protocol Amendment 3 (03-APR-2020).

Global completion of the study is required in order to provide sufficient subjects as defined in Section 10.1 Sample Size Determination.

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment (primary study)

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary card, return for follow-up visits).

- Written or witnessed/thumb printed informed consent obtained from the subject prior to performance of any study specific procedure.
- Healthy female subjects; as established by medical history and clinical examination, aged 18 to 45 years at the time of the first vaccination;
- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to primary vaccination, and
  - has a negative pregnancy test on the day of primary vaccination, and
  - has agreed to continue adequate contraception for 90 days after completion of the vaccination.
  - No local condition precluding injection in both left and right deltoid muscles.

6.2. Exclusion criteria for enrolment (primary study)

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study.

6.2.1. Medical conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines;
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);
- Hypersensitivity to latex;
- Major congenital defects, as assessed by the investigator;
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests;
- Significant or uncontrolled psychiatric illness;
- Recurrent history or un-controlled neurological disorders or seizures;
- Documented HIV-positive subject;
- History of or current autoimmune disease;
- Body mass index (BMI) > 40 kg/m^2;

- Any clinically significant hematological parameter (hemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet red blood cell count and erythrocyte mean corpuscular volume) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.
  - The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

6.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period;
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab);
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccines or planned administration during the study period;
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine dose(s). For corticosteroids, this will mean prednisone ≥5 mg/day, or equivalent. Inhaled and topical steroids are allowed;
- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after study primary vaccination, with the exception of any licensed influenza vaccine which may be administered ≥ 15 days before or after study vaccination;
- Administration of a vaccine containing diphtheria, tetanus or pertussis antigens or diphtheria and tetanus toxoids within the previous 5 years (by participant report);
- Previous experimental vaccination against RSV;

6.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device);

6.2.4. Other exclusions

- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions;
- History of alcoholism, drug abuse and/or use disorder within the past two years (as defined in DSM-5 Diagnostic Criteria) [Camargo, 1984; Christy, 1995; Hasin, 2013];
- Any study personnel or their immediate dependents, family, or household members.

6.3. Inclusion criteria for study extension

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

- Completed in primary study and received 1st dose vaccination of a study vaccine (RSVPreF3 or *Boostrix*).
- Written or witnessed/thumb printed informed consent obtained from the subject prior to performance of any study specific procedure to the study extension.

Are eligible if they meet the following criteria below

All subjects must satisfy ALL the following criteria:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary card, return for follow-up visits).
- Female subjects remain healthy; as established by medical history and clinical examination, aged 18 to 45 years at the time of the first vaccination;
- Female subjects of childbearing potential are eligible for the extension, if the subject:
  - has practiced adequate contraception for 30 days prior to 2nd vaccination
  - has a negative pregnancy test with results available on the day of 2nd vaccination
  - has agreed to continue adequate contraception for 90 days after completion of the 2nd vaccination.

6.4. Exclusion criteria for extension

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of entry to the extension. If ANY exclusion criterion applies, the subject must not be included in the extension.

6.4.1. Medical conditions for extension

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines;
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);
- Hypersensitivity to latex;
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests;
- Significant or uncontrolled psychiatric illness;
- Recurrent history or un-controlled neurological disorders or seizures;
- Documented HIV-positive subject;
- History of or current autoimmune disease;
- Body mass index (BMI) > 40 kg/m^2;
- Participants who experienced any SAE judged to be possibly or probably related to first dose vaccination of RSVPreF3, including hypersensitivity reactions.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

6.4.2. Prior/Concomitant therapy for extension (Amended 09-APR-2021)

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines during the period starting 30 days before the second dose of study vaccine (Day -29 to Day 1), or planned use during the 6 month study extension period;
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab);
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccines or planned administration during the study period;
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine dose(s). For corticosteroids, this will mean prednisone ≥5 mg/day, or equivalent. Inhaled and topical steroids are allowed;
- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after study 2nd dose vaccination*, with the exception of any licensed influenza vaccine which may be administered ≥15 days before or after study vaccination.

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the

routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or Prescribing Information and according to the local governmental recommendations.

6.4.3. Prior/Concurrent clinical study experience for extension

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device);

6.4.4. Other exclusions for extension

- Pregnant or lactating female at the time of Visit 4;
- Female planning to become pregnant or planning to discontinue contraceptive precautions;
- History of alcoholism, drug abuse and/or use disorder within the past two years (as defined in DSM-5 Diagnostic Criteria) [Camargo, 1984; Christy, 1995; Hasin, 2013];
- Any study personnel or their immediate dependents, family, or household members.

6.5. Criteria for temporary delay for enrolment and vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Haematological/biochemical values out of normal range at screening, *if* expected to be temporary. Subjects must be re-screened at a later date within the allowed time interval.
- Acute disease and/or fever at the time of enrollment;
  - Fever is defined as body temperature ≥ 38°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - For subjects with acute disease and/or fever at the time of enrollment, Visit 1 for primary vaccination and Visit 5, the 2nd vaccination will be rescheduled within the allowed window for the visit.
  - Screening hematological/biochemical do not need to be repeated if obtained within 30 days of each vaccination.

  Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

6.6. Screen and baseline failures

“Screening failures” are subjects who withdraw or are withdrawn from the study after giving informed consent, but before study eligibility (presence of all inclusion and absence of all exclusion criteria) is confirmed.

Discovery during screening of any condition that violates the requirements for study eligibility should be considered a screening failure. Discovery during Visit 1 of any condition that violates the requirements for study eligibility should also be considered a screening failure. Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

The development of such conditions (after Visit 1) does not constitute screening failure and should be captured on the eCRF, as applicable.

6.7. Screen failures to the extension

"Screening failures" for the extension are subjects who withdraw or are withdrawn from the extension after giving informed consent to the extension, but before extension eligibility (presence of all inclusion and absence of all exclusion criteria) is confirmed. Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject**.**

7.1. Treatments administered

Table 7 Treatments administered (Part 1)

	RSV MAT 120	**RSV MAT 60**	***Boostrix-ex-US (dTpa_500)***	***Boostrix-US (dTpa_300)***	**Placebo**
Vaccines /Products	RSVPreF3 high dose	RSVPreF3 mid dose	dTpa	dTpa	NaCl
	NaCl	NaCl			
Presentation	Powder for suspension for injection (vial) (174mcg/vial)	Powder for suspension for injection (vial) (87mcg/vial)	Suspension for injection (syringe)	Suspension for injection (syringe)	Solution for injection; vial)
	Solution for solution for injection; (vial)	Solution for solution for injection; (vial)			
Formulation	RSVPreF3(120 µg)/Trehalose(12.73 mg). NaCl solution (4.5 mg/0.5 mL, ~150 mM)	RSVPreF3(60 µg)/Trehalose(6.42 mg). NaCl solution (4.5 mg/0.5 mL, ~150 mM)	Diphtheria toxoid (≥ 2 IU) adsorbed on aluminium hydroxide and aluminium phosphate; Tetanus toxoid (≥ 20 IU)	Diphtheria toxoid (≥ 2 IU) adsorbed on aluminium hydroxide; Tetanus toxoid (≥ 20 IU) adsorbed on aluminium	NaCl solution (4.5 mg/0.5 mL, ~150 mM)

	RSV MAT 120	**RSV MAT 60**	***Boostrix-ex-US (dTpa_500)***	***Boostrix-US (dTpa_300)***	**Placebo**
			adsorbed on aluminium hydroxide and aluminium phosphate; Pertussis toxoid (8 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Filamentous haemagglutinin (8 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Pertactin (69 kDa outer membrane protein) (2.5 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Aluminium hydroxide (0.3 mg Al^{3+}); Aluminium phosphate (0.2 mg Al^{3+}); Sodium chloride; Water for injections q.s. 0.5 mL	hydroxide; Pertussis toxoid (8 µg) adsorbed on aluminium hydroxide; Filamentous haemagglutinin (8 µg) adsorbed on aluminium hydroxide; Pertactin (69 kDa outer membrane protein) (2.5 µg) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.3 mg Al^{3+}); Sodium chloride (4.4 mg); Water for injections q.s. 0.5 mL	
Route of Administration	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use	Intramuscular use
Administration site					
Location	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Laterality	Refer to Table 8.				
No of doses	2	1	1	1	1
Dose volume	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Packaging and Labelling	Refer to the SPM	Refer to the SPM	Refer to the SPM	Refer to the SPM	Refer to the SPM
Manufacturer	RSVPreF3: GSK Biologicals NaCl: GSK Biologicals	RSVPreF3: GSK Biologicals NaCl: GSK Biologicals	GSK Biologicals	GSK Biologicals	GSK Biologicals

The vaccinations will be administered in each arm as follows:

Table 8 Treatments administered (Part 2)

Primary Vaccination						
Group	**Formulation**	**N**		Laterality		Laterality
XRSV120_dTpa	ex-US	50	RSVPreF3=120µg	**Left Arm**	dTpa 500	**Right Arm**
Xplacebo_RSV120		50	RSVPreF3=120µg	**Left Arm**	Placebo	**Right Arm**
XRSV60_dTpa		50	RSVPreF3=60µg	**Left Arm**	dTpa 500	**Right Arm**
Xplacebo_RSV60		50	RSVPreF3=60µg	**Left Arm**	Placebo	**Right Arm**
Xplacebo_dTpa		50	Placebo	**Left Arm**	dTpa 500	**Right Arm**
URSV120_dTpa	US	50	RSVPreF3=120µg	**Left Arm**	dTpa 300	**Right Arm**
Uplacebo_RSV120		50	RSVPreF3=120µg	**Left Arm**	Placebo	**Right Arm**
URSV60_dTpa		50	RSVPreF3=60µg	**Left Arm**	dTpa 300	**Right Arm**
Uplacebo_RSV60		50	RSVPreF3=60µg	**Left Arm**	Placebo	**Right Arm**
Uplacebo_dTpa		50	Placebo	**Left Arm**	dTpa 300	**Right Arm**

2nd Vaccination				
Groups in primary vaccination	**Formulation in primary vaccination**	**N**	**Groups in 2nd vaccination**	**Laterality**
XRSV120_dTpa	ex-US	50	RSVPreF3=120µg	**Non-Dominant**
Xplacebo_RSV120		50	RSVPreF3=120µg	**Non-Dominant**
XRSV60_dTpa		50	RSVPreF3=120µg	**Non-Dominant**
Xplacebo_RSV60		50	RSVPreF3=120µg	**Non-Dominant**
Xplacebo_dTpa		50	RSVPreF3=120µg	**Non-Dominant**
URSV120_dTpa	US	50	RSVPreF3=120µg	**Non-Dominant**
Uplacebo_RSV120		50	RSVPreF3=120µg	**Non-Dominant**
URSV60_dTpa		50	RSVPreF3=120µg	**Non-Dominant**
Uplacebo_RSV60		50	RSVPreF3=120µg	**Non-Dominant**
Uplacebo_dTpa		50	RSVPreF3=120µg	**Non-Dominant**

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

Refer to the Study Procedures Manual (SPM) for detailed instructions on study vaccine reconstitution.

After completing all prerequisite procedures prior to vaccination (refer to Section 7.7 regarding the contraindications to subsequent vaccination), the assigned study vaccines (Table 9) will be administered as shown in Table 7and Table 8.

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine(s) administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 4).

The subjects will be observed closely for at least 60 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis and syncope.

7.2. Method of treatment assignment

7.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre. The subject identification number will be the same in the study extension. No new subjects will be recruited.

7.2.1.1. Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK, using MATerial Excellence (MatEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, USA) by GSK. Entire blocks will be shipped to the study centres/warehouse.

7.2.1.2. Treatment allocation to the subject

The treatment numbers will be allocated by component (2 treatment numbers will be allocated for each subject – one for each vaccine/product administered)**.**

For the second vaccination, 1 treatment number will be allocated for each subject.

7.2.1.2.1. Study group and treatment number allocation

The target will be to enrol approximately 500 eligible subjects (250 in the US and 250 ex-US). Of these, 250 subjects will be randomized to 5 study groups in a 1:1:1:1:1 ratio using SBIR in the US, and the other approximately 250 will also be randomized to 5 study groups in a 1:1:1:1:1 ratio using SBIR ex-US.

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation 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.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

After obtaining the signed or witnessed/thumb printed and dated ICF from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the formulation (US or ex-US), age, centre and the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for each dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

Note that as soon as the target number of approximately 250 subjects in the US or 250 subjects ex-US has been reached, the enrolment will be frozen for this formulation.

Since the second dose vaccination is open study, the treatment number will be allocated for each subject sequentially at each centre.

7.3. Blinding and unblinding

Data will be collected in an observer-blind manner during the primary study. By observer-blind, it is meant that during the course of the study, the vaccine(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity) will all be unaware of which vaccines were administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

Investigators will remain blinded to each subject's assigned study treatment until completion of the primary vaccination day 181 database freeze for analysis. In order to maintain this blind, a nurse or pharmacist who will not participate in any other study related activity will be responsible for the reconstitution and dispensation of all study treatment.

After the Day 181 phone contact (C1) for a given subject, the investigator will be informed of the subject's treatment assignment and will communicate this to the subject. The study extension will then be conducted as an open label study.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomisation/dispensing has been done accurately. Please refer to the SPM for details on blinding of the vaccine.

7.3.1. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 9) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

Table 9 Contact information for emergency unblinding

GSK Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email Phone: +32.2.656.68.04 For Canada, US and Puerto Rico Toll-free number: 877.870.0019 Fax: +32.2.401.25.75 email: rix.ugrdehelpdesk@gsk.com

GSK policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccine(s), prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 12.5.8).

A subject should continue in the study if that subject's treatment assignment is unblinded.

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life-threatening cases. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Handling, storage and replacement of study vaccine(s)/product(s)

7.4.1. Storage and handling of study vaccine(s)

The study vaccine(s) must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine(s).

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccine(s) must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccine(s) that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor).

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine(s).

7.4.2. Replacement of unusable vaccine(s) doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement product number. The replacement numbers will be allocated by component. The system will ensure, in a blinded manner, that the replacement product matches the formulation the subject was assigned to by randomisation.

7.5. Concomitant medication(s)/product(s) and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject.

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period of 31 days post primary vaccination and 2nd vaccination.
- Any concomitant vaccination administered in the period starting 30 days before the dose of study vaccine(s) and ending at the last study visit/contact (Day -30 to Day 181 post 2nd vaccination).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring fever is defined as temperature. 38.0°C/100.4°F regardless the location of measurement. The preferred location for measuring temperature in this study will be the oral cavity.

- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study.
- Any concomitant medications/products/vaccines relevant to an SAE to be reported as per protocol or administered at any time during the study period for the treatment of an SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination needs to be recorded on the specific page of the eCRF.
- The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.2 for populations to be analysed.

Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥5 mg/day (for adult subjects) or ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before the dose and ending 30 days after each dose of vaccine(s).

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.
- Drug and/or alcohol abuse.

7.6. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

At each study visit subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition that may lead to elimination from per protocol analysis. If it is the case, the condition(s) must be recorded in the eCRF.

For example, subjects may be eliminated from the per-protocol set for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. varicella) or are confirmed to have an alteration of their initial immune status.

7.7. Contraindications to subsequent vaccine(s) administration

N/A

7.8. Warnings and precautions

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit.

Refer to the local approved product Prescribing Information for *Boostrix*.

7.9. Treatment after completion of the study

The investigator is encouraged to share the immunological assay results for *Boostrix* non-responders with the study subjects.

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical care needed as per local/regional practices (such as re-vaccination of the subject(s)).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are described in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. The lab results will be considered valid for a period of 30 days from the date of initial screening.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. Study Procedures During Special Circumstances

During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances**:**

- Reconsent of subjects for the study extension may be placed on hold. Decisions on re-starting will be made in a manner consistent with guidance from public health and other competent authorities.

- Informed consent must take place in a face to face contact with the investigator but informing the potential subject ahead of giving written consent may be done remotely for example by mailing the informed consent or telephone or videotelephony conversation.
- Certain procedures may be performed at an alternate location. This includes, signing of informed consent, physical examination and vaccine dosing. If vaccinating in an alternate location, it must be assured that trained staff and equipment are available to manage an acute vaccine reaction. Biological samples may be collected at a different location* other than the study site or at participant's home**.** Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.
- "Medically attended visits" include instances where, due to the special circumstances, the subject cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.
- The paper Diary card provided to the subject may be transmitted from and to the site by electronic means and or conventional mail.
- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 4), then the interval may be extended up to a maximum length described in Table 10, however efforts should be made to adhere as closely as possible to the optimal timing.
- If despite best efforts it is not possible to administer the dose of study vaccine as defined in the protocol (see Table 4), a maximum dose interval described in Table 10 may be used, however efforts should be made to adhere as closely as possible to the optimal timing.

Table 10 Intervals between study visits under Special Circumstances

Interval	Optimal timing	Allowed interval	Adapted interval under special circumstances
Screening Visit →Visit 1	≤7 days	-7- 1 days	-30 to 1 days
Visit 1 → Visit 2	8 days	7- 10 days	7- 10 days
Visit 1 →Visit 3	31 days	30- 45 days	30 – 60 days
Visit 1 → Phone Contact 1	181 days	165- 195 days	165 – 195 days
Visit 4 → Visit 5		-7 to 1 days	-30 – 1 days*
Visit 1 → Visit 5	365 days	365-548 days**	
Visit 5 to Phone Contact 2	8 days	7- 10 days	7- 10 days
Visit 5 →Visit 6	31 days	30- 45 days	30 – 90 days
Visit 5 →Phone Contact 3	181 days	165- 195 days	165 – 195 days

*From 30 days prior to vaccination up to and including the day of vaccination.
** For a 6-month period ≥12 to <18 months post 1st vaccination

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.

- Any impact of above-mentioned measures on the study results will be described in the clinical study report.

* It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site.

8.2. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

8.3. Pre-vaccination procedures

8.3.1. Collection of demographic data

Record demographic data such as date of birth, sex, race and ethnicity in the subject's eCRF.

8.3.2. Medical and vaccination history (Amended 09 APR 2021)

Obtain the subject's medical and vaccination history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF. Significant medical conditions and vaccinations that occurred during the C1-V4 will be reviewed during the screening for the second vaccination and reported as medical history and concomitant medications, respectively.

8.3.3. Physical examination

- Perform a full physical examination of the subject at screening visit, including assessment of axillary or oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.
- Perform a history directed physical exam plus vital signs at Visit 1 [Day 1]
- Perform a history directed physical exam plus vital signs at Visit 4 [D-7 2nd vaccination to 2nd vaccination]. Note that laboratory assessments of haematology and biochemistry may be made on the investigator's discretion.
- Physical examinations at each study visit subsequent to the vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.
- Any vital signs measured at Visit 2 [Day 8] and Visit 5 [2nd Vaccination] should be recorded in the eCRF.

- Collected information needs to be recorded in the eCRF.
- If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the acceptable range.
- Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.3.4. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine(s) may only be administered if the pregnancy test is negative.

A serum pregnancy test instead of a urine pregnancy test should be performed if required by country, local or ethics committee regulations.

The results of the applicable test will be recorded in the eCRF. The study vaccine may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

8.3.5. Pre-vaccination body temperature

The body temperature (oral preferred) of each subject needs to be measured prior to any study vaccine(s) administration. If the subject has fever [temperature ≥38.0°C/100.4°F regardless of the location of measurement on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Section 6.5).

8.3.6. Pre-vaccination Vital Signs

Pre-vaccination vital signs: At Visit 5, the pre-vaccination vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF.

8.4. Immunogenicity assessments

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 8.4.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

8.4.1. Use of specified study materials

When materials are provided by GSK, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

8.4.2. Biological samples

Biological samples to evaluate immunogenicity and safety will be collected as specified in Section 2, Schedule of Activities (SoA). Table 11 summarizes biological samples and **minimum** total blood volumes to be collected from study subjects.

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

Table 11 Biological samples

Sample type Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information
Whole blood for hematology, biochemistry and immune response	10.5	ml	screening visit	Hematology, chemistry: 5.5 mL. Immune response: 5 mL (~ 2 mL serum).
Whole blood for immune response	5	ml	Visit 2 (Day 8)	Immune response : 5 mL (~ 2 mL serum).
Whole blood for immune response	5	ml	Visit 3 (Day 31)	Immune response : 5 mL (~ 2 mL serum).
Whole blood for hematology, biochemistry* Whole blood for immune response	10.5 or 5	ml	Visit 4 (up Day -7 prior to 2nd vaccination)	Hematology, chemistry: 5.5 mL. Immune response: 5 mL (~ 2 mL serum).
Whole blood for immune response	5	ml	Visit 6 (Day 31 post 2nd vaccination)	Immune response : 5 mL (~ 2 mL serum).
	36 or 30.5	**ml**	**Minimum Total, not including repeat or unscheduled samples**	
Urine for Pregnancy	-	-	screening visit Visit 1 (Day 1) and Visit 5 (2nd Vaccination)	

*Hematological and biochemical laboratory testing at Visit 4 (D -7 up to and including 2nd dose vaccination) at the investigator's discretion

8.4.3. Laboratory assays

Protocol-required hematology/biochemistry assays are listed in Section 12.2. Assays performed by GSK are listed below.

Please refer to Section 12.3 for the address of the clinical laboratories used for sample analysis.

Table 12 Humoral Immunity (Antibody determination)

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off	Groups	Number of subjects	Laboratory***
Screening	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 56 for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
	Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	In house	IU/mL	2.046	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Bordetella pertussis.Pertactin Ab.IgG	ELI	In house	IU/mL	2.187	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	In house	IU/mL	2.693	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	In house	IU/mL	0.030	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	In house	IU/mL	0.037	XRSV120_dTpa, XRSV60_dTpa,	300	GSK

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off	Groups	Number of subjects	Laboratory***
							Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa		
Day 8	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 56 for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
Day 31	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 56 for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
	Serum	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	ELI	In house	IU/mL	2.046	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Bordetella pertussis.Pertactin Ab.IgG	ELI	In house	IU/mL	2.187	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Bordetella pertussis.Pertussis Toxin Ab.IgG	ELI	In house	IU/mL	2.693	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa,	300	GSK

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off	Groups	Number of subjects	Laboratory***
							URSV60_dTpa, Uplacebo_dTpa		
	Serum	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	ELI	In house	IU/mL	0.030	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
	Serum	Clostridium tetani.Tetanus Toxoid Ab.IgG	ELI	In house	IU/mL	0.037	XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa	300	GSK
Day -7 up to 2nd vaccination	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 56 for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
D31 post 2nd vaccination	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 56 for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis

Ab = antibody; ELI = Enzyme-linked immunosorbent assay (ELISA); ELU=ELISA unit; 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; TBD = to be determined
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.
***GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Other assays may be performed with the aim to explore tertiary objectives of the study. The research may include, but is not limited to:

Additional testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

The GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.4.4. Biological samples evaluation

8.4.4.1. Immunological read-outs

Table 13 Immunological read-outs

Blood sampling timepoint		Subset name	Approximate No. subjects	Component	Components priority rank
Type of contact and timepoint*	Sampling timepoint				
Screening visit	Pre-Vacc	All	500	RSV-A neutralizing antibody	1
		All	500	RSVPreF3 IgG antibody concentration	2
		*Boostrix** recipients	300	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	3
		Boostrix recipients	300	Bordetella pertussis.Pertactin Ab.IgG	3
		Boostrix recipients	300	Bordetella pertussis.Pertussis Toxin Ab.IgG	3
		Boostrix recipients	300	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	4
		Boostrix recipients	300	Clostridium tetani.Tetanus Toxoid Ab.IgG	5
Visit 2 (Day 8)	Post-Vacc	All	500	RSV-A neutralizing antibody	1
		All	500	RSVPreF3 IgG antibody concentration	2
Visit 3 (Day 31)	Post-Vacc	All	500	RSV-A neutralizing antibody	1
		All	500	RSVPreF3 IgG antibody concentration	2
		Boostrix recipients	300	Bordetella pertussis.Filamentous Hemaglutinin Ab.IgG	3
		Boostrix recipients	300	Bordetella pertussis.Pertactin Ab.IgG	3
		Boostrix recipients	300	Bordetella pertussis.Pertussis Toxin Ab.IgG	3
		Boostrix recipients	300	Corynebacterium diphtheriae.Diphtheria Toxoid Ab.IgG	4
		Boostrix recipients	300	Clostridium tetani.Tetanus Toxoid Ab.IgG	5
Day -7 up to 2nd vaccination	Post-Vacc	All	500	RSV-A neutralizing antibody	1
		All	500	RSVPreF3 IgG antibody concentration	2
D31 post 2nd vaccination	Post-Vacc	All	500	RSV-A neutralizing antibody	1
		All	500	RSVPreF3 IgG antibody concentration	2

Boostrix recipients = subjects in the following study groups: -XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 13.

8.4.5. Immunological correlates of protection

8.4.5.1. RSV

No generally accepted immunological correlate of protection has been established so far for the antigen used in the RSV maternal (RSVPreF3) vaccine.

8.4.5.2. Boostrix

The following cut-offs are accepted as immunological correlates of protection:

- Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) will be measured by Enzyme-linked immunosorbent assay (ELISA). Subjects with antibody concentrations of at least 0.1 International Units per ml (IU/ml) by ELISA are deemed to be protected [Camargo, 1984; Melville-Smith, 1983]. In this study, the booster response will be defined by the percentage of subjects with concentration ≥ 1.0 IU/mL.
- No serological correlate of protection against pertussis has been established [Vidor, 2008]. Antibodies against the pertussis components pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) will be measured by ELISA. The current seropositivity cut-off is 2.693 IU/ml for anti-PT, 2.046 IU/ml for anti-FHA and 2.187 IU/ml for anti-PRN (see Table 12). Subjects with antibody concentration below the cut-off will be considered seronegative.

The immunological assay results will be communicated to the investigator within 12 months after the last study visit has been completed.

Refer to section 7.9 for details regarding treatment for non-responders.

8.5. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study**.**

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Time period and frequency for collecting AE and serious adverse event (SAE) information

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 14 . Refer to the Section 12.5.7.1 for details on the time period for recording safety information.

Table 14 Reporting periods for collecting safety information

Event	Pre-V1*		V1		V2		V3	C1	C1 to V4**	V4	V5*		C2		V6	C3
			D1	D7	D8	D30	D31	D181		D -7 up to 2nd vaccination	2nd vaccination From 12 up to 18 months post 1st vaccination	D7 post second 2nd vaccination	D8 post second 2nd vaccination	D30 post second 2nd vaccination	D31 post 2nd vaccination	181 Days post 2nd vaccination
Solicited local and general AEs																
Unsolicited AEs																
AEs leading to withdrawal from the study																
SAEs**																
SAEs related to study participation or concurrent GSK medication/vaccine																
Pregnancies***																

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: Day, M: Month

** 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. In addition, SAE related to vaccination are reported during the period C1-V4 will be reported to the Investigator at the time of awareness.

***Pregnancies that occurred during the C1-V4 period will be reported as medical history

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Section 12.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.5.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.7.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjects is the preferred method to inquire about AE occurrence.

8.5.4. Reporting of serious adverse events, pregnancies, and other - events (Amended 09-APR-2021

Table 15 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	Paper pregnancy notification report/electronic pregnancy report	24 hours*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information.

‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.5.5. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.5.5.1. Contact information for reporting of serious adverse events (SAEs), pregnancies and study holding rules (Amended 09 APR 2021)

Table 16 Contact information for reporting of serious adverse events (SAEs), pregnancies and study holding rules

Study contact for questions regarding SAEs, pregnancies and study holding rules
Refer to the local study contact information document
Study Contact for Reporting of study holding rules
As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the local contact.
Back-up Study Contact for Reporting SAEs, pregnancies and study holding rules
24/24 hour and 7/7-day availability: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: PV.ICSRManagement@gsk.com US sites only: Fax: 1-610-787-7053 Canadian sites only: Fax: 1-866-903-4718

8.5.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilised, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.10.

8.5.7. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.5.8. Clinical safety laboratory assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are associated with an underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. All laboratory tests with values considered clinically significant abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. Refer to the Section 12.5.5 for clinical laboratory abnormal assessments qualified as AEs or SAEs.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory safety assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the SoA.

8.5.9. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation, this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

8.6. Holding rules and safety monitoring

The safety holding rules are defined in Table 17. Holding rules 1a-b will be assessed by the investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of vaccination irrespective of number of subjects enrolled.

Table 17 Study holding rules

Holding Rule	Event	Number of Subjects
1a	Death or any life-threatening **SAE occurring within 30 days from vaccination**	≥1
1b	***Any*** SAE that can be reasonably attributed to the vaccination	≥1

The investigator is not permitted to start the administration of the next dose until receipt of the favourable outcome of the safety evaluation, documented and provided in writing, authorising the investigator to proceed. While vaccinations are on hold, the investigator should not consent subjects into the study.

Moreover, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. meeting of holding rules 1a-b).

The below flow of communication has to be followed:

- The concerned site staff has to put vaccination and enrolment on hold.
- The concerned site staff must immediately inform their local contact defined in the Table 16.
- The local contact will escalate the information immediately to the central study team (ie SDL and CRDL).
- The central study team will ensure SBIR is blocked and all vaccinating centres are informed.
- GSK Safety Review Team (SRT) will further evaluate the case and escalate to GSK VSMB for making the decision to stop or to restart the vaccination. All site staff will be informed about that final decision by their local GSK contact.

If the Central Team becomes aware of a holding rule being met, the below flow of communication must be followed:

- CRDL inform the local Study team (Table 16)
- The LML/delegate of each country confirm the reception of the holding rule to the CRDL and inform all the investigators.
- The concerned site staff has to put vaccination and enrolment on hold.
- The central study team will ensure SBIR is blocked and all vaccinating centres are informed.
- GSK Safety Review Team (SRT) will further evaluate the case and escalate to GSK VSMB for making the decision to stop or to restart the vaccination. All site staff will be informed about that final decision by their local GSK contact.

8.7. Genetic Research (Pharmacogenetics)

Genetics are not evaluated in this study.

8.8. Biomarkers and pharmacogenomics

Not applicable.

8.9. Economic assessment

Not applicable.

8.9.1. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation from the study

Subjects will complete the study at day 181 with a phone contact. For the subjects that enroll in the study extension, the conclusion of the study will be on Day 181 following the second immunization as described in the protocol.

From an analysis perspective, a 'withdrawal' from the study refers to any subject was not available for the concluding contact foreseen in the protocol.

All data and samples collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make 3 attempts followed by a certified letter to contact those subjects who do not return for scheduled visits or follow-up.

Primary reason for study withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse events requiring expedited reporting
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*In case a subject is withdrawn from the study because she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 12.5.10).

9.2. Discontinuation of study vaccine(s)

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- Adverse event requiring expedited reporting to GSK
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

9.3. Lost to follow-up

A subject will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

10.1.1. Hypotheses related to primary and secondary objectives

No hypothesis driven sample size calculation was conducted due to the descriptive nature of the study.

10.1.2. Sample size calculation

The sample size of 50 subjects per group and 100 subjects per group in the combined formulations at the first vaccination were planned to provide reasonable confidence to evaluate the AE rate and quantify immunogenicity interference. The table below illustrates the precision that can be obtained on the percentage of subjects with AEs following vaccination. If an AE is not observed in a given treatment group, a sample size of 50 subjects can provide at least 95% confidence to rule out an AE incidence greater than 7.1%, and a total of 100 subjects in the combined formulations can provide at least 95% confidence to rule out an AE rate greater than 3.6%. A combined 400 subjects across the RSVPreF3 groups and formulations can provide at least 95% confidence to rule out an AE incidence rate greater than 0.9%.

Furthermore, a sample size of 50 subjects per group and 100 subjects per group in the combined formulations would provide a probability of 92% or 99% to observe at least one AE respectively, if the true AE rate is 5%. In addition, a sample size of 400 when combining the RSVPreF3 groups would provide a probability of 98% to observe at least one AE if the true AE rate is only 1%.

Table 18 Exact 95% confidence interval (CI) on the probability of a subject with AEs events following vaccination of 50 subjects per group, (100 subjects per group in US and ex-US combined) and 400 subjects with RSVPreF3 groups combined

Number of subjects per group	Number (%) of subjects with an AE	Exact 95% CI	
		Lower Limit (%)	Upper Limit (%)
50	0 (0%)	0	7.1
50	5 (10%)	3.3	21.8
50	10 (20%)	10	33.7
50	15 (30%)	17.9	44.6
50	20 (40%)	26.4	54.8
50	25 (50%)	35.5	64.5
100	0 (0%)	0	3.6
100	5 (5%)	1.6	11.3
100	10 (10%)	4.9	17.6
100	15 (15%)	8.6	23.5
100	20 (20%)	12.7	29.2
100	25 (25%)	16.9	34.7
400	0 (0%)	0	0.9
400	5 (1.25%)	0.4	2.9
400	10 (2.5%)	1.2	4.5
400	15 (3.75%)	2.1	6.1
400	20 (5%)	3.1	7.6
400	25 (6.25%)	4.1	9.1

Exact 95% CI computed based on Clopper/Pearson formula

In order to evaluate the humoral response to 2 dose levels (60 and 120 μg) of RSVPreF3 when given alone, and co-administered with dTpa, the difference between co-administration with dTpa (RSVPreF3 dTpa) and RSVPreF3 alone (RSVPreF3 placebo) in terms of RSV-A neutralizing antibody (Nab) titers will be evaluated at Day 8 and Day 31 post the first vaccination.

Table 19 presents the precision estimation on the ratio of the Geometric Mean of RSV-A Nab titers (GMT) with their 90% CI between two study groups, and the power to claim non-inferiority, when the sample size is 100 subjects per group and 50 subjects per group, with a range of standard deviation (SD) of RSV-A Nab titers 0.3-0.5 on its log10 transformation and non-inferiority margin of 1.5 between RSVPreF3 alone and RSVPreF3 dTpa.

If a SD of log10 transformed RSV-A Nab of 0.4 is assumed, when the sample size is 50 subjects per group, the half width of the 90% CI on the log ratio of GMT between co-administration with dTpa and RSVPreF3 alone is 0.133. With an observed GMT ratio of 1, its 90% CI will be (0.74, 1.36). With subjects in US and ex-US combined, there will be at least 90% chance that the upper bound of one-sided 95% CI for the ratio of GMT of RSV-A Nab titer between RSVPreF3 alone and co-administration with dTpa is under 1.5-fold.

Table 19 Precision and power in terms of RSV-A neutralizing antibody titers with a sample size of 100 subjects per group and 50 subjects per group

Number of subjects per group	Ratio of GMT between two groups	SD*	90% CI	90% CI	Power for non-inferiority test (%) ***
			LL	UL	
50	0.9	0.3	0.71	1.13	97.9
50	0.9	0.4	0.66	1.22	86.6
50	0.9	0.5	0.61	1.32	71.2
50	1.0	0.3	0.79	1.26	89.8
50	1.0	0.4	0.74	1.36	70.5
50	1.0	0.5	0.68	1.47	54.1
50	1.1	0.3	0.87	1.38	72.0
50	1.1	0.4	0.81	1.49	51.0
50	1.1	0.5	0.75	1.61	37.9
100	0.9	0.3	0.77	1.06	100
100	0.9	0.4	0.73	1.11	98.8
100	0.9	0.5	0.69	1.18	93.1
100	1.0	0.3	0.85	1.17	99.4
100	1.0	0.4	0.81	1.24	92.7
100	1.0	0.5	0.76	1.31	79.8
100	1.1	0.3	0.94	1.29	93.5
100	1.1	0.4	0.89	1.36	76.6
100	1.1	0.5	0.84	1.44	60.0

*Standard deviation of log_{10} of RSV-A Nab titer. The highest standard deviation observed 30 days after vaccination in a previous GSK RSV study was 0.4.

**Precision estimation for log GMT ratio using PASS 12.0.2 (CI for two means), LL: Lower Limit, UL: Upper Limit

***PASS: Non-Inferiority Tests for Two Means using Differences with one-sided alpha 5% and Non-Inferiority Margin 0.176 on log 10 scale (corresponding to Non-Inferiority Margin 1.5 for GMT ratio).

10.2. Populations for analyses

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

10.3. Statistical analyses

10.3.1. Subjects disposition

The number of screened, enrolled, and vaccinated subjects included in each group or in total for a given age category or for all age categories will be described. These might be additionally broken down by country and/or by site.

10.3.2. Demography and baseline characteristics analyses

Demographic characteristics (age at first study vaccination in weeks, or months or years, gender, race and ethnicity [where applicable]), vaccination history, will be summarised by overall and vaccine groups 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).

10.3.3. Immunogenicity analyses

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 Exposed 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 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 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. • 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.

Endpoint	Statistical Analysis Methods
	– 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.

10.3.4. Safety analyses

The primary safety analyses will be performed on the Exposed Set. The following safety analyses will be performed based on the Exposed Set. The following safety analysis will be performed on the pooled formulations, 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 with at least one general AE and with any ("solicited or unsolicited") AE during the 7-day or 30 -day follow up is for SAE visit 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 (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) 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 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.

Endpoint	Statistical Analysis Methods
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-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 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. 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.
Tertiary	Will be described in a Statistical Analysis Plan finalised before database unblinding/freezing.

10.4. Sequence of analyses

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, 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 **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.
- 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. 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.

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

11. REFERENCES

Camargo ME, Silveira L, Furuta JA, Oliveira EP, Germek OA. Immunoenzymatic assay of anti-diphtheric toxin antibodies in human serum. *J Clin Microbiol*. 1984 Oct;20(4):772-4.

Christy C, Pichichero ME, Reed GF, Effect of Gender, Race, and Parental Education on Immunogenicity and Reported Reactogenicity of Acellular and Whole-Cell Pertussis Vaccines. Pediatrics (1995), 96(3)

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006); http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf

Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 Criteria for Substance Use Disorders: Recommendations and Rationale. *The American journal of psychiatry*. 2013;170(8):834-851. Doi:10.1176/appi.ajp.2013.12060782.

Mazzilli S, Tavoschi L, Lopalco PL. Tdap vaccination during pregnancy to protect newborns from pertussis infection. *Ann Ig.* 2018 Jul-Aug;30(4):346-363. Doi: 10.7416/ai.2018.2226.

Melville-Smith ME, Seagroatt VA, Watkins JT. A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralization test in mice as a method for the estimation of tetanus antitoxin in human sera. *J Biol Stand*. 1983 Apr;11(2):137-44.

Theeten H, Van Damme P, Hoppenbrouwers K, et al. Effects of lowering the aluminium content of a dTpa vaccine on its immunogenicity and reactogenicity when given as a booster to adolescents. *Vaccine* 23(2005) 1515–1521.

Vidor E, Plotkin SA. Immunogenicity of a two-component (PT & FHA) acellular pertussis vaccine in various combinations *Hum Vaccin*. 2008 Sep-Oct;4(5):328-40.

12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

Ab	Antibody
AE	Adverse Event
AE(s)	Adverse Event(s)
Anti-	Antibodies against
BS H	Blood Sample Humoral
CDC	Centers for Disease Control
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CoP	Correlate of Protection
COVID	Severe acute respiratory syndrome coronavirus 2
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
GSK	GlaxoSmithKline
IAF	Informed Assent Form
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
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
pIMD	Potential Immune-Mediated Disease
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
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
VSMB	Vaccine Safety Monitoring Board

12.1.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 7.3 for details on observer-blinded studies).
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS): **(Synonym of End of Trial)**	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last subject last visit (Visit X) or Last testing results released of samples collected at Visit X* * In this case EoS must be achieved no later than 8 months after LSLV.
Enrolled:	Subjects who agreed to participate in a clinical study after completion of the informed consent process. and subject is not a screen failure.

Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomisation, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardised term to replace: period, cycle, phase, stage.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.2 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative: **(The terms legal representative or legally authorised representative are used in some settings.)**	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorised use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Generic description
Boostrix	Combined diphtheria, tetanus and acellular pertussis vaccine (adsorbed)

12.2. Appendix 2: Clinical and safety laboratory tests

The tests detailed in Table 20 will be performed by the local laboratory.

All clinical and safety laboratory tests will be performed by local laboratory(ies). All assessments of immune response (Section 8.4) will be performed centrally (by GSK or by a GSK-designated laboratory).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the protocol.

The investigator is not allowed to do extra testing on samples outside of what has been agreed upon by the ethics committees.

Table 20 Protocol-Required Safety Laboratory Assessments

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Haematology[1]	Leukocytes (White Blood Cells)	As per local practice	Quantitative	At investigator's laboratory
		Lymphocytes			
		Eosinophils			
		Basophils			
		Haemoglobin			
		Platelets			
		Neutrophils			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	As per local practice	Quantitative	
		Aspartate Aminotransferase (AST)			
		Creatinine			
		Blood Urea Nitrogen (BUN)/urea]*			
Urine[1]		Pregnancy	As per local practice; dipstick provided by GSK Biologicals	Ordinal	At investigator's laboratory

* Sites not able to directly test for BUN, will test for urea and then convert urea values into BUN using the applicable established conversion factor(s).

[1] In certain labs a complete blood counts will be required per local lab practice (more than just those listed in table)

12.3. Appendix 3: Clinical laboratories

Table 21 GSK laboratories,

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89-B-1330 Rixensart-Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20-B-1300 Wavre-Belgium
GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

Table 22 Outsourced laboratories

Laboratory	Address
Nexelis *Inc.*	525, Cartier Ouest Laval Quebec Canada H7V 3S8 Nexelis Inc.

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF) or Informed Assent Form (IAF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the centre and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.4.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the subject.

Subjects who are rescreened are required to sign a new ICF.

12.4.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the frame and for the purpose of the study.

12.4.5. Committees structure

Safety oversight will be provided by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, internal safety review committee composed of GSK personnel not affiliated with the RSV program.

12.4.6. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.7. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

In addition, for studies that are in scope of the EU Clinical Trial Directive, summaries of the results of GSK interventional studies (phase I-IV) in adult population will be posted within defined timelines on the publicly available EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

	Clinicaltrial.gov	**EU**
Protocol summary	Before enrolment of subjects	As per CTA submission/Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 6 months (for paediatric population studies)/Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymised patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.4.8. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF/eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.4.9. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the glossary of terms.

12.4.10. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the/eCRF.

12.5. Appendix 5: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE Definition

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.5.1.2. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.5.3. All other AEs will be recorded as UNSOLICITED AEs.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

12.5.2. Definition of SAE

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred, or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered

serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

12.5.3. Solicited adverse events

a. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 23 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

b. Solicited general adverse events

The following general AEs will be solicited:

Table 24 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache

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

Note: subjects will be instructed to measure and record the axillary or oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the diary card.

12.5.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subjects who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalisation, or emergency room visit, or visit to/by a health care provider), or were of concern to the subjects. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects will be collected during interview with the subjects and by review of available medical records at the next visit.

12.5.5. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessment that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 12.5.1 and 12.5.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.5.6. Events or outcomes not qualifying as adverse events or serious adverse events

12.5.6.1. Pregnancy

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 12.5.8.1 and 12.5.8.4:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).

- Any congenital anomaly or birth defect identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine(s) will be reported to GSK as described in Section 12.5.8. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

12.5.7. Detecting and recording adverse events, serious adverse events and pregnancies

A Paper Diary (pDiary) hereafter referred to as Subject Diary will be used in this study to capture solicited or unsolicited adverse events. The subject should be trained on how and when to complete each field of the Subject Diary.

The subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. This individual may not be the subject, but if a person other than the subject enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit when Subject Diary is dispensed. This training must be documented in the subject's source record.

At the vaccination visit, the diary card will be provided to the subject. The subject/ will be instructed to measure and record the body temperature (oral preferred), and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after the 1st and 2nd vaccination. The subject will be instructed to return the completed diary card to the investigator at the next study visit.

12.5.7.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs during 7 days following administration of each dose vaccination of study vaccine(s) (Day 1 to Day 7 post primary vaccination and Day 1 to Day 7 post 2nd vaccination) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the receipt of study vaccine(s)/product(s).

SAEs that are related to the study vaccine(s) will be collected and recorded from the time of the receipt of study vaccine(s) until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine(s) and will end 181 days following administration of the dose of study vaccine(s). See section 12.5.8 for instructions on reporting of pregnancies.

12.5.7.2. Evaluation of adverse events and serious adverse events

12.5.7.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine(s) or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

12.5.7.2.2. Assessment of adverse events

Assessment of intensity

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

Table 25 Intensity scales for solicited symptoms in adults and children of 6 years of age or more

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

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

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

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.

An AE that is assessed as Grade 3 CCI should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 12.5.2.

Assessment of causality

The investigator is obligated to assess the relationship between study vaccine(s) and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s) cannot be determined, the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine(s) will be considered and investigated. The investigator will also consult; for the RSV maternal vaccine the IB; and for the *Boostrix* Vaccine, the SmPC and/or Prescribing Information to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine?

YES	:	There is a reasonable possibility that the study vaccine(s) contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 12.5.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s)/product(s) (delete as applicable), if applicable.
- Erroneous administration.
- Other cause (specify).

Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

12.5.7.2.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

12.5.8. Reporting of serious adverse events, pregnancies, and other events

12.5.8.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK

SAEs that occur in the time period defined in Section 12.5.7 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.7 will be reported promptly to GSK within the timeframes described in Table 15, once the investigator becomes aware of the pregnancy.

12.5.8.2. SAEs requiring expedited reporting to GSK

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the ‘reviewed’ box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

12.5.8.3. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

12.5.8.4. Completion and transmission of pregnancy reports to GSK (Amended 09-APR-2021)

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 24 HOURS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

12.5.9. Updating of SAE, pregnancy, information after removal of write access to the subject's eCRF

When additional SAE and pregnancy information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 15.

12.5.10. Follow-up of adverse events, serious adverse events, and pregnancies

12.5.10.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK (within 24 hours for SAEs; refer to Table 15).

All SAEs (serious or non-serious) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the subject.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

12.5.10.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

12.5.10.3. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE

12.6. Appendix 6: Contraceptive guidance and collection of pregnancy information

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal

  Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 26.

Table 26 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in 12.5.8. While the investigator is not obligated to actively seek this information in former study subjects, she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will continue the study.

12.7. Appendix 7: Genetics

Not applicable

12.8. Appendix 8: Country-specific requirements

Not applicable.

12.9. Appendix 9: Protocol Amendment/Administrative change History

The Protocol Amendment/Administrative change Summary of Changes Table for the current amendment/administrative change is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 6	9-APR-2021
Amendment 5	2-Nov-2020
Amendment 4	28-Aug-2020
Amendment 3	3-Apr-2020
Amendment 2	23-Jan-2020
Amendment 1	21-Oct-2019
Original Protocol	23-Aug-2019

Overall Rationale for Amendment 1: The current holding rules do not include death or life-threatening SAEs considered related to vaccination that occur > 30 days post vaccination. In order to ensure inclusion of such events as triggers for study hold, the phrase “non-life-threatening” has been removed from holding rule 1b.

Detailed description of Protocol Amendment 1

Table 16 Study holding rules

Holding Rule	Event	Number of Subjects
1a	Death or any life-threatening **SAE occurring within 30 days from vaccination**	≥1
1b	***Any*** ~~non-life-threatening~~ SAE that can be reasonably attributed to the vaccination	≥1

Overall Rationale for Amendment 2

This study has been amended to collect immunogenicity data to 12 months post dosing. Long term persistence data will be useful to inform the boosting schedule for women entering successive pregnancies. Unblinding after Day 181 will still occur and the extended study (epoch 4) will be open label.

In addition, several discrepancies with the protocol with the study procedures manual were aligned.

Detailed description of Protocol Amendment 2

Contributing authors (Cont.)

- PPD, Oversight Data Manager
- PPD, Safety Scientist
- PPD ~~,~~–Study Statistician

Objectives and Endpoints:

• 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~~**365.**	• Occurrence of SAEs from Vaccination up to Day ~~181~~ **365**.
• 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~~ **365** by formulation.	• Occurrence of SAEs from Vaccination up to Day ~~181~~**365**.
• To evaluate the safety of RSVPreF3 (pooled for all groups receiving RSVPreF3).	• Occurrence of SAEs from Vaccination up to Day ~~181~~**365**.
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**, Day 181, and Day 365** post vaccination by formulation.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8, ~~and~~ Day 31**, Day 181, and Day 365** • RSV IgG antibody concentrations at Screening, Day 8, ~~and~~ Day 31**, Day 181, and Day 365**

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], **Visit 4 [Day 181], and Visit 5 [Day 365]**, and dTpa ELISAs at Screening and Visit 3 [Day 31])
For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.

Table 3 Schedule of Activities

Epoch	Epoch 001	Epoch 002 (Vaccination)			Epoch 003 (Follow-up)[8]	**Epoch 004 (Extension Study)[8]**	
Type of contact	Screening	Visit 1	Visit 2	Visit 3	Phone Contact 1	**Visit 4**	**Visit 5**
Time points	Day -7 to Day 1	Day 1	Day 8	Day 31	Day 181	**Day 181**	**Day 365**
Sampling time points	Pre-Vacc	Vacc	Post-Vacc	Post-Vacc	**Post-Vacc**	**Post Vacc**	**Post Vacc**
Physical examination [2]	●	●	●	O		O	O
Informed consent for extension study						●	
Phone contact					●		

Epoch	Epoch 001	Epoch 002 (Vaccination)			Epoch 003 (Follow-up)[8]	**Epoch 004 (Extension Study)[8]**	
Blood sampling for humoral immune response (~5 mL) [4]	●		●	●		●	●
Recording of AE leading to withdrawal		●	●	●	●	●	●[8]
Recording of serious AE [6]	●	●	●	●	●	●	●[8]
Recording of pregnancies		●	●	●	●	●	●[8]
Recording of concomitant medications/vaccinations		●	●	●	●~~[7]~~	●	● [7, 8]
Record any intercurrent medical conditions			●	●	●	●	●[8]
Screening conclusion	●						
Investigator sign-off on eCRF before analysis	●				●[8]		●[8]
Study conclusion							●[8]

[2] Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest. Weight, height and BMI will only be collected at Screening. Physical examination at **Visit 2,** Visit 3, **Visit 4 and Visit 5**, will be performed only if deemed necessary by the investigator. **For Visit 1 and Visit 2, (if performed), only vital signs will be collected in the eCRF.**

[8] **For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact**.

Table 4 Intervals between study visits

Interval	Optimal timing	Allowed interval
Screening Visit →Visit 1	≤7 days	-7- 1 days
Visit 1 →Visit 2	8 days	7- 10 days
Visit 1 →Visit 3	31 days	30- 45 days
Visit 1→Phone Contact	181 days	165- 195 days
Phone Contact→ Visit 4		**0-30 days**
Visit 1 →Visit 5	**365 days**	**335-395 days**

5.2 Overall design

- Duration of the study: Approximately ~~6 months~~ **1 year** for each enrolled subject **that signs the addendum for the extended study phase. For those that do not sign the addendum for the extended study phase the duration of the study will last approximately 6 months.**
  - 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 **Phone C**~~e~~ontact Day 181)
  - **Epoch 004: Follow Visit 4 (Day 181) to Visit 5 (Day 365)**
- Primary completion Date (PCD): Visit 3 (Day 31) or last visit of Primary Epoch

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit **5** ~~3~~, to occur no later than 8 months after last subject last visit (LSLV), which occurs with **Visit 5** ~~Contact 1~~ on Day **365** ~~181~~.

Table 6 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)	**Epoch 004 (open study)**
XRSV120_dTpa	50	18 - 45 years	*RSV MAT 120 Boostrix*-ex-US (dTpa_500)	x	x	x	x
XPlacebo_RSV120	50	18 - 45 years	*RSV MAT 120* Placebo	x	x	x	x
XRSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-ex-US (dTpa_500)*	x	x	x	x
XPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x	x
XPlacebo_dTpa	50	18 - 45 years	*Boostrix-ex-US (dTpa_500)* Placebo	x	x	x	x
URSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-US (dTpa_300)	x	x	x	x
UPlacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	x	x	x	x
URSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-US*	x	x	x	x
UPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x	x
UPlacebo_dTpa	50	18 – 45 years	*Boostrix*-US (dTpa_300) Placebo	x	x	x	x

5.4 Subject and study completion

A subject is considered to have completed the study if ~~he/~~she is available for the concluding ~~contact~~ **visit (Visit 5**, Day ~~181~~**365**) as described in the protocol. **For those participants that do not sign the ICF amendment the EOS will be the Day 181 phone contact as described in previous version of protocol (RSV MAT-011 (209141) Protocol Amendment 1 (21-Oct-2019).**

7.3 Blinding and unblinding

After the Day 181 phone contact for a given subject, the investigator will be informed of the subject's treatment assignment and will communicate this to the subject. For Visit 4 (Day 181) and Visit 5 (Day 365), the study will continue during the extended follow-up phase as an open study.

7.5.1 Recording of concomitant medications/products and concomitant vaccinations

- Any concomitant vaccination administered in the period starting 30 days before the dose of study vaccine(s) and ending at ~~the last study visit/contact~~ (Day -30 to Day ~~181~~ **365**).

8.0 Study assessments and procedures

For subjects consenting to the extended follow-up phase, 2 additional evaluations will be performed at Day 181 (Visit 4) and Day 365 (Visit 5). The subject will be queried for the occurrence of SAE and associated concomitant medication, pregnancy, and vaccinations received. In addition, approximately 5 ml of blood will be collected for assessment of vaccine immunogenicity.

8.2.3 Physical Examination

Perform a physical examination of the subject, including assessment of axillary or oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.

Perform a full physical examination of the subject at screening visit, including assessment of axillary or oral body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.

Perform a history directed physical exam plus vital signs at Visit 1 [Day 1]

Physical examinations at each study visit subsequent to the vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate. **Any vitals signs measured at Visit 2 (Day 8) should be recorded in the eCRF).**

8.3.Immunogenicity assessments

Any sample testing will be done in line with the consent of the individual subject~~/subject's parent(s)/LAR(s).~~

Table 10 Biological samples

Sample type Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information
Whole blood for immune response*	**5**	**ml**	**Visit 4 (Day 181)**	**Immune response: 5 mL (~ 2 mL serum).**
Whole blood for immune response*	**5**	**ml**	**Visit 5 (Day 365)**	**Immune response: 5 mL (~ 2 mL serum).**
	30~~20~~.5*	**ml**	**Minimum Total, not including repeat or unscheduled samples**	

***For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol and 30.5 mL of blood will be collected in total during the study. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact and 20.5 m of blood will be collected in total during the study.**

Table 11 Humoral Immunity (Antibody determination)

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off*	Groups	Number of subjects	Laboratory
Screening	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	**Nexelis** ~~Neomed~~
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	**Nexelis** ~~Neomed~~
Day 31									
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	**Nexelis** ~~Neomed~~
Day 181*	**Serum**	**Respiratory Syncytial Virus A Ab neutralizing**	**NEU**	**In house**	**ED60 and/or IU (international unit)**	**18 for ED60 TBD for IU**	**All**	**500**	**GSK**
	Serum	**Respiratory Syncytial Virus PreF3 Ab.IgG concentration**	**ELI**	**In house**	**ELU/mL**	**25**	**All**	**500**	**Nexelis**

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off*	Groups	Number of subjects	Laboratory
Day 365*	Serum	Respiratory Syncytial Virus A Ab neutralizing	NEU	In house	ED60 and/or IU (international unit)	18 for ED60 TBD for IU	All	500	GSK
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis

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; **TBD = to be determined**

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.

*** For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.**

***GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Table 12 Immunological read-outs

Blood sampling timepoint		Subset name	**Approximate** No. subjects	Component	Components priority rank
Visit 4 (Day 181)* **	**Post-Vacc**	**All**	**500**	**RSV-A neutralizing antibody**	**1**
		All	**500**	**RSVPreF3 IgG antibody concentration**	**2**
Visit 5 (Day 365)* **	**Post-Vacc**	**All**	**500**	**RSV-A neutralizing antibody**	**1**
		All	**500**	**RSVPreF3 IgG antibody concentration**	**2**

***** For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact**.

Table 13 Reporting periods for collecting safety information

Event	Pre-V1*		V1		V2		V3	Phone contact 1	V4**	V5 (Study Conclusion
			D1	D7	D8	D30	D31	D181	D181	D365
Solicited local and general AEs										
Unsolicited AEs										
AEs leading to withdrawal from the study										
SAEs										
SAEs related to study participation or concurrent GSK medication/vaccine										
Pregnancies										

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: Day, M: Month

****For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.**

8.5 Holding rules and safety monitoring

If the Central Team becomes aware of a holding rule being met, the below flow of communication must be followed:

- **CRDL to inform the local Study team (Table 15)**
- **The LML/delegate of each country confirm the reception of the holding rule to the CRDL and inform all the investigators.**
- **The concerned site staff has to put vaccination and enrolment on hold.**
- **The central study team will ensure SBIR is blocked and all vaccinating centres are informed.**
- **GSK Safety Review Team (SRT) will further evaluate the case and escalate to GSK VSMB for making the decision to stop or to restart the vaccination. All site staff will be informed about that final decision by their local GSK contact.**

9.1 Discontinuation from the study

For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact. From an analysis perspective, a 'withdrawal' from the study refers to any subject was not available for the concluding contact foreseen in the protocol.

10.1.2 Sample size calculation

In order to evaluate the humoral response to 2 dose levels (60 and 120 μg) of RSVPreF3 when given alone, and co-administered with dTpa, the difference between co-administration with dTpa (RSVPreF3 dTpa) and RSVPreF3 alone (RSVPreF3 placebo) in terms of RSV-A neutralizing antibody (Nab) titers will be evaluated at Day 8 and-Day 31**. Additional sampling at Day 181, and Day 365 will allow evaluation of the persistence of RSVPreF3 responses.**

10.2 Populations for analyses

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**. ~~Refer to the glossary of terms for the definition of 'enrolled'~~ ~~All subjects who completed the informed consent process and signed the informed consent form~~

10.3.3 Immunogenicity analyses

Endpoint	Statistical Analysis Methods
Primary	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~~ **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.
Secondary	• **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 Day 181, and/or Day 365* pooled for all subjects.**

***For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum, will complete the study at day 181 with a phone contact.**

10.3.4 Safety analyses

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 ~~follow up is for SAE~~ **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.
Secondary	**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 as well any SAE up to 365 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 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 same analysis will be done covering the entire study period (from vaccination up to day 365) In addition, similar analyses covering the 30-day follow up period and the 365 day follow up period will be performed for pooled formulations and pooled all groups receiving RSVPreF3 SAEs.** ~~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).~~

***For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.**

10.4 Sequence of analyses

The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion **(D365)** are available.

After Day 181(Visit 4) the study participants will be unblinded and the study extension phase will continue as an open study until the final study visit (Visit 5).

Table 19 Protocol-Required Safety Laboratory Assessments

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Haematology[1]	Leukocytes (White Blood Cells)	As per local practice	Quantitative	At investigator's laboratory
		Lymphocytes			
		Eosinophils			
		Basophils			
		Haemoglobin			
		Platelets			
		Neutrophils			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	As per local practice	Quantitative	
		Aspartate Aminotransferase (AST)			
		Creatinine			
		Blood Urea Nitrogen (BUN)/urea]*			
Urine[1]		Pregnancy	As per local practice; dipstick provided by GSK Biologicals	Ordinal	At investigator's laboratory

* Sites not able to directly test for BUN, will test for urea and then convert urea values into BUN using the applicable established conversion factor(s). ~~Only BUN values will be entered into the eCRF.~~

~~Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.~~

[1] **In certain local labs a complete blood counts will be required per local laboratory practice (more than just those listed in table).**

Table 21 Outsourced laboratories

Laboratory	Address
Nexelis ~~*NÉOMED-LABS*~~ *Inc.*	525, Cartier Ouest Laval Quebec Canada H7V 3S8 **Nexelis** ~~NÉOMED-LABS~~ Inc.

12.1.1. List of abbreviations

VSMB	**Vaccine Safety Monitoring Board**

12.1.2 Glossary of terms

Enrolled	**Subjects who agreed to participate in a clinical study after completion of the informed consent process. and subject is not a screen failure.**

12.5.7.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine(s) and will end ~~181~~ **365** days following administration of the dose of study vaccine(s).

Overall Rationale for Amendment 3:

The sponsor has decided not to implement the six-month extension for prolonged immunogenicity described under Amendment 2. The rationale for taking this decision is that the sponsor intends to submit an amendment that will enroll new participants (Cohort 2) to allow a more robust assessment of non-inferiority of *Boostrix* response in co-administration with RSVPreF3. An assessment of antibody persistence and response to a second dose of RSVPreF3 will be included in these newly enrolled subjects. Hence the evaluation of prolonged immunogenicity in Cohort 1 has become redundant.

Detailed description of Protocol Amendment 3

Contributing authors (Cont.)

- PPD, Lead Statistician
- PPD PPD

Objectives and Endpoints:

• 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**~~365~~**.**	• Occurrence of SAEs from Vaccination up to Day **181** ~~365~~.
• 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** ~~365~~ by formulation.	• Occurrence of SAEs from Vaccination up to Day **181**~~365~~.
• To evaluate the safety of RSVPreF3 (pooled for all groups receiving RSVPreF3).	• Occurrence of SAEs from Vaccination up to Day **181**~~365~~.
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~~, Day 181, and Day 365~~ post vaccination by formulation.	*Immunogenicity* • RSV A neutralizing antibody titers at Screening, Day 8, **and** Day 31~~, Day 181, and Day 365~~ • RSV IgG antibody concentrations at Screening, Day 8, **and** Day 31**,** ~~Day 181, and Day 365~~

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], ~~Visit 4 [Day 181], and Visit 5 [Day 365],~~ and dTpa ELISAs at Screening and Visit 3 [Day 31])

~~For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

Table 3 Schedule of Activities

Epoch	Epoch 001	Epoch 002 (Vaccination)			Epoch 003 (Follow-up)[8]	~~Epoch 004 (Extension Study)[8]~~	
Type of contact	Screening	Visit 1	Visit 2	Visit 3	Phone Contact 1	~~Visit 4~~	~~Visit 5~~
Time points	Day -7 to Day 1	Day 1	Day 8	Day 31	Day 181	~~Day 181~~	~~Day 365~~
Sampling time points	Pre-Vacc	Vacc	Post-Vacc	Post-Vacc	**Post-Vacc**	~~Post Vacc~~	~~Post Vacc~~
Physical examination [2]	●	●	●	O		~~O~~	~~O~~
~~Informed consent for extension study~~						~~●~~	
Phone contact					●		
Blood sampling for humoral immune response (~5 mL) [4]	●		●	●		~~●~~	~~●~~
Recording of AE leading to withdrawal		●	●	●	●	~~●~~	~~●[8]~~
Recording of serious AE [6]	●	●	●	●	●	~~●~~	~~●[8]~~
Recording of pregnancies		●	●	●	●	~~●~~	~~●[8]~~
Recording of concomitant medications/vaccinations[7]		●	●	●	●~~[7]~~	~~●~~	~~●[7, 8]~~
Record any intercurrent medical conditions			●	●	●	~~●~~	~~●[8]~~
Screening conclusion	●						
Investigator sign-off on eCRF before analysis	●				●[8]		~~●[8]~~
Study conclusion					●		~~●[8]~~

[2] Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest. Weight, height and BMI will only be collected at Screening. Physical examination at Visit 2**, and** Visit 3, ~~Visit 4 and Visit 5~~, will be performed only if deemed necessary by the investigator. For Visit 1 and Visit 2, (if performed), only vital signs will be collected in the eCRF.

[8] ~~For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

Table 4 Intervals between study visits

Interval	Optimal timing	Allowed interval
Screening Visit →Visit 1	≤7 days	-7- 1 days
Visit 1→Visit 2	8 days	7- 10 days
Visit 1→Visit 3	31 days	30- 45 days
Visit 1→Phone Contact	181 days	165- 195 days
~~Phone Contact →Visit 4~~		~~0-30 days~~
~~Visit 1 →Visit 5~~	~~365 days~~	~~335-396 days~~

5.2 Overall design

- Duration of the study: Approximately **6 months** ~~1 year~~ for each enrolled subject ~~that signs the addendum for the extended study phase. For those that do not sign the addendum for the extended study phase the duration of the study will last approximately 6 months.~~
  - 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 Phone Contact **(**Day 181)
- ~~Epoch 004: Follow Visit 4 (Day 181) to Visit 5 (Day 365)~~

- Primary completion Date (PCD): Visit 3 (Day 31) or last visit of Primary Epoch

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit ~~5~~ **3**, to occur no later than 8 months after last subject last visit (LSLV), which occurs with ~~Visit 5~~ **Contact 1** on Day ~~365~~ **181**.

Table 6 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)	~~Epoch 004 (open study)~~
XRSV120_dTpa	50	18 - 45 years	*RSV MAT 120 Boostrix*-ex-US (dTpa_500)	x	x	x	~~x~~
XPlacebo_RSV120	50	18 - 45 years	*RSV MAT 120* Placebo	x	x	x	~~x~~
XRSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-ex-US (dTpa_500)*	x	x	x	~~x~~
XPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x	~~x~~
XPlacebo_dTpa	50	18 - 45 years	*Boostrix-ex-US (dTpa_500)* Placebo	x	x	x	~~x~~
URSV120_dTpa	50	18 – 45 years	*RSV MAT 120 Boostrix*-US (dTpa_300)	x	x	x	~~x~~
UPlacebo_RSV120	50	18 – 45 years	*RSV MAT 120* Placebo	x	x	x	~~x~~
URSV60_dTpa	50	18 - 45 years	*RSV MAT 60 Boostrix-US*	x	x	x	~~x~~
UPlacebo_RSV60	50	18 - 45 years	*RSV MAT 60* Placebo	x	x	x	~~x~~
UPlacebo_dTpa	50	18 – 45 years	*Boostrix*-US (dTpa_300) Placebo	x	x	x	~~x~~

5.4 Subject and study completion

A subject is considered to have completed the study if ~~he/~~she is available for the concluding **contact** visit ~~(Visit 5~~, Day **181**~~365~~) as described in the protocol. ~~For those participants that do not sign the ICF amendment the EOS will be the Day 181 phone contact as described in previous version of protocol (RSV MAT-011 (209141) Protocol Amendment 1 (21-Oct-2019).~~

7.3 Blinding and unblinding

~~After the Day 181 phone contact for a given subject, the investigator will be informed of the subject's treatment assignment and will communicate this to the subject. For Visit 4 (Day 181) and Visit 5 (Day 365), the study will continue during the extended follow-up phase as an open study.~~

7.5.1 Recording of concomitant medications/products and concomitant vaccinations

- Any concomitant vaccination administered in the period starting 30 days before the dose of study vaccine(s) and ending at ~~the last study visit/contact~~ (Day -30 to Day **181**~~365~~).

8.0 Study assessments and procedures

~~For subjects consenting to the extended follow-up phase, 2 additional evaluations will be performed at Day 181 (Visit 4) and Day 365 (Visit 5). The subject will be queried for the occurrence of SAE and associated concomitant medication, pregnancy, and vaccinations received. In addition, approximately 5 ml of blood will be collected for assessment of vaccine immunogenicity.~~

Table 10 Biological samples

Sample type Collected to Evaluate	Minimum Quantity per subject	Unit	Time point	Additional Information
~~Whole blood for immune response*~~	~~5~~	~~ml~~	~~Visit 4 (Day 181)~~	~~Immune response: 5 mL (~ 2 mL serum).~~
~~Whole blood for immune response*~~	~~5~~	~~ml~~	~~Visit 5 (Day 365)~~	~~Immune response: 5 mL (~ 2 mL serum).~~
	~~30~~**20.5**~~*~~	ml	Minimum Total, not including repeat or unscheduled samples	

~~*For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol and 30.5 mL of blood will be collected in total during the study. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact and 20.5 m of blood will be collected in total during the study.~~

Table 11 Humoral Immunity (Antibody determination)

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off*	Groups	Number of subjects	Laboratory
Screening	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
Day 31									
	Serum	Respiratory Syncytial Virus PreF3 Ab.IgG concentration	ELI	In house	ELU/mL	25	All	500	Nexelis
~~Day 181*~~	~~Serum~~	~~Respiratory Syncytial Virus A Ab neutralizing~~	~~NEU~~	~~In house~~	~~ED60 and/or IU (international unit)~~	~~18 for ED60 TBD for IU~~	~~All~~	~~500~~	~~GSK~~
	~~Serum~~	~~Respiratory Syncytial Virus PreF3 Ab.IgG concentration~~	~~ELI~~	~~In house~~	~~ELU/mL~~	~~25~~	~~All~~	~~500~~	~~Nexelis~~
~~Day 365*~~	~~Serum~~	~~Respiratory Syncytial Virus A Ab neutralizing~~	~~NEU~~	~~In house~~	~~ED60 and/or IU (international unit)~~	~~18 for ED60 TBD for IU~~	~~All~~	~~500~~	~~GSK~~
	~~Serum~~	~~Respiratory Syncytial Virus PreF3 Ab.IgG concentration~~	~~ELI~~	~~In house~~	~~ELU/mL~~	~~25~~	~~All~~	~~500~~	~~Nexelis~~

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; TBD = to be determined

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.

~~* For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

***GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany.

Table 12 Immunological read-outs

Blood sampling timepoint		Subset name	Approximate No. subjects	Component	Components priority rank
~~Visit 4 (Day 181)***~~	~~Post-Vacc~~	~~All~~	~~500~~	~~RSV-A neutralizing antibody~~	~~1~~
		~~All~~	~~500~~	~~RSVPreF3 IgG antibody concentration~~	~~2~~
~~Visit 5 (Day 365)***~~	~~Post-Vacc~~	~~All~~	~~500~~	~~RSV-A neutralizing antibody~~	~~1~~
		~~All~~	~~500~~	~~RSVPreF3 IgG antibody concentration~~	~~2~~

~~*** For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

Table 13 Reporting periods for collecting safety information

Event	Pre-V1*		V1		V2		V3	Phone contact 1	~~V4**~~	~~V5 (Study Conclusion~~
			D1	D7	D8	D30	D31	D181	~~D181~~	~~D365~~
Solicited local and general AEs										
Unsolicited AEs										
AEs leading to withdrawal from the study										
SAEs										
SAEs related to study participation or concurrent GSK medication/vaccine										
Pregnancies										

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: Day, M: Month
~~**For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

9.1 Discontinuation from the study

~~For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participants that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~ From an analysis perspective, a 'withdrawal' from the study refers to any subject was not available for the concluding contact foreseen in the protocol.

10.1.2 Sample size calculation

In order to evaluate the humoral response to 2 dose levels (60 and 120 μg) of RSVPreF3 when given alone, and co-administered with dTpa, the difference between co-administration with dTpa (RSVPreF3 dTpa) and RSVPreF3 alone (RSVPreF3 placebo) in terms of RSV-A neutralizing antibody (Nab) titers will be evaluated at Day 8 and-Day 31**.** ~~Additional sampling at Day 181, and Day 365 will allow evaluation of the persistence of RSVPreF3 responses.~~

10.3.3 Immunogenicity analyses

Endpoint	Statistical Analysis Methods
~~Secondary~~	• ~~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 Day 181, and/or Day 365* pooled for all subjects.~~

~~*For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum, will complete the study at day 181 with a phone contact.~~

10.3.4 Safety analyses

Secondary	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 as well any SAE up to **180** ~~365~~ 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~~*~~.

~~*For the participants that sign the informed consent addendum, the conclusion of the study will be on Day 365 as described in the protocol. Participant's that do not sign the informed consent addendum will complete the study at day 181 with a phone contact.~~

10.4 Sequence of analyses

The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion (D181~~365~~) are available.

~~After Day 181(Visit 4) the study participants will be unblinded and the study extension phase will continue as an open study until the final study visit (Visit 5).~~

12.5.7.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine(s) and will end **181** ~~365~~ days following administration of the dose of study vaccine(s).

Overall Rationale for Amendment 4

This study has been amended to collect immunogenicity data to 12 months post dosing. Long term persistence data will be useful to inform the boosting schedule for women entering successive pregnancies. Unblinding after Day 181 will still occur and the extended study (epoch 4) will be open label.

In addition, several discrepancies with the protocol with the study procedures manual were aligned.

Detailed description of Protocol Amendment 4

This study has been amended to administer a second dose of the 120 µg RSVPreF3 Maternal investigational vaccine to all consenting subjects within a 6-month period from the beginning of 12 months to the beginning of 18 months following initial immunization (≥12 to <18 months). This extension part of the study will use non-pregnant women as a proxy for women who may require additional dosing in successive pregnancies. Specifically, this extension will provide information on:

1. Long term immunogenicity of a 1st dose of 60 µg or 120 µg RSVPreF3 vaccine
2. Safety and immunogenicity of 2nd dose of 120 µg RSVPreF3 vaccine

In addition, this protocol amendment outlines measures that may be applicable during special circumstances (e.g., COVID-19 pandemic). The purpose of the amendment is to protect the subject's welfare, and as far as possible ensure the potential benefit to the subject and promote data integrity.

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** ~~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) **and to evaluate the safety, reactogenicity and immunogenicity of a 2nd dose of the RSV maternal vaccine.**

A Phase II study of **a primary** ~~2~~ dose ~~levels~~ of ~~an~~ investigational RSV maternal vaccine, given alone or with *Boostrix*, **with a 2nd dose investigational RSV maternal vaccine** ~~to healthy non-pregnant women.~~

Contributing authors (Cont.)

- ~~•~~ PPD , PPD
  PPD
- PPD ~~Tanvir Kaur~~, Study Delivery Lead
- PPD , Safety Physician
- PPD , Safety **Physician**~~Scientist~~

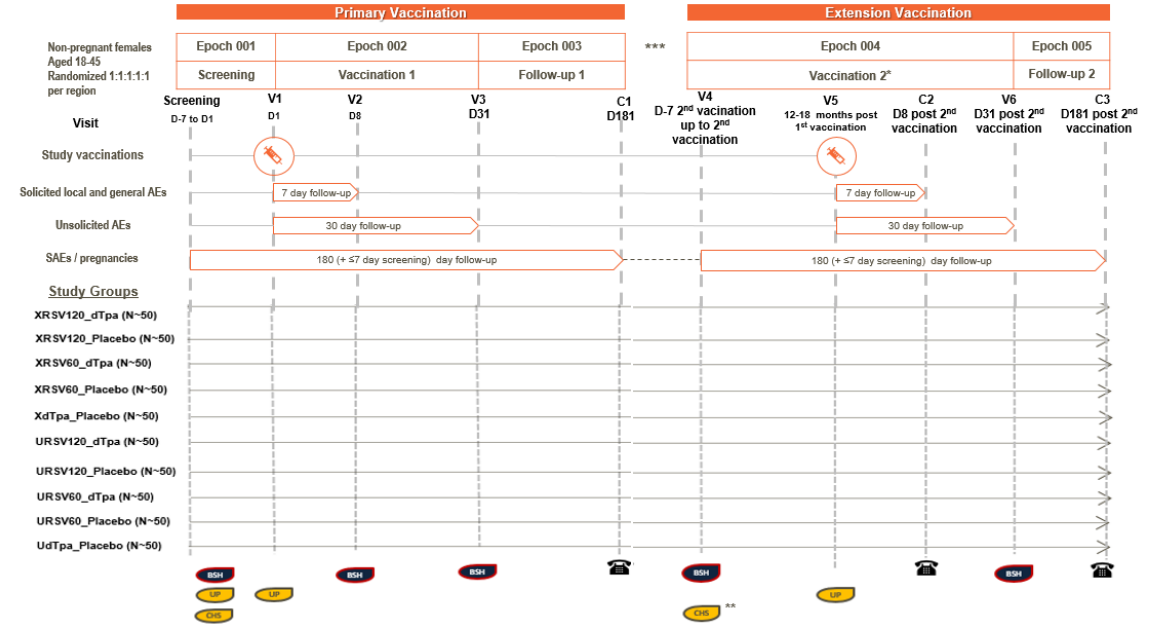
1. Synopsis

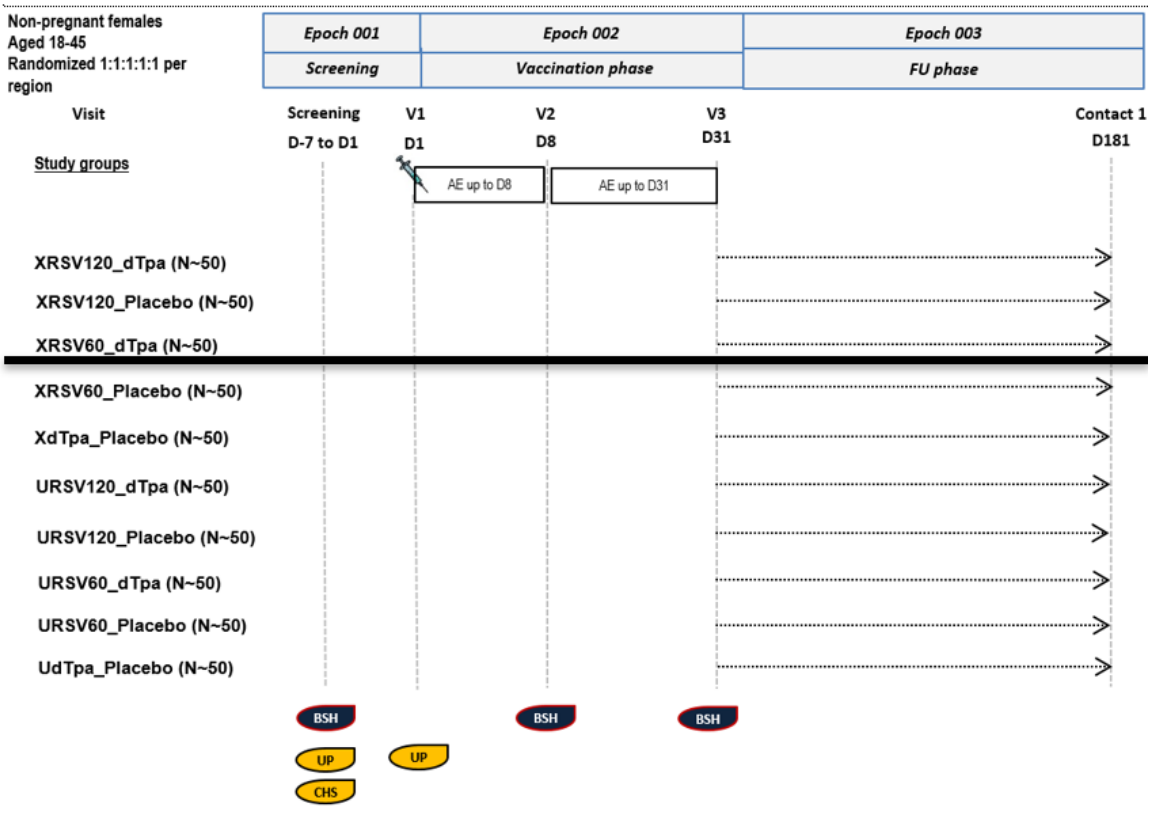
For those who provide consent, the durability of the response to RSVPreF3 will be measured from 12 to 18 months following initial vaccination. In addition, a second immunization with the RSV Maternal (120µg) vaccine will be administered from 12 months to 18 months after the first vaccination to evaluate the immunogenicity and safety profile of RSVPreF3 vaccine second dose.

Objective

• **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.**
• **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**~~31post~~ vaccination**, and at 12 to 18 months** by formulation.	Immunogenicity • RSV A neutralizing antibody titers at Screening, Day 8, ~~and~~ Day 31, **a single timepoint between 12 to 18 months post 1st vaccination**. • RSV IgG antibody concentrations at Screening, Day 8 ~~and~~ Day 31, **a single timepoint between 12 to 18 months post 1st vaccination**.
• **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.**

Overall Design





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], **Visit 4, [up to D7 prior to 2nd vaccination], and Visit 6 [D31 post 2nd vaccination]**
~~And~~ 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.**

2. Schedule of Activities

Epoch		**Epoch 004 (Vaccination 2)**				**Epoch 005 (Follow-up 2)**
Type of contact		**Visit 4**	**Visit 5**	**Phone Contact 2**	**Visit 6**	**Phone Contact 3**
Time points	**Day 181 to -7 before 2nd vaccination**	**Day -7 to Day of 2nd vaccination**	**From 12 up to 18 months post 1st vaccination**	**Day 8 post 2nd vaccination**	**Day 31 post 2nd vaccination**	**Day 181 post 2nd vaccination**
Sampling time points	**Pre-Vacc 2**	**Pre-Vacc 2**	**Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**
Informed consent		●				
Check inclusion/exclusion criteria		●				
Check contraindications to subsequent vaccine(s) administration		O	O			
Phone contact				●		●
Medical history		●				
Physical examination [2]		●			O	
Urine pregnancy test [3]			●			
Pre-vaccination body temperature and heart rate			●			
Distribution of subject card			O			
Hematological and biochemical laboratory testing (~5.5 mL)		O[8]				
Blood sampling for humoral immune response (~5 mL) [4]		●			●	
Treatment number allocation (SBIR)			O			
Vaccine administration			●			
Recording of administered treatment number			●			
60 minutes post vaccination observation period			O			
Training on use of diary cards			O			
Distribution of diary cards[5]			O			
Collection of diary cards					O	
Diary card transcription by investigator or designate					●	
Recording of solicited adverse events			●	●		
Recording of unsolicited adverse events			●	●	●	
Recording of AE leading to withdrawal			●	●	●	●
Recording of serious AE [6]		●	●	●	●	●
Recording of pregnancies		●	●	●	●	●

Epoch		**Epoch 004 (Vaccination 2)**				**Epoch 005 (Follow-up 2)**
Type of contact		**Visit 4**	**Visit 5**	**Phone Contact 2**	**Visit 6**	**Phone Contact 3**
Time points	**Day 181 to -7 before 2nd vaccination**	**Day -7 to Day of 2nd vaccination**	**From 12 up to 18 months post 1st vaccination**	**Day 8 post 2nd vaccination**	**Day 31 post 2nd vaccination**	**Day 181 post 2nd vaccination**
Sampling time points	**Pre-Vacc 2**	**Pre-Vacc 2**	**Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**	**Post-Vacc 2**
Recording of concomitant medications/vaccinations[7]		●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●
Investigator sign-off on eCRF before analysis					●	●
COVID-19 eCRFs log page		●	●	●	●	●
Study conclusion extension						●

[2] Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest. Weight, height and BMI will only be collected at Screening **and V4**. Physical examination at Visit 2,~~and~~ Visit 3, **and Visit 4** will be performed only if deemed necessary by the investigator. For Visit 1 and Visit 2 (if performed), only vital signs will be collected in the eCRF.

Table 4 Intervals between study visits

Interval	**Optimal timing**	**Allowed interval**
Screening Visit →Visit 1	≤7 days	-7- 1 days *
Visit 1→Visit 2	8 days	7- 10 days
Visit 1→Visit 3	31 days	30- 45 days
Visit 1→Phone Contact 1	181 days	165- 195 days
Visit 4→Visit 5	**≤7 days**	**-7 to 1 days***
Visit 1→Visit 5	**365 days**	**365 - 548 days****
Visit 5→Phone Contact 2	**8 days**	**7 - 10 days**
Visit 5→Visit 6	**31 days**	**30 - 45 days**
Visit 5→Phone Contact 3	**181 days**	**165 - 195 days**

***From 7 days prior to vaccination up to and including the day of vaccination.**
****For a 6-month period ≥12 to <18 months post 1st vaccination**

3.1 Study Rationale

Finally, a second dose vaccination of RSVPreF3 (120 µg) will be administered to the consenting subjects from 12 months to 18 months following initial vaccination to evaluate the immunogenicity and safety profile of RSVPreF3. This extension of the study will recruit the same non-pregnant women as a proxy for women who may require additional dosing in successive pregnancies.

4 Objectives

(See 1. Synopsis for Objectives and Outcome Table)

5.1 Scientific rationale for study design

Finally, a second dose vaccination of RSVPreF3 will be administered to consenting subjects from 12 months to 18 months following 1st vaccination to evaluate the immunogenicity and safety profile of RSVPreF3. The intention of this study extension is to assess the durability of the immune response after the first dose vaccination, and to assess the safety and immunogenicity following a second dose vaccination of the RSVPreF3 maternal vaccine. This extension of the study will recruit the same non-pregnant women as a proxy for women who may require additional dosing in successive pregnancies.

5.2 Study Design

(See 1. Synopsis for Design Figure)

- **Primary Vaccination**
- 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 **after Visit 3 (Day 31) to Phone Contact 1**~~contact~~ 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).**

- End of Study (EoS): Last testing results released of samples collected at Visit **6**~~3~~, to occur no later than 8 months after last subject last visit (LSLV), which occurs with phone contact **3**~~1~~ on Day 181 **post 2nd vaccination**.

Table 6 Study groups, treatment and epochs foreseen in the study

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 study)**	**Epoch 005 (open study)**
XRSV120_dTpa	50	18 – 45	*RSV MAT 120*	***RSV MAT 120***	x	x	x	**x**	**x**

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 study)**	**Epoch 005 (open study)**
		years	*Boostrix-ex-US (dTpa_500)*						
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**

5.4 Subject and study completion

A subject is considered to have completed the study if she is available for the concluding phone contact **3** (Day 181 **post second vaccination**) as described in the protocol.

For those subjects that do not agree to participate in the study extension, the concluding contact will be the Day 181 phone contact as described in previous version of protocol (RSV MAT-011 (209141) Protocol Amendment 3 (03-APR-2020).

6.3 Inclusion criteria for study extension

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

- **Completed in primary study and received 1st dose vaccination of a study vaccine (RSVPreF3 or *Boostrix*).**
- **Written or witnessed/thumb printed informed consent obtained from the subject prior to performance of any study specific procedure to the study extension.**

Are eligible if they meet the following criteria below

All subjects must satisfy ALL the following criteria:

- **Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary card, return for follow-up visits).**
- **Female subjects remain healthy; as established by medical history and clinical examination, aged 18 to 45 years at the time of the first vaccination;**
- **Female subjects of childbearing potential are eligible for the extension, if the subject:**
  - **has practiced adequate contraception for 30 days prior to 2nd vaccination**
  - **has a negative pregnancy test with results available on the day of 2nd vaccination**
  - **has agreed to continue adequate contraception for 90 days after completion of the 2nd vaccination.**

6.4 Exclusion criteria for extension

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of entry to the extension. If ANY exclusion criterion applies, the subject must not be included in the extension.

6.4.1 Medical conditions for extension

- **History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines;**
- **Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);**
- **Hypersensitivity to latex;**
- **Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests;**
- **Significant or uncontrolled psychiatric illness;**
- **Recurrent history or un-controlled neurological disorders or seizures;**
- **Documented HIV-positive subject;**
- **History of or current autoimmune disease;**
- **Body mass index (BMI) > 40 kg/m^2;**
- **Participants who experienced any SAE judged to be possibly or probably related to first dose vaccination of RSVPreF3, including hypersensitivity reactions.**
- **Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.**

6.4.2 Prior/Concomitant therapy for extension

- **Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccines during the period starting 30 days before the second dose of study vaccine (Day -29 to Day 1), or planned use during the 6 month study extension period;**
- **Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab);**
- **Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccines or planned administration during the study period;**
- **Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine dose(s). For corticosteroids, this will mean prednisone ≥5 mg/day, or equivalent. Inhaled and topical steroids are allowed;**

- **Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after study 2nd dose vaccination, with the exception of any licensed influenza vaccine which may be administered ≥ 15 days before or after study vaccination.**

6.4.3 Prior/Concurrent clinical study experience for extension

- **Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device);**

6.4.4 .Other exclusions for extension

- **Pregnant or lactating female at the time of Visit 4;**
- **Female planning to become pregnant or planning to discontinue contraceptive precautions;**
- **History of alcoholism, drug abuse and/or use disorder within the past two years (as defined in DSM-5 Diagnostic Criteria) [Camargo, 1984; Christy, 1995; Hasin, 2013];**
- **Any study personnel or their immediate dependents, family or household members**

6.7 Screen failures for the extension

"Screening failures" for the extension are subjects who withdraw or are withdrawn from the extension after giving informed consent to the extension, but before extension eligibility (presence of all inclusion and absence of all exclusion criteria) is confirmed. Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

7.1 Treatments administered

	RSV MAT 120	**RSV MAT 60**	***Boostrix-ex-US (dTpa_500)***	***Boostrix-US (dTpa_300)***	**Placebo**
	NaCl	NaCl			
Presentation	**Powder for suspension for injection (vial)** ~~Freeze-dried Antigen~~ (174mcg/vial)	**Powder for suspension for injection (vial)** ~~Freeze-dried Antigen~~ (87mcg/vial)	**Suspension for injection** ~~prefilled~~ syringe)	**Suspension for injection** ~~prefilled~~ syringe)	**Solution for injection; vial)**~~Clear liquid in monodose ampule or vial~~
	Solution for solution for injection; (vial)~~Clear liquid in monodose ampule or vial~~	**Solution for solution for injection; (vial)**~~Clear liquid in monodose ampule or vial~~			

	RSV MAT 120	**RSV MAT 60**	***Boostrix-ex-US (dTpa_500)***	***Boostrix-US (dTpa_300)***	**Placebo**
	NaCl	NaCl			
Formulation	RSVPreF3(**120 µg)/Trehalose(12.73 mg). NaCl solution (4.5 mg/0.5 mL, ~150 mM)** ~~NaCl=150mM~~	***RSVPreF3(60 µg)/Trehalose(6.42 mg).*** **NaCl solution (4.5 mg/0.5 mL, ~150 mM)** ~~NaCl=150mM~~	***Diphtheria toxoid (≥ 2 IU) adsorbed on aluminium hydroxide and aluminium phosphate; Tetanus toxoid (≥ 20 IU) adsorbed on aluminium hydroxide and aluminium phosphate; Pertussis toxoid (8 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Filamentous haemagglutinin (8 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Pertactin (69 kDa outer membrane protein) (2.5 µg) adsorbed on aluminium hydroxide and aluminium phosphate; Aluminium hydroxide (0.3 mg Al^{3+}); Aluminium phosphate (0.2 mg Al^{3+}); Sodium chloride; Water for injections q.s. 0.5 mL*** ~~*DT>=2IU; TT>=20IU; PT=8µg; FHA=8µg; PRN=2.5µg; Aluminium=500µg Al3+*~~	**Diphtheria toxoid (≥ 2 IU) adsorbed on aluminium hydroxide; Tetanus toxoid (≥ 20 IU) adsorbed on aluminium hydroxide; Pertussis toxoid (8 µg) adsorbed on aluminium hydroxide; Filamentous haemagglutinin (8 µg) adsorbed on aluminium hydroxide; Pertactin (69 kDa outer membrane protein) (2.5 µg) adsorbed on aluminium hydroxide; Aluminium hydroxide (0.3 mg Al^{3+}); Sodium chloride (4.4 mg); Water for injections q.s. 0.5 mL** ~~DT>=2IU; TT>=20IU; PT>=8µg; FHA=8µg; PRN=2.5µg; $Al(OH)_3$=300µg Al3+~~	**NaCl solution (4.5 mg/0.5 mL, ~150 mM)** ~~NaCl=150mM~~

	RSV MAT 120	**RSV MAT 60**	***Boostrix-ex-US (dTpa_500)***	***Boostrix-US (dTpa_300)***	**Placebo**
	NaCl	NaCl			
Route of Administration	**Intramuscular use~~IM~~**	**Intramuscular use~~IM~~**	**Intramuscular use~~IM~~**	**Intramuscular use~~IM~~**	**Intramuscular use~~IM~~**
No of doses	**2~~1~~**	1	1	1	1
Manufacturer	RSVPreF3: GSK **Biologicals** NaCl: GSK **Biologicals**	RSVPreF3: GSK **Biologicals** NaCl: GSK **Biologicals**	GSK **Biologicals**	GSK **Biologicals**	GSK **Biologicals**

Table 8 Treatments administered (Part 2)

Primary Vaccination				
2nd Vaccination				
Groups in primary vaccination	**Formulation in primary vaccination**	**N**	**Groups in 2nd vaccination**	**Laterality**
XRSV120_dTpa	**ex-US**	**50**	**RSVPreF3=120µg**	**Non-Dominant**
Xplacebo_RSV120		**50**	**RSVPreF3=120µg**	**Non-Dominant**
XRSV60_dTpa		**50**	**RSVPreF3=120µg**	**Non-Dominant**
Xplacebo_RSV60		**50**	**RSVPreF3=120µg**	**Non-Dominant**
Xplacebo_dTpa		**50**	**RSVPreF3=120µg**	**Non-Dominant**
URSV120_dTpa	**US**	**50**	**RSVPreF3=120µg**	**Non-Dominant**
Uplacebo_RSV120		**50**	**RSVPreF3=120µg**	**Non-Dominant**
URSV60_dTpa		**50**	**RSVPreF3=120µg**	**Non-Dominant**
Uplacebo_RSV60		**50**	**RSVPreF3=120µg**	**Non-Dominant**
Uplacebo_dTpa		**50**	**RSVPreF3=120µg**	**Non-Dominant**

7.2.1 Subject identification

The subject identification number will be the same in the study extension. No new subjects will be recruited.

7.2.1.2 Treatment allocation by subject

For the second vaccination, 1 treatment number will be allocated for each subject.

7.2.1.2.1 Study group and treatment number allocation

Since the second dose vaccination is open study, the treatment number will be allocated for each subject sequentially at each centre.

7.3 Blinding and unblinding

Data will be collected in an observer-blind manner **during the primary study.**

Investigators will remain blinded to each subject's assigned study treatment **until completion** ~~throughout the course~~ of the **primary vaccination day 181 database freeze for analysis**. ~~study.~~

After the Day 181 phone contact **(C1)** for a given subject, the investigator will be informed of the subject's treatment assignment and will communicate this to the subject. **The study extension will then be conducted as an open label study**.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomisation/dispensing has been done accurately. Please refer to the SPM for details on blinding of the vaccine. ~~administration.~~

8.1 Study Procedures During Special Circumstances

During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For the duration of such special circumstances:

- **Reconsent of subjects for the study extension may be placed on hold. Decisions on re-starting will be made in a manner consistent with guidance from public health and other competent authorities.**
- **Informed consent must take place in a face to face contact with the investigator but informing the potential subject ahead of giving written consent may be done remotely for example by mailing the informed consent or telephone or videotelephony conversation.**
- **Certain procedures may be performed at an alternate location. his includes, signing of informed consent, physical examination and vaccine dosing. If vaccinating in an alternate location, it must be assured that trained staff and equipment are available to manage an acute vaccine reaction. Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.**
- **Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.**
- **"Medically attended visits" include instances where, due to the special circumstances, the subject cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.**
- **The paper Diary card provided to the subject may be transmitted from and to the site by electronic means and or conventional mail.**

- **If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 4), then the interval may be extended up to a maximum length described in Table 10, however efforts should be made to adhere as closely as possible to the optimal timing.**
- **If despite best efforts it is not possible to administer the dose of study vaccine as defined in the protocol (see Table 4), a maximum dose interval described in Table 10 may be used, however efforts should be made to adhere as closely as possible to the optimal timing.**

Table 10 Intervals between study visits under Special Circumstances

Interval	Optimal timing	Allowed interval	Adapted interval under special circumstances
Screening Visit →Visit 1	≤7 days	-7- 1 days	-30 to 1 days
Visit 1 →Visit 2	8 days	7- 10 days	7- 10 days
Visit1 →Visit 3	31 days	30- 45 days	30 – 60 days
Visit 1→Phone Contact 1	181 days	165- 195 days	165 – 195 days
Visit 4→Visit 5		-7 to 1 days	-30 – 1 days*
Visit 1→Visit 5	365 days	365-548 days**	
Visit 5 to Phone Contact 2	8 days	7- 10 days	7- 10 days
Visit 5→Visit 6	31 days	30- 45 days	30 – 90 days
Visit 5→Phone Contact 3	181 days	165- 195 days	165 – 195 days

*From 30 days prior to vaccination up to and including the day of vaccination.
** For a 6-month period ≥12 to <18 months post 1st vaccination

Impact on the per protocol set for immunogenicity will be determined on a case by case basis.

- **Any impact of above-mentioned measures on the study results will be described in the clinical study report.**

* It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site.

8.3.2 Medical and vaccination history

Significant medical conditions and vaccinations that occurred during the C1-V4 will be reviewed during the screening for the second vaccination and reported as medical history.

8.3.3 Physical Exam

- **Perform a history directed physical exam plus vital signs at Visit 4 [D-7 2nd vaccination to 2nd vaccination]. Note that laboratory assessments of haematology and biochemistry may be made on the investigator's discretion.**

8.4.2 Biological samples

Whole blood for hematology, biochemistry* **Whole blood for immune response**	**10.5 or 5**	**ml**	**Visit 4 (up Day -7 prior to 2nd vaccination)**	**Hematology, chemistry: 5.5 mL. Immune response: 5 mL (~ 2 mL serum).**
Whole blood for immune response	**5**	**ml**	**Visit 6 (Day 31 post 2nd vaccination)**	**Immune response : 5 mL (~ 2 mL serum).**
	36 or 3020.5	ml	Minimum Total, not including repeat or unscheduled samples	
Urine for Pregnancy	-	-	screening visit Visit 1 (day 1) **and Visit 5 (2nd Vaccination)**	

***Hematological and biochemical laboratory testing at Visit 4 (D -7 up to and including 2nd dose vaccination) at the investigator's discretion**

8.4.3 Laboratory Assays

Table 12 Humoral Immunity (Antibody determination)

Sampling time points	System	Component	Method	Kit/ Manufacturer	Unit	Cut-off	Groups	Number of subjects	Laboratory ***
Day -7 up to 2nd vaccination	**Serum**	**Respiratory Syncytial Virus A Ab neutralizing**	**NEU**	**In house**	**ED60 and/or IU (international unit)**	**18 for ED60 56 for IU**	**All**	**500**	**GSK**
	Serum	**Respiratory Syncytial Virus PreF3 Ab.IgG concentration**	**ELI**	**In house**	**ELU/mL**	**25**	**All**	**500**	**Nexelis**
D31 post 2nd vaccination	**Serum**	**Respiratory Syncytial Virus A Ab neutralizing**	**NEU**	**In house**	**ED60 and/or IU (international unit)**	**18 for ED60 56 for IU**	**All**	**500**	**GSK**
	Serum	**Respiratory Syncytial Virus PreF3 Ab.IgG concentration**	**ELI**	**In house**	**ELU/mL**	**25**	**All**	**500**	**Nexelis**

Table 13 Immunological read-outs

Blood sampling timepoint		Subset name	Approximate No. subjects	Component	Components priority rank
Type of contact and timepoint*	Sampling timepoint				
Day -7 up to 2nd vaccination	**Post-Vacc**	**All**	**500**	**RSV-A neutralizing antibody**	**1**
		All	**500**	**RSVPreF3 IgG antibody concentration**	**2**
D31 post 2nd vaccination	**Post-Vacc**	**All**	**500**	**RSV-A neutralizing antibody**	**1**
		All	**500**	**RSVPreF3 IgG antibody concentration**	**2**

~~* The results of this testing might potentially impact the subject medical care~~
Boostrix recipients = subjects in the following study groups: -XRSV120_dTpa, XRSV60_dTpa, Xplacebo_dTpa, URSV120_dTpa, URSV60_dTpa, Uplacebo_dTpa.

8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information

Table 14 Reporting periods for collecting safety information

Event	~~Phone Contact~~ **C1**	**C1 to V4****	**V4**	**V5***		**C2**		**V6**	**C3**
	D181		**D -7 up to 2nd vaccination**	**2nd vaccination From 12 up to 18 months post 1st vaccination**	**D7 post second 2nd vaccination**	**D8 post second 2nd vaccination**	**D30 post second 2nd vaccination**	**D31 post 2nd vaccination**	**181 Days post 2nd vaccination**
Solicited local and general AEs									
Unsolicited AEs									
AEs leading to withdrawal from the study									
SAEs**									
SAEs related to study participation or concurrent GSK									

Event	~~Phone Contact~~ **C1**	**C1 to V4****	**V4**	**V5***		**C2**		**V6**	**C3**
	D181		**D -7 up to 2nd vaccination**	**2nd vaccination From 12 up to 18 months post 1st vaccination**	**D7 post second 2nd vaccination**	**D8 post second 2nd vaccination**	**D30 post second 2nd vaccination**	**D31 post 2nd vaccination**	**181 Days post 2nd vaccination**
medication/vaccine									
Pregnancies***									

**** 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. In addition, SAE related to vaccination are reported during the period C1-V4 will be reported to the Investigator at the time of awareness.**

*****Pregnancies that occurred during the C1-V4 period will be reported as medical history**

~~A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine(s), the investigator will promptly notify the Study Contact for Reporting SAEs.~~

8.5.5 Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 14. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs.

9.1 Discontinuation from the study

Subjects will complete the study at day 181 with a phone contact. For the subjects that enroll in the study extension, the conclusion of the study will be on Day 181 following the second immunization as described in the protocol.

Investigators will make **3 attempts followed by a certified letter**~~an attempt~~ to contact those subjects who do not return for scheduled visits or follow-up.

9.2 Discontinuation of study vaccine(s)

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- **Adverse event requiring expedited reporting to GSK**
- **Unsolicited non-serious adverse event**
- **Solicited adverse event**
- **Not willing to be vaccinated**
- **Other (specify).**
- ~~Not applicable~~.

10.2 Population for analysis

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.
~~Full Analysis~~	~~All subjects who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data~~
Per Protocol	All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data ~~(Full Analysis Set)~~ minus subjects with protocol deviations that lead to exclusion
~~Unsolicited Safety~~	~~All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs~~

10.3.3. Immunogenicity analysis

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 **Exposed** ~~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 the first vaccination**)*
Secondary	*(US and ex-US data to be considered pooled, then separately* **for the first vaccination)** **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.** • **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.**

10.3.4 Safety Analysis

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 ~~(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 ~~as well 180 day~~ follow up is for SAE visit 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 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.

Endpoint	Statistical Analysis Methods
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-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 ~~(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 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. 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). 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.

10.4 Sequence of analysis

- **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.**
- **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 ~~analysis~~ 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.** ~~(D181) are available. Any available tertiary endpoints will also be analyzed in this step. Individual listings will only be provided at this stage.~~ An integrated clinical study report containing all available data will be written and made available to the investigators

12.5.7.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs during 7 days following administration of **each** ~~the~~ dose **vaccination** of study vaccine(s) (Day 1 to Day 7 **post primary vaccination and Day 1 to Day 7 post 2nd vaccination**) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Overall Rationale for Amendment 5: This study has been amended to align the physical exam and vital signs throughout the study with the eCRF. In addition, several administrative changes in personnel and minor edits to the protocol are included.

Detailed description of Protocol Amendment

Contributing authors

- PPD
  PPD
- PPD Clinical **Research Development Lead**~~Expert~~
- PPD, Safety Physician
- PPD **, Safety Scientist**

2.0 Schedule of Activities (SoA)

Type of contact	Screening	Visit 1	Visit 2	Visit 3	Phone Contact 1	Visit 4	Visit 5	Phone Contact 2	Visit 6	Phone Contact 3
Pre-vaccination body temperature and heart rate		•					•			
Pre-vaccination vital sign readings[4]							•			

[2] Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) measured after at least 10 minutes of rest.

Screening: Physical exam, vital signs (blood pressure, heart rate and respiratory rate, temperature), and weight, height and BMI will be recorded in the eCRF.

Visit 1: History directed physical exam will be performed and the vital signs will be recorded in the eCRF

Visit 2 Physical examination will be performed only if deemed necessary by the investigator. If performed, only vital signs (blood pressure, heart rate and respiratory rate) will be required recorded in the eCRF

Visit 3: Physical examination will be performed only if deemed necessary by the investigator.

Visit 4: Perform history directed physical exam will be performed and vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF. Weight, height and BMI should also be recorded in the eCRF.

Visit 6: Physical examination will be performed only if deemed necessary by the investigator.

~~*Weight, height and BMI will only be collected at Screening and V4. Physical examination at Visit 2, Visit 3, and Visit 4 will be performed only if deemed necessary by the investigator. For Visit 1 and Visit 2 (if performed), only vital signs will be collected in the eCRF.*~~

[4]**Pre-vaccination vital signs: At Visit 5, the pre-vaccination vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF**

8.3.3 Physical Exam

- Any vital signs measured at Visit 2 [Day 8] **and Visit 5 [2nd Vaccination]** should be recorded in the eCRF.

8.3.6 Pre-Vaccination Vital Signs

Pre-vaccination vital signs: At Visit 5, the pre-vaccination vital signs (blood pressure, heart rate and respiratory rate, temperature) will be recorded in the eCRF.

9.1 Discontinuation from the study

*In case a subject is withdrawn from the study because she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject~~*subject's parent(s)/LAR(s),*~~ in the eCRF.

12.4.3 Informed consent process

~~*For subjects who become legally emancipated during the course of the study, e.g. become of the legal age of consent, re-consent is sought in accordance with local laws and regulations. The subject can provide consent by signing an ICF, similar to that provided to the parent(s)/LAR(s) at the study start, which summarises the study and includes a consent statement and documents that the subject agrees to continue participating in the study.*~~

A copy of the ICF(s) must be provided to the subject.~~*or the subject's parent(s)/LAR(s).*~~

~~*The study investigator is encouraged to obtain assent from the minor in addition to the consent provided by the LAR(s) when a minor is able to give assent to decisions about his/her participation in a study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.*~~

Overall Rationale for Amendment 6: This study has been amended to include a clarification in the Exclusion criteria section to align with Protocol section 7.5.2 and reflect the flexibility of reducing the interval between administration of a coronavirus disease 2019 (COVID-19) vaccine and the RSV maternal vaccine. Also, several administrative changes in personnel and minor edits to the protocol are included.

Detailed description of Protocol Amendment 6

Contributing authors (Cont.) PPD PPD, Study Delivery Lead

6.4.2 Prior/Concomitant therapy for extension

Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or Prescribing Information and according to the local governmental recommendations.

8.5.4 Reporting of serious adverse events, pregnancies, and other events

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
Pregnancies	2 weeks*	Paper pregnancy notification report/electronic pregnancy report	~~2 weeks~~ ***24 hours****	electronic pregnancy report

8.5.5.1 Contact information for reporting of serious adverse events (SAEs), pregnancies and study holding rules

24/24 hour and 7/7-day availability:

GSK Clinical Safety & Pharmacovigilance
Outside US & Canada sites:
Fax: +32 2 656 51 16 or +32 2 656 80 09
Email address: ~~Rix.CT-safety-vac@gsk.com~~ ***PV.ICSRManagement@gsk.com***

12.5.8.4 Completion and transmission of pregnancy reports to GSK

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN ~~2 WEEKS~~ ***24 HOURS***.

8.3.2 Medical and vaccination history

Significant medical conditions and vaccinations that occurred during the C1-V4 will be reviewed during the screening for the second vaccination and reported as medical history ***and concomitant medications, respectively.***

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Reason for signing: Approved	Name: Joon Hyung Kim Role: Approver Date of signature: 14-Apr-2021 19:05:50 GMT+0000

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