GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated mothers
eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
Scope:	All analyses for the primary and secondary objectives of the study.
Date of Statistical Analysis Plan	Final: 29 October 2019 Amendment 1 Final: 10 March 2020 Amendment 2 Final: 29 May 2020 ***Amendment 3 Final: 02 November 2020***

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

CONFIDENTIAL

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean of ratio
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
LRTI	Lower Respiratory Tract Illness
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NB	Newborn
PD	Protocol Deviation
PPS	Per-Protocol Set
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SPM	Study Procedures Manual
SR	Study Report
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULOQ	Upper Limit of Quantification

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29 OCT 2019	first version	Final: 09 JUL 2019
10 MAR 2020	Amendment 1	Amendment 1: 27 JAN 2020
29 MAY 2020	Amendment 2	Amendment 2: 19 MAY 2020
02 NOV 2020	**Amendment 3**	**Amendment 3: 30 SEP 2020**

Table below lists main changes in the SAP amendment 3 and their rationale

Section # and Name	Description of Change	Brief Rationale
7.1.2 Second analysis 7.1.3 Third analysis Section 3, table 2	Observer blind removed following 2nd analysis	After the second analysis, the study will not be considered observer blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Primary Safety objectives	Primary Safety endpoint(s)
To evaluate the safety and reactogenicity of a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery	Occurrence of solicited administration site and systemic events during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).
	Occurrence of any hematological (complete blood count with differential and platelet count) or biochemical (alanine amino-transferase, aspartate amino-transferase, creatinine, blood urea nitrogen) laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs (MAEs) from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery (Visit 6).	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.*
To evaluate the safety of the study vaccine, including neonatal AEs of special interest, in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 weeks after birth.	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia.* Occurrence of SAEs, AEs leading to study withdrawal and MAEs from birth up to 6 weeks after birth.

Primary Immunogenicity objectives	**Primary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects at Day 31 and at Delivery.	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).
To evaluate RSV-specific antibody levels in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine at birth j	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained).
To evaluate the transfer of RSV-specific antibodies from maternal subjects vaccinated with a single IM dose of study vaccine to their infants at the time of delivery.	The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations *or an infant blood sample collected within 3 days after birth (if no cord blood sample can be obtained).
Secondary Safety objectives	**Secondary Safety endpoints**
To evaluate the safety of a single IM dose of study vaccine in maternal subjects, up to 6 months after delivery	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs, and AEs leading to study withdrawal.
To evaluate the safety of the vaccine in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 1 year of age	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs.
To estimate the incidence of RSV-associated, medically attended RTIs (MA-RTIs) in maternal subjects vaccinated with a single IM dose of study vaccine, from vaccination up to 6 months post-delivery (Visit 8).	Occurrence of RSV-associated MA-RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)
To estimate the incidence of RSV-associated lower respiratory tract illness (LRTI), severe LRTI and very severe LRTI and RSV-associated hospitalization in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, from birth up to 6 months of age.	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions).

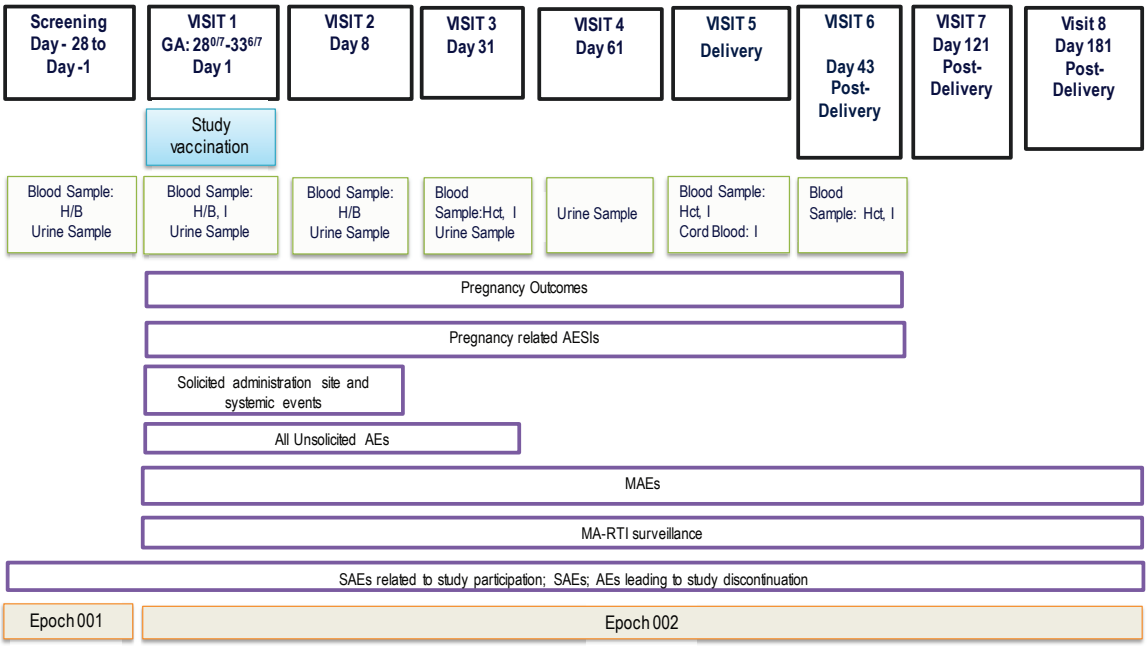
Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibodies against RSV-A at Day 43 after Delivery (Visit 6).	RSVPreF3 IgG-specific antibody concentration Neutralizing antibody titers against RSV-A Measured on the blood sample collected at Day 43 post- delivery (Visit 6).
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSV-B neutralizing antibodies at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).	Neutralizing antibody titers against RSV-B Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).
To evaluate RSV-specific antibodies in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 months after birth.	RSVPreF3 IgG-specific antibody concentration Neutralising antibody titres against RSV-A Neutralising antibody titres against RSV-B For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective). For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to treatment study intervention.
Tertiary objectives: To further evaluate the humoral response to the RSV maternal vaccine, which may include RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. To evaluate the presence of other respiratory viruses in nasal swabs collected from maternal subjects and their infants (via an Allplex Respiratory Viruses Panel or alternative, performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples.)	

*Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with GAIA assessment and level of diagnostic certainty when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category."

3. STUDY DESIGN

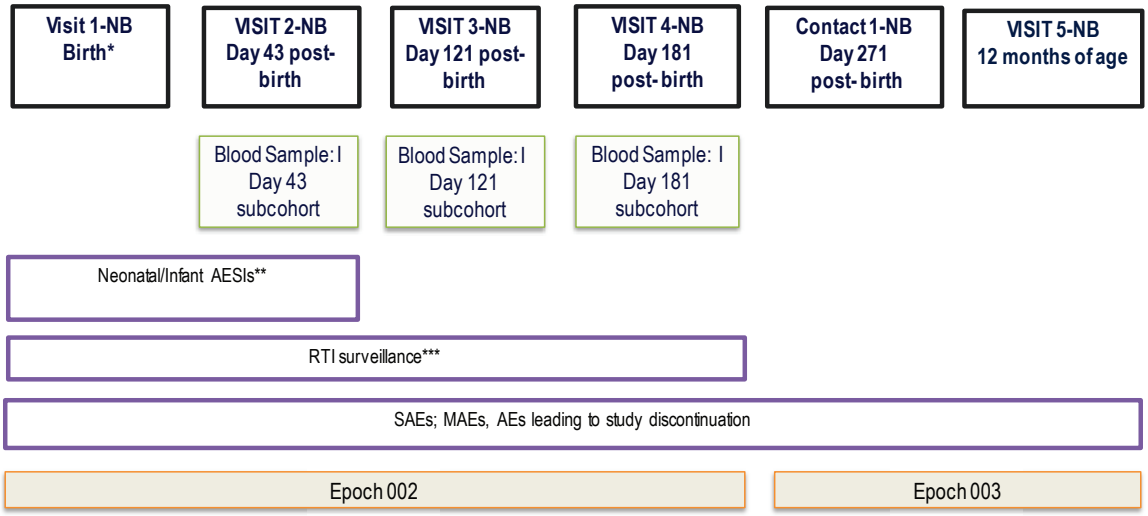
Figure 1 and Figure 2 provide overviews of the study design for maternal and infant subjects, respectively.

Figure 1 Overall design – maternal subjects



H/B= hematology/biochemistry, Hct- hematocrit; I= humoral immune response
If Screening blood sample collected ≤ 15 days before Visit 1, hematology/biochemistry not required at Visit 1
Subjects will be vaccinated year-round and will not be limited to seasonal enrolment
*Pregnancy-related AESIs identified after Day 43 will continue to be reported as such.

Figure 2 Overall design– infant subjects



NB = Newborn; I=humoral immune response: infants will be randomized 1:1:1 to one of the 3 subcohorts shown.
*Blood sample to be collected within 3 days after birth **ONLY** if a cord blood sample is not collected
**Neonatal AESIs identified after Day 43 (e.g., congenital anomalies) will continue to be reported as such.
***Infant subjects' parent(s)/LAR(s) will be contacted at least monthly to ensure RTI eDiary compliance.
Safety and disease surveillance data collected *after* Visit 4-NB will be reported in the database *in Epoch 003*.

- Study Type: self-contained.
- Experimental design: Phase II, observer-blind, randomised, placebo controlled, multi-centric, multi-country study with 3 parallel groups.
- Study Duration: Approximately 9 months (including the screening visit) for participating pregnant women; approximately 1 year after birth for participating infants.
- Control: Placebo.
- Epochs 001, 002 and 003 begin and end as described in Table 2.
- Blinding is as described in Table 2.
- Randomized intervention allocation: ***Up to*** 300 eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio) using an automated internet based system (SBIR).The system's randomisation algorithm will use a minimisation procedure accounting for maternal age at the time of vaccination (≥18 and <35 years of age or ≥ 35 years of age), gestational age at the time of vaccination ($28^{0/7}$-$31^{0/7}$; $31^{1/7}$-$33^{6/7}$) and center. Minimisation factors will have equal weight in the minimisation algorithm.
- Study (intervention) groups are described in Table 2

Table 2 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study (Amended 02-NOV-2020)

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Intervention name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)***	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	***Up to*** 100	18 – 40 years	RSVPreF3_60	BS1_60	***Up to 33***	RSVMAT60_BS1	●	●	●
				BS2_60	***Up to 33***	RSVMAT60_BS2		●	
				BS3_60	***Up to 33***	RSVMAT60_BS3		●	
RSV MAT 120	***Up to*** 100	18 – 40 years	RSVPreF3_120	BS1_120	***Up to 33***	RSVMAT120_BS1	●	●	●
				BS2_120	***Up to 33***	RSVMAT120_BS2		●	
				BS3_120	***Up to 33***	RSVMAT120_BS3		●	
Control	***Up to*** 100	18 – 40 years	Control	BS1_C	***Up to 33***	Control_BS1	●	●	●
				BS2_C	***Up to 33***	Control_BS2		●	
				BS3_C	***Up to 33***	Control_BS3		●	

M=maternal subject; I=infant; Control = Placebo; Blood sampling subcohorts are abbreviated "BS1;" "BS2;" BS3" and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.

*** After the second analysis, the study will not be considered observer blind as the investigator brochure will be updated to include safety information presented by treatment group. This could lead to inadvertent unblinding of investigators and site staff to some subjects' treatment assignments. The subjects themselves will remain blinded throughout their participation in the study.**

- Data collection: standardized Electronic Case Report Form (eCRF). Electronic diaries (e-diaries) for solicited event data, and notifications regarding occurrence of unsolicited events (including medically attended events and SAEs), and symptoms of respiratory tract illnesses in infant subjects.
- Safety monitoring: This study will be monitored by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee (IDMC) external to GSK. The analyses for IDMC safety evaluations will be described in a separate SAP for IDMC.

4. ANALYSIS SETS

4.1. Definition

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

4.1.1. Maternal Subjects

	Description
Analysis Set	**Maternal subjects**
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form.
Exposed	All maternal subjects who received at least 1 dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Full Analysis	All maternal subjects *in the Exposed set* who have post-vaccination immunogenicity data.
Per Protocol	All maternal subjects who received at least 1 dose of the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.
Unsolicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All maternal subjects ***in the*** Exposed Set who have solicited safety data

4.1.2. Infant subjects

	Description
Analysis Set	
Exposed	Infants live-born to exposed maternal subjects, whose parents/LARs completed the informed consent process and signed the informed consent form
Full Analysis	All infant subjects in the Exposed set who have post-delivery/birth immunogenicity data.
Per Protocol	All infant subjects in the Full Analysis set minus those who (a) were born less than 4 weeks post- maternal subject vaccination and/ or (b) have protocol deviations that lead to exclusion.
Unsolicited Safety	All infants in the exposed set for whom unsolicited AEs /not having unsolicited AEs are reported

4.1.3. Randomized Set

Randomized set will include all maternal subjects who are randomized and all of their randomized infants. The allocation in a group is done as function of the randomized intervention. Please note this set was not included in the protocol, but will be used later in one summary analysis, so it is added here for clarification.

4.1.4. Full Analysis Set

Full analysis set will be defined by time point. For infants, it will include all of the infants in the Exposed Set who have immunogenicity data at the corresponding time point after birth.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

Infants: Code 1030 (Study vaccine not administered at all, carry forward elimination from mother to infant), 800 (Fraudulent data), code 900 (invalid informed consent) and code 901 (invalid informed consent due to mother) will be used for identifying infants eliminated from ES

4.2.2. Elimination from Full Analysis Set (FAS)

4.2.2.1. Excluded subjects from FAS of maternal subjects

A maternal subject will be excluded from the FAS analysis under the following conditions

Table 3 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.

4.2.2.2. Excluded subjects from FAS of infant subjects

An infant subject will be excluded from the FAS analysis under the following conditions

Table 4 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all - mother	All	Safety, immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth* Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

#Carry forward elimination from mother to infant
Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
*cord blood sample or blood sample collected within 3 days after birth if cord blood sample is not collected

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

4.2.3.1. Excluded subjects from Per-protocol analysis set of maternal subjects

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

Table 5 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-40 years Gestational age at vaccination - 28 0/7 – 33 6/7	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 31, check the interval from vaccination to day 31 BS = ***20 –45*** days; • For PPS at Delivery, check the interval from delivery to delivery BS = ***(-1) – (+3)*** days; • For PPS at Day 43 post-delivery, check the interval from delivery to day 43 post-delivery BS = 40 – ***60*** days	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

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

4.2.3.2. Excluded subjects from Per-protocol analysis set of infant subjects

An infant subject will be excluded from the PPS analysis under the following conditions

Table 6 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent - infant	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
1041#*	Maternal administration of concomitant vaccine(s) forbidden in the protocol up to Delivery	All	Immunogenicity
1050#	Maternal randomisation failure	All	Immunogenicity
1060#	Maternal randomisation code was broken	All	Immunogenicity
1070#	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070#	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070#	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070#	Study treatment administered while contraindicated	All	Immunogenicity
1080#	Vaccine temperature deviation	All	Immunogenicity
1090#	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) - infant	All	Immunogenicity
2011#	Protocol violation (inclusion/exclusion criteria) - mother	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2041#*	Maternal administration of any medication forbidden by the protocol up to Delivery	All	Immunogenicity
2041#*	Device, excluded by the protocol, was administered by mother up to Delivery	All	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2050#*	Maternal intercurrent medical conditions which are exclusionary as per protocol up to Delivery	All	Immunogenicity
2060#*	Maternal concomitant infection related to the vaccine which may influence immune response up to Delivery	All	Immunogenicity
2070#*	Maternal concomitant infection not related to the vaccine but may influence immune response up to Delivery	All	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule – infant: • For infants without cord blood, check the interval from birth to Visit 1-NB birth BS = 0 – 3 days; • For PPS at Day 43 post-birth, check the interval from birth to Day 43 BS = ***28 – 60*** days; • For PPS at Day 121 post-birth, check the interval from birth to Day 121 BS = ***110 –140*** days; • For PPS at Day 181 post-birth, check the interval from birth to Day 181 BS = 165 ***– 200*** days	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2120.Vx*	Obvious incoherence or abnormality or error in data	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
3100	Delivery happens less than 4 weeks post-vaccination.	All	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
#Carry forward elimination from mother to infant
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
BS- Blood Sample.

4.2.4. Elimination from unsolicited and solicited safety set

4.2.4.1. Excluded subjects

4.2.4.1.1. *Unsolicited safety set*

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.4.1.2. *Solicited safety set*

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

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1while the study specific data derivation rules and stat methods are described in section 9.

5.1. Demography

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

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

For all maternal subjects, demographic characteristics (e.g., age at vaccination (18 - <35; ≥ 35 years), gestational age at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), geographic ancestry will be summarized by group using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics.

For their infants, demographic characteristics (e.g., gestational age at time of delivery (> 37 weeks; ≤ 37 weeks), sex, weight, length, head circumference, geographic ancestry, apgar score), and lifestyle characteristics (e.g., living environment, household composition, breastfeeding, passive smoking and extent of contact with children less than 6 years of age) will be summarised by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

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

5.1.2. Additional considerations

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

Subgroup analysis for demographic characteristics by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth (> 37 weeks or ≤ 37 weeks) for infant subjects will also be performed on Enrolled Set, ES or PPS.

Subject disposition will be summarized by group using descriptive statistics:

- Number of maternal subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- Number of infants enrolled and withdrawn including withdrawal reasons will be tabulated by group, by sub-cohort within each group and overall.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set. The parameters include but may not be limited to systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiratory rate, height, weight and body mass index.

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

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

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

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol

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

	Primary Immunogenicity Endpoints	**Statistical Analysis Methods**
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).	For each assay, at each timepoint and by study group and age category (18 - <35 years; ≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline, at day 31 and at delivery will be explored using scatter plots of individual values. Between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A will be performed at Day31 and at Delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, age category at vaccination, center and the interval between vaccination and delivery as covariates if needed.

Primary Immunogenicity Endpoints		Statistical Analysis Methods
Cord blood/ placental transfer	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A	For each assay, the following analysis will be performed by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations (GMCs) will be tabulated with 95% CI and represented graphically. • The distribution of RSV-A and RSVPreF3 IgG-specific antibody titres/concentration from cord blood will be tabulated • For each assay, relationship between maternal antibody titers/concentrations and infant antibody titers/concentrations at the time of delivery will be evaluated graphically using scatter plots of individual results.
	• The ratio between cord blood and maternal RSVPreF3 IgG-specific antibody concentrations All 3 endpoints measured on blood samples collected from maternal subjects at delivery and either cord blood, or (if cord blood cannot be collected) infant blood samples collected within 3 days after birth	• Geometric mean of placental transfer will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ≥ 1 will be tabulated with exact 95 % CI by study group. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks; ≤ 37 weeks), age category at vaccination, center and the interval between vaccination and delivery as covariates if appropriate. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at delivery will be explored using scatter plots of individual values.

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and • Neutralizing antibody titers against RSV B For RSV-A: Measured on the blood sample collected Day 43 post-delivery (Visit 6). • For RSV-B: Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3),, at Delivery (Visit 5) and at Day 43 post delivery (Visit 6).	For each assay, at each timepoint and by study group and age category (18 - <35 years ;≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at baseline, at day 31, at delivery and at day 43 post-delivery will be explored using scatter plots of individual values. In addition, between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A and RSV-B will be performed at Day31, at Delivery and at Day 43 post-delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery if available as covariates if needed.
Infant subjects	• RSVPreF3 IgG-specific antibody concentration • Neutralising antibody titres against RSV-A • Neutralising antibody titres against RSV-B For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of	For each assay, at each timepoint and by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. In addition, analyses will include exploratory evaluation of the persistence of RSV specific antibodies in infants through time, and half-life analysis modelling of logarithm transformed RSV antibody concentrations/titers over time. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery, and on blood samples collected at 6 weeks, 4 months and 6 months post-birth using a mixed effect model on the logarithm10 transformation of the concentrations/titers,

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
	these 3 cohorts at the time of maternal randomization to intervention For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective).	including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks ; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate and needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at delivery will be explored using scatter plots of individual values.

5.2.2. Additional considerations

Before unblinding occurs, the immunogenicity analysis will only be performed on Exposed Set. At the time of final analysis, the immunogenicity analysis will be performed on PPS.

5.2.2.1. Distribution analysis

RSV-A neutralizing antibody titers and RSV-B neutralizing antibody titers:

- Number and percentage of subjects with titers <128, ≥128, ≥256, ≥512, ≥1024, ≥2048, ≥4096, ≥8192 and >=16384 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 2, 4, 6, 8, 10 and 12 by pre-vaccination category (< 128, ≥128 and <256, ≥ 256 and <512, ≥ 512 and <1024, ≥1024 and <2048, ≥ 2048 and <4096, ≥ 4096 and <8192, ≥8192 and <16384) will be tabulated.

RSVPreF3 IgG-specific antibody concentrations:

- Number and percentage of subjects with concentrations <2048, ≥2048, ≥4096, ≥8192, ≥16384, ≥32768, ≥65536, ≥131072 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 4, 6, 8, 10, 12, 14 and 16 by pre-vaccination category (< 2048, ≥2048 and <4096, ≥ 4096 and <8192, ≥ 8192 and <16384, ≥16384 and <32768, ≥ 32768 and <65536, ≥ 65536 and <131072, ≥131072) will be tabulated.

The thresholds for distribution tables of titres and concentrations and fold increase may be further adjusted at analysis as needed.

In addition, to assess the effect of the interval between vaccination and delivery on the antibody transfer, geometric mean of RSV-A neutralizing antibody titers, RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers from cord blood (or blood drawn from infants within 3 days after birth) will be tabulated with different categories of time (in weeks) from vaccination to delivery. This analysis will be performed for infants born at gestational age <37 weeks and those born at gestational age >=37 weeks. Associated scatter plots may also be provided as needed.

5.2.2.2. Ratio of fold increase analysis

Fold increase of RSVPreF3 IgG-specific antibody concentrations over fold increase of RSV-A neutralizing antibody titers (ratio of fold increase post- over pre-vaccination) will be tabulated using descriptive statistics. This analysis will include calculation on:

- Geometric mean ratios with corresponding 95% CIs of RSVPreF3 IgG-specific antibody concentration over RSV-A neutralizing antibody titers at pre-vaccination for each group and
- Geometric mean ratios with corresponding 95% CIs of fold increase post/pre (Day 31, Delivery and Day 43 post-delivery/Day 1) between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody titers for each group.

Similar analysis will be performed between RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers.

5.2.2.3. Between group analysis

This analysis is exploratory.

For the analysis of maternal subjects at each time point (Day 31, Delivery, and Day 43 post-delivery), the model will be explored and fitted via the proc mixed procedure according to the following code:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group ges_age_cat age_cat center;
  MODEL log_val = baseline group ges_age_cat age_cat
inter_vac_del center /ddfm=kenwardroger outp = pred;
  /*RANDOM Subjid*/;
   LSMEANS group/pdiff cl alpha=0.05;
RUN;
```

where log_val represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, group indicates the study group, ges_age_cat is the gestational age category at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), age_cat is the age category at vaccination (18 – <35 years and ≥35 years), inter_vac_del is the interval between vaccination and delivery (days). The inclusion of age category at vaccination, interval between vaccination and delivery, and center in the model depends on the availability of the variable (inter_val_del may not be available at Day 31 analysis) and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

For the analysis of infants at each time point (cord blood at Delivery, Day 43 post-birth, Day 121 post-birth, and Day 181 post-birth), similar model will be explored:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group center ges_age_cat ges_age_birth;
  MODEL log_val = baseline group ges_age_cat /*inter_vac_del*/
ges_age_birth center /ddfm=kenwardroger outp = pred;
 /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
   RUN;
```

Baseline is pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, ges_age_birth is gestational age category at birth (> 37 weeks; ≤ 37 weeks) for infants. With the inclusion of gestational age category at vaccination (ges_age_cat) in the model, this categorical variable ges_age_birth provides similar information as continuous variable inter_vac_del, therefore the inclusion of either variable in the model could be adjusted according to the analysis needs.

The ratio of GMTs/GMCs between vaccine groups and the corresponding 95% CI will then be constructed by exponentiating the mean difference and its confidence interval between vaccine groups on the logarithm10 scale estimated from the model. Summary tables will show adjusted GMT/GMC for vaccine groups, and ratios of GMTs/GMCs between vaccine groups along with the 95% CI.

If deemed necessary, an analysis of variance model for repeated measures will be fitted to assess the mean profile in each group over time for both maternal and infant subjects separately. Below is the sample SAS code for the analysis of maternal subjects, and similar codes could be explored for the analysis of infants.

```
PROC MIXED data=sero;
    CLASS subjid group visit age_cat center ges_age_cat;
    MODEL log_val = baseline group | visit age_cat ges_age_cat
inter_vac_del center/ddfm=kenwardroger outp = pred;
    RANDOM subjid;
    /*REPEATED visit/subject=subjid(group) type=un;*/
    LSMEANS group*visit/pdiff cl alpha=0.05;
RUN;
```

Summary tables will present adjusted GMT/GMC with 95% CI for each group at each timepoint.

5.2.2.4. Persistence and Half-life analysis of antibody level over time for infant subjects

This analysis is exploratory.

The decay of infant antibody levels over time will be analysed by a linear regression of the logarithm transformed of antibody levels. This analysis will be performed on PPS for infants in RSV vaccine group in terms of RSV-A neutralizing antibody titers, RSV-B neutralizing antibody titers and RSVPreF3 IgG-specific antibody concentrations.

A true, natural decay curve will be explored by stochastically reducing the sample to uninfected subjects only. The following steps will be taken to identify infected subjects (confirmed and suspected) to be eliminated from the sample:

- STEP 1: Infants with an RSV positive nasal swab during the study before time of blood sampling will be eliminated from the analysis because RSV infection may have contributed to their antibody levels which may no longer represent what was passively transferred from the mother.
- Infants whose mothers had an RSV positive nasal swab before or up to the time of delivery will be eliminated from the analysis. Maternal infection may contribute to post-vaccination increase in the levels of maternal antibodies, leading to higher placental antibody transfer to the fetus/infant, which would not reflect the effect of vaccination alone.
- STEP 2: Run the model and compute expected value based on the decay curve
- STEP 3: Subjects with an antibody titer at the blood sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected and then eliminated and the decay curve refined.
- STEP 4: Step 3 is repeated up to 5 times until the most accurate decay curve is established.

The natural decay of antibody level will be determined using linear regression between the logarithm transformed antibody level (Y) and time t (age in days) with subject as a random effect. All infants have RSV neutralizing antibodies measured at birth (cord blood) or within 3 days after birth, and each infant in PPS sub-cohort will have blood sampling for RSV neutralizing antibodies at one of the following time points: Day 43 post-birth, Day 121 post-birth or Day 181 post-birth. Therefore, in the natural decay model, each infant will have maximum 2 RSV neutralizing antibodies measures, one at birth or within 3 days after birth and the other at Day 43 post-birth, Day 121 post-birth or Day 181 post-birth depending on the sub-cohorts where the infants are.

The following SAS code will be explored:

```
PROC MIXED DATA=<filename>;
  CLASS PID;
  MODEL LOG_Y = t /s outp=pred;
  RANDOM Int t / sub=PID type=UN G GCORR;
RUN;
```

The choice of correlation structure and other parameters may be further adjusted according to the data and analysis needs.

The predicted value will be computed using the following formula

$$A_t = A_0 \exp(-K_e t)$$

where, A_t and A_0 are antibody titres at times t and zero, respectively, K_e is the constant rate of antibody change with time, defined as the estimate of model.

In addition, the half-life ($t_{1/2}$) of antibody (i.e. the time required for titre to decrease by one-half) will be displayed using the following equations of declining antibody titre:

$$\text{when } A_t = \tfrac{1}{2} A_0$$

$$t_{1/2} = 0.693 / K_e$$

A summary table will be prepared to show the number of infants included in the model, the model estimate of the antibody decay rate, and the half-life of the antibody.

In case cord blood samples are missing in 20% or more of infants in a single study group, separate analysis for infants with cord blood and infants with a blood sample within 3 days after birth will be performed.

5.2.2.5. ROC analysis (dose characterization)

This analysis is exploratory and complementary to traditional data analysis methods comparing post-vaccination immune responses among vaccine groups and will be performed on the PPS only if deemed necessary.

If immune response between active vaccination groups can't be differentiated using traditional approach, additional analyses using a generalized ROC (Receiver Operating Characteristics) method [Yu, 2018] will be performed for both RSV-A neutralizing antibody titers and RSVPreF3 IgG specific antibody concentrations at Day 31 and Delivery, and other timepoints if needed.

Two ROC Methods will be explored:

- ROC-P (ROC of post-dose levels) method: Post-vaccination antibody levels from 2 RSV vaccine groups (RSV MAT 60 and RSV MAT 120) will be pooled and used as a reference distribution.
- ROC-B (ROC relative to baseline) method: Overall pre-vaccination antibody levels from 2 RSV groups (RSV MAT 60 and RSV MAT 120) will be used as a reference distribution.

Different percentile (0% to 100%) thresholds from the reference distribution will be obtained. The percentage of subjects with post-vaccination antibody level higher than or equal to the percentile thresholds from the reference distribution will then be calculated for each vaccine group.

A figure will be provided showing the ROC curve with x-axis the percentile of the reference distribution and y-axis the percentage of subjects in each vaccine group with post-vaccination antibody levels higher than or equal to the percentile threshold of the reference distribution.

A summary table will be provided on the thresholds of e.g. 25%, 50% and 75% percentiles of the reference distribution and the percentage of subjects in each vaccine group with post-vaccination antibody level higher than or equal to these percentile thresholds.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in **maternal subjects** will include summaries by study group and age category (18 - < 35 years of age; ≥35 years of age; overall) of hematology and biochemistry results by grade and per time point, solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant subjects** will include summaries by study group and gestational age at birth (> 37 weeks or ≤ 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

All safety analyses will be performed on the Solicited Safety or Exposed sets.

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal subjects	Occurrence of Solicited administration site and systemic events that occur during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	The number and percentage with exact 95% CI of maternal subjects reporting each **Solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day (days 1 to 7) follow-up period after vaccination will be tabulated by maximum intensity per subject for each study vaccine group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of maternal subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 7-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).
	Occurrence of any protocol-specified hematological or biochemical laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)	The number and percentage of subjects with hematology and biochemistry results outside central laboratory normal ranges will be tabulated to show Day 8 versus baseline. The maximum grading as described in [Sheffield, 2013] and in the ***SPM*** from Screening up to Day 8 will also be tabulated.

	Primary Safety Endpoints	Statistical Analysis Methods
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	The number and percentage of maternal subjects with **unsolicited** symptoms within 30 days after vaccination with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 related unsolicited symptoms and for MAEs. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 30-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for MAEs.
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).	The number and percentage of maternal subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). Outcomes are listed in Section 2.	The number and percentage of maternal subjects with each pregnancy outcome will be tabulated with its exact 95% CI by group. By subject listings of adverse pregnancy outcomes will be prepared but will not be released until the final, unblinded analysis has been completed.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post delivery; Visit 6**).** These events are listed in Section 2**.**	The number and percentage of maternal subjects with each pregnancy-related AESI will be tabulated with its exact 95% CI by group. By subject listings of pregnancy-related AESIs will be prepared but will not be released until the final, unblinded analysis has been completed.

Primary Safety Endpoints		Statistical Analysis Methods
Infant subjects	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These events are listed In Section 2. Occurrence of SAEs, AEs leading to study withdrawal and medically attended AEs from birth up to 6 weeks after birth.	The number and percentage of infant subjects with each neonatal AESI will be tabulated with its exact 95% CI by group. By-subject listings of neonatal AESIs will be prepared, but will not be released until the final, unblinded analysis has been completed. The number and percentage of infant subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
Secondary Safety Endpoints		**Statistical Analysis Methods**
Maternal subjects	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs and AEs leading to study withdrawal. Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)	The number and percentage of maternal subjects with at least one SAE, MAE from Day 1 up to 6 months after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared (but will not be released until the final, unblinded, analysis has been completed). The number and proportion of subjects with at least one RSV-associated MA- RTI (with 95 % CI) will be calculated and tabulated.
Infant subjects	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and medically attended AEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs	For each category: - SAE, - MAEs The number and proportion of infant subjects who experienced at least one event from birth up to 6 months after birth and the number and proportion of infant subjects who experienced at least one event from birth up to 1 year after birth will be tabulated with 95% CI by group. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared.
	From birth to 6 months after birth (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions in Section 4.2.6 in the protocol)	For each category: - RSV-associated LRTI, - Severe LRTI, - Very severe LRTI - RSV-associated hospitalization The number and proportion (with 95% CI) of subjects with at least one event will be calculated and tabulated by group.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

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

Table 7 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F (with 1 decimal) Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache		
Fatigue	0	Normal
Nausea	1	Mild: Easily tolerated
Vomiting	2	Moderate: Interferes with normal activity
Diarrhea	3	Severe: Prevents normal activity
Abdominal pain		

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

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

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

5.3.2.2. Exclusion of implausible solicited Event

Some local and systemic events will be directly measured by the subject and will be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 8 Implausible Solicited Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	Measurements < 0 mm For subjects ≥ 6 years: ≥ 900 mm
Swelling	Measurements < 0 mm For subjects ≥ 6 years: ≥ 500 mm

5.3.2.3. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set

5.3.2.4. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Nausea	Nausea	10028813
Vomiting	Vomiting	10047700
Diarrhea	Diarrhea	10012727
Abdominal pain	Abdominal pain	10000081
Headache	Headache	10019211

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

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

5.3.2.5. Analysis of RTI and LRTI

The analysis of RTI and LRTI will be performed on Exposed Set according to the case definitions in section 9.1.3. Separate listings of maternal MA-RTI and infant RTI/LRTI will be provided.

Further analysis with respect to the incidence of RSV LRTI by an exploratory case definition might be performed if deemed necessary.

5.3.2.6. Other analysis

Other safety analysis will be performed on Exposed Set.

For hematology and biochemistry lab results, the maximum grading as described in [Sheffield, 2013] and SPM will be used, see section 9.1.4 for details.

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination, up to 6 weeks post-delivery and up to 6 months post-delivery will be summarized by group. A listing will also be provided.

The number and percentage of infants taking concomitant medications from birth up to 6 weeks after birth, 6 months after birth and 1 year after birth will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

7.1.1. First analysis

The **first analysis** will be conducted after approximately 75 maternal subjects have completed Visit 3 (Day 31) and approximately 24 maternal subjects and their infants have completed Visit 5 / Visit 1-NB (Delivery/Birth).

By-study-group safety and immunogenicity analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

Immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.

Safety analyses will be performed by blinded treatment group, with the letters “A,” “B,” and “C” replacing treatment-specific group identifiers in all results summaries. Steps will be taken to minimize the risk of unblinding (e.g., events that happen in a single group will be masked by adding the same amount of counts to other groups). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.

Safety analyses will include all available data for:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

A report summarizing these ***safety and immunogenicity*** results will be prepared but will not be made available to investigators.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.2. Second analysis *(Amended 02-NOV-2020)*

The **second analysis** will be performed after approximately 24 maternal subjects and their infants have completed Visit 7 / Visit 3-NB (Day 121 post-delivery / birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results, at:

- Visit 1 (Day 1) and Visit 3 (Day 31).
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery).
- Visit 3-NB (Day 121 post-delivery).

By-study-group safety analyses will include the following data from those subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified). ***Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.***

Blinded SAE and AESI listings for all subjects will also be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations**.**

7.1.3. Third analysis *(Amended 02-NOV-2020)*

The **third analysis** will be performed after approximately 150 maternal and infant subjects have completed Visit 8/Visit 4-NB (Day 181 post-delivery/birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery);
- Visit 3-NB (Day 121 post-delivery)
- Visit 4-NB (Day 181 post-delivery)

By-study-group safety analyses will include the following data from all ***vaccinated*** subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified). ***Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.***

In addition, blinded SAE and AESI listings for all subjects will be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.4. Final analysis

The **final** analysis will evaluate all data pertaining to primary and secondary safety and immunogenicity endpoints. It will be performed by the GSK Biologicals biostatistics team when all primary and secondary endpoint data up to study end (last Visit 5-NB) are available.

Results will be presented in a clinical study report. This report will include results summarized by study group as well as individual (by subject) data /data listings, and will be made available to investigators.

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 clinical study report**.**

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

7.2. Statistical considerations for interim analyses

The first 3 analyses will be descriptive. Therefore, the conduct of these analyses has no impact on interpretation of study results.

8. CHANGES FROM PLANNED ANALYSES

To take a more practical approach, subgroup analysis of safety by age category at vaccination (18 - <35; ≥ 35 years) in maternal subjects will include summaries of pregnancy outcomes, pregnancy related AESIs, SAEs, MAEs and MA-RTIs.

Subgroup analysis of safety by gestational age at birth (> 37 weeks or ≤ 37 weeks) in infant subjects will include summaries of neonatal AESIs, MAEs, SAEs, and occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

Subgroup analysis on other safety summaries will be performed if deemed necessary.

Subgroup analysis of immunogenicity by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth ((> 37 weeks or ≤ 37 weeks) for infants will include analysis of GMT(C) and GMR calculation at each time point and geometric mean of placental transfer.

Subgroup analysis on other immunogenicity analysis will be performed if deemed necessary.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Data derivation

9.1.1. Gestational age at vaccination

Gestational age at vaccination in weeks for maternal subjects will be calculated based on estimated date of delivery and date of vaccination.

9.1.2. Immunogenicity

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

- For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
- For the between group assessments, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

The GMT/GMC and its 95% CI will be obtained by exponentiating the mean and its 95% CI of the log-transformed titres/concentrations. All CI computed will be two-sided 95% CI.

Placental transfer is defined as the ratio of RSVPreF3 IgG-specific antibody concentrations between cord blood (or blood sample from infants collected within 3 days after birth if cord blood is not available) and maternal blood sample at delivery (or within 3 days after delivery if blood sample is not collected during delivery).

9.1.2.1. Assay cut-offs for serology results

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

System	Component	Method	Unit	Cut-off *(LLOQ)*	*ULOQ*
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	ED60	18	***123535***
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	IU/mL	56	***217400***
Serum	RSVPreF3 IgG antibody concentrations	ELISA	EU/mL	*25*	***251 769***
Serum	RSV-B Neutralising Antibody	NEUTRALISATION	ED60	*30*	***138336***
Serum	***RSV-B Neutralising Antibody***	***NEUTRALISATION***	***IU/mL***	***44***	***171279***

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis, which would not lead to SAP amendment.

9.1.3. RTI and LRTI

Cases will be classified (during data analyses) according to the definitions that follow.

Table 9 MA-RTI case definitions for data analysis in maternal subjects

RSV-MA-RTI	Medically attended visit for RTI symptoms AND Confirmed RSV infection [1, 2]
RSV hospitalization	Confirmed RSV infection AND Hospitalized for acute medical condition [3]
All-cause MA- RTI	Medically attended visit for RTI symptoms

[1] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol
[2] RSV (nasal swab) sampling and testing as specified in Table 11 of the Protocol.
[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.
MA-RTI = Maternal, medically attended respiratory tract illness

Table 10 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection [4]
RSV-LRTI	History of cough OR difficulty in breathing [1] AND SpO_2 < 95%[2], OR RR increase [3] AND Confirmed RSV infection [4]
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%[2], OR lower chest wall in-drawing
RSV-very severe LRTI	Meeting the case definition of RSV-LRTI AND SpO2 < 90%[2], OR inability to feed OR failure to respond / unconscious
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing [1] AND SpO2 < 95% [2], OR RR increase [3]

Definitions based on [Modjarrad, 2016]
RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.
[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnea).
[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.
[3] RR increase defined as:
> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)
[4] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol
[5] RSV (nasal swab) sampling and testing as specified in Table 12 of the Protocol
[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose, wheezing or difficulty breathing with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed.

9.1.4. Hematology and Biochemistry parameters

The table below shows the toxicity grading during the second and third trimester of pregnancy based on [Sheffield, 2013]

Table 11 Laboratory values during the second and third trimester of pregnancy

Serum chemistries	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.8 mg/dL		0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
BUN	3.0-13.0 mg/dL		14.0-19.0	20.0-30.0	>30	Required dialysis
Haematology	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – gm/dL	9.7-14.8 g/dL		9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.6-14.8 x 1000cell/mm^3	High	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	0.9-3.9 x 1000cell/mm^3	High	>3.9-5.0	>5.0		
		Low	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.8-12.3 x 1000cell/mm^3		<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	155-409 x 1000 L^{-1}	Low	125-154	100-124	25-99	<25
		High	410-499	500-749	750-1000	>1000
Liver Function Tests	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	3-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate

Serum chemistries	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.9 mg/dL		1.0-1.2	1.3-1.6	1.7-2.5	>2.5 or required dialysis
BUN	3.0-11.0 mg/dL		12.0-19.0	20.0-30.0	>30	Required dialysis
Liver Function Tests	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	4-32 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-25 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Haematology	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – g/dL	9.5-15.0 g/dL		9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.9-16.9 x 1000cell/mm^3	High	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	1.0-3.6 x 1000cell/mm^3	High	>3.6-5.0	>5.0		
		Low	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.9-13.1 x 1000cell/mm^3		<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.4 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	146-429 x 1000 L^{-1}	Low	125-146	100-124	25-99	<25
		High	430-499	500-749	750-1000	>1000

Adapted from [Sheffield, 2013]
ULN: upper limit of normal.

Table below shows the toxicity grading for lab parameters that are not covered in [Sheffield, 2013] but calculated based on the references and guidance in [Abbassi-Ghanavati, 2009]

Laboratory Parameter	Grade 1	Grade 2	Grade 3
Hematocrit-2nd trimester N 30.0-39.0 (%)	27-29.9 39.1-42.9	24-26.9 43-46.8	≤ 23.9 ≥46.9
Hematocrit-3rd trimester N 28.0-40.0 (%)	25.2- 27.9 40.1-44	22.4-25.1 44.1-48	≤22.3 ≥48.1
Mean Corpuscular Volume MCV 2nd trimester N 82-97 (μm^3)	73.8-81.9 97.1-106.7	65.6-73.7 106.8-116.4	≤65.5 ≥116.5
Mean Corpuscular Volume MCV 3rd trimester N 81-99 (μm^3)	72.9-80.9 99.1-108.9	64.8-72.8 109-118.8	≤64.7 ≥118.9
RBC - 2nd trimester N 2.81 – 4.49	2.6-2.8 4.5-4.9	2.3 – 2.5 5.0-5.3	≤2.2 ≥5.4
RBC - 3rd trimester N 2.71-4.43	2.5-2.7 4.4-4.8	2.2 – 2.4 4.9-5.3	≤2.1 ≥5.4

9.2. Statistical Method

Study specific statistical methods for immunogenicity analysis are described in section 5.2.2.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event.

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. *Studies with electronic diaries*

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

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

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

10.1.3.8. Onset day

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

10.1.3.9. Duration of events

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

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

10.1.3.10. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.11. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

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

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

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

10.1.4.2. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.3. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document. Please note the protocol of this study was developed based on V17 template and the term ‘solicited administration site event’ and ‘solicited systemic event’ are used, however, at the development of the TFL TOC, only V16 standard catalog is available and still ‘solicited local adverse event’ and ‘solicited general adverse event’ are used in the TFL mocks per this standard.

11. REFERENCES

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Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments. Vaccine 2013; 31:4264-4273.

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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated mothers
eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
Scope:	All analyses for the primary and secondary objectives of the study.
Date of Statistical Analysis Plan	Final: 29 October 2019 Amendment 1 Final: 10 March 2020 ***Amendment 2 Final: 29 May 2020***

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

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMR	Geometric mean of ratio
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
LRTI	Lower Respiratory Tract Illness
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NB	Newborn
PD	Protocol Deviation
PPS	Per-Protocol Set
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SPM	Study Procedures Manual
SR	Study Report
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULOQ	Upper Limit of Quantification

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29 OCT 2019	first version	Final: 09 JUL 2019
10 MAR 2020	Amendment 1	Amendment 1: 27 JAN 2020
29 MAY 2020	***Amendment 2***	***Amendment 2: 19 MAY 2020***

Table below lists main changes in the SAP amendment 2 and their rationale

Section # and Name	Description of Change	Brief Rationale
Globally	Total number of maternal subjects / total number of infant subjects have each been changed to "up to 300." Total number of maternal subjects per group / total number of infant subjects per group have each been changed to "up to 100." Total number of infant subjects per blood sampling subcohort has been changed to "up to 33."	213 subjects were vaccinated and subsequent enrollment was halted due to COVID-19.
Section 3, Study Design, Figure 1	References to Gestational age have been removed at Visits 2, 3 and 4.	The gestational age range at each of these visits was provided as a guide only. It has created confusion, since the provided gestational age interval does not perfectly line up with the preferred visit day or allowed interval for the corresponding visits. Therefore the gestational age ranges previously provided have been removed.
Section 4.2.3 Elimination from Per-protocol analysis set Table 5, Elimination code 2090.Vx Table 6, Elimination code 2090.Vx	Allowed intervals for completion of some visits (or contacts) have been widened.	Visit windows have been widened to promote data collection and data integrity during special circumstances (such as COVID-19).
Section 7.1.1, First analysis	Updates the Sequence of Analysis section to indicate that the first safety analysis will be by study group (rather than in aggregate) and performed by an independent statistician	Per U.S. FDA request
Section 9.1.2.1	Updated the assay cut-offs	Assay cut-offs are available after the release of lab immunogenicity data

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Primary Safety objectives	Primary Safety endpoint(s)
To evaluate the safety and reactogenicity of a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery	Occurrence of solicited administration site and systemic events during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).
	Occurrence of any hematological (complete blood count with differential and platelet count) or biochemical (alanine amino-transferase, aspartate amino-transferase, creatinine, blood urea nitrogen) laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs (MAEs) from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery (Visit 6).	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.*
To evaluate the safety of the study vaccine, including neonatal AEs of special interest, in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 weeks after birth.	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia.* Occurrence of SAEs, AEs leading to study withdrawal and MAEs from birth up to 6 weeks after birth.

Primary Immunogenicity objectives	**Primary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects at Day 31 and at Delivery.	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).
To evaluate RSV-specific antibody levels in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine at birth j	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained).
To evaluate the transfer of RSV-specific antibodies from maternal subjects vaccinated with a single IM dose of study vaccine to their infants at the time of delivery.	The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations *or an infant blood sample collected within 3 days after birth (if no cord blood sample can be obtained).
Secondary Safety objectives	**Secondary Safety endpoints**
To evaluate the safety of a single IM dose of study vaccine in maternal subjects, up to 6 months after delivery	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs, and AEs leading to study withdrawal.
To evaluate the safety of the vaccine in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 1 year of age	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs.
To estimate the incidence of RSV-associated, medically attended RTIs (MA-RTIs) in maternal subjects vaccinated with a single IM dose of study vaccine, from vaccination up to 6 months post-delivery (Visit 8).	Occurrence of RSV-associated MA-RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)
To estimate the incidence of RSV-associated lower respiratory tract illness (LRTI), severe LRTI and very severe LRTI and RSV-associated hospitalization in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, from birth up to 6 months of age.	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions).

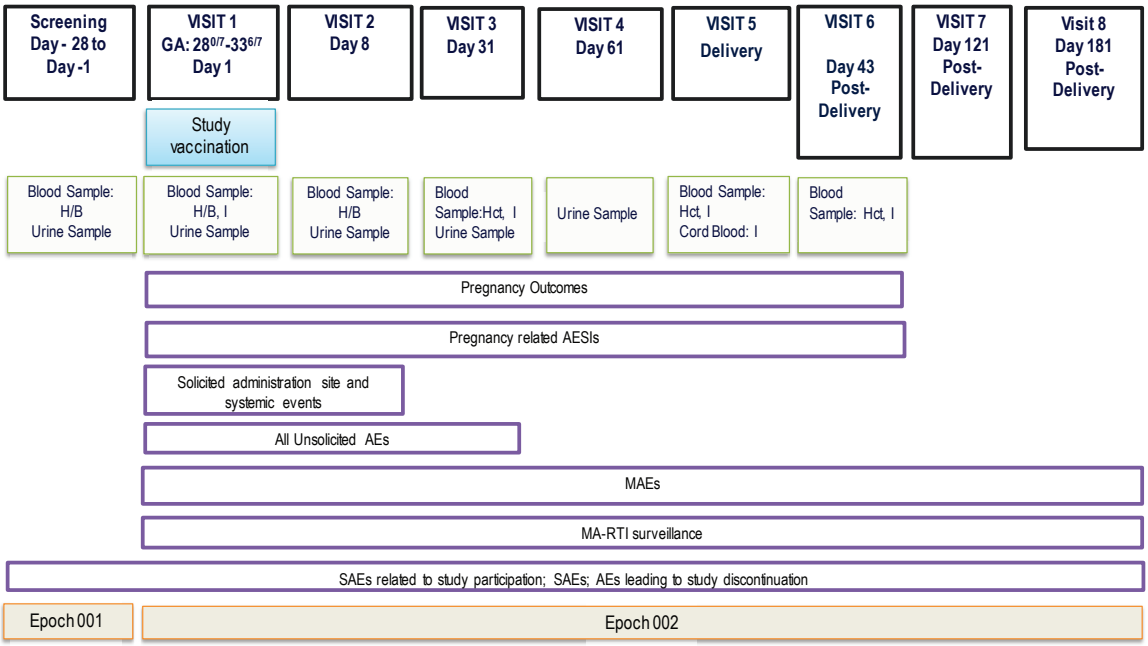
Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibodies against RSV-A at Day 43 after Delivery (Visit 6).	RSVPreF3 IgG-specific antibody concentration Neutralizing antibody titers against RSV-A Measured on the blood sample collected at Day 43 post- delivery (Visit 6).
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSV-B neutralizing antibodies at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).	Neutralizing antibody titers against RSV-B Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).
To evaluate RSV-specific antibodies in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 months after birth.	RSVPreF3 IgG-specific antibody concentration Neutralising antibody titres against RSV-A Neutralising antibody titres against RSV-B For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective). For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to treatment study intervention.
Tertiary objectives: To further evaluate the humoral response to the RSV maternal vaccine, which may include RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. To evaluate the presence of other respiratory viruses in nasal swabs collected from maternal subjects and their infants (via an Allplex Respiratory Viruses Panel or alternative, performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples.)	

*Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with GAIA assessment and level of diagnostic certainty when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category."

3. STUDY DESIGN

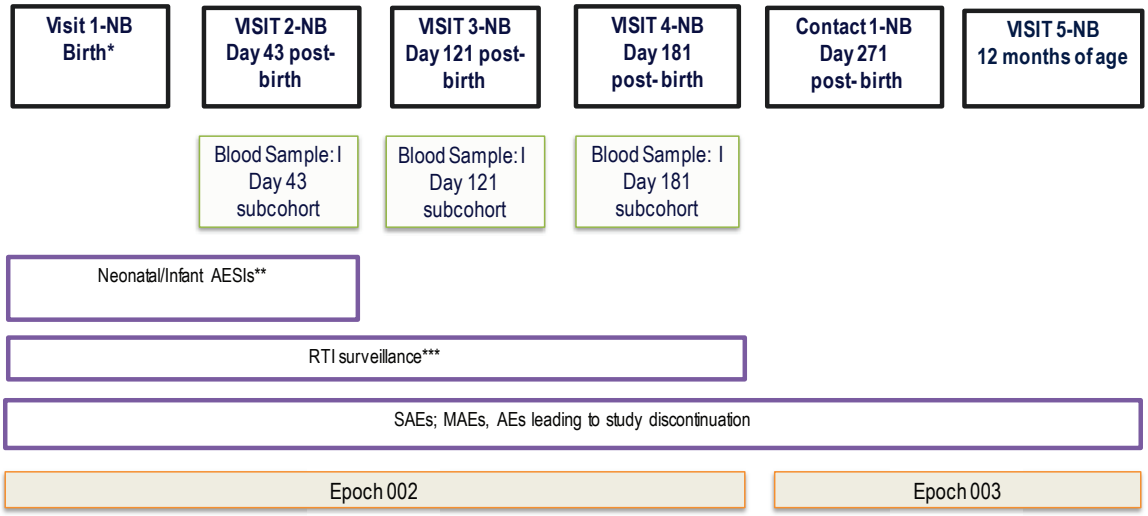
Figure 1 and Figure 2 provide overviews of the study design for maternal and infant subjects, respectively.

Figure 1 Overall design – maternal subjects (Amended 29-MAY-2020)



H/B= hematology/biochemistry, Hct- hematocrit; I= humoral immune response
If Screening blood sample collected ≤ 15 days before Visit 1, hematology/biochemistry not required at Visit 1
Subjects will be vaccinated year-round and will not be limited to seasonal enrolment
*Pregnancy-related AESIs identified after Day 43 will continue to be reported as such.

Figure 2 Overall design– infant subjects



NB = Newborn; I=humoral immune response: infants will be randomized 1:1:1 to one of the 3 subcohorts shown.
*Blood sample to be collected within 3 days after birth **ONLY** if a cord blood sample is not collected
**Neonatal AESIs identified after Day 43 (e.g., congenital anomalies) will continue to be reported as such.
***Infant subjects' parent(s)/LAR(s) will be contacted at least monthly to ensure RTI eDiary compliance.
Safety and disease surveillance data collected *after* Visit 4-NB will be reported in the database *in Epoch 003*.

- Study Type: self-contained.
- Experimental design: Phase II, observer-blind, randomised, placebo controlled, multi-centric, multi-country study with 3 parallel groups.
- Study Duration: Approximately 9 months (including the screening visit) for participating pregnant women; approximately 1 year after birth for participating infants.
- Control: Placebo.
- Epochs 001, 002 and 003 begin and end as described in Table 2.
- Blinding is as described in Table 2.
- Randomized intervention allocation: ***Up to*** 300 eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio) using an automated internet based system (SBIR).The system's randomisation algorithm will use a minimisation procedure accounting for maternal age at the time of vaccination (≥18 and <35 years of age or ≥ 35 years of age), gestational age at the time of vaccination ($28^{0/7}$-$31^{0/7}$; $31^{1/7}$-$33^{6/7}$) and center. Minimisation factors will have equal weight in the minimisation algorithm.
- Study (intervention) groups are described in Table 2

Table 2 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Intervention name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)**	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	***Up to*** 100	18 – 40 years	RSVPreF3_60	BS1_60	***Up to 33***	RSVMAT60_BS1	●	●	●
				BS2_60	***Up to 33***	RSVMAT60_BS2		●	
				BS3_60	***Up to 33***	RSVMAT60_BS3		●	
RSV MAT 120	***Up to*** 100	18 – 40 years	RSVPreF3_120	BS1_120	***Up to 33***	RSVMAT120_BS1	●	●	●
				BS2_120	***Up to 33***	RSVMAT120_BS2		●	
				BS3_120	***Up to 33***	RSVMAT120_BS3		●	
Control	***Up to*** 100	18 – 40 years	Control	BS1_C	***Up to 33***	Control_BS1	●	●	●
				BS2_C	***Up to 33***	Control_BS2		●	
				BS3_C	***Up to 33***	Control_BS3		●	

M=maternal subject; I=infant; Control = Placebo; Blood sampling subcohorts are abbreviated "BS1;" "BS2;" BS3" and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.

- Data collection: standardized Electronic Case Report Form (eCRF). Electronic diaries (e-diaries) for solicited event data, and notifications regarding occurrence of unsolicited events (including medically attended events and SAEs), and symptoms of respiratory tract illnesses in infant subjects.
- Safety monitoring: This study will be monitored by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee (IDMC) external to GSK. The analyses for IDMC safety evaluations will be described in a separate SAP for IDMC.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined (Amended 14-FEB-2020):

4.1.1. Maternal Subjects

	Description
Analysis Set	**Maternal subjects**
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form.
Exposed	All maternal subjects who received at least 1 dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Full Analysis	All maternal subjects *in the Exposed set* who have post-vaccination immunogenicity data.
Per Protocol	All maternal subjects who received at least 1 dose of the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.
Unsolicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All maternal subjects ***in the*** Exposed Set who have solicited safety data

4.1.2. Infant subjects

	Description
Analysis Set	
Exposed	Infants live-born to exposed maternal subjects, whose parents/LARs completed the informed consent process and signed the informed consent form
Full Analysis	All infant subjects in the Exposed set who have post-delivery/birth immunogenicity data.
Per Protocol	All infant subjects in the Full Analysis set minus those who (a) were born less than 4 weeks post- maternal subject vaccination and/ or (b) have protocol deviations that lead to exclusion.
Unsolicited Safety	All infants in the exposed set for whom unsolicited AEs /not having unsolicited AEs are reported

4.1.3. Randomized Set

Randomized set will include all maternal subjects who are randomized and all of their randomized infants. The allocation in a group is done as function of the randomized intervention. Please note this set was not included in the protocol, but will be used later in one summary analysis, so it is added here for clarification.

4.1.4. Full Analysis Set

Full analysis set will be defined by time point. For infants, it will include all of the infants in the Exposed Set who have immunogenicity data at the corresponding time point after birth.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

Infants: Code 1030 (Study vaccine not administered at all, carry forward elimination from mother to infant), 800 (Fraudulent data), code 900 (invalid informed consent) and code 901 (invalid informed consent due to mother) will be used for identifying infants eliminated from ES

4.2.2. Elimination from Full Analysis Set (FAS)

4.2.2.1. Excluded subjects from FAS of maternal subjects

A maternal subject will be excluded from the FAS analysis under the following conditions

Table 3 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.

4.2.2.2. Excluded subjects from FAS of infant subjects

An infant subject will be excluded from the FAS analysis under the following conditions

Table 4 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all - mother	All	Safety, immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth* Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

#Carry forward elimination from mother to infant
Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
*cord blood sample or blood sample collected within 3 days after birth if cord blood sample is not collected

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

4.2.3.1. Excluded subjects from Per-protocol analysis set of maternal subjects

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

Table 5 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-40 years Gestational age at vaccination - 28 0/7 – 33 6/7	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 31, check the interval from vaccination to day 31 BS = ***20 –45*** days; • For PPS at Delivery, check the interval from delivery to delivery BS = ***(-1) – (+3)*** days; • For PPS at Day 43 post-delivery, check the interval from delivery to day 43 post-delivery BS = 40 – ***60*** days	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

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

4.2.3.2. Excluded subjects from Per-protocol analysis set of infant subjects

An infant subject will be excluded from the PPS analysis under the following conditions

Table 6 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent - infant	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
1041#*	Maternal administration of concomitant vaccine(s) forbidden in the protocol up to Delivery	All	Immunogenicity
1050#	Maternal randomisation failure	All	Immunogenicity
1060#	Maternal randomisation code was broken	All	Immunogenicity
1070#	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070#	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070#	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070#	Study treatment administered while contraindicated	All	Immunogenicity
1080#	Vaccine temperature deviation	All	Immunogenicity
1090#	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) - infant	All	Immunogenicity
2011#	Protocol violation (inclusion/exclusion criteria) - mother	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2041#*	Maternal administration of any medication forbidden by the protocol up to Delivery	All	Immunogenicity
2041#*	Device, excluded by the protocol, was administered by mother up to Delivery	All	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2050#*	Maternal intercurrent medical conditions which are exclusionary as per protocol up to Delivery	All	Immunogenicity
2060#*	Maternal concomitant infection related to the vaccine which may influence immune response up to Delivery	All	Immunogenicity
2070#*	Maternal concomitant infection not related to the vaccine but may influence immune response up to Delivery	All	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule – infant: • For infants without cord blood, check the interval from birth to Visit 1-NB birth BS = 0 – 3 days; • For PPS at Day 43 post-birth, check the interval from birth to Day 43 BS = ***28 – 60*** days; • For PPS at Day 121 post-birth, check the interval from birth to Day 121 BS = ***110 –140*** days; • For PPS at Day 181 post-birth, check the interval from birth to Day 181 BS = 165 ***– 200*** days	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2120.Vx*	Obvious incoherence or abnormality or error in data	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
3100	Delivery happens less than 4 weeks post-vaccination.	All	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
#Carry forward elimination from mother to infant
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
BS- Blood Sample.

4.2.4. Elimination from unsolicited and solicited safety set

4.2.4.1. Excluded subjects

4.2.4.1.1. *Unsolicited safety set*

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.4.1.2. *Solicited safety set*

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

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1while the study specific data derivation rules and stat methods are described in section 9.

5.1. Demography

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

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

For all maternal subjects, demographic characteristics (e.g., age at vaccination (18 - <35; ≥ 35 years), gestational age at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), geographic ancestry will be summarized by group using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics.

For their infants, demographic characteristics (e.g., gestational age at time of delivery (> 37 weeks; ≤ 37 weeks), sex, weight, length, head circumference, geographic ancestry, apgar score), and lifestyle characteristics (e.g., living environment, household composition, breastfeeding, passive smoking and extent of contact with children less than 6 years of age) will be summarised by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

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

5.1.2. Additional considerations

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

Subgroup analysis for demographic characteristics by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth (> 37 weeks or ≤ 37 weeks) for infant subjects will also be performed on Enrolled Set, ES or PPS.

Subject disposition will be summarized by group using descriptive statistics:

- Number of maternal subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- Number of infants enrolled and withdrawn including withdrawal reasons will be tabulated by group, by sub-cohort within each group and overall.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set. The parameters include but may not be limited to systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiratory rate, height, weight and body mass index.

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

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

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

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol

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

	Primary Immunogenicity Endpoints	**Statistical Analysis Methods**
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).	For each assay, at each timepoint and by study group and age category (18 - <35 years; ≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline, at day 31 and at delivery will be explored using scatter plots of individual values. Between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A will be performed at Day31 and at Delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, age category at vaccination, center and the interval between vaccination and delivery as covariates if needed.

Primary Immunogenicity Endpoints		Statistical Analysis Methods
Cord blood/ placental transfer	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A	For each assay, the following analysis will be performed by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • The distribution of RSV-A and RSVPreF3 IgG-specific antibody titres/concentration from cord blood will be tabulated • For each assay, relationship between maternal antibody titers/concentrations and infant antibody titers/concentrations at the time of delivery will be evaluated graphically using scatter plots of individual results.
	• The ratio between cord blood and maternal RSVPreF3 IgG-specific antibody concentrations All 3 endpoints measured on blood samples collected from maternal subjects at delivery and either cord blood, or (if cord blood cannot be collected) infant blood samples collected within 3 days after birth	• Geometric mean of placental transfer will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ≥ 1 will be tabulated with exact 95 % CI by study group. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks; ≤ 37 weeks), age category at vaccination, center and the interval between vaccination and delivery as covariates if appropriate. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at delivery will be explored using scatter plots of individual values.

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and • Neutralizing antibody titers against RSV B For RSV-A: Measured on the blood sample collected Day 43 post-delivery (Visit 6). • For RSV-B: Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3),, at Delivery (Visit 5) and at Day 43 post delivery (Visit 6).	For each assay, at each timepoint and by study group and age category (18 - <35 years ;≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at baseline, at day 31, at delivery and at day 43 post-delivery will be explored using scatter plots of individual values. In addition, between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A and RSV-B will be performed at Day31, at Delivery and at Day 43 post-delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery if available as covariates if needed.
Infant subjects	• RSVPreF3 IgG-specific antibody concentration • Neutralising antibody titres against RSV-A • Neutralising antibody titres against RSV-B For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of	For each assay, at each timepoint and by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. In addition, analyses will include exploratory evaluation of the persistence of RSV specific antibodies in infants through time, and half-life analysis modelling of logarithm transformed RSV antibody concentrations/titers over time. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery, and on blood samples collected at 6 weeks, 4 months and 6 months post-birth using a mixed effect model on the logarithm10 transformation of the concentrations/titers,

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
	these 3 cohorts at the time of maternal randomization to intervention For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective).	including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks ; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate and needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at delivery will be explored using scatter plots of individual values.

5.2.2. Additional considerations

Before unblinding occurs, the immunogenicity analysis will only be performed on Exposed Set. At the time of final analysis, the immunogenicity analysis will be performed on PPS.

5.2.2.1. Distribution analysis

RSV-A neutralizing antibody titers and RSV-B neutralizing antibody titers:

- Number and percentage of subjects with titers <128, ≥128, ≥256, ≥512, ≥1024, ≥2048, ≥4096, ≥8192 and >=16384 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 2, 4, 6, 8, 10 and 12 by pre-vaccination category (< 128, ≥128 and <256, ≥ 256 and <512, ≥ 512 and <1024, ≥1024 and <2048, ≥ 2048 and <4096, ≥ 4096 and <8192, ≥8192 and <16384) will be tabulated.

RSVPreF3 IgG-specific antibody concentrations:

- Number and percentage of subjects with concentrations <2048, ≥2048, ≥4096, ≥8192, ≥16384, ≥32768, ≥65536, ≥131072 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 4, 6, 8, 10, 12, 14 and 16 by pre-vaccination category (< 2048, ≥2048 and <4096, ≥ 4096 and <8192, ≥ 8192 and <16384, ≥16384 and <32768, ≥ 32768 and <65536, ≥ 65536 and <131072, ≥131072) will be tabulated.

The thresholds for distribution tables of titres and concentrations and fold increase may be further adjusted at analysis as needed.

In addition, to assess the effect of the interval between vaccination and delivery on the antibody transfer, geometric mean of RSV-A neutralizing antibody titers, RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers from cord blood (or blood drawn from infants within 3 days after birth) will be tabulated with different categories of time (in weeks) from vaccination to delivery. This analysis will be performed for infants born at gestational age <37 weeks and those born at gestational age >=37 weeks. Associated scatter plots may also be provided as needed.

5.2.2.2. Ratio of fold increase analysis

Fold increase of RSVPreF3 IgG-specific antibody concentrations over fold increase of RSV-A neutralizing antibody titers (ratio of fold increase post- over pre-vaccination) will be tabulated using descriptive statistics. This analysis will include calculation on:

- Geometric mean ratios with corresponding 95% CIs of RSVPreF3 IgG-specific antibody concentration over RSV-A neutralizing antibody titers at pre-vaccination for each group and
- Geometric mean ratios with corresponding 95% CIs of fold increase post/pre (Day 31, Delivery and Day 43 post-delivery/Day 1) between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody titers for each group.

Similar analysis will be performed between RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers.

5.2.2.3. Between group analysis

This analysis is exploratory.

For the analysis of maternal subjects at each time point (Day 31, Delivery, and Day 43 post-delivery), the model will be explored and fitted via the proc mixed procedure according to the following code:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group ges_age_cat age_cat center;
  MODEL log_val = baseline group ges_age_cat age_cat
inter_vac_del center /ddfm=kenwardroger outp = pred;
  /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
RUN;
```

where log_val represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, group indicates the study group, ges_age_cat is the gestational age category at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), age_cat is the age category at vaccination (18 – <35 years and ≥35 years), inter_vac_del is the interval between vaccination and delivery (days). The inclusion of age category at vaccination, interval between vaccination and delivery, and center in the model depends on the availability of the variable (inter_val_del may not be available at Day 31 analysis) and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

For the analysis of infants at each time point (cord blood at Delivery, Day 43 post-birth, Day 121 post-birth, and Day 181 post-birth), similar model will be explored:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group center ges_age_cat ges_age_birth;
  MODEL log_val = baseline group ges_age_cat /*inter_vac_del*/
ges_age_birth center /ddfm=kenwardroger outp = pred;
 /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
   RUN;
```

Baseline is pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, ges_age_birth is gestational age category at birth (> 37 weeks; ≤ 37 weeks) for infants. With the inclusion of gestational age category at vaccination (ges_age_cat) in the model, this categorical variable ges_age_birth provides similar information as continuous variable inter_vac_del, therefore the inclusion of either variable in the model could be adjusted according to the analysis needs.

The ratio of GMTs/GMCs between vaccine groups and the corresponding 95% CI will then be constructed by exponentiating the mean difference and its confidence interval between vaccine groups on the logarithm10 scale estimated from the model. Summary tables will show adjusted GMT/GMC for vaccine groups, and ratios of GMTs/GMCs between vaccine groups along with the 95% CI.

If deemed necessary, an analysis of variance model for repeated measures will be fitted to assess the mean profile in each group over time for both maternal and infant subjects separately. Below is the sample SAS code for the analysis of maternal subjects, and similar codes could be explored for the analysis of infants.

```
PROC MIXED data=sero;
    CLASS subjid group visit age_cat center ges_age_cat;
    MODEL log_val = baseline group | visit age_cat ges_age_cat
inter_vac_del center/ddfm=kenwardroger outp = pred;
    RANDOM subjid;
    /*REPEATED visit/subject=subjid(group) type=un;*/
    LSMEANS group*visit/pdiff cl alpha=0.05;
RUN;
```

Summary tables will present adjusted GMT/GMC with 95% CI for each group at each timepoint.

5.2.2.4. Persistence and Half-life analysis of antibody level over time for infant subjects

This analysis is exploratory.

The decay of infant antibody levels over time will be analysed by a linear regression of the logarithm transformed of antibody levels. This analysis will be performed on PPS for infants in RSV vaccine group in terms of RSV-A neutralizing antibody titers, RSV-B neutralizing antibody titers and RSVPreF3 IgG-specific antibody concentrations.

A true, natural decay curve will be explored by stochastically reducing the sample to uninfected subjects only. The following steps will be taken to identify infected subjects (confirmed and suspected) to be eliminated from the sample:

- STEP 1: Infants with an RSV positive nasal swab during the study before time of blood sampling will be eliminated from the analysis because RSV infection may have contributed to their antibody levels which may no longer represent what was passively transferred from the mother.
- Infants whose mothers had an RSV positive nasal swab before or up to the time of delivery will be eliminated from the analysis. Maternal infection may contribute to post-vaccination increase in the levels of maternal antibodies, leading to higher placental antibody transfer to the fetus/infant, which would not reflect the effect of vaccination alone.
- STEP 2: Run the model and compute expected value based on the decay curve
- STEP 3: Subjects with an antibody titer at the blood sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected and then eliminated and the decay curve refined.
- STEP 4: Step 3 is repeated up to 5 times until the most accurate decay curve is established.

The natural decay of antibody level will be determined using linear regression between the logarithm transformed antibody level (Y) and time t (age in days) with subject as a random effect. All infants have RSV neutralizing antibodies measured at birth (cord blood) or within 3 days after birth, and each infant in PPS sub-cohort will have blood sampling for RSV neutralizing antibodies at one of the following time points: Day 43 post-birth, Day 121 post-birth or Day 181 post-birth. Therefore, in the natural decay model, each infant will have maximum 2 RSV neutralizing antibodies measures, one at birth or within 3 days after birth and the other at Day 43 post-birth, Day 121 post-birth or Day 181 post-birth depending on the sub-cohorts where the infants are.

The following SAS code will be explored:

```
PROC MIXED DATA=<filename>;
  CLASS PID;
  MODEL LOG_Y = t /s outp=pred;
  RANDOM Int t / sub=PID type=UN G GCORR;
RUN;
```

The choice of correlation structure and other parameters may be further adjusted according to the data and analysis needs.

The predicted value will be computed using the following formula

$$A_t = A_0 \exp(-K_e t)$$

where, A_t and A_0 are antibody titres at times t and zero, respectively, K_e is the constant rate of antibody change with time, defined as the estimate of model.

In addition, the half-life ($t_{1/2}$) of antibody (i.e. the time required for titre to decrease by one-half) will be displayed using the following equations of declining antibody titre:

$$\text{when } A_t = \tfrac{1}{2} A_0$$

$$t_{1/2} = 0.693 / K_e$$

A summary table will be prepared to show the number of infants included in the model, the model estimate of the antibody decay rate, and the half-life of the antibody.

In case cord blood samples are missing in 20% or more of infants in a single study group, separate analysis for infants with cord blood and infants with a blood sample within 3 days after birth will be performed.

5.2.2.5. ROC analysis (dose characterization)

This analysis is exploratory and complementary to traditional data analysis methods comparing post-vaccination immune responses among vaccine groups and will be performed on the PPS only if deemed necessary.

If immune response between active vaccination groups can't be differentiated using traditional approach, additional analyses using a generalized ROC (Receiver Operating Characteristics) method [Yu, 2018] will be performed for both RSV-A neutralizing antibody titers and RSVPreF3 IgG specific antibody concentrations at Day 31 and Delivery, and other timepoints if needed.

Two ROC Methods will be explored:

- ROC-P (ROC of post-dose levels) method: Post-vaccination antibody levels from 2 RSV vaccine groups (RSV MAT 60 and RSV MAT 120) will be pooled and used as a reference distribution.
- ROC-B (ROC relative to baseline) method: Overall pre-vaccination antibody levels from 2 RSV groups (RSV MAT 60 and RSV MAT 120) will be used as a reference distribution.

Different percentile (0% to 100%) thresholds from the reference distribution will be obtained. The percentage of subjects with post-vaccination antibody level higher than or equal to the percentile thresholds from the reference distribution will then be calculated for each vaccine group.

A figure will be provided showing the ROC curve with x-axis the percentile of the reference distribution and y-axis the percentage of subjects in each vaccine group with post-vaccination antibody levels higher than or equal to the percentile threshold of the reference distribution.

A summary table will be provided on the thresholds of e.g. 25%, 50% and 75% percentiles of the reference distribution and the percentage of subjects in each vaccine

group with post-vaccination antibody level higher than or equal to these percentile thresholds.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in **maternal subjects** will include summaries by study group and age category (18 - < 35 years of age; ≥35 years of age; overall) of hematology and biochemistry results by grade and per time point, solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant subjects** will include summaries by study group and gestational age at birth (> 37 weeks or ≤ 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

All safety analyses will be performed on the Solicited Safety or Exposed sets.

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal subjects	Occurrence of Solicited administration site and systemic events that occur during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	The number and percentage with exact 95% CI of maternal subjects reporting each **Solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day (days 1 to 7) follow-up period after vaccination will be tabulated by maximum intensity per subject for each study vaccine group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of maternal subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 7-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).
	Occurrence of any protocol-specified hematological or biochemical laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)	The number and percentage of subjects with hematology and biochemistry results outside central laboratory normal ranges will be tabulated to show Day 8 versus baseline. The maximum grading as described in [Sheffield, 2013] and in the ***SPM*** from Screening up to Day 8 will also be tabulated.

	Primary Safety Endpoints	Statistical Analysis Methods
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	The number and percentage of maternal subjects with **unsolicited** symptoms within 30 days after vaccination with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 related unsolicited symptoms and for MAEs. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 30-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for MAEs.
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).	The number and percentage of maternal subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). Outcomes are listed in Section 2.	The number and percentage of maternal subjects with each pregnancy outcome will be tabulated with its exact 95% CI by group. By subject listings of adverse pregnancy outcomes will be prepared but will not be released until the final, unblinded analysis has been completed.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post delivery; Visit 6**).** These events are listed in Section 2**.**	The number and percentage of maternal subjects with each pregnancy-related AESI will be tabulated with its exact 95% CI by group. By subject listings of pregnancy-related AESIs will be prepared but will not be released until the final, unblinded analysis has been completed.

Primary Safety Endpoints		Statistical Analysis Methods
Infant subjects	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These events are listed In Section 2. Occurrence of SAEs, AEs leading to study withdrawal and medically attended AEs from birth up to 6 weeks after birth.	The number and percentage of infant subjects with each neonatal AESI will be tabulated with its exact 95% CI by group. By-subject listings of neonatal AESIs will be prepared, but will not be released until the final, unblinded analysis has been completed. The number and percentage of infant subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
Secondary Safety Endpoints		**Statistical Analysis Methods**
Maternal subjects	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs and AEs leading to study withdrawal. Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)	The number and percentage of maternal subjects with at least one SAE, MAE from Day 1 up to 6 months after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared (but will not be released until the final, unblinded, analysis has been completed). The number and proportion of subjects with at least one RSV-associated MA- RTI (with 95 % CI) will be calculated and tabulated.
Infant subjects	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and medically attended AEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs	For each category: - SAE, - MAEs The number and proportion of infant subjects who experienced at least one event from birth up to 6 months after birth and the number and proportion of infant subjects who experienced at least one event from birth up to 1 year after birth will be tabulated with 95% CI by group. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared.
	From birth to 6 months after birth (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions in Section 4.2.6 in the protocol)	For each category: - RSV-associated LRTI, - Severe LRTI, - Very severe LRTI - RSV-associated hospitalization The number and proportion (with 95% CI) of subjects with at least one event will be calculated and tabulated by group.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

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

Table 7 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F (with 1 decimal) Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache Fatigue	0	Normal
Nausea	1	Mild: Easily tolerated
Vomiting	2	Moderate: Interferes with normal activity
Diarrhea Abdominal pain	3	Severe: Prevents normal activity

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

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

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

5.3.2.2. Exclusion of implausible solicited Event

Some local and systemic events will be directly measured by the subject and will be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 8 Implausible Solicited Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	Measurements < 0 mm For subjects ≥ 6 years: ≥ 900 mm
Swelling	Measurements < 0 mm For subjects ≥ 6 years: ≥ 500 mm

5.3.2.3. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set

5.3.2.4. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Nausea	Nausea	10028813
Vomiting	Vomiting	10047700
Diarrhea	Diarrhea	10012727
Abdominal pain	Abdominal pain	10000081
Headache	Headache	10019211

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

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

5.3.2.5. Analysis of RTI and LRTI

The analysis of RTI and LRTI will be performed on Exposed Set according to the case definitions in section 9.1.3. Separate listings of maternal MA-RTI and infant RTI/LRTI will be provided.

Further analysis with respect to the incidence of RSV LRTI by an exploratory case definition might be performed if deemed necessary.

5.3.2.6. Other analysis

Other safety analysis will be performed on Exposed Set.

For hematology and biochemistry lab results, the maximum grading as described in [Sheffield, 2013] and SPM will be used, see section 9.1.4 for details.

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination, up to 6 weeks post-delivery and up to 6 months post-delivery will be summarized by group. A listing will also be provided.

The number and percentage of infants taking concomitant medications from birth up to 6 weeks after birth, 6 months after birth and 1 year after birth will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses (Amended 14-FEB-2020)

7.1.1. First analysis *(Amended 29-MAY-2020)*

The **first analysis** will be conducted after approximately 75 maternal subjects have completed Visit 3 (Day 31) and approximately 24 maternal subjects and their infants have completed Visit 5 / Visit 1-NB (Delivery/Birth).

By-study-group ***safety and*** immunogenicity analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

Immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.

Safety analyses will be performed by blinded treatment group, with the letters "A," "B," and "C" replacing treatment-specific group identifiers in all results summaries. Steps will be taken to minimize the risk of unblinding (e.g., events that happen in a single group will be masked by adding the same amount of counts to other groups). Although the risk of unblinding may be reduced with the proposed masking, this risk may not be avoidable in certain cases.

Safety analyses will include all available data for:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

A report summarizing these ***safety and immunogenicity*** results will be prepared but will not be made available to investigators.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.2. Second analysis

The **second analysis** will be performed after approximately 24 maternal subjects and their infants have completed Visit 7 / Visit 3-NB (Day 121 post-delivery / birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results, at:

- Visit 1 (Day 1) and Visit 3 (Day 31).
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery).
- Visit 3-NB (Day 121 post-delivery).

By-study-group safety analyses will include the following data from those subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified).

Blinded SAE and AESI listings for all subjects will also be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations**.**

7.1.3. Third analysis *(Amended 29-MAY-2020)*

The **third analysis** will be performed after approximately 150 maternal and infant subjects have completed Visit 8/Visit 4-NB (Day 181 post-delivery/birth).

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results at:

- Visit 1 (Day 1) and Visit 3 (Day 31);
- Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.
- Visit 6 / Visit 2-NB (Day 43 post delivery);
- Visit 3-NB (Day 121 post-delivery)
- Visit 4-NB (Day 181 post-delivery)

By-study-group safety analyses will include the following data from all ***vaccinated*** subjects who have reached the Day 43 post-delivery visit:

- Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.
- RTI surveillance data (including nasal swab test results).

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified).

In addition, blinded SAE and AESI listings for all subjects will be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.4. Final analysis

The **final** analysis will evaluate all data pertaining to primary and secondary safety and immunogenicity endpoints. It will be performed by the GSK Biologicals biostatistics team when all primary and secondary endpoint data up to study end (last Visit 5-NB) are available.

Results will be presented in a clinical study report. This report will include results summarized by study group as well as individual (by subject) data /data listings, and will be made available to investigators.

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 clinical study report**.**

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

7.2. Statistical considerations for interim analyses (Amended 14-Feb-2020)

The first 3 analyses will be descriptive. Therefore, the conduct of these analyses has no impact on interpretation of study results.

8. CHANGES FROM PLANNED ANALYSES

To take a more practical approach, subgroup analysis of safety by age category at vaccination (18 - <35; ≥ 35 years) in maternal subjects will include summaries of pregnancy outcomes, pregnancy related AESIs, SAEs, MAEs and MA-RTIs.

Subgroup analysis of safety by gestational age at birth (> 37 weeks or ≤ 37 weeks) in infant subjects will include summaries of neonatal AESIs, MAEs, SAEs, and occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

Subgroup analysis on other safety summaries will be performed if deemed necessary.

Subgroup analysis of immunogenicity by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth ((> 37 weeks or ≤ 37 weeks) for infants will include analysis of GMT(C) and GMR calculation at each time point and geometric mean of placental transfer.

Subgroup analysis on other immunogenicity analysis will be performed if deemed necessary.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Data derivation

9.1.1. Gestational age at vaccination

Gestational age at vaccination in weeks for maternal subjects will be calculated based on estimated date of delivery and date of vaccination.

9.1.2. Immunogenicity

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

- For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
- For the between group assessments, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

The GMT/GMC and its 95% CI will be obtained by exponentiating the mean and its 95% CI of the log-transformed titres/concentrations. All CI computed will be two-sided 95% CI.

Placental transfer is defined as the ratio of RSVPreF3 IgG-specific antibody concentrations between cord blood (or blood sample from infants collected within 3 days after birth if cord blood is not available) and maternal blood sample at delivery (or within 3 days after delivery if blood sample is not collected during delivery).

9.1.2.1. Assay cut-offs for serology results

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

System	Component	Method	Unit	Cut-off *(LLOQ)*	*ULOQ*
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	ED60	18	***123535***
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	IU/mL	56	***217400***
Serum	RSVPreF3 IgG antibody concentrations	ELISA	EU/mL	*25*	***251 769***
Serum	RSV-B Neutralising Antibody	NEUTRALISATION	ED60	*30*	***138336***
Serum	***RSV-B Neutralising Antibody***	***NEUTRALISATION***	***IU/mL***	***44***	***171279***

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis, which would not lead to SAP amendment.

9.1.3. RTI and LRTI

Cases will be classified (during data analyses) according to the definitions that follow.

Table 9 MA-RTI case definitions for data analysis in maternal subjects

RSV-MA-RTI	Medically attended visit for RTI symptoms AND Confirmed RSV infection [1, 2]
RSV hospitalization	Confirmed RSV infection AND Hospitalized for acute medical condition [3]
All-cause MA- RTI	Medically attended visit for RTI symptoms

[1] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol
[2] RSV (nasal swab) sampling and testing as specified in Table 11 of the Protocol.
[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.
MA-RTI = Maternal, medically attended respiratory tract illness

Table 10 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection [4]
RSV-LRTI	History of cough OR difficulty in breathing [1] AND SpO_2 < 95%[2], OR RR increase [3] AND Confirmed RSV infection [4]
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%[2], OR lower chest wall in-drawing
RSV-very severe LRTI	Meeting the case definition of RSV-LRTI AND SpO2 < 90%[2], OR inability to feed OR failure to respond / unconscious
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing [1] AND SpO2 < 95% [2], OR RR increase [3]

Definitions based on [Modjarrad, 2016]
RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.
[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnea).
[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.
[3] RR increase defined as:
> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)
[4] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol
[5] RSV (nasal swab) sampling and testing as specified in Table 12 of the Protocol
[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose, wheezing or difficulty breathing with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed.

9.1.4. Hematology and Biochemistry parameters

The table below shows the toxicity grading during the second and third trimester of pregnancy based on [Sheffield, 2013]

Table 11 Laboratory values during the second and third trimester of pregnancy

Serum chemistries	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.8 mg/dL		0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
BUN	3.0-13.0 mg/dL		14.0-19.0	20.0-30.0	>30	Required dialysis
Haematology	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin	9.7-14.8 g/dL		9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
Change from baseline value – gm/dL			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.6-14.8 x 1000cell/mm^3	High	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	0.9-3.9 x 1000cell/mm^3	High	>3.9-5.0	>5.0		
		Low	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.8-12.3 x 1000cell/mm^3		<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	155-409 x 1000 L^{-1}	Low	125-154	100-124	25-99	<25
		High	410-499	500-749	750-1000	>1000
Liver Function Tests	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	3-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate

ALT (SGPT) Alanine transaminase	2-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Serum chemistries	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.9 mg/dL		1.0-1.2	1.3-1.6	1.7-2.5	>2.5 or required dialysis
BUN	3.0-11.0 mg/dL		12.0-19.0	20.0-30.0	>30	Required dialysis
Liver Function Tests	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	4-32 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-25 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Haematology	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – g/dL	9.5-15.0 g/dL		9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.9-16.9 x 1000cell/mm^3	High	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	1.0-3.6 x 1000cell/mm^3	High	>3.6-5.0	>5.0		
		Low	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.9-13.1 x 1000cell/mm^3		<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.4 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	146-429 x 1000 L^{-1}	Low	125-146	100-124	25-99	<25
		High	430-499	500-749	750-1000	>1000

Adapted from [Sheffield, 2013]
ULN: upper limit of normal.

Table below shows the toxicity grading for lab parameters that are not covered in [Sheffield, 2013] but calculated based on the references and guidance in [Abbassi-Ghanavati, 2009]

Laboratory Parameter	Grade 1	Grade 2	Grade 3
Hematocrit-2nd trimester N 30.0-39.0 (%)	27-29.9 39.1-42.9	24-26.9 43-46.8	≤ 23.9 ≥46.9
Hematocrit-3rd trimester N 28.0-40.0 (%)	25.2- 27.9 40.1-44	22.4-25.1 44.1-48	≤22.3 ≥48.1
Mean Corpuscular Volume MCV 2nd N 82-97 (μm^3)	73.8-81.9 97.1-106.7	65.6-73.7 106.8-116.4	≤65.5 ≥116.5
Mean Corpuscular Volume MCV 3rd N 81-99 (μm^3)	72.9-80.9 99.1-108.9	64.8-72.8 109-118.8	≤64.7 ≥118.9
RBC - 2nd trimester N 2.81 – 4.49	2.6-2.8 4.5-4.9	2.3 – 2.5 5.0-5.3	≤2.2 ≥5.4
RBC - 3rd trimester N 2.71-4.43	2.5-2.7 4.4-4.8	2.2 – 2.4 4.9-5.3	≤2.1 ≥5.4

9.2. Statistical Method

Study specific statistical methods for immunogenicity analysis are described in section 5.2.2.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event.

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. *Studies with electronic diaries*

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

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

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

10.1.3.8. Onset day

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

10.1.3.9. Duration of events

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

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

10.1.3.10. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.11. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

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

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

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

10.1.4.2. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.3. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document. Please note the protocol of this study was developed based on V17 template and the term 'solicited administration site event' and 'solicited systemic event' are used, however, at the development of the TFL TOC, only V16 standard catalog is available and still 'solicited local adverse event' and 'solicited general adverse event' are used in the TFL mocks per this standard.

11. REFERENCES

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Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments. Vaccine 2013; 31:4264-4273.

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CONFIDENTIAL

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated mothers
eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
Scope:	All analyses for the primary and secondary objectives of the study.
Date of Statistical Analysis Plan	Final: 29 October 2019 ***Amendment 1 Final: 10 March 2020***

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

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GMR	Geometric mean of ratio
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
LRTI	Lower Respiratory Tract Illness
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NB	Newborn
PD	Protocol Deviation
PPS	Per-Protocol Set
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SPM	***Study Procedures Manual***
SR	Study Report
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULOQ	Upper Limit of Quantification

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29 OCT 2019	first version	Final: 09 JUL 2019
10 MAR 2020	***Amendment 1***	***Amendment 1: 27 JAN 2020***

Table below lists main changes in the SAP amendment 1 and their rationale

Section # and Name	Description of Change	Brief Rationale
Globally	Number of maternal subjects has been increased from ~150 (i.e., ~50 per group) to ~300 (i.e, ~100 per group). Number of infant subjects has been increased from ~150 (i.e., ~50 per group) to ~300 (i.e, ~100 per group). Number of infant subjects in each blood sampling subcohort has been increased from ~ 16 per timepoint per study group to ~ 33 per timepoint per study group.	To provide additional safety and immune response data in support of subsequent studies
Section 4.2.3.1, Table 5, Elimination code 2090.Vx	The minimum interval between Visit 1 and Visit 3 is 25 rather than 28 days.	To facilitate availability of immune response data at Visit 3.
Section 3, Data collection	Reference to eDiary collection of maternal medically attended RTI data has been removed.	The eDiary captures occurrences of maternal medically attended AEs but does not specifically query for occurrences of maternal medically attended RTIs.
Section 4.1 Analysis Sets definition	Descriptions of maternal and infant subject populations for analyses have been presented separately. Descriptions of infant subject populations for analyses have been corrected.	Adjusted to clarify differences in maternal / infant subject populations for analysis and corrected to remove inappropriate references to “post-vaccination” status in infant subjects, who are not, themselves, vaccinated.
Section 7.1, Sequence of Analyses	A total of 4 rather than 5 analyses will be performed. For the first 3 analyses, cutoff dates, number of subjects to be considered and parameters to be evaluated have been updated.	Updated for consistency with the increase in enrolment from ~ 150 to ~ 300 maternal and infant subjects.
Section 7.2, Statistical considerations for interim analysis	The original reference to “final data” was incorrect and has been replaced.	To more accurately reflect the sequence of analyses described in Section 7.1.
Section 9.1.4 Toxicity grading for lab parameters not covered under [Sheffield 2013]	Toxicity grading for lab parameters not covered under [Sheffield 2013] are now based on [Abbassi-Ghanavati 2009]	The previous grading scale for those parameters were based on non-pregnant women. Upon further review, it was determined that the grading is not appropriate for the pregnant population that is being enrolled in this study.
Section 5.2.2.1	Added analysis of the effect of the interval between vaccination and delivery on the antibody transfer	To have a better understanding of the effect of the interval between

Section # and Name	Description of Change	Brief Rationale
		vaccination and delivery on the antibody transfer
Section 8	Safety report display format for the first interim analysis changed from aggregated to by study group using Group A, B, C	This change was made per regulatory feedback and request

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Primary Safety objectives	Primary Safety endpoint(s)
To evaluate the safety and reactogenicity of a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery	Occurrence of solicited administration site and systemic events during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).
	Occurrence of any hematological (complete blood count with differential and platelet count) or biochemical (alanine amino-transferase, aspartate amino-transferase, creatinine, blood urea nitrogen) laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs (MAEs) from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery (Visit 6).	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.*
To evaluate the safety of the study vaccine, including neonatal AEs of special interest, in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 weeks after birth.	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia.* Occurrence of SAEs, AEs leading to study withdrawal and MAEs from birth up to 6 weeks after birth.

Primary Immunogenicity objectives	**Primary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects at Day 31 and at Delivery.	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).
To evaluate RSV-specific antibody levels in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine at birth j	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained).
To evaluate the transfer of RSV-specific antibodies from maternal subjects vaccinated with a single IM dose of study vaccine to their infants at the time of delivery.	The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations *or an infant blood sample collected within 3 days after birth (if no cord blood sample can be obtained).
Secondary Safety objectives	**Secondary Safety endpoints**
To evaluate the safety of a single IM dose of study vaccine in maternal subjects, up to 6 months after delivery	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs, and AEs leading to study withdrawal.
To evaluate the safety of the vaccine in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 1 year of age	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs.
To estimate the incidence of RSV-associated, medically attended RTIs (MA-RTIs) in maternal subjects vaccinated with a single IM dose of study vaccine, from vaccination up to 6 months post-delivery (Visit 8).	Occurrence of RSV-associated MA-RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)
To estimate the incidence of RSV-associated lower respiratory tract illness (LRTI), severe LRTI and very severe LRTI and RSV-associated hospitalization in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, from birth up to 6 months of age.	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions).

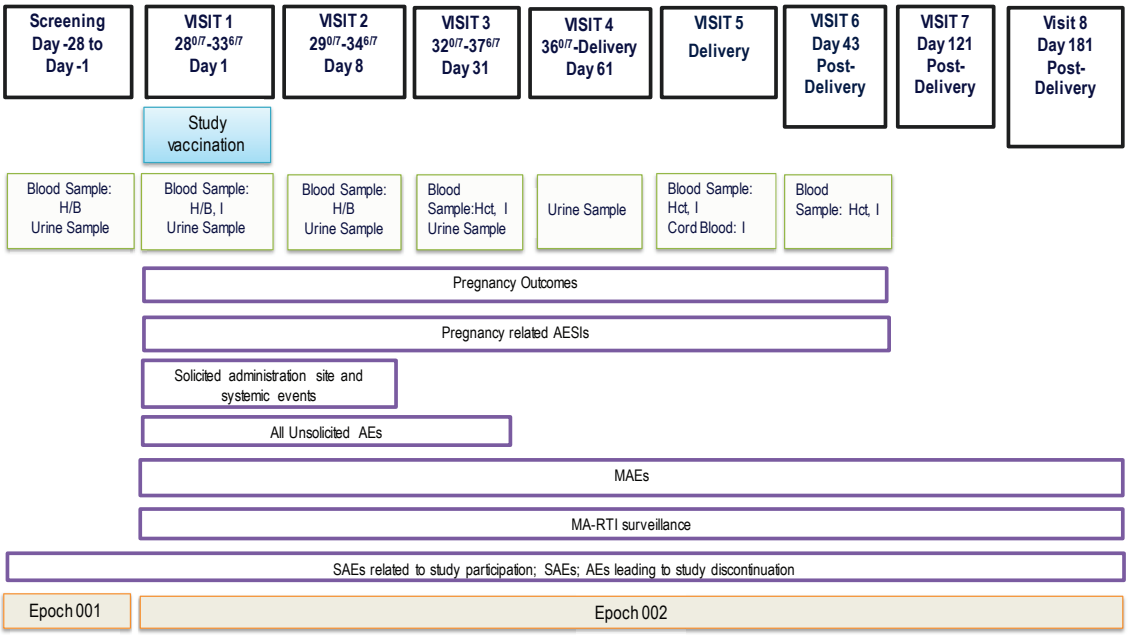
Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibodies against RSV-A at Day 43 after Delivery (Visit 6).	RSVPreF3 IgG-specific antibody concentration Neutralizing antibody titers against RSV-A Measured on the blood sample collected at Day 43 post- delivery (Visit 6).
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSV-B neutralizing antibodies at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).	Neutralizing antibody titers against RSV-B Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).
To evaluate RSV-specific antibodies in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 months after birth.	RSVPreF3 IgG-specific antibody concentration Neutralising antibody titres against RSV-A Neutralising antibody titres against RSV-B For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective). For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to treatment study intervention.
Tertiary objectives: To further evaluate the humoral response to the RSV maternal vaccine, which may include RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. To evaluate the presence of other respiratory viruses in nasal swabs collected from maternal subjects and their infants (via an Allplex Respiratory Viruses Panel or alternative, performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples.)	

*Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with GAIA assessment and level of diagnostic certainty when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category."

3. STUDY DESIGN

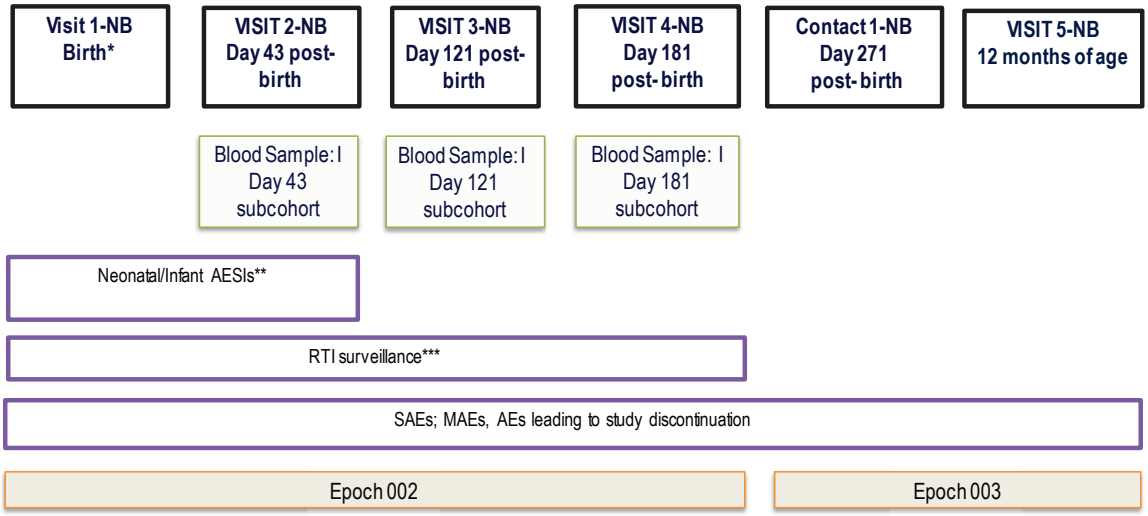
Figure 1 and Figure 2 provide overviews of the study design for maternal and infant subjects, respectively.

Figure 1 Overall design – maternal subjects



H/B= hematology/biochemistry, Hct- hematocrit; I= humoral immune response
If Screening blood sample collected ≤ 15 days before Visit 1, hematology/biochemistry not required at Visit 1
Subjects will be vaccinated year-round and will not be limited to seasonal enrolment
*Pregnancy-related AESIs identified after Day 43 will continue to be reported as such.

Figure 2 Overall design– infant subjects



NB = Newborn; I=humoral immune response: infants will be randomized 1:1:1 to one of the 3 subcohorts shown.
*Blood sample to be collected within 3 days after birth **ONLY** if a cord blood sample is not collected
**Neonatal AESIs identified after Day 43 (e.g., congenital anomalies) will continue to be reported as such.
***Infant subjects' parent(s)/LAR(s) will be contacted at least monthly to ensure RTI eDiary compliance.
Safety and disease surveillance data collected *after* Visit 4-NB will be reported in the database *in Epoch 003*.

- Study Type: self-contained.
- Experimental design: Phase II, observer-blind, randomised, placebo controlled, multi-centric, multi-country study with 3 parallel groups.
- Study Duration: Approximately 9 months (including the screening visit) for participating pregnant women; approximately 1 year after birth for participating infants.
- Control: Placebo.
- Epochs 001, 002 and 003 begin and end as described in Table 2.
- Blinding is as described in Table 2.
- Randomized intervention allocation: Approximately ***300*** eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio) using an automated internet based system (SBIR).The system's randomisation algorithm will use a minimisation procedure accounting for maternal age at the time of vaccination (≥18 and <35 years of age or ≥ 35 years of age), gestational age at the time of vaccination ($28^{0/7}$-$31^{0/7}$; $31^{1/7}$-$33^{6/7}$) and center. Minimisation factors will have equal weight in the minimisation algorithm.
- Study (intervention) groups are described in Table 2

Table 2 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Intervention name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)**	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	***100***	18 – 40 years	RSVPreF3_60	BS1_60	***33***	RSVMAT60_BS1	●	●	●
				BS2_60	***33***	RSVMAT60_BS2		●	
				BS3_60	***33***	RSVMAT60_BS3		●	
RSV MAT 120	***100***	18 – 40 years	RSVPreF3_120	BS1_120	***33***	RSVMAT120_BS1	●	●	●
				BS2_120	***33***	RSVMAT120_BS2		●	
				BS3_120	***33***	RSVMAT120_BS3		●	
Control	***100***	18 – 40 years	Control	BS1_C	***33***	Control_BS1	●	●	●
				BS2_C	***33***	Control_BS2		●	
				BS3_C	***33***	Control_BS3		●	

M=maternal subject; I=infant; Control = Placebo; Blood sampling subcohorts are abbreviated "BS1;" "BS2;" BS3" and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.

- Data collection: standardized Electronic Case Report Form (eCRF). Electronic diaries (e-diaries) for solicited ***event data, and notifications regarding occurrence of unsolicited events (including medically attended events and SAEs), and symptoms of respiratory tract illnesses in infant subjects.***
- Safety monitoring: This study will be monitored by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee (IDMC) external to GSK. The analyses for IDMC safety evaluations will be described in a separate SAP for IDMC.

4. ANALYSIS SETS

4.1. Definition

For purposes of analysis, the following analysis sets are defined ***(Amended 14-FEB-2020):***

4.1.1. Maternal Subjects

	Description
Analysis Set	**Maternal subjects**
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form.
Exposed	All maternal subjects who received at least 1 dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Full Analysis	All maternal subjects ***in the Exposed set*** who have post-vaccination immunogenicity data.
Per Protocol	All maternal subjects who received at least 1 dose of the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.
Unsolicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All maternal subjects ***in the*** Exposed Set who have solicited safety data

4.1.2. Infant subjects

	Description
Analysis Set	
Exposed	***Infants live-born to exposed maternal subjects***, whose parents/LARs completed the informed consent process and signed the informed consent form
Full Analysis	All infant subjects in the Exposed set who have post-delivery/birth immunogenicity data.
Per Protocol	All infant subjects in the Full Analysis set minus those who (a) were born less than 4 weeks post- maternal subject vaccination and/ or (b) have protocol deviations that lead to exclusion.
Unsolicited Safety	All infants in the exposed set for whom unsolicited AEs /not having unsolicited AEs are reported

4.1.3. Randomized Set

Randomized set will include all maternal subjects who are randomized and all of their randomized infants. The allocation in a group is done as function of the randomized intervention. Please note this set was not included in the protocol, but will be used later in one summary analysis, so it is added here for clarification.

4.1.4. Full Analysis Set

Full analysis set will be defined by time point. For infants, it will include all of the infants ***in the Exposed Set*** who have immunogenicity data at the corresponding time point after birth.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

Infants: Code 1030 (Study vaccine not administered at all, carry forward elimination from mother to infant), 800 (Fraudulent data), code 900 (invalid informed consent) and code 901 (invalid informed consent due to mother) will be used for identifying infants eliminated from ES

4.2.2. Elimination from Full Analysis Set (FAS)

4.2.2.1. Excluded subjects from FAS of maternal subjects

A maternal subject will be excluded from the FAS analysis under the following conditions

Table 3 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.

4.2.2.2. Excluded subjects from FAS of infant subjects

An infant subject will be excluded from the FAS analysis under the following conditions

Table 4 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all - mother	All	Safety, immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth* Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

#Carry forward elimination from mother to infant
Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
*cord blood sample or blood sample collected within 3 days after birth if cord blood sample is not collected

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

4.2.3.1. Excluded subjects from Per-protocol analysis set of maternal subjects

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

Table 5 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-40 years Gestational age at vaccination - 28 0/7 - 336/7	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 31, check the interval from vaccination to day 31 BS = 25 – 34 days; • For PPS at Delivery, check the interval from delivery to delivery BS = 0 – 3 days; • For PPS at Day 43 post-delivery, check the interval from delivery to day 43 post-delivery BS = 40 – 46 days	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

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

4.2.3.2. Excluded subjects from Per-protocol analysis set of infant subjects

An infant subject will be excluded from the PPS analysis under the following conditions

Table 6 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent - infant	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
1041#*	Maternal administration of concomitant vaccine(s) forbidden in the protocol up to Delivery	All	Immunogenicity
1050#	Maternal randomisation failure	All	Immunogenicity
1060#	Maternal randomisation code was broken	All	Immunogenicity
1070#	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070#	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070#	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070#	Study treatment administered while contraindicated	All	Immunogenicity
1080#	Vaccine temperature deviation	All	Immunogenicity
1090#	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) - infant	All	Immunogenicity
2011#	Protocol violation (inclusion/exclusion criteria) - mother	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2041#*	Maternal administration of any medication forbidden by the protocol up to Delivery	All	Immunogenicity
2041#*	Device, excluded by the protocol, was administered by mother up to Delivery	All	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2050#*	Maternal intercurrent medical conditions which are exclusionary as per protocol up to Delivery	All	Immunogenicity
2060#*	Maternal concomitant infection related to the vaccine which may influence immune response up to Delivery	All	Immunogenicity
2070#*	Maternal concomitant infection not related to the vaccine but may influence immune response up to Delivery	All	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule – infant: • For infants without cord blood, check the interval from birth to Visit 1-NB birth BS = 0 – 3 days; • For PPS at Day 43 post-birth, check the interval from birth to Day 43 BS = 40 – 46 days; • For PPS at Day 121 post-birth, check the interval from birth to Day 121 BS = 116 – 130 days; • For PPS at Day 181 post-birth, check the interval from birth to Day 181 BS = 166 - 195 days	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2120.Vx*	Obvious incoherence or abnormality or error in data	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
3100	Delivery happens less than 4 weeks post-vaccination.	All	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
#Carry forward elimination from mother to infant
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
BS- Blood Sample.

4.2.4. Elimination from unsolicited and solicited safety set

4.2.4.1. Excluded subjects

4.2.4.1.1. *Unsolicited safety set*

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.4.1.2. *Solicited safety set*

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

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1while the study specific data derivation rules and stat methods are described in section 9.

5.1. Demography

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

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

For all maternal subjects, demographic characteristics (e.g., age at vaccination (18 - <35; ≥ 35 years), gestational age at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), geographic ancestry will be summarized by group using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics.

For their infants, demographic characteristics (e.g., gestational age at time of delivery (> 37 weeks; ≤ 37 weeks), sex, weight, length, head circumference, geographic ancestry, apgar score), and lifestyle characteristics (e.g., living environment, household composition, breastfeeding, passive smoking and extent of contact with children less than 6 years of age) will be summarised by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

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

5.1.2. Additional considerations

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

Subgroup analysis for demographic characteristics by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth (> 37 weeks or ≤ 37 weeks) for infant subjects will also be performed on Enrolled Set, ES or PPS.

Subject disposition will be summarized by group using descriptive statistics:

- Number of maternal subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- Number of infants enrolled and withdrawn including withdrawal reasons will be tabulated by group, by sub-cohort within each group and overall.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set. The parameters include but may not be limited to systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiratory rate, height, weight and body mass index.

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

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

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

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol

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

	Primary Immunogenicity Endpoints	**Statistical Analysis Methods**
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).	For each assay, at each timepoint and by study group and age category (18 - <35 years; ≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline, at day 31 and at delivery will be explored using scatter plots of individual values. Between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A will be performed at Day31 and at Delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, age category at vaccination, center and the interval between vaccination and delivery as covariates if needed.

Cord blood/ placental transfer	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A	For each assay, the following analysis will be performed by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • The distribution of RSV-A and RSVPreF3 IgG-specific antibody titres/concentration from cord blood will be tabulated • For each assay, relationship between maternal antibody titers/concentrations and infant antibody titers/concentrations at the time of delivery will be evaluated graphically using scatter plots of individual results.
	• The ratio between cord blood and maternal RSVPreF3 IgG-specific antibody concentrations All 3 endpoints measured on blood samples collected from maternal subjects at delivery and either cord blood, or (if cord blood cannot be collected) infant blood samples collected within 3 days after birth	• Geometric mean of placental transfer will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer 1 will be tabulated with exact 95 % CI by study group. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks; ≤ 37 weeks), age category at vaccination, center and the interval between vaccination and delivery as covariates if appropriate. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at delivery will be explored using scatter plots of individual values.

	Secondary Immunogenicity Endpoints	**Statistical Analysis Methods**
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and • Neutralizing antibody titers against RSV B For RSV-A: Measured on the blood sample collected Day 43 post-delivery (Visit 6). • For RSV-B: Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3),, at	For each assay, at each timepoint and by study group and age category (18 - <35 years ;≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated

	Delivery (Visit 5) and at Day 43 post delivery (Visit 6).	• Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at baseline, at day 31, at delivery and at day 43 post-delivery will be explored using scatter plots of individual values. In addition, between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A and RSV-B will be performed at Day31, at Delivery and at Day 43 post-delivery using a mixed effect model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery if available as covariates if needed.
Infant subjects	• RSVPreF3 IgG-specific antibody concentration • Neutralising antibody titres against RSV-A • Neutralising antibody titres against RSV-B For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to intervention For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective).	For each assay, at each timepoint and by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. In addition, analyses will include exploratory evaluation of the persistence of RSV specific antibodies in infants through time, and half-life analysis modelling of logarithm transformed RSV antibody concentrations/titers over time. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery, and on blood samples collected at 6 weeks, 4 months and 6 months post-birth using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks ; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate and needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at delivery will be explored using scatter plots of individual values.

5.2.2. Additional considerations

Before unblinding occurs, the immunogenicity analysis will only be performed on Exposed Set. At the time of final analysis, the immunogenicity analysis will be performed on PPS.

5.2.2.1. Distribution analysis

RSV-A neutralizing antibody titers and RSV-B neutralizing antibody titers:

- Number and percentage of subjects with titers <128, ≥128, ≥256, ≥512, ≥1024, ≥2048, ≥4096, ≥8192 and >=16384 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 2, 4, 6, 8, 10 and 12 by pre-vaccination category (< 128, ≥128 and <256, ≥ 256 and <512, ≥ 512 and <1024, ≥1024 and <2048, ≥ 2048 and <4096, ≥ 4096 and <8192, ≥8192 and <16384) will be tabulated.

RSVPreF3 IgG-specific antibody concentrations:

- Number and percentage of subjects with concentrations <2048, ≥2048, ≥4096, ≥8192, ≥16384, ≥32768, ≥65536, ≥131072 will be tabulated.
- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 4, 6, 8, 10, 12, 14 and 16 by pre-vaccination category (< 2048, ≥2048 and <4096, ≥ 4096 and <8192, ≥ 8192 and <16384, ≥16384 and <32768, ≥ 32768 and <65536, ≥ 65536 and <131072, ≥131072) will be tabulated.

The thresholds for distribution tables of titres and concentrations and fold increase may be further adjusted at analysis as needed.

In addition, to assess the effect of the interval between vaccination and delivery on the antibody transfer, geometric mean of RSV-A neutralizing antibody titers, RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers from cord blood (or blood drawn from infants within 3 days after birth) will be tabulated with different categories of time (in weeks) from vaccination to delivery. This analysis will be performed for infants born at gestational age <37 weeks and those born at gestational age >=37 weeks. Associated scatter plots may also be provided as needed.

5.2.2.2. Ratio of fold increase analysis

Fold increase of RSVPreF3 IgG-specific antibody concentrations over fold increase of RSV-A neutralizing antibody titers (ratio of fold increase post- over pre-vaccination) will be tabulated using descriptive statistics. This analysis will include calculation on:

- Geometric mean ratios with corresponding 95% CIs of RSVPreF3 IgG-specific antibody concentration over RSV-A neutralizing antibody titers at pre-vaccination for each group and

- Geometric mean ratios with corresponding 95% CIs of fold increase post/pre (Day 31, Delivery and Day 43 post-delivery/Day 1) between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody titers for each group.

Similar analysis will be performed between RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers.

5.2.2.3. Between group analysis

This analysis is exploratory.

For the analysis of maternal subjects at each time point (Day 31, Delivery, and Day 43 post-delivery), the model will be explored and fitted via the proc mixed procedure according to the following code:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group ges_age_cat age_cat center;
  MODEL log_val = baseline group ges_age_cat age_cat
inter_vac_del center /ddfm=kenwardroger outp = pred;
  /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
RUN;
```

where log_val represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, group indicates the study group, ges_age_cat is the gestational age category at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), age_cat is the age category at vaccination (18 – <35 years and ≥35 years), inter_vac_del is the interval between vaccination and delivery (days). The inclusion of age category at vaccination, interval between vaccination and delivery, and center in the model depends on the availability of the variable (inter_val_del may not be available at Day 31 analysis) and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

For the analysis of infants at each time point (cord blood at Delivery, Day 43 post-birth, Day 121 post-birth, and Day 181 post-birth), similar model will be explored:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group center ges_age_cat ges_age_birth;
  MODEL log_val = baseline group ges_age_cat /*inter_vac_del*/
ges_age_birth center /ddfm=kenwardroger outp = pred;
 /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
   RUN;
```

Baseline is pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, ges_age_birth is gestational age category at birth (> 37 weeks; ≤ 37 weeks) for infants. With the inclusion of gestational age category at vaccination (ges_age_cat) in the model, this categorical variable ges_age_birth provides similar information as continuous variable inter_vac_del, therefore the inclusion of either variable in the model could be adjusted according to the analysis needs.

The ratio of GMTs/GMCs between vaccine groups and the corresponding 95% CI will then be constructed by exponentiating the mean difference and its confidence interval between vaccine groups on the logarithm10 scale estimated from the model. Summary tables will show adjusted GMT/GMC for vaccine groups, and ratios of GMTs/GMCs between vaccine groups along with the 95% CI.

If deemed necessary, an analysis of variance model for repeated measures will be fitted to assess the mean profile in each group over time for both maternal and infant subjects separately. Below is the sample SAS code for the analysis of maternal subjects, and similar codes could be explored for the analysis of infants.

```
PROC MIXED data=sero;
    CLASS subjid group visit age_cat center ges_age_cat;
    MODEL log_val = baseline group | visit age_cat ges_age_cat
inter_vac_del center/ddfm=kenwardroger outp = pred;
    RANDOM subjid;
    /*REPEATED visit/subject=subjid(group) type=un;*/
    LSMEANS group*visit/pdiff cl alpha=0.05;
RUN;
```

Summary tables will present adjusted GMT/GMC with 95% CI for each group at each timepoint.

5.2.2.4. Persistence and Half-life analysis of antibody level over time for infant subjects

This analysis is exploratory.

The decay of infant antibody levels over time will be analysed by a linear regression of the logarithm transformed of antibody levels. This analysis will be performed on PPS for infants in RSV vaccine group in terms of RSV-A neutralizing antibody titers, RSV-B neutralizing antibody titers and RSVPreF3 IgG-specific antibody concentrations.

A true, natural decay curve will be explored by stochastically reducing the sample to uninfected subjects only. The following steps will be taken to identify infected subjects (confirmed and suspected) to be eliminated from the sample:

- STEP 1: Infants with an RSV positive nasal swab during the study before time of blood sampling will be eliminated from the analysis because RSV infection may have contributed to their antibody levels which may no longer represent what was passively transferred from the mother.
- Infants whose mothers had an RSV positive nasal swab before or up to the time of delivery will be eliminated from the analysis. Maternal infection may contribute to post-vaccination increase in the levels of maternal antibodies, leading to higher placental antibody transfer to the fetus/infant, which would not reflect the effect of vaccination alone.
- STEP 2: Run the model and compute expected value based on the decay curve

- STEP 3: Subjects with an antibody titer at the blood sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected and then eliminated and the decay curve refined.
- STEP 4: Step 3 is repeated up to 5 times until the most accurate decay curve is established.

The natural decay of antibody level will be determined using linear regression between the logarithm transformed antibody level (Y) and time t (age in days) with subject as a random effect. All infants have RSV neutralizing antibodies measured at birth (cord blood) or within 3 days after birth, and each infant in PPS sub-cohort will have blood sampling for RSV neutralizing antibodies at one of the following time points: Day 43 post-birth, Day 121 post-birth or Day 181 post-birth. Therefore, in the natural decay model, each infant will have maximum 2 RSV neutralizing antibodies measures, one at birth or within 3 days after birth and the other at Day 43 post-birth, Day 121 post-birth or Day 181 post-birth depending on the sub-cohorts where the infants are.

The following SAS code will be explored:

```
PROC MIXED DATA=<filename>;
  CLASS PID;
  MODEL LOG_Y = t /s outp=pred;
  RANDOM Int t / sub=PID type=UN G GCORR;
RUN;
```

The choice of correlation structure and other parameters may be further adjusted according to the data and analysis needs.

The predicted value will be computed using the following formula

$$A_t = A_0 \exp(-K_e t)$$

where, A_t and A_0 are antibody titres at times t and zero, respectively, K_e is the constant rate of antibody change with time, defined as the estimate of model.

In addition, the half-life ($t_{1/2}$) of antibody (i.e. the time required for titre to decrease by one-half) will be displayed using the following equations of declining antibody titre:

$$\text{when } A_t = \tfrac{1}{2} A_0$$

$$t_{1/2} = 0.693 / K_e$$

A summary table will be prepared to show the number of infants included in the model, the model estimate of the antibody decay rate, and the half-life of the antibody.

In case cord blood samples are missing in 20% or more of infants in a single study group, separate analysis for infants with cord blood and infants with a blood sample within 3 days after birth will be performed.

5.2.2.5. ROC analysis (dose characterization)

This analysis is exploratory and complementary to traditional data analysis methods comparing post-vaccination immune responses among vaccine groups and will be performed on the PPS only if deemed necessary.

If immune response between active vaccination groups can't be differentiated using traditional approach, additional analyses using a generalized ROC (Receiver Operating Characteristics) method [Yu, 2018] will be performed for both RSV-A neutralizing antibody titers and RSVPreF3 IgG specific antibody concentrations at Day 31 and Delivery, and other timepoints if needed.

Two ROC Methods will be explored:

- ROC-P (ROC of post-dose levels) method: Post-vaccination antibody levels from 2 RSV vaccine groups (RSV MAT 60 and RSV MAT 120) will be pooled and used as a reference distribution.
- ROC-B (ROC relative to baseline) method: Overall pre-vaccination antibody levels from 2 RSV groups (RSV MAT 60 and RSV MAT 120) will be used as a reference distribution.

Different percentile (0% to 100%) thresholds from the reference distribution will be obtained. The percentage of subjects with post-vaccination antibody level higher than or equal to the percentile thresholds from the reference distribution will then be calculated for each vaccine group.

A figure will be provided showing the ROC curve with x-axis the percentile of the reference distribution and y-axis the percentage of subjects in each vaccine group with post-vaccination antibody levels higher than or equal to the percentile threshold of the reference distribution.

A summary table will be provided on the thresholds of e.g. 25%, 50% and 75% percentiles of the reference distribution and the percentage of subjects in each vaccine group with post-vaccination antibody level higher than or equal to these percentile thresholds.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in **maternal subjects** will include summaries by study group and age category (18 - < 35 years of age; ≥35 years of age; overall) of hematology and biochemistry results by grade and per time point, solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant subjects** will include summaries by study group and gestational age at birth (> 37 weeks or ≤ 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to

study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

All safety analyses will be performed on the Solicited Safety or Exposed sets.

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal subjects	Occurrence of Solicited administration site and systemic events that occur during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	The number and percentage with exact 95% CI of maternal subjects reporting each **Solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day (days 1 to 7) follow-up period after vaccination will be tabulated by maximum intensity per subject for each study vaccine group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of maternal subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 7-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).
	Occurrence of any protocol-specified hematological or biochemical laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)	The number and percentage of subjects with hematology and biochemistry results outside central laboratory normal ranges will be tabulated to show Day 8 versus baseline. The maximum grading as described in [Sheffield, 2013] and in the ***SPM*** from Screening up to Day 8 will also be tabulated.
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	The number and percentage of maternal subjects with **unsolicited** symptoms within 30 days after vaccination with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 related unsolicited symptoms and for MAEs. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 30-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for MAEs.
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically	The number and percentage of maternal subjects with - at least one SAE;

	attended AEs from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).	- at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). Outcomes are listed in Section 2.	The number and percentage of maternal subjects with each pregnancy outcome will be tabulated with its exact 95% CI by group. By subject listings of adverse pregnancy outcomes will be prepared but will not be released until the final, unblinded analysis has been completed.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post delivery; Visit 6**).** These events are listed in Section 2**.**	The number and percentage of maternal subjects with each pregnancy-related AESI will be tabulated with its exact 95% CI by group. By subject listings of pregnancy-related AESIs will be prepared but will not be released until the final, unblinded analysis has been completed.
Infant subjects	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These events are listed In Section 2. Occurrence of SAEs, AEs leading to study withdrawal and medically attended AEs from birth up to 6 weeks after birth.	The number and percentage of infant subjects with each neonatal AESI will be tabulated with its exact 95% CI by group. By-subject listings of neonatal AESIs will be prepared, but will not be released until the final, unblinded analysis has been completed. The number and percentage of infant subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
Secondary Safety Endpoints		**Statistical Analysis Methods**
Maternal subjects	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs and AEs leading to study withdrawal. Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)	The number and percentage of maternal subjects with at least one SAE, MAE from Day 1 up to 6 months after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared (but will not be released until the final, unblinded, analysis has been completed). The number and proportion of subjects with at least one RSV-associated MA- RTI (with 95 % CI) will be calculated and tabulated.
Infant subjects	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study	For each category: - SAE,

	withdrawal, and medically attended AEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs	- MAEs The number and proportion of infant subjects who experienced at least one event from birth up to 6 months after birth and the number and proportion of infant subjects who experienced at least one event from birth up to 1 year after birth will be tabulated with 95% CI by group. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared.
	From birth to 6 months after birth (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions in Section 4.2.6 in the protocol)	For each category: - RSV-associated LRTI, - Severe LRTI, - Very severe LRTI - RSV-associated hospitalization The number and proportion (with 95% CI) of subjects with at least one event will be calculated and tabulated by group.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

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

Table 7 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F (with 1 decimal) Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache		
Fatigue	0	Normal
Nausea	1	Mild: Easily tolerated
Vomiting	2	Moderate: Interferes with normal activity
Diarrhea	3	Severe: Prevents normal activity
Abdominal pain		

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

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

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

5.3.2.2. Exclusion of implausible solicited Event

Some local and systemic events will be directly measured by the subject and will be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 8 Implausible Solicited Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema	Measurements < 0 mm For subjects ≥ 6 years: ≥ 900 mm
Swelling	Measurements < 0 mm For subjects ≥ 6 years: ≥ 500 mm

5.3.2.3. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set

5.3.2.4. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Nausea	Nausea	10028813
Vomiting	Vomiting	10047700
Diarrhea	Diarrhea	10012727

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Abdominal pain	Abdominal pain	10000081
Headache	Headache	10019211

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

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

5.3.2.5. Analysis of RTI and LRTI

The analysis of RTI and LRTI will be performed on Exposed Set according to the case definitions in section 9.1.3. Separate listings of maternal MA-RTI and infant RTI/LRTI will be provided.

Further analysis with respect to the incidence of RSV LRTI by an exploratory case definition might be performed if deemed necessary.

5.3.2.6. Other analysis

Other safety analysis will be performed on Exposed Set.

For hematology and biochemistry lab results, the maximum grading as described in [Sheffield, 2013] and ***SPM*** will be used, see section 9.1.4 for details.

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination, up to 6 weeks post-delivery and up to 6 months post-delivery will be summarized by group. A listing will also be provided.

The number and percentage of infants taking concomitant medications from birth up to 6 weeks after birth, 6 months after birth and 1 year after birth will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses *(Amended 14-FEB-2020)*

7.1.1. First analysis

The **first analysis** will *be conducted after approximately 75 maternal subjects have completed Visit 3 (Day 31) andapproximately 24 maternal subjects and their infants have completed Visit 5 / Visit 1-NB (Delivery/Birth).*

By-study-group immunogenicity analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding). These analyses will include all available test results at:

- ***Visit 1 (Day 1) and Visit 3 (Day 31);***
- ***Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.***

Aggregate (blinded) safety analyses will be performed by the GSK Biologicals biostatistics team. These analyses will include all available data for:

- ***Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.***
- ***RTI surveillance data (including nasal swab test results).***

A report summarizing these results will be prepared but will not be made available to investigators.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.2. Second analysis

The **second analysis** will *be performed after approximately 24 maternal subjects and their infants have completed Visit 7 / Visit 3-NB (Day 121 post-delivery / birth).*

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results, at:

- ***Visit 1 (Day 1) and Visit 3 (Day 31).***
- ***Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.***

- ***Visit 6 / Visit 2-NB (Day 43 post delivery).***
- ***Visit 3-NB (Day 121 post-delivery).***

By-study-group safety analyses will include the following data from those subjects who have reached the Day 43 post-delivery visit:

- ***Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.***
- ***RTI surveillance data (including nasal swab test results).***

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified).

Blinded SAE and AESI listings for all subjects will also be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.3. Third analysis

The **third analysis** will be performed ***after approximately 150 maternal and infant subjects have completed Visit 8/Visit 4-NB (Day 181 post-delivery/birth).***

By-study-group immunogenicity and by-study-group safety analyses will be performed by an independent statistician not affiliated with the project (to preserve the observer blinding).

By-study-group immunogenicity analyses will include all available test results at:

- ***Visit 1 (Day 1) and Visit 3 (Day 31);***
- ***Visit 5 (delivery; maternal blood sample and cord blood). If no cord blood was collected, test results for the infant blood sample collected within 3 days post birth (Visit 1-NB) will also be evaluated.***
- ***Visit 6 / Visit 2-NB (Day 43 post delivery);***
- ***Visit 3-NB (Day 121 post-delivery)***
- ***Visit 4-NB (Day 181 post-delivery)***

By-study-group safety analyses will include the following data from all ~300 subjects who have reached the Day 43 post-delivery visit:

- ***Solicited events, unsolicited AEs for 30 days post-dose, MAEs, SAEs and AESIs.***
- ***RTI surveillance data (including nasal swab test results).***

Safety results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be masked (i.e. the group in which this event occurred will not be identified).

In addition, blinded SAE and AESI listings for all subjects will be provided.

The results will be summarized in an Investigator Brochure update.

No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.4. Final analysis

The **final** analysis ***will evaluate all data pertaining to primary and secondary safety and immunogenicity endpoints.*** It will be performed ***by the GSK Biologicals biostatistics team*** when all ***primary and secondary endpoint*** data up to study end ***(last Visit 5-NB)*** are available.

Results will be presented in a clinical study report. This report will include results summarized by study group as well as individual (by subject) data / data listings, and will be made available to investigators.

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 ***clinical*** study report**.**

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

7.2. Statistical considerations for interim analyses *(Amended 14-Feb-2020)*

The first 3 analyses will be descriptive. Therefore, the conduct of these analyses has no impact on interpretation of study results.

8. CHANGES FROM PLANNED ANALYSES

To take a more practical approach, subgroup analysis of safety by age category at vaccination (18 - <35; ≥ 35 years) in maternal subjects will include summaries of pregnancy outcomes, pregnancy related AESIs, SAEs, MAEs and MA-RTIs.

Subgroup analysis of safety by gestational age at birth (> 37 weeks or ≤ 37 weeks) in infant subjects will include summaries of neonatal AESIs, MAEs, SAEs, and occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

Subgroup analysis on other safety summaries will be performed if deemed necessary.

Subgroup analysis of immunogenicity by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth ((> 37 weeks or ≤ 37 weeks) for infants will include analysis of GMT(C) and GMR calculation at each time point and geometric mean of placental transfer.

Subgroup analysis on other immunogenicity analysis will be performed if deemed necessary.

After protocol amendment 1 was finalized, FDA requested that safety data for the first interim analysis be summarized by-study-group and performed by an independent statistician not affiliated with the project. Results will be presented in a blinded manner: Groups will be labelled A, B, C instead of using the real study group labels. For each study group, summary tables may indicate only the number of subjects who reported the event (neither total N per group nor percentages will be supplied). Where indicated the number of subjects who reported the event might in itself pose a risk of unblinding, additional masking will be performed by the independent statistician. Detailed information can be found in the TFL TOC document.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Data derivation

9.1.1. Gestational age at vaccination

Gestational age at vaccination in weeks for maternal subjects will be calculated based on estimated date of delivery and date of vaccination.

9.1.2. Immunogenicity

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

- For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
- For the between group assessments, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

The GMT/GMC and its 95% CI will be obtained by exponentiating the mean and its 95% CI of the log-transformed titres/concentrations. All CI computed will be two-sided 95% CI.

Placental transfer is defined as the ratio of RSVPreF3 IgG-specific antibody concentrations between cord blood (or blood sample from infants collected within 3 days after birth if cord blood is not available) and maternal blood sample at delivery (or within 3 days after delivery if blood sample is not collected during delivery).

9.1.2.1. Assay cut-offs for serology results

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

System	Component	Method	Unit	Cut-off *(LLOQ)*	*ULOQ*
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	ED60	18	*21654*
Serum	RSVPreF3 IgG antibody concentrations	ELISA	EU/mL	*25*	*143000*
Serum	RSV-B Neutralising Antibody	NEUTRALISATION	ED60	*TBD*	*TBD*

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis, ***which would not lead to SAP amendment.***

9.1.3. RTI and LRTI

Cases will be classified (during data analyses) according to the definitions that follow.

Table 9 MA-RTI case definitions for data analysis in maternal subjects

RSV-MA-RTI	Medically attended visit for RTI symptoms AND Confirmed RSV infection [1, 2]
RSV hospitalization	Confirmed RSV infection AND Hospitalized for acute medical condition [3]
All-cause MA- RTI	Medically attended visit for RTI symptoms

[1] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol

[2] RSV (nasal swab) sampling and testing as specified in Table 11 of the Protocol.

[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

MA-RTI = Maternal, medically attended respiratory tract illness

Table 10 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection [4]
RSV-LRTI	History of cough OR difficulty in breathing [1] AND SpO_2 < 95%[2], OR RR increase [3] AND Confirmed RSV infection [4]
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%[2], OR lower chest wall in-drawing
RSV-very severe LRTI	Meeting the case definition of RSV-LRTI AND SpO2 < 90%[2], OR inability to feed OR failure to respond / unconscious
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing [1] AND SpO2 < 95% [2], OR RR increase [3]

Definitions based on [Modjarrad., 2016]
RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.

[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnea).

[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.

[3] RR increase defined as:
> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)

[4] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol

[5] RSV (nasal swab) sampling and testing as specified in Table 12 of the Protocol

[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose, wheezing or difficulty breathing with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed.

9.1.4. Hematology and Biochemistry parameters

The table below shows the toxicity grading during the second and third trimester of pregnancy based on [Sheffield, 2013]

Table 11 Laboratory values during the second and third trimester of pregnancy

Serum chemistries	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.8 mg/dL		0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
BUN	3.0-13.0 mg/dL		14.0-19.0	20.0-30.0	>30	Required dialysis
Haematology	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – gm/dL	9.7-14.8 g/dL		9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.6-14.8 x 1000cell/mm^3	High	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	0.9-3.9 x 1000cell/mm^3	High	>3.9-5.0	>5.0		
		Low	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.8-12.3 x 1000cell/mm^3		<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	155-409 x 1000 L^{-1}	Low	125-154	100-124	25-99	<25
		High	410-499	500-749	750-1000	>1000
Liver Function Tests	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	3-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate

Serum chemistries	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.9 mg/dL		1.0-1.2	1.3-1.6	1.7-2.5	>2.5 or required dialysis
BUN	3.0-11.0 mg/dL		12.0-19.0	20.0-30.0	>30	Required dialysis
Liver Function Tests	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	4-32 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-25 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Haematology	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – g/dL	9.5-15.0 g/dL		9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.9-16.9 x 1000cell/mm^3	High	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	1.0-3.6 x 1000cell/mm^3	High	>3.6-5.0	>5.0		
		Low	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.9-13.1 x 1000cell/mm^3		<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.4 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	146-429 x 1000 L^{-1}	Low	125-146	100-124	25-99	<25
		High	430-499	500-749	750-1000	>1000

Adapted from [Sheffield, 2013]
ULN: upper limit of normal.

Table below shows the toxicity grading for lab parameters that are not covered in [Sheffield, 2013] but calculated based on the references and guidance in ***[Abbassi-Ghanavati, 2009]***

Laboratory Parameter	Grade 1	Grade 2	Grade 3
Hematocrit-2nd trimester N 30.0-39.0 (%)	27-29.9 39.1-42.9	24-26.9 43-46.8	≤ 23.9 ≥46.9
Hematocrit-3rd trimester N 28.0-40.0 (%)	25.2- 27.9 40.1-44	22.4-25.1 44.1-48	≤22.3 ≥48.1
Mean Corpuscular Volume MCV 2nd N 82-97 (μm^3)	73.8-81.9 97.1-106.7	65.6-73.7 106.8-116.4	≤65.5 ≥116.5
Mean Corpuscular Volume MCV 3rd N 81-99 (μm^3)	72.9-80.9 99.1-108.9	64.8-72.8 109-118.8	≤64.7 ≥118.9
RBC - 2nd trimester N 2.81 – 4.49	2.6-2.8 4.5-4.9	2.3 – 2.5 5.0-5.3	≤2.2 ≥5.4
RBC - 3rd trimester N 2.71-4.43	2.5-2.7 4.4-4.8	2.2 – 2.4 4.9-5.3	≤2.1 ≥5.4

9.2. Statistical Method

Study specific statistical methods for immunogenicity analysis are described in section 5.2.2.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event.

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

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

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. *Studies with electronic diaries*

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

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

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

10.1.3.8. Onset day

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

10.1.3.9. Duration of events

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

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

10.1.3.10. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.11. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

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

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

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

10.1.4.2. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.3. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document. Please note the protocol of this study was developed based on V17 template and the term ‘solicited administration site event’ and ‘solicited systemic event’ are used, however, at the development of the TFL TOC, only V16 standard catalog is available and still ‘solicited local adverse event’ and ‘solicited general adverse event’ are used in the TFL mocks per this standard.

11. REFERENCES

Abbassi-Ghanavati M, Greer LG, and Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Laboratory Values in Pregnancy. 2009, VOL. 114 NO. 6.

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Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS; WHO RSV Vaccine Consultation Expert Group. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. Vaccine. 2016;34(2):190-7.

Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments. Vaccine 2013; 31:4264-4273.

Yu L, Esser M, Falloon J et. al. Generalized ROC methods for immunogenicity data analysis of vaccine phase I studies in a seropositive population, Human Vaccines & Immunotherapeutics. 2018; 14 (11):2692-2700.

	Statistical Analysis Plan
Detailed Title:	A Phase II, randomised, observer-blind, placebo controlled multi-country study to assess the safety, reactogenicity and immunogenicity of a single intramuscular dose of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women aged 18 to 40 years and infants born to vaccinated mothers
eTrack study number and Abbreviated Title	209544 (RSV MAT-004)
Scope:	All analyses for the primary and secondary objectives of the study.
Date of Statistical Analysis Plan	Final: 29 October 2019

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

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GMR	Geometric mean of ratio
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
LRTI	Lower Respiratory Tract Illness
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NB	Newborn
PD	Protocol Deviation
PPS	Per-Protocol Set
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULOQ	Upper Limit of Quantification

1. DOCUMENT HISTORY

Date	Description	Protocol Version
29 OCT 2019	first version	Final: 09 JUL 2019

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Primary Safety objectives	Primary Safety endpoint(s)
To evaluate the safety and reactogenicity of a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery	Occurrence of solicited administration site and systemic events during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).
	Occurrence of any hematological (complete blood count with differential and platelet count) or biochemical (alanine amino-transferase, aspartate amino-transferase, creatinine, blood urea nitrogen) laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs (MAEs) from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single IM dose of study vaccine administered to maternal subjects, from Visit 1 up to 6 weeks after delivery (Visit 6).	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include live birth with no congenital anomalies, live birth with congenital anomalies, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with congenital anomalies, elective/therapeutic termination with no congenital anomalies and elective/therapeutic termination with congenital anomalies.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.*
To evaluate the safety of the study vaccine, including neonatal AEs of special interest, in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 weeks after birth.	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia.* Occurrence of SAEs, AEs leading to study withdrawal and MAEs from birth up to 6 weeks after birth.

Primary Immunogenicity objectives	**Primary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects at Day 31 and at Delivery.	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).
To evaluate RSV-specific antibody levels in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine at birth j	RSVPreF3 IgG-specific antibody concentration, and Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained).
To evaluate the transfer of RSV-specific antibodies from maternal subjects vaccinated with a single IM dose of study vaccine to their infants at the time of delivery.	The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations *or an infant blood sample collected within 3 days after birth (if no cord blood sample can be obtained).
Secondary Safety objectives	**Secondary Safety endpoints**
To evaluate the safety of a single IM dose of study vaccine in maternal subjects, up to 6 months after delivery	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs, and AEs leading to study withdrawal.
To evaluate the safety of the vaccine in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 1 year of age	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs.
To estimate the incidence of RSV-associated, medically attended RTIs (MA-RTIs) in maternal subjects vaccinated with a single IM dose of study vaccine, from vaccination up to 6 months post-delivery (Visit 8).	Occurrence of RSV-associated MA-RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)
To estimate the incidence of RSV-associated lower respiratory tract illness (LRTI), severe LRTI and very severe LRTI and RSV-associated hospitalization in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, from birth up to 6 months of age.	From birth to 6 months (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions).

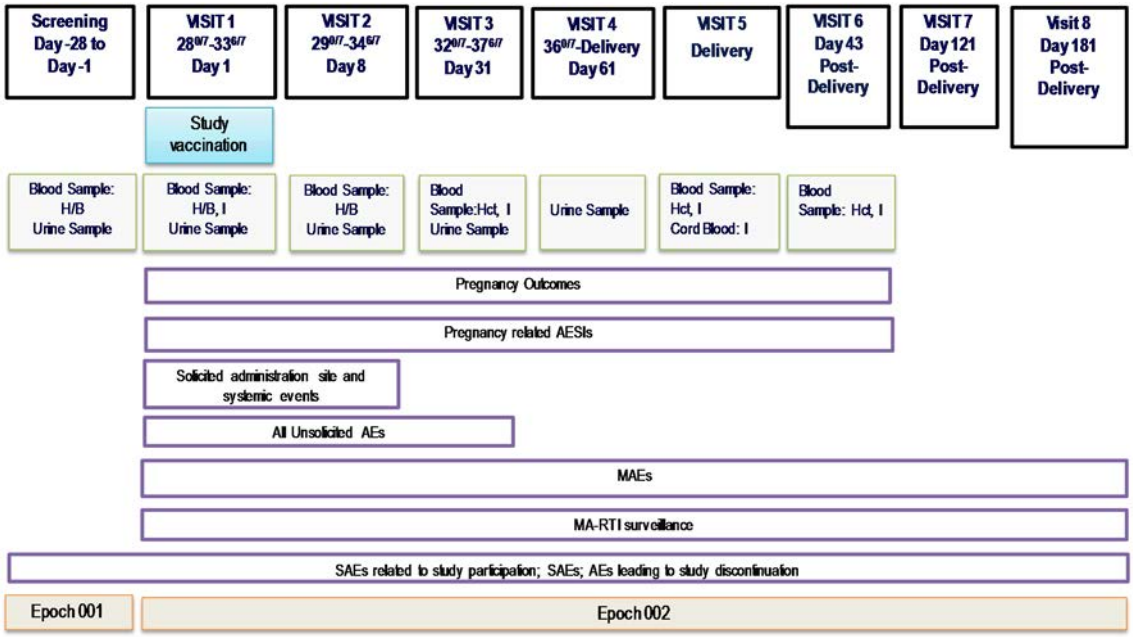
Secondary immunogenicity objectives	**Secondary Immunogenicity endpoints**
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibodies against RSV-A at Day 43 after Delivery (Visit 6).	RSVPreF3 IgG-specific antibody concentration Neutralizing antibody titers against RSV-A Measured on the blood sample collected at Day 43 post- delivery (Visit 6).
To evaluate the immunogenicity of a single IM dose of study vaccine in maternal subjects in terms of RSV-B neutralizing antibodies at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).	Neutralizing antibody titers against RSV-B Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), at Delivery (Visit 5) and at Day 43 post-delivery (Visit 6).
To evaluate RSV-specific antibodies in infants born to maternal subjects who were vaccinated with a single IM dose of study vaccine, up to 6 months after birth.	RSVPreF3 IgG-specific antibody concentration Neutralising antibody titres against RSV-A Neutralising antibody titres against RSV-B For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective). For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to treatment study intervention.
Tertiary objectives: To further evaluate the humoral response to the RSV maternal vaccine, which may include RSVpreF3 specific IgG subclasses, antibodies competing for binding to specific RSVpreF3 epitopes, and other exploratory endpoints. To evaluate the presence of other respiratory viruses in nasal swabs collected from maternal subjects and their infants (via an Allplex Respiratory Viruses Panel or alternative, performed for RSV A/B-positive samples and if deemed necessary for RSV A/B-negative samples.)	

*Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with GAIA assessment and level of diagnostic certainty when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category."

3. STUDY DESIGN

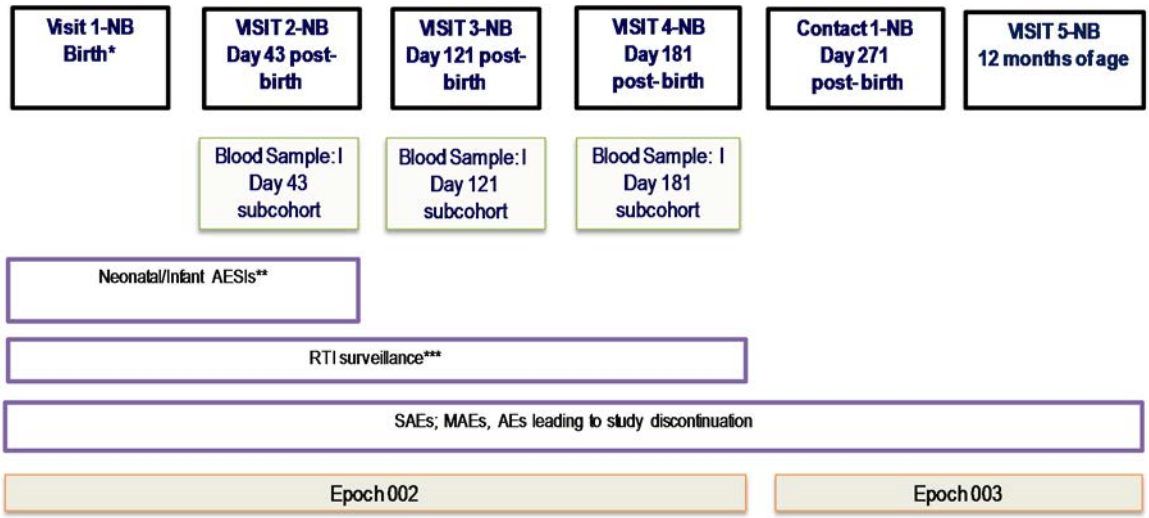
Figure 1 and Figure 2 provide overviews of the study design for maternal and infant subjects, respectively.

Figure 1 Overall design – maternal subjects



H/B= hematology/biochemistry, Hct- hematocrit; I= humoral immune response
If Screening blood sample collected ≤ 15 days before Visit 1, hematology/biochemistry not required at Visit 1
Subjects will be vaccinated year-round and will not be limited to seasonal enrolment
*Pregnancy-related AESIs identified after Day 43 will continue to be reported as such.

Figure 2 Overall design– infant subjects



NB = Newborn; I=humoral immune response: infants will be randomized 1:1:1 to **one** of the 3 subcohorts shown.
*Blood sample to be collected within 3 days after birth **ONLY** if a cord blood sample is not collected
**Neonatal AESIs identified after Day 43 (e.g., congenital anomalies) will continue to be reported as such.
***Infant subjects' parent(s)/LAR(s) will be contacted at least monthly to ensure RTI eDiary compliance.
Safety and disease surveillance data collected *after* Visit 4-NB will be reported in the database *in Epoch 003*.

- Study Type: self-contained.
- Experimental design: Phase II, observer-blind, randomised, placebo controlled, multi-centric, multi-country study with 3 parallel groups.
- Study Duration: Approximately 9 months (including the screening visit) for participating pregnant women; approximately 1 year after birth for participating infants.
- Control: Placebo.
- Epochs 001, 002 and 003 begin and end as described in Table 2.
- Blinding is as described in Table 2.
- Randomized intervention allocation: Approximately 150 eligible pregnant women will be randomly assigned to 3 study (intervention) groups in a 1:1:1 ratio and at the same time, their (as yet unborn) infants will be randomly assigned to 3 blood sampling subcohorts (also in a 1:1:1 ratio) using an automated internet based system (SBIR).The system's randomisation algorithm will use a minimisation procedure accounting for maternal age at the time of vaccination (≥18 and <35 years of age or ≥ 35 years of age), gestational age at the time of vaccination ($28^{0/7}$-$31^{0/7}$; $31^{1/7}$-$33^{6/7}$) and center. Minimisation factors will have equal weight in the minimisation algorithm.
- Study (intervention) groups are described in Table 2

Table 2 Study groups, subcohorts, interventions, epochs and blinding foreseen in the study

							Epochs (Blinding)		
Study groups (Maternal subjects, allocated 1:1:1)	**Approximate Number of maternal subjects**	**Age of maternal subject at enrolment (Min/Max)**	**Intervention name**	**Blood sample subcohorts (infant subjects, allocated 1:1:1 within each maternal study group)**	**Approximate Number of infant subjects**	**Study groups for randomization (Allocation 1:1:1:1:1:1:1:1:1)**	**Epoch 001 Maternal subjects Only (Screening)**	**Epoch 002 Maternal subjects V1-V8 Infant subjects V1-NB – V4NB (observer-blind)**	**Epoch 003 Infant subjects only Contact 1-NB – V5-NB (single-blind)**
RSV MAT 60	50	18 – 40 years	RSVPreF3_60	BS1_60	16	RSVMAT60_BS1	●	●	●
				BS2_60	16	RSVMAT60_BS2		●	
				BS3_60	16	RSVMAT60_BS3		●	
RSV MAT 120	50	18 – 40 years	RSVPreF3_120	BS1_120	16	RSVMAT120_BS1	●	●	●
				BS2_120	16	RSVMAT120_BS2		●	
				BS3_120	16	RSVMAT120_BS3		●	
Control	50	18 – 40 years	Control	BS1_C	16	Control_BS1	●	●	●
				BS2_C	16	Control_BS2		●	
				BS3_C	16	Control_BS3		●	

M=maternal subject; I=infant; Control = Placebo; Blood sampling subcohorts are abbreviated “BS1;” “BS2;” BS3” and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.

- Data collection: standardized Electronic Case Report Form (eCRF). Electronic diaries (e-diaries) for solicited adverse events and medically attended respiratory tract illnesses in maternal subjects, and for respiratory tract illnesses in infant subjects.
- Safety monitoring: This study will be monitored by a blinded safety review team (SRT) composed of GSK RSV team members, and by an unblinded, independent data monitoring committee (IDMC) external to GSK. The analyses for IDMC safety evaluations will be described in a separate SAP for IDMC.

4. ANALYSIS SETS

4.1. Definition

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

Analysis Set	Description
Enrolled	All maternal subjects who completed / infant subjects whose parents/LARs completed the informed consent process and signed the informed consent form
Exposed	All maternal subjects who received at least 1 dose of the study intervention, and all of their enrolled infants. The allocation in a group is done in function of the administered intervention.
Full Analysis	All maternal subjects who received at least 1 dose of the study intervention and have post-vaccination immunogenicity data. All of their enrolled infants who have post-vaccination immunogenicity data.
Per Protocol	All maternal subjects who received at least 1 dose of the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion. All of their enrolled infants in the Full Analysis set minus those with protocol deviations that lead to exclusion and/or who delivered less than 4 weeks post-vaccination.
Unsolicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs. All of their enrolled infants who report unsolicited AEs/report not having unsolicited AEs.
Solicited Safety	All maternal subjects who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data

4.1.1. Randomized Set

Randomized set will include all maternal subjects who are randomized and all of their randomized infants. The allocation in a group is done as function of the randomized intervention. Please note this set was not included in the protocol, but will be used later in one summary analysis, so it is added here for clarification.

4.1.2. Full Analysis Set

Full analysis set will be defined by time point. For infants, it will include all of the enrolled infants who have immunogenicity data at the corresponding time point after birth.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Exposed Set (ES)

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

Infants: Code 1030 (Study vaccine not administered at all, carry forward elimination from mother to infant), 800 (Fraudulent data), code 900 (invalid informed consent) and code 901 (invalid informed consent due to mother) will be used for identifying infants eliminated from ES

4.2.2. Elimination from Full Analysis Set (FAS)

4.2.2.1. Excluded subjects from FAS of maternal subjects

A maternal subject will be excluded from the FAS analysis under the following conditions

Table 3 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.

4.2.2.2. Excluded subjects from FAS of infant subjects

An infant subject will be excluded from the FAS analysis under the following conditions

Table 4 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all - mother	All	Safety, immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth* Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity

#Carry forward elimination from mother to infant
Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
*cord blood sample or blood sample collected within 3 days after birth if cord blood sample is not collected

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

4.2.3.1. Excluded subjects from Per-protocol analysis set of maternal subjects

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

Table 5 Elimination code and condition for maternal subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 18-40 years Gestational age at vaccination - 28 0/7 - 336/7	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 31, check the interval from vaccination to day 31 BS = 28 – 34 days; • For PPS at Delivery, check the interval from delivery to delivery BS = 0 – 3 days; • For PPS at Day 43 post-delivery, check the interval from delivery to day 43 post-delivery BS = 40 – 46 days	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2100.Vx	Serological results not available post-vaccination	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 3/Day 31, Visit 5/Delivery Visit 6/Day 43 Post-Delivery	Immunogenicity

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

4.2.3.2. Excluded subjects from Per-protocol analysis set of infant subjects

An infant subject will be excluded from the PPS analysis under the following conditions

Table 6 Elimination code and condition for infant subjects

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent - infant	All	All
901#	Invalid informed consent - mother	All	All
1030#	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
1041#*	Maternal administration of concomitant vaccine(s) forbidden in the protocol up to Delivery	All	Immunogenicity
1050#	Maternal randomisation failure	All	Immunogenicity
1060#	Maternal randomisation code was broken	All	Immunogenicity
1070#	Subjects got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070#	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
1070#	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070#	Study treatment administered while contraindicated	All	Immunogenicity
1080#	Vaccine temperature deviation	All	Immunogenicity
1090#	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) - infant	All	Immunogenicity
2011#	Protocol violation (inclusion/exclusion criteria) - mother	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2041#*	Maternal administration of any medication forbidden by the protocol up to Delivery	All	Immunogenicity
2041#*	Device, excluded by the protocol, was administered by mother up to Delivery	All	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response - infant	Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2050#*	Maternal intercurrent medical conditions which are exclusionary as per protocol up to Delivery	All	Immunogenicity
2060#*	Maternal concomitant infection related to the vaccine which may influence immune response up to Delivery	All	Immunogenicity
2070#*	Maternal concomitant infection not related to the vaccine but may influence immune response up to Delivery	All	Immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2090.Vx	Subjects did not comply with blood sample schedule – infant: • For infants without cord blood, check the interval from birth to Visit 1-NB birth BS = 0 – 3 days; • For PPS at Day 43 post-birth, check the interval from birth to Day 43 BS = 40 – 46 days; • For PPS at Day 121 post-birth, check the interval from birth to Day 121 BS = 116 – 130 days; • For PPS at Day 181 post-birth, check the interval from birth to Day 181 BS = 166 - 195 days	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2100.Vx	Serological results not available	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth Visit3-NB/Day 121 post-birth Visit4-NB/Day 181 post-birth	Immunogenicity
3100	Delivery happens less than 4 weeks post-vaccination.	All	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
#Carry forward elimination from mother to infant
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
BS- Blood Sample.

4.2.4. Elimination from unsolicited and solicited safety set

4.2.4.1. Excluded subjects

4.2.4.1.1. *Unsolicited safety set*

Code 1030 (Study vaccine not administered at all), code 800 (fraudulent data) and code 900 (invalid informed consent) and code 1150 (no post-vaccination safety data) will be used for identifying subjects eliminated from the unsolicited safety set.

4.2.4.1.2. *Solicited safety set*

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

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1while the study specific data derivation rules and stat methods are described in section 9.

5.1. Demography

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

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

For all maternal subjects, demographic characteristics (e.g., age at vaccination (18 - <35; ≥ 35 years), gestational age at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), geographic ancestry will be summarized by group using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics.

For their infants, demographic characteristics (e.g., gestational age at time of delivery (> 37 weeks; ≤ 37 weeks), sex, weight, length, head circumference, geographic ancestry, apgar score), and lifestyle characteristics (e.g., living environment, household composition, breastfeeding, passive smoking and extent of contact with children less than 6 years of age) will be summarised by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

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

5.1.2. Additional considerations

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

Subgroup analysis for demographic characteristics by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth (> 37 weeks or ≤ 37 weeks) for infant subjects will also be performed on Enrolled Set, ES or PPS.

Subject disposition will be summarized by group using descriptive statistics:

- Number of maternal subjects screened, randomised, vaccinated and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- Number of infants enrolled and withdrawn including withdrawal reasons will be tabulated by group, by sub-cohort within each group and overall.

Vital signs will be summarized by group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and Per-protocol Set. The parameters include but may not be limited to systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiratory rate, height, weight and body mass index.

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

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

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

5.2. Immunogenicity

5.2.1. Analysis of immunogenicity planned in the protocol

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

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3), and at Delivery (Visit 5).	For each assay, at each timepoint and by study group and age category (18 - <35 years; ≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline, at day 31 and at delivery will be explored using scatter plots of individual values. Between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A will be performed at Day31 and at Delivery using a mixed effect model on the logarithm_{10} transformation of the concentrations/titers, and including the pre-vaccination logarithm_{10} transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, age category at vaccination, center and the interval between vaccination and delivery as covariates if needed.
Cord blood/ placental transfer	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A	For each assay, the following analysis will be performed by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • Geometric Mean Titers (GMTs)/ Geometric Mean Concentrations(GMCs) will be tabulated with 95% CI and represented graphically. • The distribution of RSV-A and RSVPreF3 IgG-specific antibody titres/concentration from cord blood will be tabulated • For each assay, relationship between maternal antibody titers/concentrations and infant antibody titers/concentrations at the time of delivery will be evaluated graphically using scatter plots of individual results.

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
	• The ratio between cord blood and maternal RSVPreF3 IgG-specific antibody concentrations All 3 endpoints measured on blood samples collected from maternal subjects at delivery and either cord blood, or (if cord blood cannot be collected) infant blood samples collected within 3 days after birth	• Geometric mean of placental transfer will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ≥ 1 will be tabulated with exact 95 % CI by study group. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks; ≤ 37 weeks), age category at vaccination, center and the interval between vaccination and delivery as covariates if appropriate. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at delivery will be explored using scatter plots of individual values.

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal subjects	• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and • Neutralizing antibody titers against RSV B For RSV-A: Measured on the blood sample collected Day 43 post-delivery (Visit 6). • For RSV-B: Measured on blood samples collected from vaccinated maternal subjects at Day 1 before vaccination (Visit 1), Day 31 (Visit 3),, at Delivery (Visit 5) and at Day 43 post delivery (Visit 6).	For each assay, at each timepoint and by study group and age category (18 - <35 years ;≥ 35 - years; overall): • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference. • Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI. • The distribution of antibody titres/concentration will be tabulated • Distribution of the fold increase of the antibody titres/concentrations (post- versus pre-vaccination) will be tabulated by pre-specified pre-vaccination titre category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at baseline, at

Primary Immunogenicity Endpoints		Statistical Analysis Methods
		day 31, at delivery and at day 43 post-delivery will be explored using scatter plots of individual values. In addition, between group evaluation of vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations and Neutralizing antibody titers against RSV-A and RSV-B will be performed at Day31, at Delivery and at Day 43 post-delivery using a mixed effect model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers, the vaccine groups, gestational age at vaccination, and the interval between vaccination and delivery if available as covariates if needed.
Infant subjects	• RSVPreF3 IgG-specific antibody concentration • Neutralising antibody titres against RSV-A • Neutralising antibody titres against RSV-B For all 3 RSV-specific antibody assessments: measured in a subcohort of infants at Day 43 after birth (sub-cohort V2-NB), in a subcohort of infants at Day 121 (sub-cohort V3-NB) after birth and in a subcohort of infants at D181 after birth (sub-cohort V4-NB). Each infant will be randomly assigned to 1 of these 3 cohorts at the time of maternal randomization to intervention For neutralizing antibody titers against RSV-B only: measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained). (Note: RSV-A neutralizing antibody at birth is a primary immunogenicity objective).	For each assay, at each timepoint and by study group • Antibody titres/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. In addition, analyses will include exploratory evaluation of the persistence of RSV specific antibodies in infants through time, and half-life analysis modelling of logarithm transformed RSV antibody concentrations/titers over time. Between group evaluation on vaccine formulations in terms of RSVPreF3 IgG-specific antibody concentrations / neutralizing antibody titers will be performed on cord blood at Delivery, and on blood samples collected at 6 weeks, 4 months and 6 months post-birth using a mixed effect model on the logarithm10 transformation of the concentrations/titers, including the pre-vaccination logarithm$_{10}$ transformation of the concentrations/titers from maternal subjects, the vaccine groups, gestational age at vaccination, gestational age at birth (> 37 weeks ; ≤ 37 weeks), and the interval between vaccination and delivery as covariates if appropriate and needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers and persistence of RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 3 days after birth. The relationship between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSV-B neutralizing antibody and RSVPreF3 IgG-specific antibody concentration at delivery will be explored using scatter plots of individual values.

5.2.2. Additional considerations

Before unblinding occurs, the immunogenicity analysis at Day 31, Delivery, Day 43 post-delivery will only be performed on Exposed Set. At the time of 6 month post-delivery and final analysis, the immunogenicity analysis will be performed on PPS.

5.2.2.1. Distribution analysis

RSV-A neutralizing antibody titers and RSV-B neutralizing antibody titers:

- Number and percentage of subjects with titers <128, ≥128, ≥256, ≥512, ≥1024, ≥2048, ≥4096, ≥8192 will be tabulated.

- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 2, 4, 6, 8, 10 and 12 by pre-vaccination category (< 128, ≥128 and <256, ≥ 256 and <512, ≥ 512 and <1024, ≥1024 and <2048, ≥ 2048 and <4096, ≥ 4096 and <8192, ≥8192) will be tabulated.

RSVPreF3 IgG-specific antibody concentrations:

- Number and percentage of subjects with concentrations <2048, ≥2048, ≥4096, ≥8192, ≥16384, ≥32768, ≥65536, ≥131072 will be tabulated.

- For distribution of fold increase, number and percentage of subjects with a fold increase above or equal to 4, 6, 8, 10, 12, 14 and 16 by pre-vaccination category (< 2048, ≥2048 and <4096, ≥ 4096 and <8192, ≥ 8192 and <16384, ≥16384 and <32768, ≥ 32768 and <65536, ≥ 65536 and <131072, ≥131072) will be tabulated.

The thresholds for distribution tables of titres and concentrations and fold increase may be further adjusted at analysis as needed.

5.2.2.2. Ratio of fold increase analysis

Fold increase of RSVPreF3 IgG-specific antibody concentrations over fold increase of RSV-A neutralizing antibody titers (ratio of fold increase post- over pre-vaccination) will be tabulated using descriptive statistics. This analysis will include calculation on:

- Geometric mean ratios with corresponding 95% CIs of RSVPreF3 IgG-specific antibody concentration over RSV-A neutralizing antibody titers at pre-vaccination for each group and
- Geometric mean ratios with corresponding 95% CIs of fold increase post/pre (Day 31, Delivery and Day 43 post-delivery/Day 1) between RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody titers for each group.

Similar analysis will be performed between RSVPreF3 IgG-specific antibody concentrations and RSV-B neutralizing antibody titers.

5.2.2.3. Between group analysis

This analysis is exploratory.

For the analysis of maternal subjects at each time point (Day 31, Delivery, and Day 43 post-delivery), the model will be explored and fitted via the proc mixed procedure according to the following code:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group ges_age_cat age_cat center;
  MODEL log_val = baseline group ges_age_cat age_cat
inter_vac_del center /ddfm=kenwardroger outp = pred;
  /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
RUN;
```

where log_val represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, group indicates the study group, ges_age_cat is the gestational age category at vaccination ($28^{0/7}$ - $31^{0/7}$, $31^{1/7}$ - $33^{6/7}$ weeks), age_cat is the age category at vaccination (18 – <35 years and ≥35 years), inter_vac_del is the interval between vaccination and delivery (days). The inclusion of age category at vaccination, interval between vaccination and delivery, and center in the model depends on the availability of the variable (inter_val_del may not be available at Day 31 analysis) and the necessity, therefore, the above SAS code serves as a reference and may be adjusted according to the analysis needs.

For the analysis of infants at each time point (cord blood at Delivery, Day 43 post-birth, Day 121 post-birth, and Day 181 post-birth), similar model will be explored:

```
PROC MIXED data=sero;
  CLASS /*subjid*/ group center ges_age_cat ges_age_birth;
  MODEL log_val = baseline group ges_age_cat /*inter_vac_del*/
ges_age_birth center /ddfm=kenwardroger outp = pred;
 /*RANDOM Subjid*/;
  LSMEANS group/pdiff cl alpha=0.05;
   RUN;
```

Baseline is pre-vaccination logarithm10 transformation of the concentrations/titers from maternal subjects, ges_age_birth is gestational age category at birth (> 37 weeks; ≤ 37 weeks) for infants. With the inclusion of gestational age category at vaccination (ges_age_cat) in the model, this categorical variable ges_age_birth provides similar information as continuous variable inter_vac_del, therefore the inclusion of either variable in the model could be adjusted according to the analysis needs.

The ratio of GMTs/GMCs between vaccine groups and the corresponding 95% CI will then be constructed by exponentiating the mean difference and its confidence interval between vaccine groups on the logarithm10 scale estimated from the model. Summary tables will show adjusted GMT/GMC for vaccine groups, and ratios of GMTs/GMCs between vaccine groups along with the 95% CI.

If deemed necessary, an analysis of variance model for repeated measures will be fitted to assess the mean profile in each group over time for both maternal and infant subjects separately. Below is the sample SAS code for the analysis of maternal subjects, and similar codes could be explored for the analysis of infants.

```
PROC MIXED data=sero;
    CLASS subjid group visit age_cat center ges_age_cat;
    MODEL log_val = baseline group | visit age_cat ges_age_cat
inter_vac_del center/ddfm=kenwardroger outp = pred;
    RANDOM subjid;
    /*REPEATED visit/subject=subjid(group) type=un;*/
    LSMEANS group*visit/pdiff cl alpha=0.05;
RUN;
```

Summary tables will present adjusted GMT/GMC with 95% CI for each group at each timepoint.

5.2.2.4. Persistence and Half-life analysis of antibody level over time for infant subjects

This analysis is exploratory.

The decay of infant antibody levels over time will be analysed by a linear regression of the logarithm transformed of antibody levels. This analysis will be performed on PPS for infants in RSV vaccine group in terms of RSV-A neutralizing antibody titers, RSV-B neutralizing antibody titers and RSVPreF3 IgG-specific antibody concentrations.

A true, natural decay curve will be explored by stochastically reducing the sample to uninfected subjects only. The following steps will be taken to identify infected subjects (confirmed and suspected) to be eliminated from the sample:

- STEP 1: Infants with an RSV positive nasal swab during the study before time of blood sampling will be eliminated from the analysis because RSV infection may have contributed to their antibody levels which may no longer represent what was passively transferred from the mother.
- Infants whose mothers had an RSV positive nasal swab before or up to the time of delivery will be eliminated from the analysis. Maternal infection may contribute to post-vaccination increase in the levels of maternal antibodies, leading to higher placental antibody transfer to the fetus/infant, which would not reflect the effect of vaccination alone.
- STEP 2: Run the model and compute expected value based on the decay curve
- STEP 3: Subjects with an antibody titer at the blood sampling time that is more than 2-fold above the expected value based on their baseline (cord blood) value and the established decay curve will be considered to have been infected and then eliminated and the decay curve refined.
- STEP 4: Step 3 is repeated up to 5 times until the most accurate decay curve is established.

The natural decay of antibody level will be determined using linear regression between the logarithm transformed antibody level (Y) and time t (age in days) with subject as a random effect. All infants have RSV neutralizing antibodies measured at birth (cord blood) or within 3 days after birth, and each infant in PPS sub-cohort will have blood

sampling for RSV neutralizing antibodies at one of the following time points: Day 43 post-birth, Day 121 post-birth or Day 181 post-birth. Therefore, in the natural decay model, each infant will have maximum 2 RSV neutralizing antibodies measures, one at birth or within 3 days after birth and the other at Day 43 post-birth, Day 121 post-birth or Day 181 post-birth depending on the sub-cohorts where the infants are.

The following SAS code will be explored:

```
PROC MIXED DATA=<filename>;
  CLASS PID;
  MODEL LOG_Y = t /s outp=pred;
  RANDOM Int t / sub=PID type=UN G GCORR;
RUN;
```

The choice of correlation structure and other parameters may be further adjusted according to the data and analysis needs.

The predicted value will be computed using the following formula

$$A_t = A_0 \exp(-K_e t)$$

where, A_t and A_0 are antibody titres at times t and zero, respectively, K_e is the constant rate of antibody change with time, defined as the estimate of model.

In addition, the half-life ($t_{1/2}$) of antibody (i.e. the time required for titre to decrease by one-half) will be displayed using the following equations of declining antibody titre:

$$\text{when } A_t = \tfrac{1}{2} A_0$$
$$t_{1/2} = 0.693 / K_e$$

A summary table will be prepared to show the number of infants included in the model, the model estimate of the antibody decay rate, and the half-life of the antibody.

In case cord blood samples are missing in 20% or more of infants in a single study group, separate analysis for infants with cord blood and infants with a blood sample within 3 days after birth will be performed.

5.2.2.5. ROC analysis (dose characterization)

This analysis is exploratory and complementary to traditional data analysis methods comparing post-vaccination immune responses among vaccine groups and will be performed on the PPS only if deemed necessary.

If immune response between active vaccination groups can't be differentiated using traditional approach, additional analyses using a generalized ROC (Receiver Operating Characteristics) method [Yu, 2018] will be performed for both RSV-A neutralizing antibody titers and RSVPreF3 IgG specific antibody concentrations at Day 31 and Delivery, and other timepoints if needed.

Two ROC Methods will be explored:

- ROC-P (ROC of post-dose levels) method: Post-vaccination antibody levels from 2 RSV vaccine groups (RSV MAT 60 and RSV MAT 120) will be pooled and used as a reference distribution.
- ROC-B (ROC relative to baseline) method: Overall pre-vaccination antibody levels from 2 RSV groups (RSV MAT 60 and RSV MAT 120) will be used as a reference distribution.

Different percentile (0% to 100%) thresholds from the reference distribution will be obtained. The percentage of subjects with post-vaccination antibody level higher than or equal to the percentile thresholds from the reference distribution will then be calculated for each vaccine group.

A figure will be provided showing the ROC curve with x-axis the percentile of the reference distribution and y-axis the percentage of subjects in each vaccine group with post-vaccination antibody levels higher than or equal to the percentile threshold of the reference distribution.

A summary table will be provided on the thresholds of e.g. 25%, 50% and 75% percentiles of the reference distribution and the percentage of subjects in each vaccine group with post-vaccination antibody level higher than or equal to these percentile thresholds.

5.3. Analysis of safety and reactogenicity

5.3.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in **maternal subjects** will include summaries by study group and age category (18 - < 35 years of age; ≥35 years of age; overall) of hematology and biochemistry results by grade and per time point, solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant subjects** will include summaries by study group and gestational age at birth (> 37 weeks or ≤ 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

All safety analyses will be performed on the Solicited Safety or Exposed sets.

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal subjects	Occurrence of Solicited administration site and systemic events that occur during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	The number and percentage with exact 95% CI of maternal subjects reporting each **Solicited administration site event** (any grade, each grade,) and **solicited systemic event** (any, each grade) during the 7-day (days 1 to 7) follow-up period after vaccination will be tabulated by maximum intensity per subject for each study vaccine group. **For fever** during the 7-day follow-up period after vaccination, the number and percentage of maternal subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments, any Grade 3 fevers, will be reported. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 7-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).
	Occurrence of any protocol-specified hematological or biochemical laboratory abnormality at baseline (up to 15 days before vaccination) and Day 8 (Visit 2)	The number and percentage of subjects with hematology and biochemistry results outside central laboratory normal ranges will be tabulated to show Day 8 versus baseline. The maximum grading as described in [Sheffield, 2013] and in the Laboratory Manual from Screening up to Day 8 will also be tabulated.
	Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	The number and percentage of maternal subjects with **unsolicited** symptoms within 30 days after vaccination with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulations will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 related unsolicited symptoms and for MAEs. The number and percentage of maternal subjects with at least one **administration site AE** (**solicited *and* unsolicited**), with at least one **systemic AE** (**solicited *and* unsolicited)** and with **any AE** during the 30-day follow-up period after vaccination will be tabulated with exact 95% confidence interval (CI) by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for MAEs.
	Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and medically attended AEs from Visit 1 (Day 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6).	The number and percentage of maternal subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Primary Safety Endpoints		Statistical Analysis Methods
		By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 6). Outcomes are listed in Section 2.	The number and percentage of maternal subjects with each pregnancy outcome will be tabulated with its exact 95% CI by group. By subject listings of adverse pregnancy outcomes will be prepared but will not be released until the final, unblinded analysis has been completed.
	Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post delivery; Visit 6**).** These events are listed in Section 2**.**	The number and percentage of maternal subjects with each pregnancy-related AESI will be tabulated with its exact 95% CI by group. By subject listings of pregnancy-related AESIs will be prepared but will not be released until the final, unblinded analysis has been completed.
Infant subjects	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These events are listed In Section 2. Occurrence of SAEs, AEs leading to study withdrawal and medically attended AEs from birth up to 6 weeks after birth.	The number and percentage of infant subjects with each neonatal AESI will be tabulated with its exact 95% CI by group. By-subject listings of neonatal AESIs will be prepared, but will not be released until the final, unblinded analysis has been completed. The number and percentage of infant subjects with - at least one SAE; - at least one MAE from Visit 1 (Day 1) up to 6 weeks after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal, and MAEs will be prepared (but will not be released until the final, unblinded analysis has been completed).
Secondary Safety Endpoints		**Statistical Analysis Methods**
Maternal subjects	From Day 1 (Visit 1) through 6 months after delivery (Visit 8), occurrences of SAEs, MAEs and AEs leading to study withdrawal. Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) up to 6 months post-delivery (Visit 8)	The number and percentage of maternal subjects with at least one SAE, MAE from Day 1 up to 6 months after delivery with exact 95% CIs will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared (but will not be released until the final, unblinded, analysis has been completed). The number and proportion of subjects with at least one RSV-associated MA- RTI (with 95 % CI) will be calculated and tabulated.
Infant subjects	From birth through 6 months (Visit 4-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and medically attended AEs	For each category: - SAE, - MAEs The number and proportion of infant subjects who experienced at least one event from birth up to 6 months after birth and the number and proportion of infant subjects who

Primary Safety Endpoints		Statistical Analysis Methods
	From birth through 1 year (Visit 5-NB) after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAEs	experienced at least one event from birth up to 1 year after birth will be tabulated with 95% CI by group. By-subject listings of SAEs, AEs leading to study withdrawal and MAEs will be prepared.
	From birth to 6 months after birth (Visit 4-NB), occurrences of RSV-associated LRTI(s), Severe LRTI(s), very severe LRTIs and RSV-associated hospitalizations (according to the case definitions in Section 4.2.6 in the protocol)	For each category: - RSV-associated LRTI, - Severe LRTI, - Very severe LRTI - RSV-associated hospitalization The number and proportion (with 95% CI) of subjects with at least one event will be calculated and tabulated by group.

5.3.2. Additional considerations

5.3.2.1. Analysis of solicited events

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

Table 7 Intensity scales for solicited symptoms in adults

Adults/Child (≥6 years)		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature		Record temperature in °C/°F (with 1 decimal) Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache		
Fatigue	0	Normal
Nausea	1	Mild: Easily tolerated
Vomiting	2	Moderate: Interferes with normal activity
Diarrhea	3	Severe: Prevents normal activity
Abdominal pain		

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

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

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

5.3.2.2. Exclusion of implausible solicited Event

Some local and systemic events will be directly measured by the subject and will be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings. Implausible measurements are summarized in the table below:

Table 8 Implausible Solicited Events

Parameter	Implausible measurements	
Body temperature	≤ 33°C or ≥ 42°C	
Erythema	Measurements < 0 mm For subjects ≥ 6 years: ≥ 900 mm	
Swelling	Measurements < 0 mm For subjects ≥ 6 years: ≥ 500 mm	

5.3.2.3. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on Exposed Set

5.3.2.4. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of subjects with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Nausea	Nausea	10028813
Vomiting	Vomiting	10047700
Diarrhea	Diarrhea	10012727

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Abdominal pain	Abdominal pain	10000081
Headache	Headache	10019211

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

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

5.3.2.5. Analysis of RTI and LRTI

The analysis of RTI and LRTI will be performed on Exposed Set according to the case definitions in section 9.1.3. Separate listings of maternal MA-RTI and infant RTI/LRTI will be provided.

Further analysis with respect to the incidence of RSV LRTI by an exploratory case definition might be performed if deemed necessary.

5.3.2.6. Other analysis

Other safety analysis will be performed on Exposed Set.

For hematology and biochemistry lab results, the maximum grading as described in [Sheffield, 2013] and Laboratory Manual will be used, see section 9.1.4 for details

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal subjects taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days following vaccination, 30 days following vaccination, up to 6 weeks post-delivery and up to 6 months post-delivery will be summarized by group. A listing will also be provided.

The number and percentage of infants taking concomitant medications from birth up to 6 weeks after birth, 6 months after birth and 1 year after birth will be summarized by group. A listing will also be provided.

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

7.1.1. First, second and third analyses

The **first analysis** will evaluate maternal safety and immunogenicity data, and will be performed when **50% of maternal subjects** have completed visits up to (and including) Visit 3 (Day 31).

The **second analysis** will evaluate maternal safety and immunogenicity data, and will be performed when **all maternal subjects** have completed visits up to (and including) Visit 3 (Day 31) and the data are available. At this time, any available infant safety data and cord blood (or an infant blood sample collected within 3 days after delivery, if a cord blood sample is not available) immunogenicity data will also be provided.

The **third analysis** will be performed to evaluate **maternal and infant** safety data up to (and including) Day 43 post-delivery (Visit 6 mothers/ Visit 2-NB infants), maternal immunogenicity data up to (and including) delivery (Visit 5), and immunogenicity data based on analyses of cord blood (Visit 5) or an infant blood sample collected within 3 days after delivery (Visit 1-NB – if a cord blood sample could not be collected). The analysis will be performed when the respective visits are completed and the data are available.

To maintain the blind during each of these analyses, analysis by group will be performed by an independent statistician not affiliated with the project. Results that would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). A report will be prepared and released to regulatory agencies but will not be provided to site personnel. No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

7.1.2. Fourth analysis

The **fourth analysis** will take place after **maternal and infant** subjects have completed their Month 6 post-delivery/birth visits (Visit 8 mothers / Visit 4-NB infants. This analysis will evaluate**:**

- Immunogenicity data up to (and including) Day 43 post-delivery for the mother and Month 4 for the infant (Visit 6 mothers / Visit 3-NB infants), and
- Safety data, including RTI surveillance, up to (and including) Month 6 post-delivery / birth in both mother and infant (Visit 8 mothers/ Visit 4-NB infants).

A statistical report will be prepared. Only analysis results summarized by study group will be released. No individual (by-subject) data / data listings will be provided, except for SUSARs which will be reported to regulatory authorities in compliance with the regulations.

Results of this analysis will be summarized in an Investigator Brochure update that will be provided to regulators, Investigators, and IECs/IRBs before initiating the Phase III study in pregnant women.

Visits conducted subsequent to this analysis will be considered "single blinded," since release of the summary results may inadvertently inform sponsor or site personnel of specific intervention assignments (for example, if an event of interest only occurs in a single subject, in a single study group, and is not masked in the statistical report). Steps will be taken during preparation of the statistical report to minimize this risk.

7.1.3. Final analysis

The **final** analysis will be performed when all data up to study end are available. A clinical study report including all available data will be written and made available to the investigators at that time.

The clinical 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**.**

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final Analysis (E1_01)	Public disclosure, Study report
First Analysis (E1_02)	Internal
Second Analysis (E1_03)	Internal
Third Analysis (E1_04)	Internal
Fourth Analysis (E1_05)	Public disclosure

7.2. Statistical considerations for interim analyses

No interim analyses are planned. However, analyses to evaluate objectives and endpoints will be performed in steps as described above.

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

8. CHANGES FROM PLANNED ANALYSES

To take a more practical approach, subgroup analysis of safety by age category at vaccination (18 - <35; ≥ 35 years) in maternal subjects will include summaries of pregnancy outcomes, pregnancy related AESIs, SAEs, MAEs and MA-RTIs.

Subgroup analysis of safety by gestational age at birth (> 37 weeks or ≤ 37 weeks) in infant subjects will include summaries of neonatal AESIs, MAEs, SAEs, and occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, very severe LRTIs and RSV-associated hospitalizations.

Subgroup analysis on other safety summaries will be performed if deemed necessary.

Subgroup analysis of immunogenicity by age category at vaccination (18 - <35; ≥ 35 years) for maternal subjects and by gestational age at birth ((> 37 weeks or ≤ 37 weeks) for infants will include analysis of GMT(C) and GMR calculation at each time point and geometric mean of placental transfer.

Subgroup analysis on other immunogenicity analysis will be performed if deemed necessary.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Data derivation

9.1.1. Gestational age at vaccination

Gestational age at vaccination in weeks for maternal subjects will be calculated based on estimated date of delivery and date of vaccination.

9.1.2. Immunogenicity

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

- For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
- For the between group assessments, statistical model will be fitted based on the subjects having a result at both the baseline and the considered timepoint.

The GMT/GMC and its 95% CI will be obtained by exponentiating the mean and its 95% CI of the log-transformed titres/concentrations. All CI computed will be two-sided 95% CI.

Placental transfer is defined as the ratio of RSVPreF3 IgG-specific antibody concentrations between cord blood (or blood sample from infants collected within 3 days after birth if cord blood is not available) and maternal blood sample at delivery (or within 3 days after delivery if blood sample is not collected during delivery).

9.1.2.1. Assay cut-offs for serology results

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

System	Component	Method	Unit	Cut-off *(LLOQ)*	*ULOQ*
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	ED60	18	*21654*
Serum	RSVPreF3 IgG antibody concentrations	ELISA	EU/mL	*25*	*143000*
Serum	RSV-B Neutralising Antibody	NEUTRALISATION	ED60	*TBD*	*TBD*

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis.

9.1.3. RTI and LRTI

Cases will be classified (during data analyses) according to the definitions that follow.

Table 9 MA-RTI case definitions for data analysis in maternal subjects

RSV-MA-RTI	Medically attended visit for RTI symptoms AND Confirmed RSV infection [1, 2]
RSV hospitalization	Confirmed RSV infection AND Hospitalized for acute medical condition [3]
All-cause MA- RTI	Medically attended visit for RTI symptoms

[1] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol
[2] RSV (nasal swab) sampling and testing as specified in Table 11 of the Protocol.
[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.
MA-RTI = Maternal, medically attended respiratory tract illness

Table 10 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection [4]
RSV-LRTI	History of cough OR difficulty in breathing [1] AND SpO_2 < 95%[2], OR RR increase [3] AND Confirmed RSV infection [4]
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%[2], OR lower chest wall in-drawing
RSV-very severe LRTI	Meeting the case definition of RSV-LRTI AND SpO2 < 90%[2], OR inability to feed OR failure to respond / unconscious
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing [1] AND SpO2 < 95% [2], OR RR increase [3]

Definitions based on [Modjarrad., 2016]

RTI = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.

[1] Based on history reported by parents/LARs and includes difficulty in breathing (e.g. showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnea).

[2] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.

[3] RR increase defined as:

> 60/minute (< 2 months of age)
> 50/minute (2 to < 12 months of age)
> 40/minute (12 to 24 months of age)

[4] Confirmed RSV infection defined in Section 4.2.6.3 of the Protocol

[5] RSV (nasal swab) sampling and testing as specified in Table 12 of the Protocol

[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose, wheezing or difficulty breathing with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed.

9.1.4. Hematology and Biochemistry parameters

The table below shows the toxicity grading during the second and third trimester of pregnancy based on [Sheffield, 2013]

Table 11 Laboratory values during the second and third trimester of pregnancy

Serum chemistries	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	0.4-0.8 mg/dL		0.9-1.2	1.3-1.6	1.7-2.5	>2.5 or requires dialysis
BUN	3.0-13.0 mg/dL		14.0-19.0	20.0-30.0	>30	Required dialysis
Haematology	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin	9.7-14.8 g/dL		9.0-9.6	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
Change from baseline value – gm/dL			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.6-14.8 x 1000cell/mm^3	High	>14.8-16.0	>16.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.5-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	0.9-3.9 x 1000cell/mm^3	High	>3.9-5.0	>5.0		
		Low	<0.9-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.8-12.3 x 1000cell/mm^3		<3.8-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	155-409 x 1000 L^{-1}	Low	125-154	100-124	25-99	<25
		High	410-499	500-749	750-1000	>1000
Liver Function Tests	**Normal range for 2nd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	3-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-33 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Serum chemistries	**Normal range for 3rd trimester**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**

	or uncomplicated pregnancy					
Creatinine	0.4-0.9 mg/dL		1.0-1.2	1.3-1.6	1.7-2.5	>2.5 or required dialysis
BUN	3.0-11.0 mg/dL		12.0-19.0	20.0-30.0	>30	Required dialysis
Liver Function Tests	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT) Aspartate transaminase	4-32 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
ALT (SGPT) Alanine transaminase	2-25 U/L		>1.0-1.2xULN	>1.2-3.0xULN	>3.0-8.0xULN	>8.0xULN cirrhosis transplant candidate
Haematology	**Normal range for 3rd trimester or uncomplicated pregnancy**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin Change from baseline value – g/dL	9.5-15.0 g/dL		9.0-9.4	8.0-8.9	7.0-7.9 or requires a transfusion	<7.0 or li-threatening acute blood loss
			1.6-2.0	2.1-4.5	4.6-5.0	>5.0
WBC	5.9-16.9 x 1000cell/mm^3	High	>16.9-18.0	>18.0-20.0	>20.0-25.0	>25.0 Signs of septic shock
		Low	<5.9-3.5	<3.5-1.4	<1.4-1.0	<1.0 Signs of septic shock
Lymphocytes	1.0-3.6 x 1000cell/mm^3	High	>3.6-5.0	>5.0		
		Low	<1.0-0.75	<0.75-0.5	<0.5-0.25	<0.25
Neutrophils Absolute neutrophil count	3.9-13.1 x 1000cell/mm^3		<3.9-2.0	<2.0-1.0	<1.0-0.5	<0.5
Eosinophils	0-0.6 x 1000cell/mm^3		>0.6-1.5	>1.5-5.0	>5.0	Hypereosinophilic syndrome
Monocytes	0.1-1.4 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Basophils	0-0.1 x 1000cell/mm^3		≤10% outside of normal rage	>10% outside of normal rage: clinical correlation may be necessary and grading according to it		
Platelets	146-429 x 1000 L^{-1}	Low	125-146	100-124	25-99	<25
		High	430-499	500-749	750-1000	>1000

Adapted from [Sheffield, 2013]
ULN: upper limit of normal.

Table below shows the toxicity grading for lab parameters that are not covered in [Sheffield, 2013] but calculated based on the grading references and guidance in [Sheffield, 2013].

Parameter (unit)	Gender & Age range		Grade 1	Grade 2	Grade 3	Grade 4
Hematocrit (%) – 2nd Trimester	F 18-64y		27.0-29.0 Conv	24.0-26.9 Conv	21.0-23.9 Conv	<21.0 Conv
			44.5-48.9 Conv	49.0-53.2 Conv	>53.2 Conv	N/A
	F 18-64y		0.270 – 0.290 SI	0.240-0.269 SI	0.210-0.239 SI	<0.210 SI
			0.445-0.489 SI	0.490-0.532 SI	>0.532 SI	N/A
Hematocrit (%) – 3rd Trimester	F 18-64y		27.0-28.4 Conv	24.0-26.9 Conv	21.0-23.9 Conv	<21.0 Conv
			45.1-50.0 Conv	50.1-54.0 Conv	>54.0 Conv	
	F 18-64y		0.270 – 0.284 SI	0.240-0.269 SI	0.210-0.239 SI	<0.210 SI
			0.451-0.500 SI	0.501-0.540 SI	>0.540 SI	
MCV (FL)	0-199y		100.1-110.0 Conv	110.1-120.0 Conv	>120.0 Conv	
			72.0-79.0 Conv	64.0-71.9 Conv	<64.0 Conv	N/A
	0-199y		100.1-110.0 SI	110.1-120.0 SI	>120.0 SI	
			72.0-79.0 SI	64.0-71.9 SI	<64.0 SI	N/A
RBC (mill/mcl)	F 18-64y		3.5-3.8 Conv	3.1-3.4 Conv	<3.4 Conv	
			5.3-5.7 Conv	5.8-6.2 Conv	>6.2 Conv	N/A
RBC (TI/L)	F 18-64y		3.5-3.8 SI	3.1-3.4 SI	<3.4 SI	N/A
			5.3-5.7 SI	5.8-6.2 SI	>6.2 SI	

9.2. Statistical Method

Study specific statistical methods for immunogenicity analysis are described in section 5.2.2.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event.

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

10.1.2. Handling of missing data

10.1.2.1. Dates

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

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

The following exceptions apply:

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

year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

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

10.1.2.2. Laboratory data

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

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. *Studies with electronic diaries*

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

10.1.2.4. Unsolicited adverse events

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

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

10.1.3. Data derivation

10.1.3.1. Age at vaccination in years

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

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

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

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Height

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

Height in centimeters = Height in inches x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. Temperature

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

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

10.1.3.6. Numerical serology results

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

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

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

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

10.1.3.8. Onset day

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

10.1.3.9. Duration of events

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

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

10.1.3.10. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.11. Counting rules for occurrences of solicited adverse events

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

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

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

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

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

10.1.4.2. Demographic/baseline characteristics statistics

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

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

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

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

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

10.1.4.3. Serological summary statistics

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

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

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

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

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

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

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document. Please note the protocol of this study was developed based on V17 template and the term ‘solicited administration site event’ and ‘solicited systemic event’ are used, however, at the development of the TFL TOC, only V16 standard catalog is available and still ‘solicited local adverse event’ and ‘solicited general adverse event’ are used in the TFL mocks per this standard.

11. REFERENCES

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