Statistical Analysis Plan

Study ID: 214725

Official Title of Study: A Phase III, double-blind, randomized, placebo-controlled study to evaluate the safety, reactogenicity and immune response of a single intramuscular dose of unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.

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TITLE PAGE

Protocol Title:	A Phase III, double-blind, randomized, placebo-controlled study to evaluate the safety, reactogenicity and immune response of a single intramuscular dose of unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.
Study Number:	214725 (RSV MAT-012)
Compound Number:	GSK3888550A
Abbreviated Title:	A study on the safety and immune response to an unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s): 2021-000994-96

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	17 August 2021	Final (12 March 2021)	Not Applicable	Original version
SAP Amendment 1	01 Jun 2022	Amendment 1 (15 March 2022)	The SAP was amended to align to changes performed in the Protocol Amendment 1.	This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants, conduct of the trial and scientific value of the trial.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 214725 (RSV MAT-012). Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Study objectives, estimands and endpoints

Objectives	Endpoints & Estimands
Primary	
Safety assessment: **Maternal participants:**	
• To evaluate the safety and reactogenicity of a single IM dose of study intervention (RSV maternal vaccine or placebo) administered to maternal participants up to 42 days post-delivery.	• Number and percentage of maternal participants reporting: – Solicited administration site and systemic events during a 7-day follow-up period after dosing (i.e. Day 1 to Day 7 included). – Unsolicited AEs that occur during a 30-day follow-up period after dosing (i.e. Day 1 to Day 30 included). – SAEs, (S)AEs leading to study withdrawal and MAEs from Day 1 up to 42 days post-delivery.
• To evaluate the pregnancy outcomes and pregnancy-related AESIs up to 42 days post-delivery, in maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Number and percentage of maternal participants reporting: – Pregnancy outcomes * from Day 1 up to 42 days post-delivery. * These include live birth with no congenital anomalies, live birth with minor congenital anomaly(ies) only; live birth with at least one major congenital anomaly, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with only minor congenital anomalies, fetal death/still birth (antepartum or intrapartum) with at least 1 major congenital anomaly; elective/therapeutic termination with no congenital anomalies; elective/therapeutic termination with only minor congenital anomalies, and elective/therapeutic termination with at least 1 major congenital anomaly [1]. – Pregnancy-related AESIs * and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery. * These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth) and chorioamnionitis.[1]

Objectives	Endpoints & Estimands
Infant participants: • To evaluate safety up to 42 days post-birth in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Number and percentage of infant participants reporting: – Neonatal / infant AESIs * from birth up to 42 days post-birth. * These include small for gestational age, low birth weight including very low and extremely low birth weight (<2500 g, <1500g, <1000g), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in an extremely preterm birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth) and preterm birth.[1] – SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 42 days post-birth.
• To evaluate safety up to 365 days post-birth (1 year of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Number and percentage of infant participants reporting: – SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 180 days post-birth. – SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 365 days post-birth.
Immunogenicity assessment: **Maternal participants:** • To evaluate the immunogenicity of a single IM dose of study intervention (RSV maternal vaccine or placebo) administered to maternal participants, at delivery. *Cord blood/ placental transfer:* • To evaluate the transfer of RSV-specific antibodies from maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo) to their infants at delivery. **Infant participants:** • To evaluate the RSV-specific antibody levels at birth in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Humoral immune responses at pre-dosing (Day 1) and at delivery: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A • Ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations at delivery *or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained). • Humoral immune responses at delivery*: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A *Measured in cord blood sample collected at delivery or in infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).
Secondary	
Safety assessment: **Maternal participants:** • To evaluate the safety of a single IM dose of study intervention (RSV maternal vaccine and placebo) administered to maternal participants, up to 180 days post-delivery.	• Number and percentage of maternal participants reporting: – SAEs, (S)AEs leading to study withdrawal and MAEs from Day 1 up to 180 days post-delivery.

Objectives	Endpoints & Estimands
• To evaluate the worsening of pre-existing medical conditions and/or obstetric complications up to 180 days post-delivery, in maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Number and percentage of maternal participants reporting: – Worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery.
• To evaluate the occurrence of RSV-associated MA-RTIs in maternal participants who received a single IM dose of study intervention (RSV maternal vaccine and placebo) up to 180 days post-delivery.	• Number and percentage of maternal participants reporting: – RSV-associated MA-RTIs from Day 1 up to180 days post-delivery.
Infant participants:	
• To evaluate the occurrence of medically assessed, RSV-associated LRTIs up to 365 days post-birth (12 months of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated LRTIs of any severity and severe RSV-associated LRTIs (according to the cases definitions).
• To evaluate the occurrence of medically assessed, RSV-associated hospitalization up to 365 days post-birth (12 months of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated hospitalizations (according to the cases definitions).
Immunogenicity assessment: **Maternal participants:**	
• To evaluate the immunogenicity of a single IM dose of study intervention (RSV maternal vaccine or placebo) administered to maternal participants up to delivery.	• Humoral immune responses at Day 31 post-dosing: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A • Humoral immune responses at pre-dosing (Day 1), at Day 31 post-dosing and at delivery: – Neutralizing antibody titers against RSV-B
Infant participants:	
• To evaluate neutralizing antibody titers against RSV-B at birth in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Humoral immune responses at delivery*: – Neutralizing antibody titers against RSV-B * Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).

Objectives	Endpoints & Estimands
• To evaluate RSV-specific antibodies up to Day 181 post-birth (6 months of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Humoral immune responses at Day 43*, at Day 121* and at Day 181*: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A and RSV-B * Measured in infant blood samples collected at Day 43 (sub-cohort 1, V2-NB), at Day 121 (sub-cohort 2, V3-NB) and at Day 181 (sub-cohort 3, V4-NB) post-birth. Each infant will be randomly assigned (1:1:1) to one of 3 sub-cohorts.
Tertiary	
CCI [redacted]	

AE = adverse event; **IM** = intramuscular; **AESI** = adverse event of special interest; **LRTI** = lower respiratory tract illness; **MAE** = medically attended adverse event; **NB** = newborn; **RSV** = respiratory syncytial virus; **RSV-A/B** = respiratory syncytial virus subtype A/B; **MA-RTI** = medically attended respiratory tract illness; **RSVPreF3 IgG** = respiratory syncytial virus PreF3 immunoglobulin G; **SAE** = serious adverse event; **GMT** = Geometric mean titer; **GMC** = Geometric mean concentration

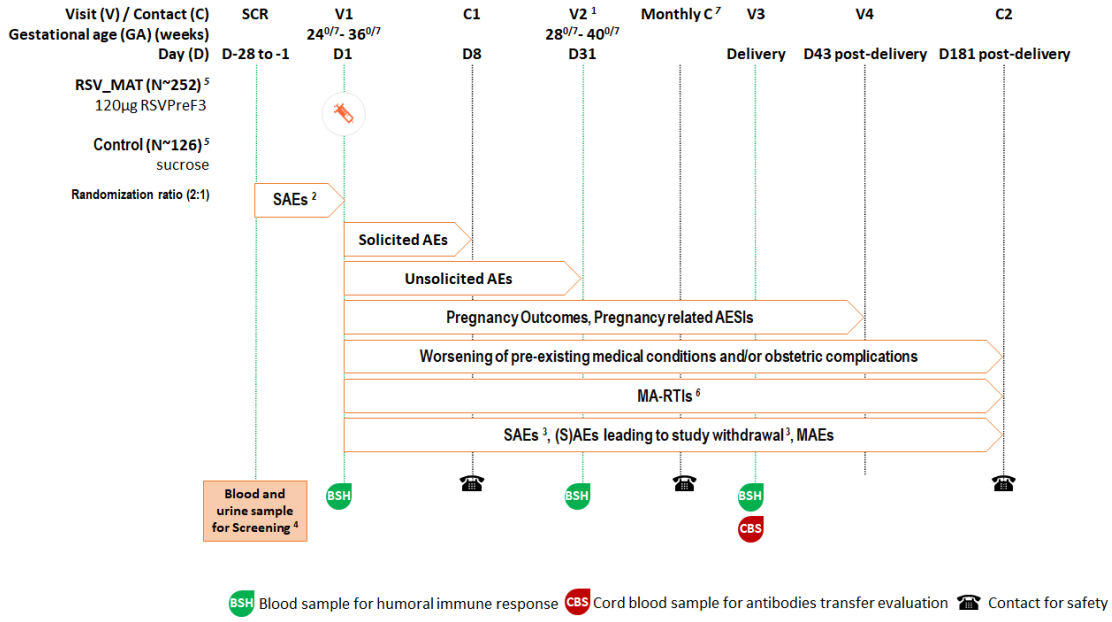
[1] Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with assessment of level of diagnostic certainty by Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) definitions when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorders of pregnancy is an event with 3 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.

1.2. Study Design

Overview of Study Design and Key Features

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

Figure 1 Study design overview – Maternal participants



MAE = medically attended adverse event; **MA-RTI** = medically attended respiratory tract illness; **(S)AE** = (serious) adverse event; **SCR** = screening

[1] Visit 2 (Day 31) may be replaced by Visit 3 (Delivery) in case of premature delivery. If the delivery date occurs prior to Day 31 post-study intervention, there will be no Visit 2 (Day 31).

[2] SAEs related to study participation are to be collected from screening to Visit 1 (Day 1 pre-study intervention).

[3] Following study invervention (RSV maternal vaccine or placebo) administration, SAEs and (S)AEs leading to study withdrawal are to be collected from Day 1 (Visit 1) up to 180 days post-delivery (Contact 2).

[4] If not performed as part of the routine care, the blood and urine samples for screening should be collected within 15 days prior to study intervention administration.

[5] Due to the recent safety signal in RSV-MAT-009, there will be no further enrollment and vaccination of maternal participants. Refer to Protocol section 2.3 for further details.

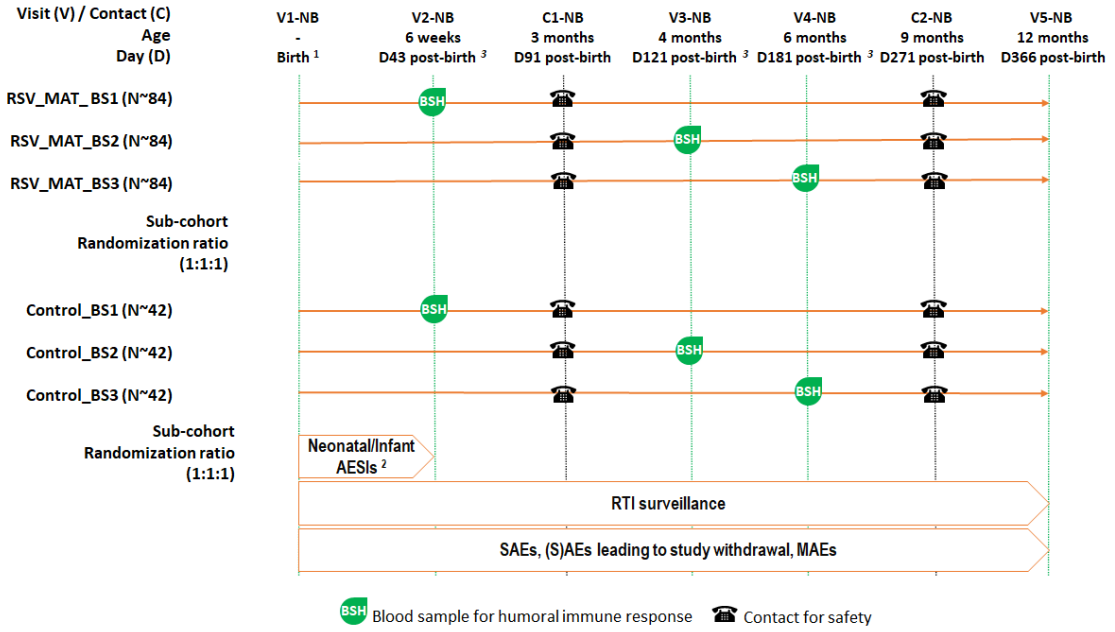
[6] Due to the change in the study requirements, MA-RTIs experienced by the maternal pariticipants will no longer be collected.

[7] In addition to the monthly contacts between Visit-2 and the Delivery visit, additional not pre-specified contacts and/or visits can be made more often (at any desired frequency), as per investigator's, maternal participant's or LAR's discretion.

Note: Placenta samples will be collected at delivery from all maternal participants, whenever feasible. These samples may be tested to support possible safety assessments, if necessary. Additional details are provided in the study procedures manual (SPM).

Overview of Study Design and Key Features

Figure 2 Study design overview – Infant participants



AESI = adverse event of special interest; **MAE** = medically attended adverse event; **RTI** = respiratory tract illness;**(S)AE** = (serious) adverse event
Infant sub-cohorts are abbreviated "BS1", "BS2" and "BS3" correspond to Visit 2-NB (Day 43 post-birth), Visit 3-NB (Day 121 post-birth) and Visit 4-NB (Day 181 post-birth), respectively.
RSV_MAT_BS1, _BS2, _BS3 = infants born to women in the RSV_MAT group and evaluated for immunogenicity at the designated timepoint (Day 43, Day 121 or Day 181 post-birth).
Control_BS1, _BS2, _BS3 = infants born to women in the Control group evaluated for immunogenicity at the designated timepoint (Day 43, Day 121 or Day 181 post-birth)
[1] If cord blood was not collected at delivery/birth, a blood sample should be collected from the infant within 72 hours post-birth.
[2] Any neonatal / infant AESIs identified after 42 days post-birth should also be reported.
[3] Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.
Note:
An additional recommended safety contact may be performed ~7 days post-birth if deemed necessary by the investigator or by the parent/ LAR(s).

Design Features	**Study Type:** self-contained. **Experimental design**: Phase III, double-blind*, randomized, placebo-controlled, multi-center, multi-country study with 1 investigational RSV MAT vaccine group in a parallel design. **** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.*** **Study Population**: High risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.

Overview of Study Design and Key Features	
	Duration of the study: The intended duration of the study for maternal participant is approximately 10 to 11 months (including screening visit, from informed consent/assent until 180 days post-delivery) and approximately 12 months for infant participants (from birth until 365 days post-birth), which is expected to cover at least 1 complete RSV season. **Control**: Placebo control. **Blinding:** Double-blind*, as described in Table 2. **** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.***
Study intervention	**Study (intervention) groups** are single 120 µg dose of the investigational RSV vaccine and Placebo control, as described in Table 2.
Study intervention Assignment	**Study intervention schedule***: 1 single dose administered IM between 24 and 36 weeks of gestation (at Visit 1, Day 1) to maternal participants. **** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.*** **Randomized study intervention allocation*** is 2:1 (investigational vaccine: placebo), as described in Table 2. **** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
Conduct of Analyses	No analysis requiring statistical adjustment will be performed. However, analyses to evaluate objectives and endpoints will be performed in steps. Refer to Section 4.7 for details.

Table 2 Study groups, intervention and blinding

Study groups	Maternal participants				Infant participants			Blinding		
	~Number	Age in years (Min-Max)	Intervention name	Study groups for randomization (Allocation 2:1)	Infant Blood Sampling sub-cohorts		Sub-cohorts for randomization (Allocation 1:1:1)	M + I Up to Day 43 post-delivery/birth	M + I Up to Day 181 post-delivery/birth	I only From Day 182 to Day 366 post-delivery/birth
					Name	~Number		Double-blind**	Single-blind**	Single-blind**
RSV_MAT	~252 *	15 – 49	RSV MAT	RSV_MAT	RSV_MAT_BS1	~84	RSV_MAT_BS1	●	●	●
					RSV_MAT_BS2	~84	RSV_MAT_BS2			
					RSV_MAT_BS3	~84	RSV_MAT_BS3			
Control	~126 *	15 – 49	Control	Control	Control_BS1	~42	Control_BS1	●	●	●
					Control_BS2	~42	Control_BS2			
					Control_BS3	~42	Control_BS3			

Control = Placebo; **M** = maternal participants; **I** = infant participants

Infant sub-cohorts are abbreviated "BS1", "BS2" and "BS3" correspond to Visit 2-NB (Day 43 post-birth), Visit 3-NB (Day 121 post-birth) and Visit 4-NB (Day 181 post-birth), respectively.

RSV_MAT_BS1, _BS2, _BS3 = infants born to women in the RSV_MAT group and evaluated for immunogenicity at the designated timepoint (Day 43, Day 121 or Day 181 post-birth).

Control_BS1, _BS2, _BS3 = infants born to women in the Control group evaluated for immunogenicity at the designated timepoint (Day 43, Day 121 or Day 181 post-birth)

* The double-blinding will apply from Day 1 pre-study intervention to Day 43 post-delivery/birth visit after which the first analysis will be conducted and treatment-level unblinded summaries will be provided to GSK and regulatory agency for review. No individual treatment code will be shared with investigators, site staff and participants until the end of the study

**** Due to the recent safety signal in RSV-MAT-009, there will be no further enrollment and vaccination of maternal participants.***

***** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants***

2. STATISTICAL HYPOTHESES

No statistical hypotheses will be tested. All statistical analyses are descriptive.

2.1. Multiplicity Adjustment

No analysis requiring statistical adjustment will be performed.

3. ANALYSIS SETS

3.1. Definition

Table 3 Maternal Participants

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All maternal participants who completed the informed consent process and signed the informed consent form ***and were determined as eligible for study participation***.	Study Population
Exposed	All maternal participants who received 1 dose of a study intervention. The allocation in a group is done in function of the administered intervention.	Safety
Full Analysis Immunogenicity	All maternal participants in the Exposed set who have at least one post-dosing immunogenicity data. It will be defined by timepoint, e,g. FAS at Day 31	Immunogenicity
Per-Protocol Immunogenicity	All maternal participants in the Full Analysis (Immunogenicity) minus participants with protocol deviations that lead to exclusion. The analysis will be done according to the study interventions that participants received. It will be defined by timepoint, e.g. PPS at Day 31.	Immunogenicity
Solicited Safety	All maternal participants in the Exposed set who have solicited safety data.	Safety

FAS = **Full Analysis Set**; PPS = **Per Protocol Set**

Table 4 Infant Participants

Analysis Set	Definition / Criteria	Analyses Evaluated
Exposed	Infants live-born to exposed maternal participants, whose parents/LARs completed the informed consent process and signed the informed consent form.	Safety
Full Analysis Immunogenicity	All infant participants in the Exposed set who have at least one post-delivery/birth immunogenicity data. The analysis will be done according to the study intervention that maternal participants received. It will be defined by timepoint, e.g. FAS at Day 31	Immunogenicity
Per-Protocol Immunogenicity	All infant participants in the Full Analysis (Immunogenicity) set minus those who (a) were born less than 4 weeks post-maternal participant dosing and/ or (b) have protocol deviations that lead to exclusion. It will be defined by timepoint, e.g. PPS at Day 31	Immunogenicity

FAS = Full Analysis Set; **PPS** = Per Protocol Set

3.2. Criteria for eliminating data from Analysis Sets

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

3.2.1. Elimination from Exposed Set (ES)

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

3.2.2. Elimination from Full Analysis Set (FAS) - Immunogenicity

3.2.2.1. Excluded participants from FAS of maternal participants

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

Table 5 Elimination code and condition for maternal participants

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 2/Day 31, Visit 3/Delivery	Immunogenicity

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

3.2.2.2. Excluded participants from FAS of infant participants

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

Table 6 Elimination code and condition for infant participants

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 participants whose immunogenicity data will be eliminated from a specific visit.

*cord blood sample or blood sample collected within 72 hours after birth if cord blood sample is not collected

3.2.3. Elimination from Per-protocol analysis Set (PPS) - Immunogenicity

3.2.3.1. Excluded participants from Per-protocol analysis set of maternal participants

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

Table 7 Elimination code and condition for maternal participants

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1060	Randomisation code was broken	All	Immunogenicity
1070**	Participants 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

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 15-49 years Gestational age at vaccination - $28^{0/7}$ - $36^{0/7}$	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2040.Vx+*	Device, excluded by the protocol, was administered	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 31, Visit 3/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 day before to 3 days after delivery;	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2100.Vx	Serological results not available post-vaccination	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 2/Day 31, Visit 3/Delivery	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 2/Day 31, Visit 3/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
BS- Blood Sample.

3.2.3.2. Excluded participants from Per-protocol analysis set of infant participants

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

Table 8 Elimination code and condition for infant participants

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#	Maternal participants 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

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
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

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
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	Participants 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 – 72 hours; • For PPS at Day 43 post-birth, check the interval from birth to Day 43 BS = 30 – 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

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	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.

3.2.4. Elimination from 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 participants eliminated from the solicited safety set.

4. STATISTICAL ANALYSES

4.1. General Considerations

Unless otherwise specified, reactogenicity analysis will be performed on Solicited Safety Set for maternal participants, and other safety analyses will be performed on Exposed Sets for both maternal and infant participants.

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

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

95% confidence interval (CI) for proportion will be based on exact Clopper-Pearson confidence interval [Clopper, 1934].

95% CI for group difference in proportion will be based on Miettinen and Nurminen confidence interval [Miettinen, 1985].

95% CI for GMT(C) will be based on a back transformation of student confidence interval for the mean of log-transformation.

95% CI for GMT(C) ratio between groups will be based on a back transformation of confidence interval for the mean difference on log-transformation.

For a given participant and given immunogenicity measurement, missing or non-evaluable measurements will neither be imputed nor be replaced, and therefore will not be included in immunogenicity analysis.

For between group statistical modelling analysis, participants having a result at both the baseline and the considered timepoint will be included in the analysis.

4.1.2. Definition

4.1.2.1. Baseline definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.2.2. Worsening of pre-existing medical conditions and/or obstetric complications

Worsening of the pre-existing medical condition and/or obstetric complication will be considered by the investigator, using clinical judgment and the following criteria:

- Change in medication and/or medication dose
- Medically attended event in relation to pre-existing condition and/or obstetric complication that are outside the routine management of the condition/complication
- SAE and/or hospitalization in relation to pre-existing condition and/or obstetric complication

Worsening of the pre-existing medical condition and/or obstetric complication will be collected from Day 1 (Visit 1) up to Day 181 post-delivery as AESI.

4.1.2.3. RSV infection

The sponsor will analyse nasal swabs by quantitative reverse transcription polymerase chain reaction (qRT-PCR) for the presence of RSV-A/B. A positive (RSV-A or B) test result constitutes a case of RSV infection. Refer to Table 10, Table 12 and section 8.4 of the Protocol.

In the event the collection of a nasal swab for testing by the sponsor is impossible, results from locally collected samples, tested with locally approved tests, may also be considered for the determination of a case of RSV infection.

Note: Due to the change in the study requirements, RTI surveillance of the maternal participants will no longer be performed.

4.1.2.4. RTI and LRTI

RTI cases will be classified (during data analyses) according to the definitions provided in Table 9***** and Table 10.

**** Due to the change in the study requirements, RTI surveillance of the maternal participants will no longer be performed.***

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

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 4.2.5.3 of the Protocol
[2] RSV (nasal swab) sampling and testing as specified in Table 10 of the Protocol.
[3] Hospitalization is defined as admission for observation or treatment based on the judgment of a health care provider.
MA-RTI = Maternal, medically attended respiratory tract illness
Note: Due to the change in the study requirements, RTI surveillance of the maternal participants will no longer be performed.

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, **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]
All-cause LRTI hospitalization	Hospitalized due to all-cause LRTI as defined above

Definitions are modified from [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.
[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 4.2.5.3 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 judgment 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.

4.2. Primary Endpoint(s) Analyses

4.2.1. Safety

4.2.1.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in maternal participants will include summaries by study group and age category (<18 years; ≥ 18 years; overall) of solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, (S)AEs leading to study withdrawal, worsening of pre-existing medical conditions and/or obstetric complications, pregnancy outcomes and pregnancy-related AESIs.

Safety analyses in infant participants will include summaries by study group and gestational age at birth (≥ 37 weeks; <37 weeks; overall) of neonatal AESIs, MAEs, SAEs, (S)AEs leading to study withdrawal, and occurrence of RSV- associated LRTIs, severe LRTIs, RSV-associated hospitalization.

The reactogenicity analysis will be performed on Solicited Safety Set for maternal participants, and other safety analyses will be performed on the Exposed Sets for both maternal and infant participants.

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting solicited administration site and systemic events during a 7-day (i.e. Day 1 to Day 7 included) follow-up period after dosing.	The number and percentage with exact 95% CI of maternal participants reporting each solicited administration site event (any grade, each grade,) and solicited systemic event (any, each grade) during the 7-day (7 days post-study intervention, Day 1 included) follow-up period after dosing will be tabulated by maximum intensity per participant for each study group. The number and percentage of maternal participants reporting: • at least one administration site AE (solicited and unsolicited) • at least one systemic AE (solicited and unsolicited) • any AE during the 7-day (7 days post-study intervention, Day 1 included) follow-up period after dosing will be tabulated with exact 95% CI by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any unsolicited AEs considered related to study intervention, for any Grade 3 unsolicited AEs considered related to study intervention and for any solicited and unsolicited AEs resulting in a medically attended visit (i.e., MAEs).
	Number and percentage of maternal participants reporting unsolicited AEs that occur during a 30-day (i.e. Day 1 to Day 30 included) follow-up period after dosing.	The number and percentage of maternal participants reporting unsolicited AEs within 30 days (30 days post-study intervention, Day 1 included) after dosing with exact 95% CIs will be tabulated by group and by MedDRA preferred term. Similar tabulations will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 related unsolicited AEs and for MAEs.

	Primary Safety Endpoints	Statistical Analysis Methods
	Number and percentage of maternal participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from Day 1 up to 42 days post-delivery.	The number and percentage of maternal participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-delivery with exact 95% CIs will be tabulated by group and by Medical MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal, and MAEs will be prepared.
	Number and percentage of maternal participants reporting pregnancy outcomes * from Day 1 up to 42 days post-delivery. *These include live birth with no congenital anomalies, live birth with minor congenital anomalies only; live birth with at least one major congenital anomaly, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with only minor congenital anomalies, fetal death/still birth (antepartum or intrapartum) with at least 1 major congenital anomaly; elective/therapeutic termination with no congenital anomalies; elective/therapeutic termination with only minor congenital anomalies, and elective/therapeutic termination with at least 1 major congenital anomaly.	The number and percentage of maternal participants reporting each pregnancy outcome from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of adverse pregnancy outcomes will be prepared.
	Number and percentage of maternal participants reporting pregnancy-related AESIs * and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery. * These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth) and chorioamnionitis.	The number and percentage of maternal participants reporting each pregnancy-related AESI and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of pregnancy-related AESIs and worsening of pre-existing medical conditions and/or obstetric complications will be prepared.

	Primary Safety Endpoints	Statistical Analysis Methods
Infant participants	Number and percentage of infant participants reporting neonatal / infant AESIs * from birth up to 42 days post-birth. * These include small for gestational age, low birth weight including very low and extremely low birth weight (<2500 g, <1500g, <1000g), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in an extremely preterm birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth) and preterm birth.	The number and percentage of infant participants reporting each neonatal / infant AESI from birth up to 42 days post-birth will be tabulated with its exact 95% CI by group. By participant listings of neonatal / infant AESIs will be prepared.
	Number and percentage of infant participants reporting SAE, (S)AEs leading to study withdrawal, and MAEs from birth up to 42 days post-birth.	The number and percentage of infant participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-birth with exact 95% CIs will be tabulated by group and by MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 180 days post-birth.	The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 180 days post-birth will be tabulated with 95% CI by group. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 365 days post-birth.	The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 365 days post-birth will be tabulated with 95% CI by group. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.

AE= Adverse event; **CI**= Confidence interval; **MAE** = medically attended adverse event; **MedRA** = Medical dictionary for regulatory activities; **SPM** = study procedure manual

4.2.1.2. Additional considerations

Refer to Section 4.3.1.2

4.2.2. Immunogenicity

4.2.2.1. Analysis of immunogenicity planned in the protocol

The primary analysis for immunogenicity will be based on the PPS for analysis of immunogenicity.

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal participants	• Humoral immune responses at pre-dosing (Day 1) and at delivery: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A	For each assay, at each timepoint and by study group and age category (<18 years; ≥ 18 years; overall): • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • GMR of antibody titers/concentrations at delivery over pre-dosing will be tabulated with 95% CI. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A will be performed at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.
Cord blood/ placental transfer	Ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations at delivery. *or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	• Geometric mean of placental transfer ratio will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ratio ≥ 1 will be tabulated with exact 95 % CI by study group.

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
Infant participants	• Humoral immune responses at delivery*: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A *Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	For each assay, the following analysis will be performed by study group • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A will be performed at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if 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 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 72 hours after birth.

ANCOVA = Analysis of covariance; **CI** = Confidence interval; **GMR** = Geometric mean of ratio; **GMT/ C** = Geometric mean titer/ concentration; **RSV-A** = Respiratory syncytial virus subtype A; **RSVPreF3 IgG** = Respiratory syncytial virus PreF3 immunoglobulin G

4.2.3. Sensitivity analyses

Refer to Section 4.3.3

4.3. Secondary Endpoint(s) Analyses

4.3.1. Safety

4.3.1.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in maternal participants will include summaries by study group and age category (<18 years; ≥ 18 years; overall) of solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, MA-RTIs, RSV-associated MA-RTIs, (S)AEs leading to study withdrawal, worsening of pre-existing medical conditions and/or obstetric complications, pregnancy outcomes and pregnancy-related AESIs.

Safety analyses in infant participants will include summaries by study group and gestational age at birth (≥ 37 weeks; <37 weeks; overall) of neonatal AESIs, MAEs, SAEs, (S)AEs leading to study withdrawal, and occurrence of RSV- associated LRTIs, severe LRTIs, RSV-associated hospitalization.

The reactogenicity analysis will be performed on Solicited Safety Set for maternal participants, and other safety analyses will be performed on the Exposed Sets for both maternal and infant participants.

	Secondary Safety Endpoints	**Statistical Analysis Methods**
Maternal participants	Number and percentage of maternal participants reporting SAEs, (S)AEs leading to study withdrawal and MAEs from Day 1 up to 180 days post-delivery.	The number and percentage of maternal participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 180 days post-delivery with exact 95% CIs will be tabulated by group and by MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.
	Number and percentage of maternal participants reporting worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery.	The number and percentage of maternal participants reporting each worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of worsening of pre-existing medical conditions and/or obstetric complications will be prepared.
	Number and percentage of maternal participants reporting RSV-associated MA-RTIs from Day 1 up to 180 days post-delivery.	The number and proportion of participants reporting at least one RSV-associated MA-RTI from Day 1 up to 180 days post-delivery with exact 95% CIs will be calculated and tabulated.
Infant participants	From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated LRTIs of any severity and severe RSV-associated LRTIs (according to the case definitions).	The number and percentage of infant participants reporting: • at least one medically assessed, RSV-associated LRTI of any severity • at least one medically assessed, severe RSV-associated LRTI from birth up to 365 days post-birth (12 months of age) will be calculated and tabulated by group.
	From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated hospitalizations (according to the cases definitions).	The number and percentage of infant participants reporting at least one medically assessed, RSV-associated hospitalization from birth up to 365 days post-birth (12 months of age) will be calculated and tabulated by group.

AE = Adverse event; **LRTI** = Lower respiratory tract illness; **MAE** = medically attended adverse event; **NB** = Newborn; **RSV-MA-RTI** = respiratory syncytial virus associated medically attended respiratory tract illness; **SAE** = serious adverse event

4.3.1.2. Additional considerations

4.3.1.2.1. Analysis of solicited events

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

Table 11 Intensity scales for solicited events in adults

Adults			
Event		**Intensity grade**	**Parameter**
Solicited administration site events	**Pain at administration site**	0	None
		1	Mild: Any pain neither interfering with nor preventing normal everyday 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 administration site		Greatest surface diameter in mm
	Swelling at administration site		Greatest surface diameter in mm
Solicited systemic events	**Temperature***		Record temperature in °C/°F with 1 decimal Temperature will be analyzed 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		

* Refer to Section 1.3 of the Protocol for the definition of fever and the preferred location for temperature measurement.

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 study intervention 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 6.2.4.9.

4.3.1.2.2. Exclusion of implausible solicited events

Some local and systemic events will be directly measured by the participant 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 12 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

4.3.1.2.3. Analysis of unsolicited adverse events

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

4.3.1.2.4. Analysis of pregnancy outcome

The analysis of pregnancy outcome will be performed on Exposed Set.

Still births, preterm births and spontaneous abortions will be counted per pregnancy, regardless of the number of fetuses in the concerned pregnancy.

4.3.1.2.5. Analysis of RTI and LRTI

The analysis of RTI and LRTI will be performed on Exposed Set according to the case definitions in section 4.1.2.4. Separate listings of maternal RSV associated MA-RTI and infant RSV associated LRTI/hospitalization will be provided.

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

4.3.2. Immunogenicity

4.3.2.1. Analysis of immunogenicity planned in the protocol

The secondary analysis for immunogenicity will be based on the Per Protocol – Immunogenicity Set.

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal participants	• Humoral immune responses at Day 31 post-dosing: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A • Humoral immune responses at pre-dosing (Day 1), at Day 31 post-dosing and at delivery:	For each assay, at each timepoint and by study group and age category (<18 years; ≥ 18 years; overall): • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • GMR of antibody titers/concentrations at each post-dosing timepoint over pre-dosing will be tabulated with 95% CI. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody

	Secondary Immunogenicity Endpoints	**Statistical Analysis Methods**
	– Neutralizing antibody titers against RSV-B.	titers against RSV-A will be performed at Day 31 post-dosing, and against RSV-B at Day 31 post-dosing and at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.
Infant participants	• Humoral immune responses at delivery*: – Neutralizing antibody titers against RSV-B * Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	For each assay, the following analysis will be performed by study group: • Antibody titers will be displayed using reverse cumulative curves. • GMTs will be tabulated with 95% CI and represented graphically. Between group evaluation in terms of neutralizing antibody titers against RSV-B will be performed at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if 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 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 72 hours after birth.
	• Humoral immune responses at Day 43*, at Day 121* and at Day 181* after birth: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A and RSV-B * Measured in infant blood samples collected at Day 43 (sub-cohort 1, V2-NB), at Day 121 (sub-cohort 2, V3-NB) and at Day 181 (sub-cohort 3, V4-NB) after birth. Each infant will be randomly assigned (1:1:1) to one of 3 sub-cohorts.	For each assay, at each timepoint and by study group: • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A and RSV-B at Day 43 (sub-cohort 1, V2-NB), at Day 121 (sub-cohort 2, V3-NB) and at Day 181 (sub-cohort 3, V4-NB) after birth using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.

ANCOVA = Analysis of covariance; **CI** = Confidence interval; **GMR** = Geometric mean of ratio; **GMT/ C** = Geometric mean titer/ concentration; **NB** = Newborn; **RSV-A / B** = Respiratory syncytial virus subtype A / B; **RSVPreF3 IgG** = Respiratory syncytial virus PreF3 immunoglobulin G

4.3.3. Sensitivity analyses

For primary and secondary immunogenicity endpoints, between study group comparisons will also be explored through statistical modelling. This analysis is exploratory.

For the analysis of maternal participants at each time point (Day 31, Delivery), the ANCOVA model will be explored and fitted via the proc GML procedure according to the following code:

```
PROC GLM data=adis_moth;
   BY atptn atpt;
   CLASS tr01aga gagevg1 agegr3;
   MODEL aval = base tr01aga gagevg1 agegr3 vacdel;
   LSMEANS tr01aga/pdiff cl alpha=0.05;
RUN;
```

where aval represents the log-transformed antibody value of the immunogenicity variable at a given post baseline timepoint, group indicates the study group, gagevg1 is the gestational age category at study intervention administration ($<28^{0/7}$, $\geq 28^{0/7}$ weeks), agegr3 is the age category at study intervention administration (<18 years and ≥18 years), vacdel is the interval between vaccination and delivery (days). The inclusion of age category at study intervention administration, interaction term between age category and gestational age category and interval between study intervention administration and delivery in the model depends on the availability of the variables (vacdel 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. Other possible co-variates which could be included in the model, but not limited to, are pre-existing HIV infection status, CD4 count, COVID-related complications.

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 GLM data=adis;
   BY atptn atpt;
   CLASS tr01aga gagevg1 gagebg1 agegr3;
   MODEL aval = base tr01aga gagevg1 gagebg1 agegr3;
   LSMEANS tr01aga/pdiff cl alpha=0.05;
   RUN;
```

Baseline is pre-vaccination logarithm10 transformation of the concentrations/titers from maternal participants, gagebg1 is gestational age category at birth (> 37 weeks; ≤ 37 weeks) for infant participants. With the inclusion of gestational age category at vaccination (gagevg1) in the model, this categorical variable gagebg1 provides similar information as continuous variable vacdel, therefore the inclusion of either variable in the model could be adjusted according to the analysis needs. Other possible co-variates which could be included in the model, but not limited to, are maternal pre-existing HIV infection status, CD4 count, COVID-related complications, infant HIV infection status.

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

Summary tables will present number of observations included in the model, the model adjusted GMT/GMC for each group and between group adjusted GMT/GMC ratio with the corresponding 95% CIs at each timepoint.

4.4. Tertiary Endpoint(s) Analyses

CCI [redacted]

4.5. Other Safety Analyses

Other safety analyses will be based on the Exposed Set, unless otherwise specified.

4.5.1. COVID-19 Assessment and COVID-19 AEs

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment electronic Case Report Form (eCRF).

Numbers and percentage of participants with a suspected, probable or confirmed COVID-19 infection will be summarized by group based on Exposed Set.

Number and percentage of participants who had a COVID-19 test performed and number and percentage of participants with positive, negative and indeterminate results will be summarized by group on Exposed Set.

4.5.2. Additional Safety Assessments (if applicable)

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 (SBP), diastolic blood pressure

(DBP), temperature, heart rate, respiratory rate, height, weight and body mass index (BMI).

4.5.3. Combined solicited and unsolicited events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A summary of participants 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.

4.6. Other Analyses

4.6.1. Other analyses for adolescent maternal participants

Sub-analyses to evaluate objectives and endpoints will be performed on the 15-17 Years of Age (YOA) sub-group.

4.6.1.1. Safety

Due to small number of adolescent maternal participants in this trial, a Bayesian approach will be applied to predict the probability of AEs in this population. It is assumed a specific AE in an adolescent maternal participant receiving the RSV-MAT vaccine is a binary outcome (yes/no) with p as a probability that the outcome is “yes”; it is further assumed that p is a random variable having beta distribution as a prior, which will be estimated from other data sources. The prior beta distribution will be developed based on data collected in RSV-MAT vaccine recipients above 17 YOA in this trial. With the data observed in RSV-MAT vaccine recipients 15-17 YOA, a Bayesian approach will be applied to estimate the posterior distribution of p. Similar procedures will be used for estimating the posterior distribution of p_0 (the probability of having this AE for an adolescent maternal participant in placebo group). However, the prior distribution for p_0 will be assumed as a mixture of beta distributions based on both the data collected in participants above 17 YOA in the placebo group in this trial and the adolescents younger

than 17 YOA in EPI-RSV-015 study [EPI-RSV-015, 2020]. Lastly, the predictive probability of the occurrence of this AE in an adolescent maternal participant 15-17 YOA will be calculated separately in the RSV-MAT vaccine group and the placebo group. A predictive probability in an adolescent maternal participant in RSV-MAT vaccine group no worse than that in placebo group will provide reassurance that vaccination does not result in higher risk of AE.

4.6.1.2. Immunogenicity

The immunogenicity data collected in adolescent maternal participants 15 to 17 YOA in this trial will be descriptively summarized by treatment group. In addition, a Bayesian approach will be used for further extrapolation of the immune response. It is assumed that the log transformed immune response (for example neutralizing antibody titers) in adolescent maternal participants follows a normal distribution with the mean μ and SD of σ; it is further assumed that the mean μ is a random variable and has a normal distribution as a prior. The prior normal distribution for the mean μ will be developed based on data collected in maternal participants above 17 YOA in this trial. With the data observed in adolescent maternal participants 15-17 YOA in this trial, a Bayesian approach will be applied to estimate the posterior distribution of the mean μ and the predictive probability of observing a high immune response (for instance, 6 fold increase) for an adolescent maternal participant 15-17 YOA in the RSV-MAT vaccine group. A high predictive probability of having at least 6-fold increase 1 month post-study intervention from baseline in a pregnant adolescent RSV-MAT vaccine recipient will provide reassurance of immune response for an adolescent maternal participant 15-17 YOA receiving the RSV-MAT vaccine.

4.6.2. Subgroup analyses

Subgroup analyses of the primary endpoints will be made to assess consistency of the intervention effect across the following subgroups:

- Age group (for maternal participants): < 18 vs ≥ 18 years
- Gestational age at birth (for infant participants): ≥ 37 weeks; < 37 weeks (as assessed by the GAIA gestational age definition*)

  * Additional statistical analyses may also be performed by using the Intergrowth-21st (IG-21) standard definition [Villar, 2014].
- Pre-existing HIV infection status: present vs absent (for maternal participants ≥18 YOA only)
- Pre-existing obstetric complications: present vs absent (for maternal participants ≥18 YOA only)

Except for maternal age group, if the number of participants is too small (less than 10%) within above mentioned subgroup, then the subgroup categories may be redefined prior to final analysis.

To take a more practical approach, subgroup analysis of safety by age category at study intervention administration (< 18; ≥ 18 years) in maternal participants will include summaries of solicited administration site and systemic events, unsolicited AEs, MAEs, SAEs, RSV-associated MA-RTIs, (S)AEs leading to study withdrawal, worsening of pre-existing medical conditions and/or obstetric complications, pregnancy outcomes and pregnancy-related AESIs.

Subgroup analysis of safety by gestational age at birth (≥ 37 weeks; <37 weeks) in infant participants will include summaries of neonatal AESIs, MAEs, SAEs, (S)AEs leading to study withdrawal, and occurrence of RSV- associated LRTIs, any severity and severe LRTIs, RSV-associated hospitalization.

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

Subgroup analysis of immunogenicity by age category at study intervention administration (< 18; ≥ 18 years) for maternal participants and by gestational age at birth (≥ 37 weeks; < 37 weeks) for infant participants 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.

4.7. Conduct of Analyses

No analysis requiring statistical adjustment will be performed.

4.7.1. Sequence of analyses

The **final** analysis will be performed when all data up to study end are available. A CSR including all available data will be written and made available to the investigators at that time.

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

4.8. Changes to Protocol Defined Analyses

The distribution analysis for antibody titers/concentration and scatter plots for individual immunogenicity data, which were originally planned statistical analysis specified in the protocol Amendment 1 (Dated: 15-MARCH-2022), are removed from this SAP as the sufficient relevant information has been obtained from other RSV MAT Phase I/II studies.

5. SAMPLE SIZE DETERMINATION

Approximately 378 maternal participants* will be randomized in a 2:1 ratio to achieve at least 340 evaluable maternal participants (including at least 16 evaluable adolescents from 15 to less than 18 YOA).

Participants who withdraw from the study will not be replaced.

**** Due to the recent safety signal in RSV-MAT-009, there will be no further enrollment and vaccination of maternal participants.***

5.1. Safety

A sample size of 252 participants in RSV-MAT vaccine group will provide a probability of 72%, 92% or 98% to observe at least one participant with AE, if the true AE rate is 0.5%, 1% or 1.5%, respectively.

Table 13 presents the precision one can get on the percentage of participants with AEs following dosing in study vaccine group.

If no AE was observed in RSV-MAT vaccine group, the exact, two-sided 95% confidence interval (CI) would rule out an AE rate of 1.5% or more. The current sample size also provides the precision on estimating the probability of observing AEs following dosing in RSV-MAT vaccine group. If 5% of the participants experienced an AE among 252 participants following vaccination with the RSV-MAT vaccine, an exact 95% CI would be (2.7%, 8.5%).

Table 13 Exact 95% confidence interval (CI) on the percentage of participants with adverse events (AEs) following dosing in RSV-MAT vaccine group

252 participants in RSV-MAT vaccine group		
Number (%) of participants with an AE	Exact 95% CI	
	Lower Limit	Upper Limit
0 (0)	0.0	1.5
3 (1)	0.2	3.2
5 (2)	0.7	4.6
8 (3)	1.3	5.9
10 (4)	1.9	7.2
13 (5)	2.7	8.5
15 (6)	3.4	9.7
18 (7)	4.2	10.9
20 (8)	5	12.1
23 (9)	5.8	13.2
25 (10)	6.6	14.4
38 (15)	10.8	20.0
50 (20)	15.2	25.5
63 (25)	19.8	30.8
75 (30)	24.4	36.1

Note: Precision estimation using PASS2019 19.0.1 (Confidence Interval [CI] for one proportion) [Hahn, 1991]
Exact 95% CI computed based on Clopper/ Pearson formula [Newcombe, 1998]

5.2. Immunogenicity

With at least 226 evaluable maternal participants for immunogenicity in the RSV-MAT vaccine group (assuming a 10% non-evaluable rate), the current sample size can provide an adequate precision for estimating the fold increase.

Table 14 presents the precision estimation of the fold increase from Day 1 to delivery based on standard deviation (SD) of log10 transformed titer for neutralizing antibody RSV-A and half width of the fold increase.

If at least a 9-12 fold increase from Day 1 to delivery in terms of RSV-A neutralizing antibody is anticipated, then assuming a log 10 SD of 0.4, a 95% CI for a 9-fold increase would be (7.6, 10.7), and a 95% CI for a 12-fold increase would be (10.1, 14.2).

Table 14 Precision estimation on fold increase and its 95% CI with 226 participants in RSV-MAT vaccine group

Standard Deviation[1]	Fold Increase from Day 1 to delivery	No. of participants in RSV-MAT vaccine group	Half Width[2]	95% LL	95% UL	Log 10 Fold
0.3	5	226	0.056	4.4	5.7	0.699
0.3	6	226	0.056	5.3	6.8	0.778
0.3	7	226	0.056	6.2	8.0	0.845
0.3	8	226	0.056	7.0	9.1	0.903
0.3	9	226	0.056	7.9	10.2	0.954
0.3	10	226	0.056	8.8	11.4	1
0.3	11	226	0.056	9.7	12.5	1.041
0.3	12	226	0.056	10.5	13.7	1.079
0.4	5	226	0.074	4.2	5.9	0.699
0.4	6	226	0.074	5.1	7.1	0.778
0.4	7	226	0.074	5.9	8.3	0.845
0.4	8	226	0.074	6.7	9.5	0.903
0.4	9	226	0.074	7.6	10.7	0.954
0.4	10	226	0.074	8.4	11.9	1
0.4	11	226	0.074	9.3	13.0	1.041
0.4	12	226	0.074	10.1	14.2	1.079

[1] Standard deviation on log10 transformed RSV-A neutralizing antibody titer based on previous studies on PreF2 vaccine.

[2] Precision estimation using PASS2019 19.0.1 (Confidence Interval [CI] for one mean) [Hahn, 1991]
LL=10^(log10(fold increase)-half width); UL=10^(log10(fold increase)+half width)

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

Participant disposition will be summarized by group using descriptive statistics:

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

6.1.2. Demographic and Baseline Characteristics

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

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

For all maternal participants, demographic characteristics (e.g., age at study intervention administration (<18 years; ≥ 18 years; overall), gestational age at study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), geographic ancestry) will be summarized by group using descriptive statistics. The interval in days between maternal study intervention 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 YOA) will be summarized 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, SD and range will be provided for continuous data such as age.

6.1.2.2. Additional considerations

Demographic characteristics for maternal and infant participants will also be summarized on Enrolled Set for web public disclosure.

Subgroup analysis for demographic characteristics by age category at study intervention administration (<18 years; ≥ 18 years; overall) for maternal participants and by

gestational age at birth (≥ 37 weeks; < 37 weeks) for infant participants will also be performed on Exposed Set and PPS.

Subject disposition will be summarized by group using descriptive statistics:

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

Summary of past medical history and current medical conditions will be performed on Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) term. Un-coded medical conditions or medical history will be summarized under 'Other' category.

Vaccination history will be coded using GSK Drug dictionaries. Summary of vaccination history will be performed on Exposed Set by group.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized based on Exposed Set by group.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.
- The summary will include number and percentage of participants with important protocol deviations by deviation category for each study group.
- An individual listing of protocol deviation will also be provided.

Protocol deviations which result in exclusion from the analysis set will also be summarized based on Exposed Set by group.

- Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

In addition to the overall summary of important protocol deviations, separate summaries may be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively if deemed necessary.

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

6.1.4. Concomitant Medications and Vaccinations

Concomitant medications and vaccinations will be coded using the GSK Drug dictionary.

- The number and percentage of maternal participants taking concomitant medications /vaccinations within 7 days following vaccination, 30 days following study intervention administration, up to 42 days post-delivery and up to 180 days 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 42 days after birth, 180 days after birth and 365 days after birth will be summarized by group. A listing will also be provided.
- The number and percentage of infants taking concomitant vaccinations from birth up to 42 days after birth and 180 days after birth will be summarized by group. A listing will also be provided.

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

Depending on how the Covid-19 situation evolves, the SAP might be amended to reflect the analysis corresponding to Covid-19.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.2. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant 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 case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If ‘after study dose’ is selected, the relative dose for the event will be the one administered on the start day of the event. If ‘before study dose’ is selected, the relative dose for the event will be the dose prior to this one.

6.2.3. Handling of missing data

6.2.3.1. Dates

When partially completed dates (i.e. dates missing a day and/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 study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before study dose' 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 study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before study dose' 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.

6.2.3.2. Laboratory data

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

6.2.3.3. Daily recording of solicited events

6.2.3.3.1. Studies with electronic diaries

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

6.2.3.4. Unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

Missing severity, relationship with study intervention, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

6.2.4. Data derivation

6.2.4.1. Age at first dose in years

When age at first dose 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 first dose. For example:

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

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

6.2.4.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

6.2.4.3. 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

6.2.4.4. Body mass index (BMI)

BMI will be calculated as follows:

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

6.2.4.5. 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

6.2.4.6. 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

The cut-off tests for immunogenicity evaluation will be as per following:

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

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis when notified by the lab.

6.2.4.7. 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. Non quantifiable antibody titres or concentrations will be converted as described in section 6.2.4.6 for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis.

6.2.4.8. Onset day

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

6.2.4.9. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date 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 event period.

6.2.4.10. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs 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.

6.2.4.11. Counting rules for occurrences of solicited events

When the occurrences of solicited 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 interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

6.2.5. Display of decimals

6.2.5.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.2.5.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.5.3. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, BMI, pre-dose 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 minimum and maximum of transformed height variables will be displayed with no decimals.

The minimum and maximum 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.

6.2.5.4. Serological summary statistics

The number of decimals used when displaying GMT or GMC and their confidence limits is assay specific based on the magnitude of the assay result post-dose and the clinically relevant assay threshold. The same number of decimals will be used for a given assay regardless of the timepoint presented.

Lowest clinically relevant threshold	Example	Number of decimals to display
<0.3	Diphtheria, tetanus, anti-PRP	3
>=0.3 and <4	*Streptococcus pneumoniae*, Meningococcal bactericide	2
>=4 and <1000	Measles, rubella, varicella, polio	1
>=1000	CMI	0

GMT/GMC fold increase from pre-dose follows the same principle. Namely when the lowest clinically relevant threshold is 2-fold, 2 decimals are displayed while when the lowest clinically relevant threshold is 4-fold, 1 decimal is displayed.

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

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