Statistical Analysis Plan

Title:	A Phase III, randomized, double-blind, placebo-controlled multi-country study to demonstrate efficacy of a single dose of unadjuvanted RSV Maternal vaccine, administered IM to pregnant women 18 to 49 years of age, for prevention of RSV associated LRTI in their infants up to 6 months of age
eTrack study number and Abbreviated Title	212171 (RSV MAT-009)
Scope:	All analyses for the primary and secondary objectives of the study. Analysis details for tertiary objectives may be described in an SAP Amendment.
Date of Statistical Analysis Plan	Amendment 5 Final: 21 Sep 2023

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
eCRF	Electronic Case Report Form
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
HIC	High Income Countries
IDMC	Independent Data Monitoring Committee
LL	Lower Limit of the confidence interval
LLOQ	Lower Limit of Quantification
LMIC	Low-middle Income Countries
LRTI	Lower Respiratory Tract Illness
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NB	Newborn
PD	Protocol Deviation
PPS	Per-Protocol Set
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model

1. DOCUMENT HISTORY

Date	Description	Protocol Version
02 Nov 2020	Final	Amendment 1: 05 Oct 2020
01 Nov 2021	Amendment 1	Amendment 2: 23 Jun 2021
17 Nov.2022	Amendment 2	Amendment 4: 15 Mar 2022
03 Jan 2023	Amendment 3	Amendment 4: 15 Mar 2022
09 Mar 2023	Amendment 4	Amendment 5: 23 Feb 2023
21 Sep 2023	Amendment 5	Amendment 5: 23 Feb 2023

2. OBJECTIVES/ENDPOINTS

Table 1 Study objectives and endpoints

Primary objectives	**Primary endpoints**
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing *medically assessed*[1], RSV-associated severe LRTIs in their infant[3] participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of *medically assessed*[1], *RSV-associated* severe LRTIs according to the case definitions[2].
	OR
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing *medically assessed*[1], RSV-associated LRTIs of any severity in their infant[3] participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any *medically assessed*[1], RSV-associated LRTIs according to the case definitions[2].
	AND
To evaluate the safety of the RSV Maternal vaccine in infants born to mothers who were vaccinated with a single IM dose of study vaccine, up to 12 months after birth.	Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 6 months after birth[5]. Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 12 months after birth[5].
Secondary efficacy objectives	**Secondary efficacy endpoints**
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing RSV-associated hospitalization in their infant[3] participants up to 6 months of age.	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of RSV-associated hospitalizations according to the case definitions[2].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their infant[3] participants up to 6 months of age, all cause LRTI	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTI.
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their infant[3] participants up to 6 months of age, all cause LRTI with hospitalization.	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTI with hospitalization.
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed[1], RSV-associated severe LRTIs in their infant[3] participants up to 12 months of age.	From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of medically assessed, RSV-associated severe (including very severe) LRTIs according to the case definitions[2].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed[1], RSV-associated LRTIs of any severity in their infant[3] participants up to 12 months of age.	From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions[2].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing severe medically assessed[1], RSV-associated LRTIs for each RSV	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of severe medically assessed[1], RSV-associated LRTIs according to the case definition[2], for RSV subtype A and RSV subtype B separately.

subtype (A and B) separately in their infant[3] participants up to 6 months of age	
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing any medically assessed[1], RSV-associated LRTIs for each RSV subtype (A and B) separately in their infant[3] participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed[1], RSV-associated LRTIs according to the case definition[2], for RSV subtype A and RSV subtype B separately.
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed[1], RSV-associated severe LRTIs in their infant[3] participants up to 4 months of age	From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of severe medically assessed[1], RSV-associated LRTIs according to the case definitions[2].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed[1], RSV-associated LRTIs of any severity in their infant[3] participants up to 4 months of age	From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of any medically assessed[1], RSV-associated LRTIs according to the case definitions[2]
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their infant[3] participants up to 6 months of age, all cause pneumonia.	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause pneumonia.
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing RSV-associated hospitalization in their infant[3] participants up to 12 months of age.	From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of RSV-associated hospitalizations according to the case definitions[2].
To assess the efficacy of a single dose of RSV Maternal vaccine administrated to maternal participants in preventing, in all vaccinated maternal participants up to 6 months post-delivery, RSV associated medically attended RTIs (MA-RTIs)	From study intervention administration (Visit 1) to 6 months post-delivery (Contact 1), occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) [2].
Secondary immunogenicity objectives	**Secondary immunogenicity endpoints**
To evaluate the immunogenicity of the RSV Maternal vaccine in a sub-cohort of maternal participants 30 days after the study intervention, and at delivery.	Neutralizing antibody titers against RSV-A Measured on blood samples collected at Day 1 before the study intervention (Visit 1), at Day 31 (Visit 2), and at delivery (Visit 3).
To evaluate the immunogenicity of the RSV Maternal vaccine in a sub-cohort of infants in Stage A, at birth and up to 6 months after birth	Neutralizing antibody titers against RSV-A. Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 72 hours after birth (if no cord blood sample can be obtained) Measured on a blood sample collected at Day 43 (Visit 2-NB), Day 121 (Visit 3-NB), or Day 181 (Visit 4-NB) after birth in 3 sub-cohorts of infants. Infants born to women in the immunogenicity sub-cohort will be randomly assigned (1:1:1) to sample collection at 1 of the 3 timepoints noted.

To evaluate the transfer of RSV-specific antibodies from a sub-cohort of maternal participants vaccinated with a single IM dose of the RSV Maternal vaccine to their infants at the time of delivery.	***RSVPreF3 IgG-specific antibody concentration measured on blood samples collected at Delivery and cord blood**** The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations * or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).
Secondary safety objectives	**Secondary safety endpoints**
To evaluate reactogenicity of a single IM dose of the RSV Maternal vaccine in stage A maternal participants, during a 7 day follow up period after the study intervention.	Occurrence of solicited administration site and systemic events in stage A maternal participants, during a 7-day follow-up period after the study intervention (i.e. the day of the intervention and 6 subsequent days).
To evaluate the safety of a single IM dose of the RSV Maternal vaccine in all maternal participants, during a 30 day follow up period after the study intervention.	Occurrence of unsolicited adverse events (AEs) in all maternal participants during a 30-day follow-up period after the study intervention (i.e. the day of the intervention and 29 subsequent days).
To evaluate the safety of a single IM dose of the RSV Maternal vaccine in all maternal participants, from Visit 1 up to 6 months after delivery	Occurrence of serious adverse events (SAEs) [5], AEs leading to study termination, and medically attended RTIs in all maternal participants from Visit 1 (Day 1) up to 6 months after delivery. Occurrence of all other medically attended AEs in all maternal participants from Visit 1 (Day 1) up to Day 42 after delivery.
To evaluate pregnancy outcomes and pregnancy-related adverse events of special interest after a single IM dose of the RSV Maternal vaccine administered to maternal participants, from Visit 1 up to 6 weeks after delivery (Visit 4).	Pregnancy outcomes[5] from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 4). 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.
	Pregnancy-related adverse events (AEs) of special interest from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 4). These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), gestational diabetes mellitus, chorioamnionitis. [4,5]
To evaluate the occurrence of neonatal AEs of special interest (reported up to 6 weeks after birth), in infants born to mothers who were vaccinated with a single IM dose of the RSV Maternal vaccine	The occurrence of neonatal AEs of special interest (reported up to 6 weeks after 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), preterm birth. [4,5]

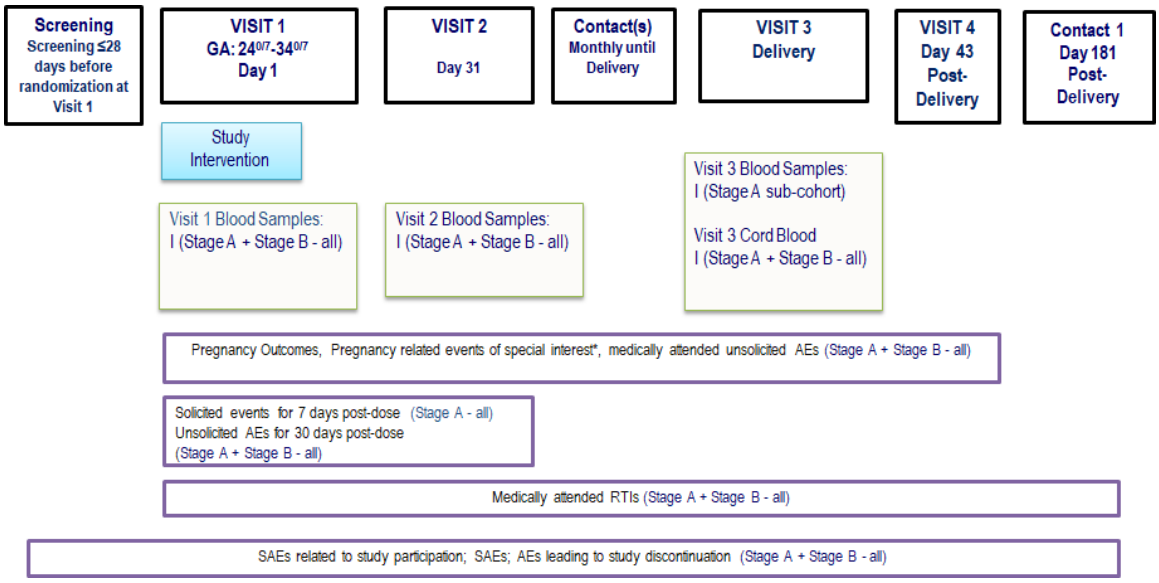
Tertiary objectives:
CCI [redacted]

[1]By "medically assessed" it is meant that the infant was evaluated by a healthcare professional (physician, nurse, etc) for the lower respiratory tract illness.
[2]Case definitions for ***RSV-associated medically attended RTIs,*** RSV associated LRTIs, surveillance for potential LRTIs, are briefly summarized in Section 9.2.2.
[3]An infant is defined as a child younger than 1 year of age; a neonate is defined as an infant 28 days old or less.
[4]Maternal and neonatal AESI and pregnancy outcomes should be recorded in the eCRF along with assessment of level of diagnostic certainty by GAIA definitions when applicable. Of note, some events of interest fall under a single category but have multiple subcategories. For example, hypertensive disorder of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.
[5]The following adverse events are listed by GAIA as events of interest, but will not, for purposes of this study, be reported as AESIs. If any of these events meets the definition for an SAE, the event should be reported as such in the eCRF and the SAE narrative should contain enough information to permit assessment of level of diagnostic certainty by GAIA criteria:

- Pregnancy-related: antenatal bleeding (morbidly adherent placenta, placental abruption, cesarean scar pregnancy, uterine rupture), postpartum hemorrhage, non-reassuring fetal status, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.
- Neonatal: neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, failure to thrive, large for gestational age, macrosomia.

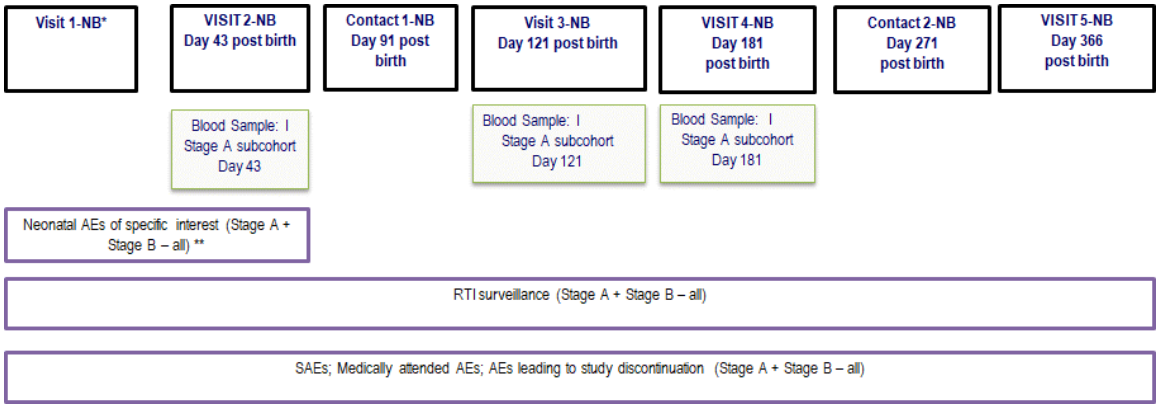
3. STUDY DESIGN

Figure 1 Study design overview – maternal participants



GA = Gestational age; I = immune response; (S)AE = (serious) adverse event; RTI = respiratory tract illness
Visit 2 may be replaced by Visit 3 in case of premature delivery.
All = all participants
Refer to Protocol Amendment 5 Section 6.3.2 for detailed description of Stage A and Stage B. Refer to Protocol Amendment 5 Section 6.3.2.1.1 for additional description of the Stage A sub-cohort.
Solicited events will be evaluated for all participants in **Stage A only**
* Any pregnancy-related event of special interest identified after Visit 4 should also be reported.
In addition to the monthly contacts between Visit-2 and the Delivery visit, additional not pre-specified visits and contacts (any desired frequency) can be made between Visit-2 and the Delivery visit, as per investigator's or maternal participant's discretion.
As from protocol Amentment 4, blood samples will be collected at delivery from all maternal participants. Placental samples will be collected at delivery from all maternal participants, if feasible
Due to the stop on study enrolment and vaccination, nasal swab samples will no longer be collected from any maternal participant and no MA-RTI assessment visit will be performed, but the MAEs associated with an RTI will continue to be reported, as applicable.

Figure 2 Study design overview – infant participants



I = immune response; (S)AE = (serious) adverse event; RTI = respiratory tract illness
Stage A + Stage B – all participants:
*If cord-blood was not collected at delivery/birth, a blood sample should be collected from the infant **within 72 hours post birth**. Applies to all participants in Stage A and Stage B.
**Any Neonatal AE of specific interest identified *after* Day 43 should also be reported.
An additional recommended safety contact may be performed 8-days post-birth if deemed necessary by the investigator or by the parent/LAR(s).
Due to the stop on study enrolment and vaccination, blood samples will no longer be collected at V2-NB, V3-NB or V4-NB.

- Study Type: self-contained
- Study Duration: Approximately 10 to 11 months (including the screening visit) for maternal participants; approximately 1 year after birth for infant participants.
- Blinding is as described in Table 2 and Table 3.
- Randomized intervention allocation: A minimum of 4600 and up to a maximum of 10,000 pregnant women (maternal participants) will be randomly assigned (2:1) to receive the investigational vaccine or control (placebo) at Visit 1. Randomization will take place in 2 sequential stages, A and B. Approximately 4,600 maternal participants will be randomized into Stage A. Stage B will only start after the last participant is randomized in Stage A. Participants in stage A will be randomized (12:2:2:2:6:1:1:1 ratio) to be in the RSV group, in one of the 3 infant blood sampling sub-cohorts and receiving the investigational vaccine (RSVMAT_BS1 (Day 43), RSVMAT_BS2 (Day 121), RSVMAT_BS3 (Day 181)), in the Control group, or in one of the 3 infant blood sampling sub-cohorts receiving placebo (Control_BS1 (Day 43), Control_BS2 (Day 121), Control_BS3 (Day 181)). Randomization will be via the automated internet-based system (SBIR). The system's randomisation algorithm of maternal enrolment will use a minimisation procedure accounting for maternal age at the time of the study intervention (18-34, 35-39, ≥40 years of age), gestational age at the time of the study intervention ($24^{0/7}$-$28^{0/7}$; $28^{1/7}$-$34^{0/7}$), and center. Minimisation factors will have equal weight in the minimisation algorithm.
- Study (intervention) groups are described in Table 2 and Table 3
- Data collection: standardized Electronic Case Report Form (eCRF). E-Diaries will be used to collect solicited event data.

- Safety monitoring will be conducted by an unblinded Independent Data Monitoring Committee (IDMC) and by an unblinded Safety Review Team*. The analyses for IDMC safety evaluations will be described in a separate SAP for IDMC.

  **** Due to the safety signal observed, the study was fully unblinded to ensure the safety of the participants.***

Table 2 Study groups, sub-cohorts, interventions, and blinding foreseen in the study: Stage A

Approximately 4,600 maternal participants will be randomized during Stage A.

									Blinding		
Study groups	**Maternal participants (M)**					**Infant participants (I)**		**Study Groups for Randomization**	**M only**	**M + I**	**I only**
	~Number	**Age in Years (Min/Max)**	**Intervention name**	**Maternal Blood Sampling Sub-cohorts**		**Infant Blood Sampling sub-cohorts**		**(Allocation 12:2:2:2:6:1:1:1)**	**Screen-ing**	**Up to D181 post delivery/birth**	**D271, D366 post delivery/birth**
				Name	~Number	Name	~Number		-	Double blind	Double blind
RSV_MAT	~3,067	18-49	RSV_MAT	RSV_MAT_0	~2,040	RSV_MAT_0	~2,040	RSVMAT_0	●	●	●
		18-49	RSV_MAT	RSV_MAT_I	~1020	RSV_MAT_BS1	~340	RSVMAT_BS1		●	
						RSV_MAT_BS2	~340	RSVMAT_BS2		●	
						RSV_MAT_BS3	~340	RSVMAT_BS3		●	
Control	~1,533	18-49	Control	Control_0	~1020	Control_0	~1020	Control_0	●	●	●
		18-49	Control	Control_I	~510	Control_BS1	~170	Control_BS1		●	
						Control_BS2	~170	Control_BS2		●	
						Control_BS3	~170	Control_BS3		●	

Control = Placebo; Infant sub-cohorts are abbreviated "BS1;" "BS2;" BS3" and correspond to visits 2-NB (Day 43), 3-NB (Day 121) and 4-NB (Day 181), respectively.
RSVMAT_0 and Control_0 = maternal and infant participants who are not in a sub-cohort for immune response assessment.
RSVMAT_I and Control_I = maternal sub-cohorts for immune response assessment.
RSVMAT_BS1, _BS2, _BS3 = infants born to women in the RSVMAT_I sub-cohort and evaluated for immune response at the designated timepoint (D43, D121 or D181).
Control_BS1, _BS2, _BS3 = infants born to women in the Control_I sub-cohort evaluated for immune response at the designated timepoint (D43, D121 or D181).

Table 3 Study groups, sub-cohorts, interventions, and blinding foreseen in the study: Stage B

Approximately a maximum of 5,400 maternal participants may be randomized during Stage B.

Stage B will only start after the last participant is randomized in Stage A.

Study groups	Number of maternal participants	Age of maternal participant at enrolment (Min/Max)	Intervention name	Study groups for randomization (Allocation 2:1)	Blinding		
					Maternal participants Only (Screening)	Maternal participants V1-C1 Infant participants V1-NB – V4NB (double-blind)	Infant participants only Contact 2-NB – V5-NB (double blind)
RSV_MAT	~3,600	18 – 49 years	RSV_MAT	RSV_MAT	●	●	●
Control	~1,800	18 – 49 years	Control	Control	●	●	●

4. ANALYSIS SETS

4.1. Definition

For the purpose of the analysis the following analysis sets are defined.

Table 4 Maternal Participants

Analysis Set	Description
Enrolled	All maternal participants who completed the informed consent process and signed the informed consent form.
Exposed	All maternal participants who received the study intervention. The allocation in a group is done in function of the administered intervention.
Per Protocol - Immunogenicity	All maternal participants who received the study intervention to which they were randomised and have post-vaccination data minus participants with protocol deviations that lead to exclusion.
Solicited Safety – Stage A only	All maternal participants in the Exposed Set who have solicited safety data

Table 5 Infant participants

Analysis Set	Description
Exposed	Infants live-born to exposed maternal participants, whose parents/LARs completed the informed consent process and signed the informed consent form.
Per Protocol - Immunogenicity	All infant participants in the Exposed set minus those who (a) were born less than 4 weeks post- maternal participant vaccination and/ or (b) have protocol deviations that lead to exclusion.
Full Analysis - Efficacy	All infant participants in the Exposed set.
Modified Full Analysis - Efficacy	All infant participants in the Exposed set who were born after at least 4 weeks of vaccination.
Per Protocol - Efficacy	All infant participants in the Modified Full Analysis – Efficacy set minus those who have protocol deviations that lead to exclusion.

Table 6 Overview of analysis sets and exclusion codes

	Code	Description	Maternal analysis set				Infant analysis set				
Determined in mother or infant			Enrolled	Exposed	Per Protocol - Immunogenicity	Solicited Safety	Exposed	Per Protocol - Immunogenicity	Modified Full Analysis - Efficacy	Full Analysis - Efficacy	Per Protocol - Efficacy
Mother	800, 800#	Fraudulent Data	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mother	900, 900#	Invalid informed consent	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mother	1030, 1030#	Study vaccine not administered		Y	Y	Y	Y	Y	Y	Y	Y
Mother	1040.Vx+*, 1040#	Administration of concomitant vaccine(s) forbidden in the protocol			Y			Y			Y
Mother	1050, 1050#	Randomisation failure			Y			Y			Y
Mother	1060, 1060#	Randomisation code was broken[a]			Y			Y			Y
Mother	1070, 1070#	Mother got vaccinated with the correct vaccine but incorrect volume			Y			Y			Y
Mother	1070, 1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)			Y			Y			Y
Mother	1070, 1070#	Study treatment not prepared as per protocol (e.g. reconstitution)			Y			Y			Y
Mother	1070, 1070#	Other deviations related to wrong study treatment/ administration/dose			Y			Y			Y

	Code	Description	Maternal analysis set				Infant analysis set				
Determined in mother or infant			Enrolled	Exposed	Per Protocol - Immunogenicity	Solicited Safety	Exposed	Per Protocol - Immunogenicity	Modified Full Analysis - Efficacy	Full Analysis - Efficacy	Per Protocol - Efficacy
Mother	1070, 1070#	Study treatment administered while contraindicated			Y			Y			Y
Mother	1080, 1080#	Vaccine temperature deviation			Y			Y			Y
Mother	1090, 1090#	Expired vaccine administered			Y			Y			Y
Mother	1160	No post-vaccination solicited safety data- Stage A participants only				Y					
Mother	2010, 2010#	Protocol violation (inclusion/exclusion criteria)			Y			Y			Y
Mother	2040.Vx+*, 2040#	Administration of any medication/product forbidden by the protocol			Y			Y			Y
Mother	2050.Vx+*, 2050#	Intercurrent medical conditions/concomitant medications which are exclusionary as per protocol			Y			Y			Y
Mother	2060.Vx+*, 2060#	Concomitant infection related to the vaccine which may influence the immune response			Y			Y			Y
Mother	2070.Vx+*, 2070#	Concomitant infection not related to the vaccine but may influence the immune response			Y			Y			Y

	Code	Description	Maternal analysis set				Infant analysis set				
Determined in mother or infant			Enrolled	Exposed	Per Protocol - Immunogenicity	Solicited Safety	Exposed	Per Protocol - Immunogenicity	Modified Full Analysis - Efficacy	Full Analysis - Efficacy	Per Protocol - Efficacy
Mother	2090.Vx	Participant did not comply with blood sample schedule			Y						
Mother	2100.Vx	Serology result not available (immunogenicity sample collected but invalid/no result)			Y						
Mother	2120.Vx	Obvious incoherence or abnormality or error in the data			Y						
Mother	2130.Vx	Testing performed on serology samples not aligned with ICF			Y						
Mother	2110.Vx	Immunogenicity sample collected but GSK decided not to test			Y						
Infant	800	Fraudulent Data					Y	Y	Y	Y	Y
Infant	900	Invalid informed consent					Y*	Y	Y	Y	Y
Infant	2010	Protocol violation (inclusion/exclusion criteria)						Y			Y
Infant	2050.Vx	Intercurrent medical conditions which are exclusionary as per protocol						Y			Y
Infant	2090.Vx	Participant did not comply with blood sample schedule						Y			

	Code	Description	Maternal analysis set				Infant analysis set				
Determined in mother or infant			Enrolled	Exposed	Per Protocol - Immunogenicity	Solicited Safety	Exposed	Per Protocol - Immunogenicity	Modified Full Analysis - Efficacy	Full Analysis - Efficacy	Per Protocol - Efficacy
Infant	2100.Vx	Serology result not available (immunogenicity sample collected but invalid/no result)						Y			
Infant	2120.Vx	Obvious incoherence or abnormality or error in the data						Y			
Infant	2130.Vx	Testing performed on serology samples not aligned with ICF						Y			
Infant	2131.Vx	Testing performed on nasal samples not aligned with ICF									Y
Infant	2110.Vx	Immunogenicity sample collected but GSK decided not to test						Y			
Infant	2040.Vx+, 2040#	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-E and PPS-I)						Y			Y
Infant	2140Vx+	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-I)						Y			
Infant	2240	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-E)									Y

	Code	Description	Maternal analysis set				Infant analysis set				
Determined in mother or infant			Enrolled	Exposed	Per Protocol - Immunogenicity	Solicited Safety	Exposed	Per Protocol - Immunogenicity	Modified Full Analysis - Efficacy	Full Analysis - Efficacy	Per Protocol - Efficacy
Infant	2060.Vx, 2060#	Concomitant infection related to the vaccine which may influence immune response						Y			Y
Infant	2070.Vx, 2070#	Concomitant infection not related to the vaccine but may influence immune response						Y			Y
Infant	3100	Birth is less than 4 weeks post-vaccination						Y	Y		Y

* in case a mother withdraws consent or does not consent for the baby, we still report SAEs/AESIs for the infants if collected
.Vx indicates participants whose data will be eliminated from a specific endpoint/visit
.Vx+ indicates participants whose data will be eliminated from a specific endpoint/visit onwards
Y indicates exclusion
Carry forward elimination from mother to infant
[a] Randomization code was broken (1060, 1060#) does not apply to the unblinding of all participants during the study due to the stop on study enrollment and vaccination and the study was fully unblinded

4.2. Criteria for eliminating data from Analysis Sets

CCI [redacted]

4.2.1. Elimination from Exposed Set (ES)

CCI [redacted]

4.2.2. Elimination from Modified Full Analysis Set for Efficacy (modified FAS-E)

4.2.2.1. Excluded Infants from Modified Full Analysis Set for Efficacy

An infant will be excluded from the modified FAS efficacy analysis under the following conditions:

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800, 800#	Fraudulent data	All
900, 900#	Invalid informed consent	All
1030#	Study vaccine not administered	All
3100	Birth is less than 4 weeks post-vaccination	All

Carry forward elimination from mother to infant

4.2.3. Elimination from Full Analysis Set for Efficacy (FAS-E)

4.2.3.1. Excluded Infants from Full Analysis Set for Efficacy

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

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800, 800#	Fraudulent data	All
900, 900#	Invalid informed consent	All
1030#	Study vaccine not administered	All

Carry forward elimination from mother to infant

4.2.4. Elimination from Per protocol analysis set for Efficacy (PPS-E)

4.2.4.1. Excluded Infants from Per protocol analysis set for Efficacy (PPS-E)

A participant will be excluded from the PPS efficacy analysis under following conditions:

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800, 800#	Fraudulent data	All
900, 900#	Invalid informed consent	All
1030#	Study vaccine not administered	All
3100	Birth/Delivery is less than 4 weeks post-vaccination	All
1040#	Administration of concomitant vaccine(s) forbidden in the protocol	All
1050#	Randomisation failure	All
1060#	Randomisation code was broken	All
1070#	Mother got vaccinated with the correct vaccine but containing an incorrect volume	All
1070#	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All
1070#	Study treatment not prepared as per protocol (e.g. reconstitution)	All
1070#	Other deviations related to wrong study treatment/administration/dose	All
1070#	Study treatment administered while contraindicated	All
1080#	Vaccine temperature deviation	All
1090#	Expired vaccine administered	All
2010, 2010#	Protocol violation (inclusion/exclusion criteria)	All
2040*	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-E and PPS-I)	All
2240*	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-E)	All
2040*	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-E and PPS-I)	All
2050.Vx*	Intercurrent medical conditions/concomitant medications which are exclusionary as per protocol	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
2050#*	Maternal intercurrent medical conditions which are exclusionary as per protocol	All
2060#* 2060*	Concomitant infection related to the vaccine which may influence immune response	All
2070#* 2070*	Concomitant infection not related to the vaccine but may influence immune response	All
2120.Vx	Obvious incoherence or abnormality or error in data	All
2131.Vx	Testing performed on nasal samples not aligned with ICF	All

.Vx indicates participants whose efficacy data will be eliminated from a specific endpoint
Carry forward elimination from mother to infant
* Attribution of these elimination codes to participant need CRDL review of individual listing

4.2.5. Elimination from Per-protocol analysis Set for Immunogenicity (PPS-I)

4.2.5.1. Excluded participants from Per-protocol analysis set for immunogenicity of maternal participants

A participant will be excluded from the PPS immunogenicity 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
800	Fraudulent data	All
900	Invalid informed consent	All
1030	Study vaccine not administered	All
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	All
1050	Randomisation failure	All
1060	Randomisation code was broken	All
1070*	Mother got vaccinated with the correct vaccine but incorrect volume	All
1070*	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All
1070*	Study treatment not prepared as per protocol (e.g. reconstitution)	All
1070*	Other deviations related to wrong study treatment/administration/dose	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
1070*	Study treatment administered while contraindicated	All
1080	Vaccine temperature deviation	All
1090	Expired vaccine administered	All
2010	Protocol violation (inclusion/exclusion criteria)	All
2040.Vx+*	Administration of any medication/product forbidden by the protocol	Visit 2/Day 31, Visit 3/Delivery
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 2/Day 31, Visit 3/Delivery
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 31, Visit 3/Delivery
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 31, Visit 3/Delivery
2090.Vx	Participants did not comply with blood sample schedule: • For PPS at Visit 2/Day 31, check the interval from vaccination to day 31 BS = -10/+15 days; • For PPS at Visit 3/Delivery, check the interval from delivery to delivery BS = -1/+3 days	Visit 2/Day 31, Visit 3/Delivery
2100.Vx	Serological results not available (immunogenicity sample collected but invalid/no result)	Visit 1/Day 1 Visit 2/Day 31, Visit 3/Delivery
2120.Vx	Obvious incoherence or abnormality or error in the data	Visit 2/Day 31, Visit 3/Delivery
2130.Vx	Testing performed on serology samples not aligned with ICF	Visit 2/Day 31, Visit 3/Delivery
2110.Vx	Immunogenicity sample collected but GSK decided not to test	Visit 1/Day 1 Visit 2/Day 31, Visit 3/Delivery

* Attribution of these elimination codes to participant need CRDL review of individual listing

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

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

4.2.5.2. Excluded participants from Per-protocol immunogenicity (PPS-I) analysis set of infant participants

An infant participant will be excluded from the PPS immunogenicity analysis under 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
800, 800#	Fraudulent data	All
900, 900#	Invalid informed consent	All
1030#	Study vaccine not administered	All
1040.Vx#+*	Administration of concomitant vaccine(s) forbidden in the protocol	All
1050#	Randomisation failure	All
1060#	Randomisation code was broken	All
1070#*	Mother got vaccinated with the correct vaccine but incorrect volume	All
1070#*	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All
1070#*	Study treatment not prepared as per protocol (e.g. reconstitution)	All
1070#*	Other deviations related to wrong study treatment/administration/dose	All
1070#*	Study treatment administered while contraindicated	All
1080#	Vaccine temperature deviation	All
1090#	Expired vaccine administered	All
2010, 2010#	Protocol violation (inclusion/exclusion criteria)	All
2040#*	Administration of any medication/product forbidden by the protocol	All
2140.#*	Administration of any medication/product forbidden by the protocol	All
2040Vx*	Administration of any medication/product forbidden by the protocol	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
2140Vx*	Administration of any medication/product forbidden by the protocol (leading to elimination from PPS-I)	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
2050.Vx#*	Intercurrent medical conditions which are exclusionary as per protocol	All
2050.Vx*	Intercurrent medical conditions which are exclusionary as per protocol	All
2060.Vx#+* 2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	All
2070.Vx#+* 2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	All
2090.Vx	Participants did not comply with blood sample schedule • For PPS at Visit 1/Day 1 check the interval of day 1 BS -0/+3 days; • For PPS at Visit 2/Day 43 post-birth, check the interval of day 43 BS -12/+18 days; • For PPS at Visit 3/Day 121 post-birth, check the interval of day 121 BS -10/+20 days; • For PPS at Visit 4/Day 181 post-birth, check the interval of day 181 -15/+20 days	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
2100.Vx	Serological results not available (immunogenicity sample collected but invalid/no result)	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
2120.Vx	Obvious incoherence or abnormality or error in the data	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
2130.Vx	Testing performed on serology samples not aligned with ICF	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
2110.Vx	Immunogenicity sample collected but GSK decided not to test	Visit 1-NB/Birth Visit 2-NB/Day 43 post-birth[a] Visit 3-NB/Day 121 post-birth[a] Visit 4-NB/Day 181 post-birth[a]
3100	Birth is less than 4 weeks post-vaccination.	All

* Attribution of these elimination codes to participant need CRDL review of individual listing

Carry forward elimination from mother to infant
Vx+ indicates participants whose immunogenicity data will be eliminated from a specific visit onwards;
Vx indicates participants whose immunogenicity data will be eliminated from a specific visit.
[a] As per Protocol Amendment 4, infant blood samples will not be collected at V2-NB, V3-NB and V4-NB. 2090.Vx, 2100.Vx, 2120.Vx, 2130.Vx will not be applicable to infant participants whose blood samples are not collected under Protocol Amendment 4.

4.2.6. Elimination from solicited safety set

4.2.6.1. Excluded participants from Solicited safety set

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

5. STATISTICAL ANALYSES

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

5.1. Demography

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

These analyses will be performed on the Exposed set (ES) for maternal and infant participants and on the modified Full Analysis - Efficacy set (modified FAS-E) for infant participants. Analysis may also be repeated on the Per Protocol set for immunogenicity for maternal as well as infant participants.

For all maternal participants, demographic characteristics (e.g., age at vaccination (18-34, 35-39, ≥40 years of age), gestational age at vaccination ($24^{0/7}$ - $28^{0/7}$, $28^{1/7}$ - $34^{0/7}$weeks), geographic ancestry) will be summarized by group and overall using descriptive statistics. The interval in days between maternal vaccination and delivery will be calculated and summarized by group using descriptive statistics.

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

- Frequency tables will be generated for categorical variables such as gestational age at time of delivery (≥ 37 weeks; < 37 weeks).
- Mean, median, standard deviation and range will be provided for continuous data such as age.

Demographics and baseline characteristics as well as the lifestyle characteristics may be reported by geographic region and by economic region (LMIC and HIC).

5.1.2. Additional considerations

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

Subgroup analysis for demographic characteristics by age category at vaccination (18 – 34, 35-39; ≥ 40 years) for maternal participants and by gestational age at birth (≥ 37 weeks or < 37 weeks) for infant participants will also be performed on ES or modified FAS-E for infant participants.

Participants disposition will be summarized by group using descriptive statistics:

- Number of maternal participants enrolled, randomised, vaccinated, eligible for maternal efficacy populations and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- Number of infants enrolled, eligible for infant efficacy populations and withdrawn including withdrawal reasons will be tabulated by group, by sub-cohort within each group and overall.

Vital signs will not be summarized for this study.

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

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

5.2. Efficacy

5.2.1. Analysis of primary efficacy endpoints planned in the protocol

The primary analysis of vaccine efficacy (VE) will be based on the modified Full Analysis - Efficacy set for infants (modified FAS-E). A secondary analysis based on the Full Analysis – Efficacy set (FAS-E) and the Per Protocol - Efficacy set for infants will be performed to complement the modified FAS-E analysis.

Primary Efficacy Endpoints – Infant participants	**Statistical Analysis Methods**
From birth to 6 months, occurrences of medically assessed, RSV-associated severe LRTIs according to the case definitions. OR From birth to 6 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	CCI [redacted]

CCI [redacted]

CCI

[redacted]

5.2.1.1. Sensitivity Analyses

Supportive analysis of time to confirmed RSV-LRTI of any severity and time to confirmed severe RSV-LRTI will be conducted by using Kaplan-Meier cumulative incidence curves.

Sub-group analyses by regions and by key demographic characteristics may also be explored. In addition, efficacy analyses stratified by VE reported for geographic regions (North America, Central America & Caribbean, and South America), economic regions (LMIC and HIC), RSV type and RSV seasonality (year-round circulation and seasonal circulation) may be included in the clinical study report.

Supportive analyses on primary efficacy endpoints based on the modified FAS-E will also be conducted for RSV-associated LRTI cases confirmed by central laboratory tests and PCR confirmed local laboratory tests and by all RSV tests (central and all local laboratory tests).

5.2.2. Analysis of secondary efficacy endpoints planned in the protocol

The primary analysis of VE on secondary efficacy endpoints **in infants** will be based on the modified Full Analysis - Efficacy set (modified FAS-E). **The analysis of vaccine efficacy in maternal participants will be based on the Exposed set.**

Secondary Efficacy Endpoints	**Statistical Analysis Methods**
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of RSV-associated hospitalizations according to the case definitions. From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTIs	CCI [redacted]
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTIs with hospitalization	
From birth (Visit 1-NB) to 12 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions	
From birth (Visit 1-NB) to 12 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definition, for RSV subtype A and RSV subtype B separately.	
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definition, for RSV subtype A and RSV subtype B separately.	

Secondary Efficacy Endpoints	Statistical Analysis Methods
From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definition.	CCI [redacted]
From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions	
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause pneumonia	
From study intervention administration (Visit 1) to 6 months post-delivery (Contact 1), occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs)	
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of RSV-associated hospitalizations according to the case definitions.	

CCI [redacted]

CCI [redacted]

5.3. Immunogenicity

5.3.1. Analysis of immunogenicity planned in the protocol

All immunogenicity analyses in stage A will be based on the Per Protocol - Immunogenicity set.

Note: In the immunogenicity sub-cohort, only those samples for which a pair (both maternal and respective infant) exist will be analyzed to evaluate secondary immunogenicity objectives and to assess antibody persistence in infants.

When performing experiments to monitor the stability of the RSV NEUT A assay overtime, a QC panel excursion was observed for tests performed after May 2023. Consequently, the testing was temporarily paused and not all samples were tested.

Secondary Immunogenicity Endpoints – Maternal Participants	**Statistical Analysis Methods**
• Neutralizing antibody titers against RSV-A Measured on blood samples collected at Day 1 before vaccination (Visit 1), at Day 31 (Visit 2), and at delivery (Visit 3).	CCI [redacted]

Secondary Immunogenicity Endpoints – Cord blood / placental transfer	Statistical Analysis Methods
• ***RSVPreF3 IgG-specific antibody concentration measured on blood samples collected at Delivery and cord blood**** • The ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations * or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	CCI [redacted]
Secondary Immunogenicity Endpoints – Infant Participants	
• Neutralizing antibody titers against RSV-A. Measured ***on the cord blood sample collected at delivery (or on a blood sample collected from the infant within 72 hours after birth if no cord blood sample can be obtained) and*** at Day 43 (Visit 2-NB), Day 121 (Visit 3-NB), or Day 181 (Visit 4-NB) after delivery in 3 sub-cohorts of infants. Infants born to women in the immunogenicity sub-cohorts will be randomly assigned (1:1:1) to sample collection at 1 of the 3 timepoints noted.	

5.3.2. Additional considerations

5.3.2.1. Sensitivity analysis

A sensitivity analysis will be performed based on the Per Protocol-Immunogenicity set excluding participants in Bangladesh.

5.3.2.2. Between group analysis

CCI [redacted]

CCI

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

Safety analyses in **maternal participants** will include summaries by study group and age category (18-34, 35-39, ≥40 years of age; overall) of solicited administration site and systemic events (for stage A subjects), unsolicited AEs, MAEs, SAEs, MA-RTIs (RSV-associated MA-RTIs and all-cause MA-RTIs), AEs leading to study withdrawal, pregnancy outcomes and pregnancy related AESIs.

Safety analyses in **infant participants** will include summaries by study group, overall and gestational age at birth (≥ 37 weeks or < 37 weeks) of neonatal AESIs, MAEs, SAEs, AEs leading to study withdrawal, and the occurrence of RSV-associated RTIs, LRTIs, severe LRTIs, RSV-associated hospitalizations, all-cause RTI and all-cause LRTI.

Safety analyses for maternal participants and infants may also be reported by economic region (LMIC and HIC).

Analyses of solicited AEs will be performed on the Solicited Safety set (maternal participants only). Analyses of unsolicited AEs will be performed on the ES.

Primary Safety Endpoints – Infant Participants	**Statistical Analysis Methods**
Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 6 months after birth Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 12 months after birth.	CCI [redacted]
Secondary Safety Endpoints – Maternal Participants	**Statistical Analysis Methods**
Occurrence of solicited injection site and systemic events in Stage A participants during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days).	CCI [redacted]
Occurrence of unsolicited adverse events (AEs) in all maternal participants during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days).	

	CCI [redacted]
Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 4). 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 minor congenital anomalies only, 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 minor congenital anomalies only, and elective/therapeutic termination with at least 1 major congenital anomaly.	
Pregnancy-related adverse events (AEs) of special interest from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 4). These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), gestational diabetes mellitus, chorioamnionitis.	
Occurrence of serious adverse events (SAEs), AEs leading to study termination, and medically attended AEs in all maternal participants from Visit 1 (Day 1) up to 6 months after delivery.	
Secondary Safety Endpoints – Infant Participants	
The occurrence of neonatal AEs of special interest (reported up to 6 weeks after 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 pre-term birth (22≤GA<28 weeks), in a preterm live birth (28≤GA<37 weeks), or in a term live birth), preterm birth.	

5.4.2. Additional considerations

5.4.2.1. Analysis of solicited events

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

Table 9 Intensity scales for solicited symptoms in adults

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

* Preferred location for measurement will be the oral cavity. “Fever” = temperature ≥38.0°C/100.4°F regardless of the location of measurement.

The maximum intensity of local injection site (redness and swelling) will be scored at GSK Biologicals as follows:

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

Duration in days of solicited administration site and systemic events within 7 days after vaccination will be tabulated by study group and overall, and if needed by age group. The derivation rule of duration in days for solicited events is detailed in section 10.1.2.11.

5.4.2.2. Exclusion of implausible solicited Event

Some local and systemic events will be directly measured by the participant and cannot be changed 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 10 Implausible Solicited Events

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

5.4.2.3. Analysis of Unsolicited Adverse Events

The analysis of unsolicited events will be performed on ES

5.4.2.4. Combined Solicited and Unsolicited Adverse Events

The combined analysis of solicited and unsolicited events will be performed on ES. A summary of participants with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA.

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

5.4.2.5. Other analysis

Other safety analysis will be performed on ES.

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal participants taking concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) within 7 days

following vaccination, 30 days following vaccination, up to 6 weeks post-delivery and up to 6 months post-delivery will be summarized by group. A listing will also be provided.

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

6. ANALYSIS INTERPRETATION

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

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

An interim analysis of safety endpoints for both maternal and infant participants has been performed, with the focus on demonstrating the safety profile at Day 43 post-delivery. The interim analysis was deemed necessary following the identification of the safety signals documented in protocol amendment 4, which assisted in the better characterization of the safety information including the signals. The interim analysis was performed after all infants completed the 43 days post-delivery timepoint. The safety endpoints are identical to those listed in section 2, and the statistical analysis methods are similar to section 5.4.1. with minor modifications. In addition, summaries of demographics, participant disposition, concomitant medication/vaccinations and medical history was included. This analysis was performed by an external Independent Data Analysis Center (IDAC). In addition, monthly safety analyses are conducted, where most of the analyses have been generated by IDAC and monitored by the SRT on a monthly basis and by an Independent Data Monitoring Committee (IDMC) on a bi-monthly basis. Additional non-standardized ad-hoc analyses (safety signal deep dive) are performed by internal GSK.

6 Month Post-delivery interim analysis occurred as described below:

- When all maternal and infant participants enrolled completed 6 months follow-up post-delivery/birth (to evaluate primary and secondary efficacy endpoints, reactogenicity and safety)

Final analysis will occur as described below:

- When all infant participants have completed Visit 5-NB (month 12, LSLV), a final safety analysis (for all maternal and infant participants in both Stage A and Stage B), a final secondary efficacy analysis up to 12 months follow up post birth, and a final immunogenicity analysis will be performed. Analyses of any evaluated tertiary endpoints may also be performed.

6 Month Post-delivery interim analysis was performed by internal GSK, so will be the final analysis.

If the data for tertiary endpoints becomes available at a later stage, (an) additional analysis/analyses will be performed.

Description	Disclosure Purpose
Day 43 post-delivery interim analysis	Internal
6 Month post-delivery interim analysis	Public Disclosure.
Final Analysis at Month 12 post birth	Public Disclosure, Study Report

7.2. Statistical considerations for interim analyses

Not applicable.

8. CHANGES FROM PLANNED ANALYSES

- By-participant listings of SAEs, AEs leading to study withdrawal, MAEs, adverse pregnancy outcomes and pregnancy related AESIs will be prepared and released. Such listings have already been released in earlier analyses. Due to study enrolment/vaccination stop, the study has been unblinded already before the final analysis.
- A sensitivity analysis for immunogenicity results excluding participants from Bangladesh, for which HIV testing was not performed before their enrollment into the study, has been added.
- Between group evaluations for immunogenicity analysis was clarified to be performed among RSV MAT and Control instead of vaccination groups, the wording has been corrected.
- In February 2022, enrollment and vaccination were stopped because of an imbalance in preterm births and associated neonatal deaths observed between the RSVPreF3-Mat and placebo groups. Subsequently the study was unblinded, and therefore the presented VE endpoints are descriptive.
- Subgroup analyses by economic region (LMIC and HIC) will be performed for demography, efficacy, and safety evaluations.
- Subgroup analyses by gestational age at birth will be performed for demography and safety evaluations.
- Sensitivity analysis for primary efficacy endpoints by using a negative binominal regression model have been removed.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

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

9.1. Gestational age at vaccination

Gestational age at vaccination in weeks for maternal participants will be entered by the investigator and used for our analyses. It will not be derived from the estimated date of delivery.

9.2. Immunogenicity

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

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

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

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

9.2.1. Assay cut-offs

9.2.1.1. Assay cut-offs for serology results

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

System	Component	Method	Unit	Cut-off *(LLOQ)*	*ULOQ*
Serum	RSV-A Neutralising Antibody	CCI [redacted]			
Serum	RSVPreF3 IgG antibody concentrations				
Serum	RSV-B Neutralising Antibody*				

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis.
*: RSV-B neutralizing antibody titers will no longer be assessed as part of the secondary immunogenicity endpoints.

9.2.1.1.1. Assay cut-offs for central nasal swabs

System	Component	Method	Unit	Cut-off
Nasal Swab	RSV-A positive	CCI [redacted]		
Nasal Swab	RSV-B positive			

9.2.2. RTI and LRTI

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

Table 11 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 4.2.6.3 of the Protocol
[2] RSV (nasal swab) sampling and testing as specified in Table 14 of the Protocol.
[3] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.
MA-RTI = Maternal, medically attended respiratory tract illness

Table 12 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, **OR** Blocked nose, **OR** Cough **AND** Confirmed RSV infection [4,5]
RSV-LRTI	History of cough **OR** difficulty in breathing [1] **AND** SpO_2 < 95%[2], **OR** RR increase [3] **AND** Confirmed RSV infection [4,5]
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 [4,5] **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 based on [Modjarrad, 2016]; except that definitions for severe and very severe RSV LRTI have been merged. **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
[5] RSV (nasal swab) sampling and testing
[6] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

For 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.

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.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough and/or difficulty in breathing with an interval of at least 7 consecutive days without cough and/or difficulty in breathing since the last/previous episode of RTI.

9.2.2.1. Alternative LRTI / Severe LRTI case definitions for data analysis in infants

To meet an alternative case definition, a participant must have at least one item from each column.

Note: As per protocol amendment 5, the alternative case definitions will no longer be considered for data analysis in infants.

Table 13 Alternative LRTI / Severe LRTI case definitions in infants

	RSV confirmed	Documented PE findings indicating lower respiratory tract involvement	Objective measures of clinical severity
LRTI	Confirmed RSV infection	Rhonchi Crackles (Rales) Wheeze	Increased respiratory rate (bpm) • ≥ 60 for < 2 mo • ≥ 50 for 2-6 mo
			Hypoxemia • SpO2 <95% at ≤1800 meters • SpO2 <92% at > 1800 meters
			New onset apnea
			Nasal flaring
			Retractions
			Grunting
Severe LRTI	Confirmed RSV infection	Rhonchi Crackles (Rales) Wheeze	Hypoxemia • Sp02 <93% at ≤1800 meters • Sp02 <90% at > 1800 meters
			Acute hypoxic or ventilatory failure
			Dehydration due to respiratory distress requiring IV hydration
			Failure to respond or unconscious

9.2.3. Hematology and Biochemistry parameters

In order to assess the impact of fluid shifts on the antibody concentration/titer, hematocrit will be evaluated at all three blood sampling timepoints (Day 1, Day 31, and delivery) for a subset of maternal (Stage A) participants in the immunogenicity sub-cohort, if deemed necessary.

Note that hematocrit sample collection will end once Protocol Amendment 2 becomes effective in the different countries/sites.

9.3. Statistical Method

Study Specific statistical methods for immunogenicity analysis are described in section 5.3.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

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

10.1.1. Handling of missing data

CCI

CCI

[redacted]

10.1.2. Data derivation

10.1.2.1. Age at vaccination in days

When age at vaccination is to be displayed in days, it will be calculated as:

Age = date of vaccination minus date of birth

10.1.2.2. Age at vaccination in months

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

DOB = 10JUN2017, Date of vaccination = 09JUL2018 -> Age = 12 months

DOB = 10JUN2017, Date of vaccination = 10JUL2018 -> Age = 13 months

10.1.2.3. Age at vaccination in years

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

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

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

10.1.2.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

Weight in grams = (Weight in pound / 2.2) ·1000

10.1.2.5. Height/Length

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

Height/Length in centimeters = Height/Length in inches x 2.54

10.1.2.6. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.2.7. Temperature

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

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

10.1.2.8. Numerical serology results

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

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

10.1.2.9. 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 10.1.2.8 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

10.1.2.10. Onset day

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

The onset day for an event (e.g. neonatal AEs, SAEs, AEs of special interest) for infants is the number of days between birth and the start date of the event (or date of diagnosis). This is 1 for an event occurring on the same day as birth.

10.1.2.11. Duration of events

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

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

10.1.2.12. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.2.13. Counting rules for occurrences of solicited adverse events

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

10.1.3. Display of decimals

10.1.3.1. Percentages

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

10.1.3.2. Differences in percentages

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

10.1.3.3. Demographic/baseline characteristics statistics

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

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

The maxima and minima of transformed height/length/weight variables will be displayed without decimals, with the exception of infant studies where three decimals will be displayed for transformed birth weight.

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

10.1.3.4. Serological summary statistics

The number of decimals used when displaying geometric mean titers (GMT) or concentrations (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*, Meningococal 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.

10.1.4. Statistical methodology

10.1.4.1. Exact confidence intervals around proportions

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

10.1.4.2. Standardized asymptotic confidence intervals around differences in proportions

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

10.1.4.3. Adjusted GMT or GMC ratios

The CI for GMC ratio and adjusted CMT will be obtained using an ANOVA model on the logarithm transformed titers. The ANOVA model will include the vaccine group as the fixed effect (3 groups) and the country effect. The GMC ratio and their 95% CI will be derived by exponential transformation of the corresponding group contrast in the model.

When between-group GMT or GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure. It should also be clear whether the model is limited to the data from some groups.

10.2. TFL TOC

The Table Figure Listing (TFL) TOC which itemizes the planned list of TFL and their associated lay-out is developed as a separate document. There will be one TOC document for the interim analysis of Day43PD and another for the 6-month PD interim analysis and the final analysis.

11. REFERENCES

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

Miettinen, O.S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985; 4: 213-226.

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