Protocol Amendment 5

Study ID: 212171

Official Title of Study: 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

NCT number: NCT04605159

Date of Document: 03-Mar-2023

Clinical Study Protocol

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

Primary Study vaccine/product and number(s)	GlaxoSmithKline (GSK) Respiratory Syncytial Virus (RSV) Maternal (RSVPreF3) Vaccine (GSK3888550A)
Other Study vaccine/product	Placebo (Lyophilized sucrose reconstituted with saline [NaCl] solution)
eTrack study number and abbreviated title	212171 (RSV MAT-009)
EudraCT number	2020-001355-40
Date of protocol	Final: 26 June 2020
Date of protocol amendment	Amendment 5 Final: 23 February 2023 Amendment 4 Final: 15 March 2022 Amendment 3 Final: 10 February 2022 Amendment 2 Final: 23 June 2021 Amendment 1 Final: 5 October 2020
Study Acronym	GRACE Investi**G**ational **R**SV M**A**ternal Va**C**cin**E**
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
Short title	A Phase III double-blind study to assess safety and efficacy of an RSV Maternal unadjuvanted vaccine, in pregnant women and infants born to vaccinated mothers

Based on GSK Biologicals' Protocol WS v17.0

PROTOCOL AMENDMENT 5 SPONSOR SIGNATORY APPROVAL

eTrack study number and Abbreviated Title	212171 (RSV MAT-009)
EudraCT number	2020-001355-40
Date of protocol	Final: 26 June 2020
Date of protocol amendment	Amendment 5 Final: 23 February 2023
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
Sponsor signatory	Joon Hyung Kim Clinical and Epidemiology Project Lead, RSV Maternal
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

PROTOCOL AMENDMENT 5 INVESTIGATOR AGREEMENT

I agree:

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

Hence, I:

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

eTrack study number and Abbreviated Title	212171 (RSV MAT-009)
EudraCT number	2020-001355-40
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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Central Back-up Study Contact for Reporting SAEs: refer to the protocol section 8.3.3.1.

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

5. GSK Biologicals' Helpdesk for Emergency Unblinding

Refer to the protocol section 6.3.6.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5 (23 February 2023):

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 scientific value of the trial due to changes made to the secondary objectives of the study.

Overall rationale for the current amendment:

This protocol has been amended to reflect the following:

- The Benefit/Risk assessment has been updated to clarify that:
  - The observed numerical imbalance in neonatal deaths is not an independent safety signal but a consequence of the validated signal of preterm births.
  - Based on the evaluation of the Study Day 43 post-birth interim analysis, GSK concluded that preterm birth is an identified risk for the pregnant women population, for the RSV Maternal vaccine candidate.
  - GSK has discontinued the work on this RSV Maternal vaccine candidate and is closing out all ongoing vaccine trials. GSK will continue to monitor and follow-up the immunized participants in the trials for the duration specified in the respective protocols.
- For vaccine efficacy (VE) related objectives, the sensitivity and supportive analyses will be only conducted for primary efficacy endpoints, but the sensitivity analysis using the negative binomial model has been removed.
- The following changes have been made to the secondary efficacy endpoints:
  - For efficacy endpoint from birth to 7 months and above, only the efficacy endpoints of “From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of severe medically assessed, RSV-associated LRTIs” and “From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed, RSV-associated LRTIs” will be kept, and the analyses will be conducted by using Kaplan-Meier curves from birth to 12 month, so that the VE changes across time can be observed.
  - “From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed, RSV-associated LRTIs by alternative case definitions” has been removed.
  - “From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of severe medically assessed, RSV-associated LRTIs according to the case definition” has been removed.
  - “From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition” has been removed.

- Secondary efficacy endpoints on infant participants will only be assessed in the Modified Full Efficacy set (FAS) and Secondary efficacy endpoints on maternal participants will only be assessed in the Exposed Set (ES).
- Secondary immunogenicity endpoints will be assessed in a sub-cohort of maternal-infant pairs including only those maternal-infant pairs from the per protocol set whose babies had blood collected for immunogenicity assessments at the allocated time-point.
- RSVPreF3 IgG antibody concentrations will be assessed only in maternal blood samples collected at delivery and cord blood (or blood samples collected from their respective infants within 72 hours after birth, if no cord blood available).
- RSV-B neutralizing antibody titers will no longer be assessed as part of the secondary immunogenicity endpoints.
- CCI [redacted]
- CCI [redacted]
- The following populations for analyses have been removed:
  - Maternal participants :- Full Analysis – Immunogenicity, Full Analysis – Efficacy
  - Infant participants:- Full analysis – Immunogenicity
- Country-specific requirements have been added in Appendix 10.6 for Spain and Argentina.

Also, this amendment includes editorial changes to improve the consistency and typographical error corrections.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 2.3 Benefit/Risk assessment	Updated to clarify the status of the safety signals after GSK's signal validation process.	Updated to reflect the changes in the benefit/risk profile.
Section 3 Objectives and Endpoints	Updated the objectives and endpoints plan.	Immunogenicity testing, secondary efficacy and tertiary analyses are being limited as a consequence of the premature stop of enrollment.
Section 4.2.4 Sub-cohorts, Section 6.3.2.1.1 Stage A, Section 8.1.3 Immunological read-outs	Updated to note that secondary immunogenicity endpoints will be assessed only when blood samples from a maternal-infant pair are available.	Secondary immunogenicity testing is being limited as a consequence of the premature stop of enrollment.

Section # and title	Description of change	Brief rationale
Section 4.2.6.2/Table 9 Alternative LRTI / Severe LRTI case definitions for data analysis in infants	Added a note to indicate that the alternative case definitions will not be used for secondary efficacy analyses.	The secondary efficacy objective using alternative case definitions has been removed.
Section 8.1.2 Laboratory assays/Table 15, Section 8.1.3 Immunological read-outs/Table 16	RSV-B neutralizing antibody assessment has been removed. Updated to indicate that RSVPreF3 IgG Ab concentrations will be assessed only in maternal blood samples collected at delivery, and cord blood. CCI [redacted]	Secondary immunogenicity testing is being limited as a consequence of the premature stop of enrollment. CCI [redacted]
Section 9.3 Populations for analyses /Table 22/Table 23	Updated to reflect the changes to populations for analyses.	Updated to reflect the change to study's statistical analysis plan following the decision to stop further enrollment and vaccination.
Section 9.4: Statistical analyses	Updated to reflect changes to secondary efficacy endpoints.	Updated to reflect changes to secondary efficacy endpoints.
Section 10.6 Appendix 6: Country-specific requirements	Updated to add country-specific requirements for Spain and Argentina.	Updated to add country-specific requirements for Spain (regarding "COMPENSATION") and Argentina (concerning "STUDY POPULATION").

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

RSV MAT-009 will evaluate:

- The efficacy, safety, reactogenicity, and immunogenicity of the investigational RSV maternal vaccine when administered to pregnant women between 24 and 34 weeks gestational age (inclusive) and
- The effects of maternal immunization on the infants born to these vaccinated women.

In the RSV maternal program to date, a Phase 1/2 study (RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 years of age to determine the safety and immunogenicity of 3 dose levels of the RSV (RSVPreF3) maternal vaccine (30, 60 and 120 µg) compared to placebo has been completed. No safety concerns have been identified.

Based on *preliminary* results of RSV MAT-001, the 60 and 120 µg dose-levels were selected for further evaluation in the following 2 additional studies, which are ongoing:

- RSV-MAT 004 (NCT 04126213): A Phase II observer-blind study to assess safety, reactogenicity, and immunogenicity of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women and infants born to vaccinated mothers
- RSV-MAT 011 (NCT 04138056): A Phase II study of 2 dose levels of an investigational RSV maternal vaccine, given alone or with *Boostrix*, to healthy non-pregnant women to assess safety, reactogenicity, and immunogenicity.

Based on the *final* results of RSV MAT-001, which are summarized in a clinical study report, and on the Day 31 results of RSV MAT-004 and -011, the 120 µg dose-level has been selected for evaluation in RSV MAT-009.

RSV MAT-009 will only be initiated after a favorable evaluation of all available safety data from completed/ongoing non-clinical studies and from the ongoing RSV MAT-004 and -011 studies.

Note: Based on all available safety information following vaccination with the RSV MAT vaccine, there will be no further enrollment and vaccination of maternal participants. However, monitoring will continue for rest of the study. All planned objectives ***described in the latest protocol amendment*** will be assessed for the participants enrolled so far.

Objectives and Endpoints are presented in Table 4.

1.2. Schema

This is a multi-center, randomized, double-blinded, placebo-controlled study. Maternal participants 18 to 49 years of age (inclusive, at the time of the study intervention) will be assigned to one of 2 study groups and will receive a single intramuscular injection between 24 $^{0/7}$ to 34 $^{0/7}$ weeks of gestation (inclusive).

Up to approximately 10 000 participants will be enrolled; it is expected that at least 20% of these participants will be enrolled at centers located in the U.S.

Enrollment will occur in 2 sequential stages, A and B.

In Stage A, approximately 4600 maternal participants will be enrolled as follows:

- RSV Maternal (RSVPreF3) vaccine, 120 µg (N ~ 3067),
- Control (Lyophilized sucrose placebo; N ~ 1533).

In Stage B, an additional approximately 5,400 maternal participants will be enrolled:

- RSV Maternal (RSVPreF3) vaccine, 120 µg (N ~ 3600),
- Control (Lyophilized sucrose placebo; N ~ 1800).

During both stages, maternal participants who receive the study intervention will be followed for safety for up to approximately 10 to 11 months (from screening until 6 months after delivery). Infant participants will be evaluated for the occurrence of medically assessed, RSV-associated lower respiratory tract ***illnesses*** and safety for 12 months after birth.

In addition, during Stage A:

- All maternal participants will be evaluated for reactogenicity;
- A sub-cohort of approximately 1533 maternal participants will be evaluated for immune response, including maternal – infant RSV-specific antibody transfer (approximately 1020 study vaccine recipients; approximately 510 control recipients);
- Sub-cohorts of infant participants whose mothers were in the immunogenicity sub-cohort referred to above, will be evaluated for RSV-specific antibody levels post-birth (in total, approximately 1020 infants born to vaccine recipients evaluated for immune response and approximately 510 infants born to control recipients evaluated for immune response).

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, since sample collection in infants was discontinued following stop of enrollment.

Section 4.1 provides an overview of the study design.

All safety data will be reviewed by a blinded Safety Review Team (SRT)* and an unblinded Independent Data Monitoring Committee (IDMC) on an on-going basis.

A firewall will be established to ensure that data are not inadvertently unblinded. Details are provided in a separate Firewall charter.

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

1.3. Schedules of Activities (SoAs)

For maternal participants, Table 1 presents the Schedule of Activities (SoA). For infant participants, Table 2 presents the SoA. Table 3 describes the allowed study visit intervals for both maternal and infant participants.

Whenever possible, the investigator should arrange study visits within the allowed study visit intervals. Immunogenicity data from blood samples collected outside an allowed interval may not be considered in the associated per protocol set (PPS) for analysis.

Please note:

- **Study visits, assessments and procedures do not replace local standards of care.** If local standard of care recommends additional visits/medical evaluations (for maternal participants or their infants), participants should comply with these local recommendations.
- Any adverse event / potential adverse event identified during a study visit or procedure should be treated according to local standards of care or by referral to an appropriate health care provider
- Maternal participant visits at Screening / Visit 1 (Day 1) may take place at the study site or another medical facility.
- When a maternal participant completes Visit 1 (study intervention), and again at Visit 3 (delivery), site staff should, in so far as possible, ensure all site study obstetrician(s) and pediatrician(s) are informed. This will help to ensure that study pediatrician(s) and/or staff are aware of the maternal participant's (approximate) date of delivery and potential enrolment of the neonate.
- Maternal participant Visits 2 and 4, infant participant Visits 1-NB, 2-NB, 3-NB, 4-NB and 5-NB, and maternal and infant respiratory tract illness (RTI) assessment visits may take place at the investigator's clinical facility, another medical facility, or via a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).
- The site must have appropriate infrastructure and logistics to complete ALL study procedures if a visit is to be conducted at the participant's home. Blood samples for immunogenicity collected during a home visit must be centrifuged within, *at most*, 24 hours after collection. Cord blood samples must be centrifuged within, *at most*, 24 hours after collection.

- Contact may be via telephone, SMS, email, videotelephony/telemedicine or other means, depending on local best practice. If the study site is the participant's primary healthcare facility, contact with study personnel may also be made in the context of a visit for routine or event-driven care.

Table 1 Schedule of activities for maternal participants

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
Informed consent	●										Section 10.1.3
Check Inclusion/exclusion criteria	●	O									Sections 5.1.1, 5.1.2
Assign maternal participant study number	●										Section 6.3.1
Register maternal participant in SBIR	O										Section 6.3.1
Assign infant participant study number		O									Section 6.3.1
Record Demographic data	●										Section 5.3
Record lifestyle characteristics	●										
Review & collect Medical and vaccination history	O	●									Section 8.2.1.1
Record outcome of fetal morphology ultrasound scan	●										

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
Record obstetric history from past and current pregnancies	● (current pregnancy)	● (past pregnancy/ies)									
Record Travel history to or living in Zika virus endemic countries/regions	●	●	●	●	●			●			During the current pregnancy only
General and/or obstetrical examination	●	●	●		●	●			If needed	If needed	General and/or Obstetrical exam is symptom directed at V4, & event-driven visits. Vaginal exams are symptom directed. See Section 8.2.1.2
Pre-vaccination body temperature		●									Preferred location for measurement will be the oral cavity. "Fever" = temperature ≥38.0°C/100.4°F regardless of the location of measurement.
Blood sample (immunogenicity ~ 10 ml)		●	●		Sub-cohort ●						At V1 and V2, collected from all participants in both Stage A and Stage B. At V3, collected only from a sub-

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
											cohort in Stage A. See Table 12 and Sections 8.1.1 and 8.1.3 As from protocol amendment 4 Blood sample at delivery to be collected from all participants.
Cord blood (~ 5 to 10 ml)					•						Collected from all participants in both Stage A and Stage B. See Table 13 and Sections 8.1.1 and 8.1.3.
Placenta sample					•						Collect from all participants, if feasible.
Nasal swab										•	See Table 12 and Sections 8.1.1, 8.1.3, and 8.4.4. Note: As from protocol amendment 4 nasal swab from maternal participants will no longer be collected and MA-RTI visit is no longer required.
Check contraindications to and criteria for temporary delay for vaccination		O									Section 7.1

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
Allocate maternal study group, intervention number		O									Sections 6.3.2, 6.3.3 Recording will be done at Visit 1, upon maternal participant randomization but the eCRF entry will be done on the demography screen
Record maternal sub-cohort for immunogenicity assessment		●									
Allocate infant sub-cohorts for immunogenicity assessment		O									
Administer Study Intervention (study vaccine / placebo)		●									Sections 6.1, 6.2
Record administered intervention number		●									
Observe for 30 minutes post-dose		O									
Distribute maternal participant card	O	O									At screening or at Visit 1 as per local practice. Section 8.3.6
Record Labor / Delivery information					●						
Record pregnancy / delivery outcomes					●						Submit Expedited AE report for an adverse pregnancy outcome (Section 8.3.3)

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
Train maternal participant /LAR on use of electronic diary		O Stage A									Section 10.3.8
Distribute electronic diary to maternal participant / LAR.		O Stage A									
Review electronic diary entries			O Stage A								Section 8.3.1
Return electronic diary			O Stage A								
Concomitant medications / vaccinations		●	●	●	●	●	●	●	●	●	Sections 6.5.1 and 6.5.3
All unsolicited AEs (Days 1 to 30)		●	●						●	●	Sections 8.3.1, 10.3.4 and 10.3.8
Pregnancy-related AESIs		●	●	●	●	●	●	●	●		Table 4, Sections 8.3.1, 8.3.3, 8.3.4, and 10.3.5. Must submit an Expedited AE report.
MAEs other than MA-RTIs		●	●	●	●	●		●	●		Medically attended RTIs to be reported up to C1.
MA-RTI signs										●	Sections 8.3.1, 8.3.3, 8.4 Note: As from protocol amendment 4 nasal swab

Visit / Contact	**Screening**	**V1**	**V2***	**Contacts (Monthly)**	**V3**	**V4**	**C1**	**Event Driven**			
Gestational Age (GA)	**≤ 28 days before V1**	**$24^{0/7}$ – $34^{0/7}$**		**Until Delivery**	**Delivery**			**Additional contact(s)[1]**	**Safety visit**	**MA-RTI visit**	For monthly contacts: Section 8.2.1.2.2. Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.
Visit Day	**D-28 – D1 before randomization**	**D1**	**D31**		**D1PD**	**D43 PD**	**D181 PD**	**V2-Delivery**			Table 3
											from maternal participants will no longer be collected and MA-RTI visit is no longer required.
SAEs, MA-RTI associated AEs and AEs leading to study withdrawal		●	●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1 and 10.3.8
SAEs related to study participation or concurrent GSK medication/vaccine	●	●									Sections 8.3.1 and 10.3.8
Subsequent pregnancies						●	●		●	●	Sections 8.3.1 and 10.3.8
Record interest in joining future extension study	○						●				Section 6.7
Screening conclusion	●										
Study conclusion							●				Section 4.4
Investigator sign-off at study conclusion							●				

The timing of an event-driven site visit (e.g., to further evaluate a potential AE or MA-RTI) cannot be defined with precision in the protocol. Event-driven visits may occur throughout the study. ● is used to indicate a study procedure that requires documentation in the individual eCRF. ○ is used to indicate a study procedure that does not require documentation in the individual eCRF. V = visit; D = day; GA = gestational age; MA-RTI = medically attended respiratory tract illness; PD = post delivery.

* V2 may be replaced by V3, depending on delivery date.

[1] 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.

Table 2 Schedule of activities for infant participants

Visit / Contact	V1-NB[1]	Safety contact (recommended)[1]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	**Birth**	**8 days**	**6 weeks**	**3 months**	**4 months**	**6 months**	**9 months**	**12 months**	**Contacts**	**Visits**	
Visit Day	**D 1-21**	**D8 (7 days post-birth)**	**D43**	**D91**	**D121**	**D181**	**D271**	**D366**	**Birth – D366**		**See Table 3 for intervals between visits, contacts.** Sections 5.1.2 and 5.2.2
Check Inclusion / exclusion criteria	●										
Re-consent / Consent for infant participation *if required by local regulations*	●										
Record infant participant study number	●										
Record sub-cohort for immunogenicity assessment, if applicable	●										Section 6.3.2.1.2
Distribute infant's participant card	O										Section 8.3.6
Distribute infant RTI-diary card	O	O	O	O	O	O	O			O	Distribute at V1-NB: Distribute additional RTI-diary cards as needed. Section 8.4.2.2 and SPM
Review infant RTI-diary card		O	O	O	O	O	O	O		O	
Collect infant RTI-diary card		O	O	O	O	O	O	O		O	Collect RTI-diary cards that are fully filled out. Section 8.4.2.2 and SPM
Transcribe applicable infant RTI-diary card data to eCRF		●	●	●	●	●	●	●		●	

Visit / Contact	V1-NB[1]	Safety contact (recommended)[1]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	**Birth**	**8 days**	**6 weeks**	**3 months**	**4 months**	**6 months**	**9 months**	**12 months**	**Contacts**	**Visits**	
Visit Day	**D 1-21**	**D8 (7 days post-birth)**	**D43**	**D91**	**D121**	**D181**	**D271**	**D366**	**Birth – D366**		**See Table 3 for intervals between visits, contacts.**
Demographic data	●										Section 5.3 Record at Visit 1-NB and if changes in lifestyle characteristics thereafter
Lifestyle characteristics	●		●	●	●	●	●	●			
Apgar score	●										At 1, 5 and (if available/performed) at 10 minutes,
Weight, length, head circumference, physical examination	●		●		●	●		●			Section 8.2.2
Blood sample if no cord blood ~2.5 ml	●										Adjust volume if weight ≤ 2.5 Kg. Refer to Table 14
Blood sample (immunology, infants) ~2.5 ml			● Sub cohort 1		● Sub cohort 2	● Sub cohort 3					1 sample at one of these visits, as per infant's assigned sub-cohort. Adjust volume if weight ≤ 2.5 Kg. Refer to Table 14 As from protocol amendment 4, Blood samples will no longer be collected at V2-NB, V3-NB or V4-NB.
Concomitant vaccinations	●	●	●	●	●	●					
Concomitant medications	●	●	●	●	●	●	●	●	●	●	Sections 6.5.2 and 6.5.3
Neonatal AESIs	●	●	●								Table 4, Sections 8.3.1, 8.3.3, 8.3.4, and 10.3.5.

Visit / Contact	V1-NB[1]	Safety contact (recommended)[1]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	**Birth**	**8 days**	**6 weeks**	**3 months**	**4 months**	**6 months**	**9 months**	**12 months**	**Contacts**	**Visits**	
Visit Day	**D 1-21**	**D8 (7 days post-birth)**	**D43**	**D91**	**D121**	**D181**	**D271**	**D366**	**Birth – D366**		**See Table 3 for intervals between visits, contacts.**
											Must submit an Expedited AE report. An additional recommended safety contact may be performed ~8 days post-birth if deemed necessary to closely monitor the newborn and support collection and reporting of any neonatal AESI(s).
SAEs, MAEs and AEs leading to study withdrawal	●	●	●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1, and 10.3.8
Symptom-directed physical examination (includes RTI signs, symptoms)										●	Section 8.4.4
Nasal swab										●	Sections 8.1.1 , 8.4.4.2, Table 14
Study conclusion								●			Section 4.4
Investigator sign-off at study conclusion								●			

The timing of an event-driven visit cannot be defined with precision in the protocol. ● indicates a study procedure that requires documentation in the individual eCRF. ○ indicates a study procedure that does not require documentation in the individual eCRF. LAR = legally acceptable representative; V=visit; D=day; NB = newborn.

[1] An additional optional but recommended safety contact may be performed on ~Day 8 (7 days post-birth) if deemed necessary by the investigator or by the parent/LAR(s).

Table 3 Intervals between study visits and contacts

Interval	Optimal interval in Days	Allowed interval in Days	Additional Information
Maternal participants			
Screening to V1	0	0– 28	The screening interval extends from Day -28 to Day 1 before randomization. If all eligibility criteria can be confirmed on the day of screening and all required procedures can be performed, then, "Screening" and "Visit 1" may occur on the same day (refer to Section 8.2.1.2). Data from all screening procedures must be available and eligibility must be confirmed before the participant is randomized. If a participant is screened but not vaccinated within the allowed interval, a re-screening should be done to establish the participant's eligibility. Please make sure the participant's gestational age is still within the allowed range, refer to Section 10.8 for guidance on gestational age assessment.
V1 to V2	30	20 - 45	If this visit occurs *before* Day 25, the site must contact the participant to collect information about any additional unsolicited adverse events that may occur between the date of the visit and Day 31.
Monthly contacts	~ every 25 – 35		Monthly beginning after Visit 2 until Delivery. Contacts are additional to and do not replace protocol specified Visits. Additional contact(s)/visit(s) can be made more often if deemed necessary by the investigator or the maternal participant.
V3 (delivery)	0	1 day before to 3 days after delivery	For maternal participants in the Stage A immunogenicity sub-cohort: collect maternal blood sample at any point from the start of labor up to delivery. (NOTE: For participants for which a cesarean section is planned, the sample may be collected as soon as the participant arrives at the clinic and the intravenous line is inserted to prepare them for the cesarean section). If blood is not collected during delivery, collect maternal blood sample no later than 72 hours after delivery. For all participants in both Stage A and Stage B: A cord blood sample should be collected at the time of delivery. If cord blood cannot be collected at delivery, a blood sample should be collected from the infant participant as soon as possible and no later than 72 hours after birth.
V3 to V4	42	30 – 60	If this visit occurs *before* Day 43, the site must contact the participant to collect information about any additional AESIs that may have been identified or may have occurred between the date of the visit and Day 43.
V3 to C1	180	165 – 200	
Infant participants			
Birth to V1-NB	0	0 – 21	If no cord blood was collected, a blood sample must be collected **within 72 hours** after birth. Consent (if required) should be obtained before any infant study-specific procedures are performed If written consent cannot be readily provided by the parent(s)/LAR(s) post-birth, and in order to be able to comply with RTI surveillance and other protocol required procedures, **verbal consent** – if permitted per local regulation -- may be sought from the parent(s) / LAR(s) instead.

Interval	Optimal interval in Days	Allowed interval in Days	Additional Information
			Verbal consent should be documented in the source data by the investigator or delegate. The parent(s) / LAR(s) will provide additional, written informed consent by (or before) (Visit 2-NB) Refer to the SPM for additional details.
Infant participants			
Birth to recommended safety contact	8		Safety contact (recommended, in interval between Day 7 to Day 10)
Birth to V2-NB	42	30 - 60	
Birth to C1-NB	90	83 – 97	
Birth to V3-NB	120	110 - 140	Visit may coincide with infant participant's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule
Birth to V4-NB	180	165 - 200	Visit may coincide with infant participant's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule
Birth to C2-NB	270	256 – 286	
Birth to V5-NB	365	330 - 400	Visit may coincide with infant participant's routine vaccination visit if consistent with the participating country's routine infant vaccination schedule
RTI surveillance contacts (Birth to V5-NB) *			
Seasonal RSV transmission	Weekly during RSV season Monthly outside the RSV season		
Year-round RSV transmission	Every 2 weeks year-round		

RTI = respiratory tract illness; V= Visit; C = Contact; NB=Newborn

* In special circumstances, the frequency of active contacts may be temporarily adapted, refer to Section 8.4.2.2.1 for guidance

2. INTRODUCTION

2.1. Study rationale *(Amended 23 February 2023)*

GSK is developing an investigational Respiratory Syncytial Virus (RSV) vaccine for administration to pregnant women, with the aim of preventing medically assessed, RSV-associated lower respiratory tract illnesses (LRTIs) in their infants by transfer of maternal antibodies. The vaccine candidate is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation.

In the RSV maternal program to date, a Phase 1/2 study (RSV MAT-001; NCT 03674177) in healthy non-pregnant women 18-45 years of age to determine the safety and immunogenicity of 3 dose levels of RSV (RSVPreF3) maternal vaccine (30, 60 and 120 µg) compared to placebo has been completed. No safety concerns have been identified.

Based on *preliminary* results of RSV MAT-001, the 60 and 120 µg dose-levels were selected for further evaluation in the following 2 additional studies, which are ongoing:

- RSV-MAT 004 (NCT 04126213): A Phase II observer-blind study to assess safety, reactogenicity, and immunogenicity of GSK Biologicals' investigational RSV Maternal unadjuvanted vaccine (GSK3888550A), in healthy pregnant women and infants born to vaccinated mothers
- RSV-MAT 011 (NCT 04138056): A Phase II study of 2 dose levels of an investigational RSV maternal vaccine, given alone or with *Boostrix*, to healthy non-pregnant women to assess safety, reactogenicity, and immunogenicity.

Based on the *final* results of RSV MAT-001, which are summarized in [GSK Study Report 208068/001], and on the Day 31 results of RSV MAT-004 and -011, the 120 µg dose-level has been selected for evaluation in RSV MAT-009.

Participants will be vaccinated year-round and will not be limited to seasonal enrollment.

Reactogenicity and safety of the candidate vaccine will be evaluated in maternal participants for up to 6 months after delivery. Safety in infants will be evaluated for up to 12 months after birth. Safety evaluation will include assessment of medically attended adverse events, serious adverse events, pregnancy outcomes, and pregnancy-related and neonatal adverse events of special interest (AESIs).

Immunogenicity of the candidate vaccine will be evaluated in maternal participants through delivery. The transfer of RSV-specific antibodies from vaccinated maternal participants to infant participants will be evaluated at delivery. RSV-specific antibody levels will be evaluated in infant participants for up to 6 months after birth.

The study will also evaluate the incidence of medically attended RSV-associated respiratory tract illnesses (MA-RTI) in maternal participants for up to 6 months after

delivery, and the incidence of medically assessed, RSV-associated respiratory tract / lower respiratory tract illnesses (RTI/LRTI) in infants for up to 12 months after birth.

Note: Due to the stop on study enrollment and vaccination, nasal swabs from maternal participants will not be collected and no MA-RTI assessment visit will be performed. Assessment of incidence of MA-RTI in maternal participants will be limited to cases where a nasal swab was collected before study enrollment stop.

2.2. Background

Please refer to the current Investigator's Brochure (IB) for background information on RSV infection, the rationale for the maternal immunization approach described in this protocol, and information regarding pre-clinical and clinical studies of the RSV Maternal (RSVPreF3) vaccine.

2.3. Benefit/Risk assessment

GSK has included provisions in this trial to ensure participant's safety. Safety monitoring has been and will be conducted throughout this study by an unblinded Independent Data Monitoring Committee (IDMC) and by the Sponsor. The study includes the establishment of a surveillance system which may facilitate detection of respiratory tract infections, in particular lower respiratory tract ***illness*** (LRTIs) in infants enrolled in the study. Measures to suspend the study should a potential safety issue be identified are described in Section 8.2.3.

In February 2022, the Independent Data Monitoring Committee (IDMC) for the RSV MAT-009 study observed an imbalance in the proportion of preterm births in the active versus the placebo group and recommended that study enrollment be paused. As a result, GSK voluntarily paused the enrollment, randomization, and vaccination of participants in its active pregnant women studies to investigate this safety signal.

Following a review of additional unblinded data from the RSV MAT-009 study, the imbalance in preterm births was noted to persist across a range of risk factors. A higher proportion of neonatal deaths reported in the active group compared to the placebo group was also observed. GSK then decided to stop enrollment and vaccination in all ongoing trials of RSV Maternal Vaccine (RSVPreF3) as a precautionary measure.

The observed numerical imbalance in neonatal deaths is not an independent safety signal but a consequence of the validated signal of preterm birth. No numerical imbalance in neonatal deaths was observed in the cohort of infants born at term. An in-depth qualitative review of the clinical information available for each neonatal death concluded that the events leading to neonatal death (e.g., very low or low birth weight, sepsis, necrotizing colitis, pneumonia, respiratory distress syndrome, hypoxic-ischemic injury) are commonly observed in preterm-born infants, particularly those who are extremely and very preterm, and there is no consistent temporal pattern of events from birth or from maternal vaccination.

In January 2023, following assessment of the Study Day 43 post-birth interim analysis (DLP 04 October 2022) with data from 5328 maternal participants (3557 in the active group) and 5235 infant participants (3496 in the active group), the imbalance in preterm birth remains statistically significant (RR 1.38 (95% CI 1.08, 1.75); p value: 0.0090) and persists across a range of risk factors. The overall incidence of preterm birth in the study is low in both groups and remains below the preterm birth background rates for the majority of the participating countries. The imbalance in preterm births was observed more with low and middle-income countries (RR: 1.57, 95% CI: 1.17–2.10) than high-income countries (RR: 1.04, 95% CI: 0.68–1.58). In low and middle-income countries, the preterm birth imbalance peaked from August to December 2021 and was not observed consistently from January 2022 onward.

GSK concluded that preterm birth is an identified risk for the pregnant women population, for the RSV Maternal vaccine candidate. GSK has discontinued the work on this RSV maternal candidate vaccine and is closing out all ongoing trials. Additionally, GSK continues to monitor and follow up those participants immunized in the trials. Another study (RSV MAT-015) has been initiated to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or control in previous RSV MAT studies, including the RSV MAT-009 study, during any pregnancy conceived post-vaccination or post-control.

3. OBJECTIVES AND ENDPOINTS

Table 4 Study objectives and endpoints *(Amended 23 February 2023)*

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 LRTIs according to the case definitions[2].

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 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 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 severe 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 LRTIs of any severity, 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.

Secondary safety objectives	Secondary safety endpoints
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 pre-term 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]	

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-MA-RTIs),*** RSV associated LRTIs and surveillance for potential LRTIs are briefly summarized in Section 4.2.6.
[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 disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.
[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.

4. STUDY DESIGN

4.1. Overall design

The study is a Phase III, double-blind, randomized, placebo controlled, multi-centric, multi-country study with 2 parallel groups. At least 20% of participants will be enrolled at centers in the U.S.

The study design is adaptive, with recruitment and randomization occurring in 2 sequential stages, A and B. Stage B may begin immediately after the last participant is randomized in Stage A.

To encourage participation in the study and to achieve recruitment targets on time, the study sites will be encouraged to manage recruitment plans using methods that are acceptable within local regulations such as advertisements in news media and/or use of posters and fliers. All such recruitment materials will be approved by the local ethics committees.

Following verification that inclusion/exclusion criteria are met, all maternal participants will be randomized 2:1 to receive either GSK Biologicals' RSV Maternal (RSVPreF3) vaccine or the placebo control.

Study procedures in Stage A differ from those in Stage B in 2 ways.

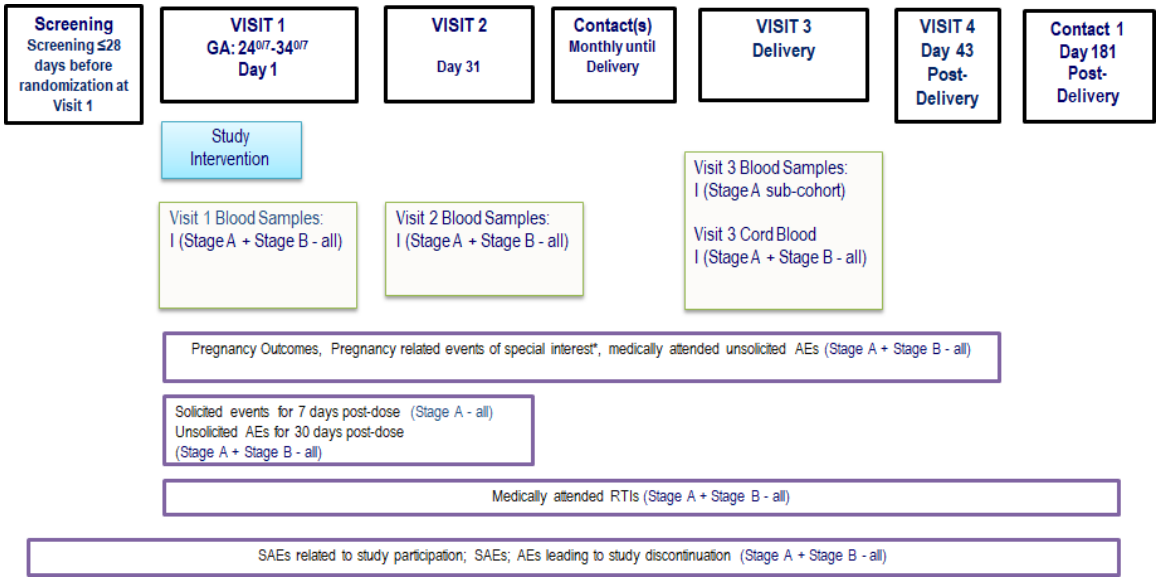
During Stage A only:

- All maternal participants will be asked to report solicited events during the 7 days post-dose, and
- Maternal and (as yet unborn) infant participants will be further randomized into sub-cohorts for blood sample collection for the assessment of immune response.

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

Section 1.3 provides Schedules of Activities (SoAs) for maternal and infant participants. Section 9.5.1 describes the sequence of analyses for maternal and infant participant data.

Figure 1 Study design overview – maternal participants (*Amended 23 February 2023)*



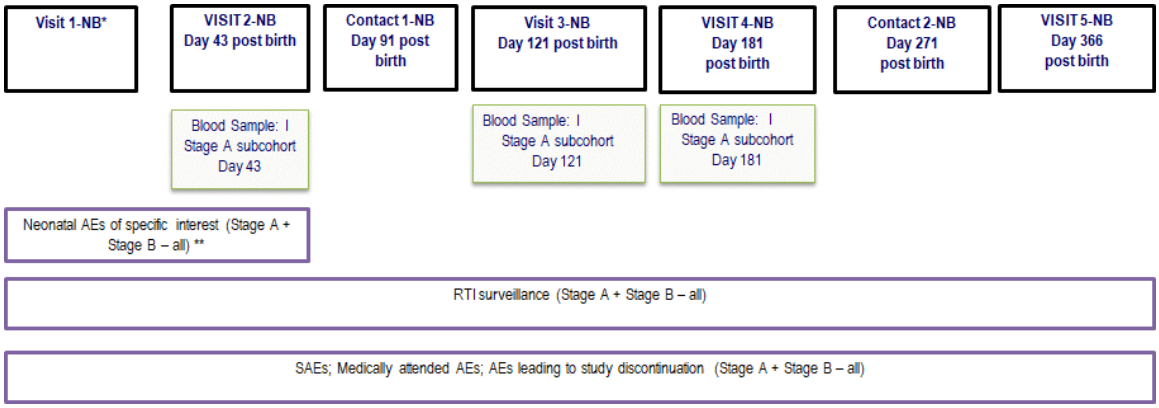
GA = Gestational age; I = immune response; (S)AE = (serious) adverse event; RTI = respiratory tract illness
Visit 2 may be replaced by Visit 3 in case of premature delivery.
All = all participants
Refer to Section 6.3.2 for detailed description of Stage A and Stage B. Refer to Section 6.3.2.1.1 for additional 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 monthy 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 enrollment 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).

NOTE: Due to the stop on study enrollment 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 5 and Table 6.
- Randomized intervention allocation is described in Table 5, Table 6, and Section 6.3.
- Study (intervention) groups are described in Table 5 and Table 6.
- Data collection: standardized Electronic Case Report Form (eCRF) e-Diaries will be used to collect solicited event data (Stage A mothers only). Unsolicited Adverse event data will be collected through questioning at study visits/contacts and reported into the eCRF, as appropriate. Parent(s) / LAR(s) will use a Paper Diary to record RTI symptoms experienced by infant participants; these data will be transcribed into the eCRF as appropriate.
- Safety monitoring will be conducted by an unblinded Independent Data Monitoring Committee (IDMC) and by an unblinded Safety Review Team* (Section 8.2.3).

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

Table 5 Study groups, sub-cohorts, interventions, and blinding foreseen in the study: Stage A

Approximately 4600 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	~3067	18-49	RSV_MAT	RSV_MAT_0	~2040	RSV_MAT_0	~2040	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	~1533	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 6 Study groups, sub-cohorts, interventions, and blinding foreseen in the study: 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	~3600	18 – 49 years	RSV_MAT	RSV_MAT	●	●	●
Control	~1800	18 – 49 years	Control	Control	●	●	●

4.2. Scientific rationale for study design

4.2.1. Study population

The study population mirrors that of the intended indication: pregnant women between $24^{0/7}$ and $34^{0/7}$ weeks gestational age (inclusive).

4.2.2. Use of placebo

The placebo group serves as a control for safety, reactogenicity, immunogenicity and efficacy assessments. No licensed vaccine against RSV is currently available.

4.2.3. Randomization ratio

A 2:1 randomization ratio was chosen to permit efficient evaluation of vaccine safety and efficacy without compromising statistical rigor. Ratios greater than 1:1 for vaccinated vs. placebo recipients increase the likelihood that reported events may occur among vaccine recipients. It is possible that a higher number of reported events among vaccine recipients may be attributed to the greater randomization ratio, the vaccine itself, or due to chance. GSK plans to mitigate the potential risk associated with the increased randomization of vaccinated to placebo participants by: a) improving standardization of reporting of predefined pregnancy related and neonatal AESI using GAIA definitions; b) conducting both epidemiological database studies and observational natural history studies to determine background rates for these events in different countries; and c) establishing processes for continuous review of blinded safety data by the SRT* and unblinded safety data by the IDMC.

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

4.2.4. Sub-cohorts

4.2.4.1. Safety assessment in maternal participants

Assessment of vaccine reactogenicity (solicited events) in the 7 days post dose has been limited to Stage A to reduce the burden for maternal participants while ensuring enough observations to support robust evaluation.

4.2.4.2. Blood sampling and immune response assessment *(Amended 23 February 2023)*

A sub-cohort for maternal blood sampling and assessment (immune response at Day 1 (Visit 1), Day 31 (Visit 2), and Delivery) has been defined to limit discomfort and risk while ensuring enough observations to support robust evaluation of secondary maternal immunogenicity objectives (see also Table 3).

Sub-cohorts for infant blood sampling have been defined to limit discomfort and risk while ensuring enough observations to support robust evaluation of immune response in maternal – infant pairs.

Note however that blood samples for assessment of immune response at Day 1 (Visit 1), Day 31 (Visit 2), and delivery (Visit 3) will be collected from *all* maternal participants. Cord blood will also be collected from all participants. These samples may also be tested to support possible safety assessments, if necessary.

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.

4.2.5. Adaptive design

This adaptive trial design will provide evidence for the efficacy of the RSV maternal vaccine in the prevention of medically assessed, RSV-associated LRTI of any severity and medically assessed, RSV-associated severe LRTI. The design has 90% power to detect the target vaccine efficacies of 70% and 50% on severe and any-severity LRTI, respectively. If the vaccine meets these target VE estimates, this design offers the opportunity to identify this benefit with an expected sample size of approximately 7598 maternal participants, which may obviate the need to enroll the maximum sample size of 10 000.

Additional details are provided in Section 9.

4.2.6. Case definitions

Cases will be classified (during data analyses) according to the definitions that follow. Case definitions should not be confused with the definitions study personnel use during RTI surveillance (Section 8.4).

4.2.6.1. Maternal, medically attended respiratory tract illness (MA-RTI)

Table 7 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

[2] RSV (nasal swab) sampling and testing as specified in Table 12.

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

4.2.6.2. Respiratory tract illness (RTI) / Lower respiratory tract illness (LRTI) in infants

Table 8 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 defined in Section 4.2.6.3

[5] RSV (nasal swab) sampling and testing as specified in Table 14.

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

Table 9 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: The alternative case definitions will no longer be considered for data analysis in infants.

	RSV confirmed	Documented Physical Examination (PE) findings indicating lower respiratory tract involvement	Objective measures of clinical severity
LRTI	Confirmed RSV infection as defined in Section 4.2.6.3	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 as defined in Section 4.2.6.3	Rhonchi Crackles (Rales) Wheeze	Hypoxemia • SpO2 <93% at ≤1800 meters • SpO2 <90% at > 1800 meters
			Acute hypoxic or ventilatory failure
			Dehydration due to respiratory distress requiring nasogastric/IV hydration
			Failure to respond or unconscious

4.2.6.3. RSV infection

The sponsor will analyze 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 12, Table 14 and Section 8.4.

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.

CCI [redacted]

4.3. Justification for dose

A single formulation of the investigational RSV maternal vaccine (containing 120µg of the RSVPreF3 antigen) is planned. Currently available data suggest that the 120 µg formulation has an acceptable safety profile and tends to elicit stronger immune responses in non-pregnant women (RSV MAT-001 and RSV MAT-011) and pregnant women (RSV MAT-004), which is likely to result in higher placental transfer of antibodies to the fetus than formulations containing 30 or 60 µg of the RSVPreF3 antigen. Available results from these studies are included in the Investigator Brochure.

Because re-infection with RSV occurs throughout an individual's lifetime, it is extremely unlikely that an adult (in this case, a maternal participant) *would not* have been naturally infected with RSV before. Results of study RSV MAT-001 in non-pregnant women indicate that a single dose of the study vaccine is sufficient to boost the neutralizing antibodies induced by previous natural infections.

The study vaccine will be administered between $24^{0/7}$ and $34^{0/7}$ weeks of gestation (inclusive). This gestational age range is considered optimal for both immunogenicity and safety. It allows enough time to (a) induce high neutralizing antibody levels in maternal participants before delivery and (b) ensure these antibody levels are elevated during the period of greatest placental antibody transfer to the fetus. Moreover, it is after the critical period for organogenesis (i.e. after the period when most congenital abnormalities develop).

4.4. End of Study definition

A participant is considered to have completed the study if he/she returns for the last visit as described in the protocol.

The Primary Completion Date (PCD) occurs on completion of the Month 12 post-delivery visit (Contact 1 for the maternal participants and Visit 5-NB for the infant participants).

End of Study (EoS) occurs with the date of last (infant) participant last visit (LSLV) or the last testing/reading released of the human biological samples related to primary and secondary endpoints, whichever comes last. EoS must be achieved no later than 8 months after LSLV.

5. STUDY POPULATION

5.1. Inclusion criteria for enrolment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety.

5.1.1. Maternal participants

Maternal participants must satisfy all the following criteria at study entry:

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of diaries, return for follow-up visits).
- Participants who give written or witnessed/thumb printed informed consent after the study has been explained according to local regulatory requirements, and before any study specific procedures are performed. The informed consent given at screening should (consistent with local regulations / guidelines) either:
  - include consent for both the maternal participant's participation and participation of the infant after the infant's birth, or
  - include consent for the maternal participant's participation and expressed willingness to consider permitting the infant to take part after the infant's birth (if local regulations/guidelines require parent(s) to provide an additional informed consent after the infant's birth).
  - Both mother and father should consent if local regulations/guidelines require it.
- Age 18 to 49 years, inclusive, at the time of study intervention.
- Pre-pregnancy BMI (based on participant's report) 17.0 to 39.9 kg/m^2, inclusive.
- In good general maternal health as established by medical history and clinical examination before entering into the study.
- Singleton pregnancy (including instances where the singleton pregnancy derives from a vanishing twin syndrome).
- At 24 $^{0/7}$ to 34 $^{0/7}$ weeks of gestation at the time of study vaccination (Visit 1), as established by:
  - Last menstrual period (LMP) date corroborated by first or second trimester ultrasound examination (U/S) i.e. at or before 28 weeks of gestation.
  - 1st or 2nd trimester U/S only, if LMP is unknown/uncertain
  - Certain LMP, corroborated by an U/S performed after 28 weeks of gestation is also acceptable.

  NOTES: If pregnancy resulted from assisted reproductive technologies, LMP date may be replaced by IUI (intrauterine insemination) or ET (embryo-transfer) date.

  If LMP (or IUI or ET) and U/S performed before 28 weeks of gestation, do not correlate, default to U/S gestational age assessment.

  If the first U/S is only performed after 28 weeks of gestation (i.e. 3rd trimester) and there is no other basis for estimating gestational age, or the only other basis is fundal height, then the GA calculation is uncertain and the woman should be excluded.

  The level of diagnostic certainty of the gestational age should be established by using the Global Alignment of Immunisation safety Assessment in pregnancy (GAIA) gestation age assessment tool (Section 10.8).

- No fetal genetic abnormalities (based on genetic testing, if performed).
- No significant congenital malformations (such as abnormal fetal morphology, abnormal amniotic fluid levels, significant abnormalities in placenta or umbilical cord), as assessed by fetal anomaly ultrasound scan (also known as a level 2 ultrasound or fetal morphology assessment) conducted at or beyond 18 weeks of gestation.
- Willing to provide cord blood.
- Who do not plan to give their child for adoption.
- Who plan to reside in the study area for at least one year after delivery.
- Willing to have the infant followed-up after delivery for a period of 12 months.

Note that women whose pregnancies resulted from Assisted Reproductive Technologies may be enrolled if they meet all inclusion criteria and none of the exclusion criteria.

5.1.2. Infant participants

Infant participants must satisfy all the following criteria at study entry:

- Live-born from the study pregnancy.
- If required per local regulations / guidelines, re-signed (confirmed) written or witnessed/thumb printed informed consent for study participation of the infant obtained from the infant's mother and/or father and/or LAR, before performing any study specific procedure. To comply with RTI surveillance and other protocol-required procedures that begin immediately after birth: If written consent cannot be provided by the parent(s)/LAR(s) readily post-birth, verbal consent – if permitted per local regulation – may be sought from the parent(s) / LAR(s) instead. Verbal consent should be documented in the source data by the investigator or delegate. The parent(s) / LAR(s) will provide additional, written informed consent by (or before) Visit 2-NB.

5.2. Exclusion criteria for enrolment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Maternal participants

5.2.1.1. Medical conditions

- History of allergic disease or reactions likely to be exacerbated by any component of the RSV vaccine.

- Hypersensitivity to latex.
- Significant (as per Investigator's judgement) complications in the current pregnancy such as:
  - Gestational hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria in a woman with a previously normal blood pressure [ACOG, 2019]. Women with gestational hypertension who maintain blood pressure in the normal range (<140 mmHg and <90 mmHg) through diet and/or on anti-hypertensive medications would be eligible.
  - Gestational diabetes which is not controlled by medication, diet and/or exercise (Gestational diabetes is defined as absence of pre-gestational diabetes and hyperglycemia during pregnancy, which is not due to other known causes, confirmed based on positive oral glucose tolerance test or based on fasting plasma glucose levels in venous or capillary blood samples [Kachikis, 2017]).
  - Pre-eclampsia (defined as Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and proteinuria or, in the absence of proteinuria, the new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or headache unresponsive to medication [ACOG, 2019].
  - Eclampsia (defined as occurrence of new-onset seizures, in the absence of other causative conditions, in a woman with a hypertensive disorder of pregnancy) [ACOG, 2019].
  - Intrauterine Growth Restriction/Fetal Growth Restriction defined as a fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age with increasing specificity for adverse perinatal outcome below the third percentile (see Table 32).
  - Placenta previa (unless there is documented sonographic evidence that the placenta has moved up before enrolment).
  - Placental abruption, placenta accreta/percreta/increta, chorioamnionitis or any abnormalities that in the opinion of Investigator can impair the maternal-fetal circulation.
  - Polyhydramnios (defined as either a deepest vertical pocket (DPV) of > 8 cm or an amniotic fluid index (AFI) > 95th percentile for the corresponding gestational age) (see Table 37).
  - Oligohydramnios (defined as an amniotic fluid index (AFI) < 8 cm or a deepest vertical pocket (DPV) < 2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology) (see Table 37).
  - Preterm labour or history of preterm labour in the current pregnancy.
  - Any intervention to prevent preterm delivery or medical treatment for suspected preterm delivery, including administration of systemic corticosteroids for fetal lung maturation.

Note: pregnant women under progesterone treatment beyond the 1st trimester of pregnancy, exclusively based on a prior pregnancy which resulted in preterm delivery/birth, but without any medical/clinical finding(s) which would lead to suspecting that there is a risk of preterm delivery in the current pregnancy (e.g. shortened cervical length, etc), would not be considered as meeting this exclusion criterion.

- Cholestasis (defined as unexplained pruritus and/or abnormal liver function tests and/or raised bile acids, based on investigator's clinical judgement) [RCOG, 2011].
- Other pregnancy-related complications that in the Investigator's judgement would preclude participation of the participants in an investigational vaccine trial or might pose risk to the participant due to participation in the study.

- Significant (as per Investigator's judgement) structural abnormalities of the uterus or cervix.
- History of 2 or more prior stillbirths or neonatal deaths, or history of multiple (2 or more) preterm births at ≤ 34 weeks gestation, or multiple (3 or more) *consecutive* spontaneous abortions.

  Note: Still births, pre-terms births and spontaneous abortions will be counted per pregnancy (i.e. regardless of the number of fetuses in the concerned pregnancy).
- Known HIV infection, as assessed by local standard of care serologic tests conducted during the current pregnancy and prior to enrolment.
- Known or suspected HBV or HCV infection, based on medical history and clinical presentation (no laboratory testing is required).
- Known or suspected infection during the current pregnancy with Toxoplasma, Parvovirus B19, Syphilis, Zika, Rubella, Varicella, CMV or primary genital Herpes Simplex, based on medical history and clinical presentation (no laboratory testing is required).
- Active infection with tuberculosis, based on medical history and clinical presentation (no lab testing is required).
- Known or suspected impairment of the immune system.
- Current autoimmune disorder (based on medical history and physical examination; no laboratory testing required), for which the participant has received immune-modifying therapy within 6 months before study vaccination, or plans administration through delivery.
- Lymphoproliferative disorder or malignancy within 5 years before study vaccination (excluding effectively treated non-melanoma skin cancer).
- Acute or chronic clinically significant abnormality or poorly controlled pre-existent co-morbidities or any other clinical conditions, as determined by physical examination or standard of care laboratory tests, that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

- Any conditions that, in the investigator's judgement, may interfere with participant's ability to comply with study procedures or receipt of prenatal care, such as behavioral or cognitive impairment or neuropsychiatric illness.
- Any condition which, in the investigator's opinion, would increase the risks of study participation to the unborn infant.

5.2.1.2. Prior/Concomitant therapy

- Prior receipt of an RSV vaccine in the current pregnancy.
- Use of any investigational or non-registered product other than the study vaccine/product as described below, or planned use during the study period:
  - **For a drug, vaccine or medical device:** 29 days before the dose of study vaccine/product (Day -28 to Day 1).
  - **For immunoglobulins:** 3 months before the dose of study vaccine/product.

The exception to this is investigational products (drugs / vaccines / immunoglobulins) administered in the setting of a pandemic. Administration in this case should respect the same period outlined above prior to vaccination, but may be allowed following delivery.

- Planned administration/administration of any vaccine within 29 days before study vaccine administration (Day -28 to Day 1) or planned administration through delivery (Visit 3), except:
  - Seasonal influenza vaccines, tetanus vaccines, dTpa/Tdap – alone vaccines, dTpa/Tdap vaccines that also contain other antigens and Hepatitis B vaccines, all of which may be administered according to standard of care ≥ 15 days before or after study vaccination.

Note that if public health authorities organize an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) outside the routine immunisation program, then the intervals described above can be reduced if necessary for that mass vaccination vaccine, provided the vaccine is licensed and used according to its Product Information. In that sense, COVID-19 vaccines will be allowed, when administered ≥ 15 days before or after study vaccination.

- Administration of immunoglobulins (except anti-Rh0D IG, which may be administered at any time), blood products or plasma derivatives within 3 months before study vaccination or planned administration through delivery (Visit 3).
- Administration of immune-modifying therapy within 6 months before the study vaccination, or planned administration through delivery. This includes but is not limited to:
  - Azathioprine, mycophenolate mofetil, 6-mercaptopurine, cyclosporine, tacrolimus, monoclonal or polyclonal antibodies;
  - Prednisone ≥ 5 mg/day or equivalent for ≥ 14 days. Inhaled. Intra-articular/intra-bursal and topical steroids are allowed.
  - Corticosteroids administered for fetal lung maturation.

5.2.1.3. Prior/Concurrent clinical study experience

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

5.2.1.4. Other exclusions

- Alcoholism or substance use disorder within the past 24 months based on the presence of two or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglect of major roles to use, withdrawal, tolerance, use of larger amounts or longer, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving (based on the DSM-5 criteria, [Hasin, 2013]).
- A local condition that in the opinion of the Investigator precludes injection of the study vaccine/product or precludes assessment of local (administration site) reactogenicity.
- Consanguinity of maternal participant and her partner (second degree cousins or closer)
- Any study personnel or their immediate dependents, family, or household members.

5.2.2. Infant participants

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- Any condition which, in the investigator's opinion, would increase the risks of study participation to the infant.
- Child in care

Please refer to Section 10.7.2 for the definition of child in care.

5.3. Lifestyle considerations

5.3.1. Demographic data

Demographic data for maternal and infant participants includes geographic ancestry (race)*, ethnicity*, month of birth (if allowed per local regulation) and year of birth.

*Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013] have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all study participants.

5.3.2. Lifestyle characteristics

5.3.2.1. Maternal participants

Lifestyle characteristics may include highest level of education, smoking status/exposures, household environment, and other factors that could place study participants at risk of adverse study outcomes.

5.3.2.2. Infant participants

Lifestyle characteristics may include living environment, household composition, breastfeeding (breastfeeding only / breastfeeding with supplementation / no breastfeeding), passive smoking, and extent of contact with children less than 6 years of age.

5.4. Screen failures

Screen failures are maternal participants who consent to take part in this study but are not subsequently randomly assigned to a study intervention.

Limited data for screening failures (including reason for screening failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF.

6. STUDY INTERVENTION

A ‘study intervention’ is defined as a set of investigational or marketed product(s) or marketed product(s) or placebo intended to be administered to a participant during the study.

Refer to the Study Procedures Manual (SPM) for additional details.

6.1. Study intervention(s) administered

Table 10 Study intervention(s) administered

Study Intervention Name:	RSV MAT		Control	
Vaccine/product name	RSVPreF3	NaCl_solution	Sucrose_Lyo	NaCl_solution
Presentation	Powder for solution for injection, vial	Solution for solution for injection; syringe	Powder for solution for injection, vial	Solution for solution for injection; syringe
Vaccine/product formulation:	RSVPreF3 (120 µg)	Sodium chloride (NaCl) (0.9%); Water for injections**	Sucrose	Sodium chloride (NaCl) (0.9%); Water for injections**
Route of Administration	Intramuscular use		Intramuscular use	
Administration site: Location Laterality *	Deltoid Non-dominant		Deltoid Non-dominant	
Number of doses to be administered:	1		1	
Volume to be administered**	Whole content		Whole content	
Packaging and Labelling	Refer to the SPM		Refer to the SPM	
Manufacturer	GSK Biologicals		GSK Biologicals	

*The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed

** The entire contents of the pre-filled NaCl syringe will be transferred into the vial for reconstitution. The entire contents of the reconstituted vaccine/product will be withdrawn for administration. Refer to the SPM for additional information.

Maternal participants must be observed closely for at least 30 minutes after the administration of the vaccine/product. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

6.2. Preparation/Handling/Storage/Accountability

The study vaccine/product must be stored in a safe, locked place at the temperature specified on the vaccine/product label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Only authorised study personnel should be allowed access to the study vaccine/product. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine/product.

6.3. Measures to minimise bias: randomisation and blinding

6.3.1. Participant identification

Maternal identification numbers will be assigned sequentially to pregnant women who have consented to participate in the study, according to the range of participant identification numbers allocated to each study center.

Maternal participants who have provided informed consent will be registered into an automated internet based system (SBIR) at the time of screening. SBIR will be further used to confirm eligibility to participate in the study, to randomize each maternal participant to an intervention, and to confirm that an intervention has been administered (see Section 6.3.3).

The maternal participant's (as yet unborn) *infant* will be assigned an identification number, according to the range of numbers allocated to each study center, AFTER the maternal participant has been randomized (and vaccinated) at Visit 1.

Maternal and infant identification numbers will be linked.

6.3.2. Randomization to study intervention

6.3.2.1. Randomization to maternal study intervention group

Up to (approximately) 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.

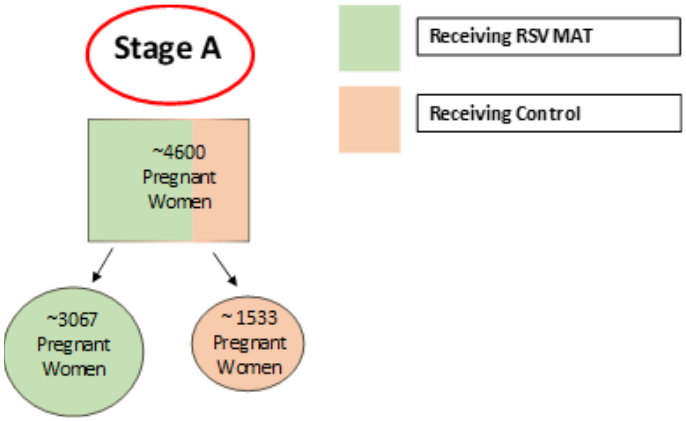
6.3.2.1.1. Stage A (Amended 23 February 2023)

Stage A begins when the first maternal participant is randomized.

Randomization to a study intervention

Approximately 4600 maternal participants will be randomized to Stage A and dosed as shown in Figure 3.

Figure 3 Randomization Overview – Stage A



All maternal participants in Stage A will:

- provide reactogenicity (solicited event) data for the first 7 days post-vaccination.
- have blood samples collected at Day 1 (Visit 1) and Day 31 (Visit 2) and Delivery (Visit 3).

At delivery, a cord blood sample will also be collected from all participants. (If it is not possible to collect cord blood, a blood sample will be collected from the neonate within 72 hours post birth).

All these samples may also be tested to support possible safety assessments, if necessary.

Randomization to the immunogenicity subcohort:

When they are randomized to a study intervention, maternal participants in Stage A (as well as their as yet unborn infants) will *also* be randomized either to participate in the immunogenicity sub-cohort (N ~ 1533) or to not participate (N ~ 3067).

For the ~ 1533 maternal participants in the immunogenicity sub-cohort, an additional blood sample will be collected at delivery.

For the ~ 1533 infant participants in the immunogenicity sub-cohort:

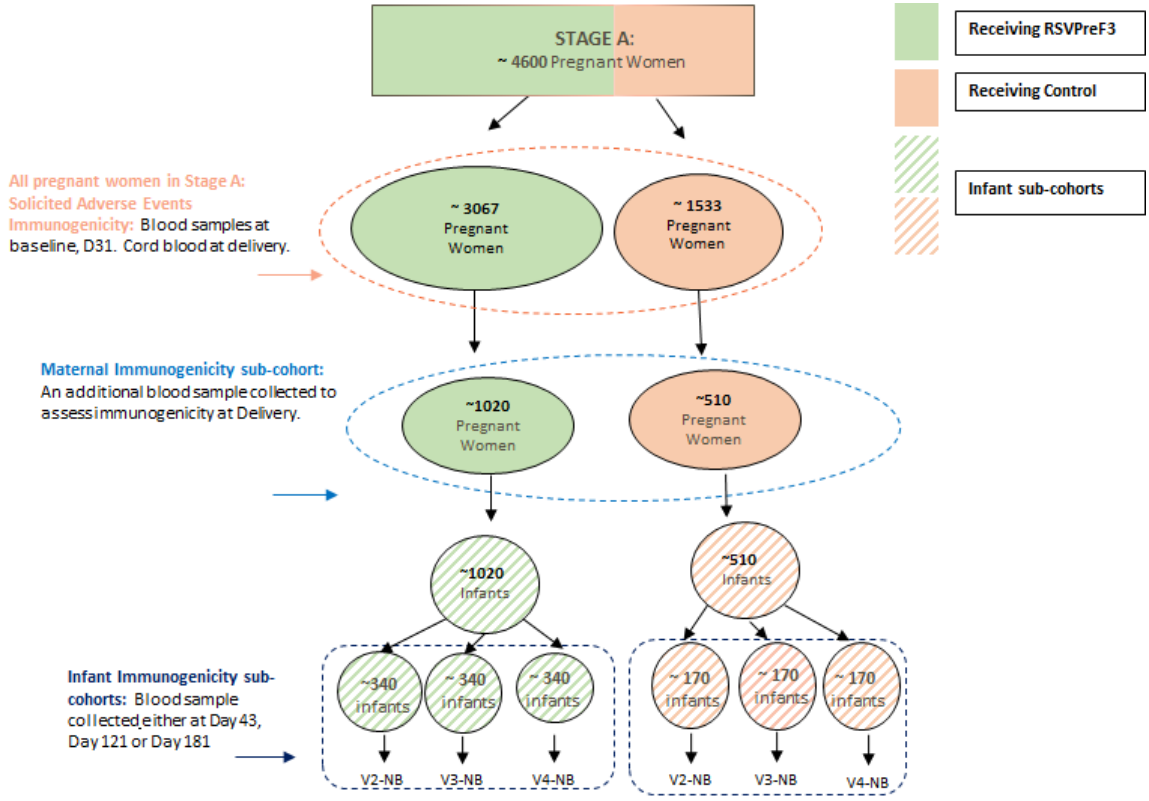
- Randomization will identify a single timepoint post-birth (Day 43 (Visit 2-NB), or Day 121 (Visit 3-NB), or Day 181 (Visit 4-NB)) at which each (as yet unborn) infant will have a blood sample collected. Thus, at each of the 3 post-birth immunogenicity timepoints, a sample will be collected from approximately one third of the infants in the sub-cohort (N ~510).

Note that due to the stop on study enrollment and vaccination, there will no longer be collection of blood samples from the infants at V2-NB, V3-NB and V4-NB.

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.

Refer to Figure 4 and Table 5 for additional information.

Figure 4 Stage A Sub-Cohort Distributions



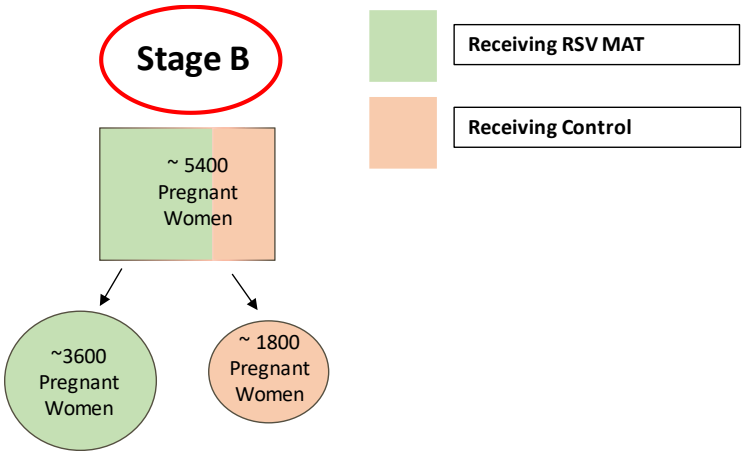
Note: As per Amendment 4, blood samples were to be collected from all maternal participants at Delivery (Visit 3). However, infant immunogenicity sub-cohort blood samples at Day 43 (V2-NB), Day 121 (V3-NB) or Day 181 (V4-NB) were no longer collected.

6.3.2.1.2. Stage B

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

Up to approximately 5400 maternal participants will be randomized and dosed as shown in Figure 5.

Figure 5 Randomization Overview – Stage B



All maternal participants in Stage B will have blood samples collected at Day 1 (Visit 1), Day 31 (Visit 2) and Delivery (Visit 3). Cord blood (or if not possible, neonatal blood within 72 hours from birth) will also be collected from all participants. These samples may also be tested to support possible safety assessments, if necessary.

Reactogenicity (solicited events) will not be evaluated in Stage B. There will be no blood sampling sub-cohorts for maternal or infant participants.

6.3.3. Intervention allocation to the participant

An automated internet based system (SBIR) will be used. The system's randomisation algorithm 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.

At Visit 1, site personnel will:

- Verify eligibility of the maternal participant.
- Access SBIR and
  - Select the maternal participant's identification number previously entered in the application (at the time of screening).
  - Verify that the maternal participant's calendar age and gestational age (GA) are correctly represented in SBIR. Entries in SBIR should reflect: calendar age at the time of V1/randomization, and GA based on LMP/IUI/ET and/or ultrasound results (as applicable).
  - Proceed to intervention allocation

The randomisation system will then determine the maternal participant's study group and provide the intervention number to be used for the study intervention.

In Stage A, the randomisation system will also determine:

- Whether or not the maternal participant and her (as yet unborn) infant are in the immunogenicity sub-cohort and
- For maternal and (as yet unborn) infant participants assigned to the immunogenicity sub-cohort, the post-birth timepoint at which blood sample will be collected from the infant.

When the automated, Internet-based system (SBIR) is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about intervention number allocation.

6.3.4. Randomization of supplies

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

To allow GSK to take advantage of greater rates of recruitment in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

6.3.5. Allocation of participants to assay subsets

Not applicable.

6.3.6. Blinding and unblinding

To minimize the introduction of bias, this study will be double-blinded*. Participants will not have access to their randomization assignment, and investigators and their staff will be blinded to the participant's assigned study intervention throughout the course of the study.

The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample.

A firewall will be established to ensure that data are not inadvertently unblinded. Details are provided in a separate Firewall charter.

* *Following the decision to stop enrollment and vaccination, the study/site staff and maternal participants no longer stay blinded. Refer to Section 2.3 for details.*

6.3.6.1. Emergency unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

A participant may continue in the study even if that participant's intervention assignment is unblinded.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via an automated Internet-based system (SBIR). Investigators are cautioned not to share this knowledge with sponsor staff, or with study staff who do not need it, in order to ensure that other members of the study team remain blinded.

As back up process, the investigator has the option of contacting a GSK Biologicals' Helpdesk (refer to the Table 11) if he/she needs help performing the unblinding (i.e. he/she cannot access the automated Internet-based system).

A non-investigator physician (e.g. physician from emergency room) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Biologicals' Helpdesk (back up process). The maternal and infant participant cards list contact information for both the investigator and GSK Biologicals' Helpdesk.

Table 11 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days	
The Helpdesk is available by phone, fax and email Phone : Fax : Email :	 +32 2 656 68 04 +32 2 401 25 75 rix.ugrdehelpdesk@gsk.com
Toll-free numbers are available for the following countries.	
Country	**Toll free number**
Canada	877.870.0019 or 1 833 541 0263
United States and Puerto Rico	877.870.0019 or 1 844 446 3133
Australia	0011 800 4344 1111
Belgium, Estonia, France, Germany, Spain,	00 800 4344 1111
Italy	800 879 197
Finland	999 800 4344 1111
Philippines	00 800 4344 1111, fixed line only
Russia	810 800 4344 1111
South Korea, Thailand	001 800 4344 1111

United Kingdom	0 800 056 7221
Brazil	0 800 891 2906
India	000 800 919 0928
Mexico	800 123 3102
South Africa	0800 984 003

6.3.6.2. Emergency unblinding prior to regulatory reporting of SAEs

GSK policy (which incorporates ICH E2A guidance, the EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any unexpected SAE and which is attributable/suspected to be attributable to the study vaccine/product, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a Serious Adverse Event that is fatal or life threatening. If the SAE requires an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

Before dosing, a qualified member of the study staff other than the person administering the dose will confirm that the intervention number is correct. The intervention number administered, and the administration date and time will be recorded in the source documents.

6.5. Concomitant therapy

At the timepoints indicated in the SoA, the investigator or delegate should question the maternal participant and/or the infant participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant.

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

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Maternal participants

- **All folate and iron supplements** beginning the month before the estimated date of conception and continuing through delivery (i.e., through Visit 3). These supplements should be reported when taken independently and/or when included in a multivitamin mineral supplement.

- All antibiotics, antivirals, analgesics and anti-pyretics taken within 7 days before dose administration.
- All concomitant **vaccines** beginning the month before the estimated date of conception and throughout the study (i.e., through Contact 1).
- **Prophylactic medication** related to the effects (actual or anticipated) of study vaccine/product administration (e.g., medication administered either in the absence of ANY symptom and in anticipation of a reaction to the study vaccine, or to prevent re-occurrence of one or more post-vaccination AEs such as headache).
- Any concomitant **medications/products** given for pre-existing medical conditions, beginning at Visit 1 and ending at Contact 1 (Day 1 to Day 181).
- Any concomitant **medications/products** associated with a solicited event or with an unsolicited adverse event, beginning at Visit 1 and ending at Visit 2 (Day 1 to Day 31).
- Any **corticosteroids for fetal lung maturation** administered prior to/during labour or delivery, as well as any **antibiotics** administered in the last week prior to delivery and/or during labor. Note: Standard of care medications/products administered routinely during labor/delivery (e.g., General/regional/local anesthetics, analgesics, etc) do not need to be reported.
- Any concomitant **medications/products** associated with a medically attended adverse event (MAE) other than an MA-RTI beginning at Visit 1 and ending at Visit 4 (Day 1 to Day 43 post delivery).
- Any concomitant **medications/products** associated with an MA-RTI beginning at Visit 1 and ending at Contact 1 (Day 1 to Day 181 post delivery).

6.5.2. Infant participants

- Vaccinations administered from Birth (Visit 1-NB) through the 6-month visit (Visit 4-NB)
- Medications administered in relation to RTIs/LRTIs from Birth (Visit 1-NB) through the 12-month visit (Visit 5-NB).
- Medications/products administered in relation to MAEs from Birth (Visit 1-NB) through the 12-month visit (Visit 5-NB).

6.5.3. Maternal and Infant participants

- Any concomitant medications/products/vaccines leading to a participant's non-eligibility (Sections 5.2.1 and 5.2.2) or potential non-evaluability (Section 9.3.1.1), or to a participant's withdrawal from the study.
- Any concomitant medications/products/vaccines relevant to an SAE/Adverse Event of Special interest (AESI) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI. Concomitant medications relevant to SAEs / AESIs must also be recorded on the Expedited Adverse Event report.

6.6. Dose modification

Not applicable.

6.7. Intervention after the end of the study

If a participant is not interested in taking part in the booster study, the reason for refusal will be documented, when available, in the participant's eCRF. Refusal to participate in the extension study will not prevent participants from enrolling in the RSV MAT-009 study.

There will be no access to study intervention after the end of the study, because of the safety signal identified, leading to stopping of further enrolment and vaccination.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Criteria for discontinuation of study vaccines / products do not apply since this is a single dose study. However, administration of the study's single dose may be *delayed* if the criteria presented in Section 7.1.1 are met.

7.1.1. Criteria for temporary delay for enrolment and/or vaccination

Vaccination must be postponed until transient circumstances cited below are resolved:

- Acute disease and/or fever within 48 hours before study vaccination. Fever is defined as temperature ≥38ºC by any age appropriate route (oral route preferred). Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.
- Use of systemic antibiotic or antiviral treatment within 48 hours before study vaccination.

Note: vaccination must be completed within the permitted time interval. If a participant is screened but not vaccinated within the allowed interval, a re-screening should be done to establish the participant's eligibility. Please make sure the participant's gestational age is still within the allowed range.

Refer to SPM for further guidance.

7.1.2. Contraindications to subsequent vaccine/product administration

Not applicable.

7.2. Participant discontinuation/withdrawal from the study

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

From an analysis perspective, a 'withdrawal' from the study refers to any participant who did not return for the concluding visit/was not available for the concluding contact foreseen in the protocol.

Investigators will attempt to contact those participants who do not return for scheduled visits or follow-up.

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

The primary reason for study withdrawal will be documented in the eCRF based on the list below:

- Adverse events requiring expedited reporting to GSK (Section 10.3.10.1)
- Unsolicited non- serious adverse event
- Solicited adverse event (maternal participants)
- Protocol deviation
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because she/the participant's parent(s)/LAR(s) has withdrawn consent and provided the reason for the withdrawal, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as a result of an SAE/AE until the event is resolved. (see Section 10.3.8.3).

7.3. Lost to follow-up

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

An infant participant will be considered 'lost to follow-up' if his or her parent(s)/LAR(s) fail to return for scheduled visits and are unable to be contacted by the study site.

Please refer to the SPM for a description of the actions to be taken before considering the participant as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoAs (Section 1.3). Information not provided in the SoAs follows.

As a reminder: study visits, assessments and procedures *do not* replace local standards of care, and that any adverse event / potential adverse event identified during a study visit or procedure should be treated according to local medical practice or by referral to an appropriate health care provider.

Adherence to the protocol is required for study conduct.

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

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the IEC/IRB.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team is aware of them.

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a screening log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles, Ultrasounds, HIV testing, etc.) and obtained before the participant signed the Informed Consent Form (ICF) may be used for screening and/or for establishing a clinical baseline, provided the procedure met protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3) and/or the eligibility criteria (Sections 5.1 and 5.2).

The SPM provides the investigator and site personnel with administrative and detailed technical information that does not impact participant safety.

Study Procedures During Special Circumstances
During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For guidance regarding the temporary delay of study intervention administration because of exposure to COVID-19, please refer to the SPM for details.

For the duration of such special circumstances:

- Enrolment of ADDITIONAL maternal participants may be placed on hold. Decisions on re-starting enrolment to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.
- The following measures may be implemented for enrolled participants:
  - If it is not possible to conduct a protocol-specified, scheduled or event-driven visit as described in Section 1.3, the visit may be replaced with a contact conducted by SMS, email, telephone, videotelephony or telemedicine. In such cases:
    - Protocol-specified clinical data that
      - cannot be collected by study staff during the contact (e.g., physical examination results; SpO_2 results) BUT
      - are available within the allowed interval (Table 3) in the participant's medical records and can be obtained by site staff (as allowed by local law), may be recorded in the participant's source document and entered into the eCRF.
      - Whenever possible, as appropriate per the judgement of the investigator and as allowed by local law, arrangements should be made for qualified personnel to collect any protocol-specified biological samples at an alternate location within the visit interval (Table 3).
        - Samples should not be collected if they cannot be processed in a timely manner and / or appropriately stored until the intended use.
        - Nasal swabs for central testing must be collected using GSK-provided supplies. (note: if collection at either the study site, participant's home or an alternate location is not possible, participants may be instructed to collect nasal swab samples by themselves/for their infant. Collection will be done using GSK-provided supplies and all the corresponding detailed instructions to allow such collection will be provided along with the nasal swab sampling kit)
        - Blood / cord blood samples for assessment of immune response must be retrieved, processed and stored in accordance with the Investigator Laboratory Manual.
- "Medically attended visits" will include instances where, due to the special circumstances, the participant cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.

- The frequency of RTI surveillance contacts by site personnel may be temporarily adapted.

Impact on the analysis sets for efficacy and immunogenicity will be determined on a case by case basis.

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic for more details.

8.1. Efficacy and/or immunogenicity assessments

Collected biological samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. Therefore, all participants in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

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

Sample testing will be done in accordance with the recorded consent of the individual maternal participant/infant participant's parent(s)/LAR(s).

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

8.1.1. Biological samples

Table 12 Biological samples – maternal participants

Maternal Sample type	Collected to Evaluate	Minimum Quantity per participant	Unit	Time point	Additional Information
Whole blood	Immune response	~10	ml	Visit 1 (Day 1) pre dose Visit 2 (Day 31) Visit 3 (Delivery)	*Visit 1 and Visit 2: Applies to all participants, Stages A & B* *Visit 3: Applies to Stage A Immunogenicity sub-cohort only#*
		~30 ~20	ml ml	Estimated TOTAL if assigned to the immunogenicity sub-cohort# Estimated TOTAL if NOT assigned to the immunogenicity sub-cohort	
Nasal Swab*	Presence of:RSV A / B	-	-	MA RTI Assessment Visit	Collect a nasal swab from any maternal participant who reports a medically attended (MA) RTI
		-	-	RTI hospitalization	Collect a nasal swab (if possible) from any maternal participant hospitalized with a RTI (or soon after discharge, as long as symptoms are ongoing).

Volume of the blood sample collected for immune response assessment may be reduced to ~5 ml at investigator's discretion. Refer to the laboratory manual for additional information.
Collection of a nasal swab for sponsor testing is additional to and **DOES NOT REPLACE** any specimen collection (per local standard of care) for testing by the local laboratory to establish a fast and accurate diagnosis for the hospitalization. In the case of hospitalization, local testing for RSV infection should be performed if feasible.
If other nasal swab specimens are collected and tested locally as per local standard of care, results will be recorded in the eCRF. In principle only the sponsor laboratory results will be used when applying the case definitions for data analysis in Section 4.2.6.3. Thus, where mandated by the protocol, every effort should be made to obtain nasal swab samples that can be analyzed by the sponsor (or sponsor-designated) laboratory. Results of locally tested samples, with locally approved tests may be used when applying case definitions only in the event the nasal swab for central testing was impossible to collect.
* Due to the stop on study enrollment and vaccination, nasal swab samples will no longer be collected from any maternal participant and no MA-RTI assessment visit will be performed.
# Following protocol amendment 4, blood samples will be collected at delivery from all maternal participants. Hence, even if not assigned to the immunogenicity sub-cohort, the estimated total volume of blood for all maternal participants will be ~30mL. In addition, placental samples will also be collected at delivery, whenever feasible.

Table 13 Biological samples – Cord Blood

Sample type	Collected to Evaluate	Minimum Quantity per participant	Unit	Time point	Additional Information
Cord blood	Immune Response	~5, up to ~10	ml	Visit 3 (Delivery)	-

Table 14 Biological samples – infant participants

Infant Sample type	Collected to Evaluate	Minimum Quantity per participant	Unit	Time point	Additional Information
Whole Blood	Immune response - IF cord blood not collected	~2.5 - Stages A and B	ml	Visit 1-NB (Within 3 days after birth)	Volume must be reduced if weight ≤ 2.5 kg. [Trial-related blood loss for infant participants should be ≤ 1 % at each timepoint. Total blood volume is estimated at 80 to 90 ml/kg body weight, and venipuncture should not exceed ~ 1.6 ml for a 2kg baby or 2.0 ml for a 2.5 kg baby.] Refer to the Laboratory Manual and/or SPM for additional information. All minimum totals given below assume a body weight > 2.5 kg.
	Immune response – sub-cohort*#	~2.5* - Stage A immunogenicity sub-cohort only	ml	Either Visit 2-NB (Day 43) or Visit 3-NB (Month 4) or Visit 4-NB (Month 6)	
		~2.5	ml	Estimated TOTAL if cord blood NOT collected	
		~2.5	ml	Estimated TOTAL if assigned to one of the three blood sampling sub-cohorts in Stage A	
		~5.0	ml	Estimated TOTAL if assigned to a blood sampling sub-cohort in Stage A AND cord blood NOT collected	
Nasal swab	Presence of RSV A / B	-	-	LRTI Assessment Visit	Collect at least one nasal swab for each potential LRTI reported. If more than one follow-up assessment visit is conducted, additional nasal swabs may be collected at the Investigator's discretion.
		-	-	RTI hospitalization	Collect (if possible) from any participant hospitalized with a RTI (or soon after release, as long as symptoms are ongoing).

*Only from infant participants in the sample collection sub-cohort for the visit. Each infant is assigned to a single sub-cohort.

Due to the stop on study enrollment and vaccination, there will no longer be collection of blood samples from the infants at V2-NB, V3-NB and V4-NB

Collection of a nasal swab for sponsor testing is additional to and **DOES NOT REPLACE** any specimen collection (per local standard of care) for **testing by the local laboratory** to establish a fast and accurate diagnosis for the hospitalization. In the case of hospitalization, local testing for RSV infection should be performed if feasible.

If other nasal swab specimens are collected and tested locally as per local standard of care, results will be recorded in the eCRF. In principle only the sponsor laboratory results will be used when applying the case definitions for data analysis in Section 4.2.6.3. Thus, where mandated by the protocol, every effort should be made to obtain nasal swab samples that can be analyzed by the sponsor (or sponsor-designated) laboratory. Results of locally tested samples, with locally approved tests may be used when applying case definitions only in the event the nasal swab for central testing was impossible to collect.

8.1.2. Laboratory assays

Table 15 Laboratory assays

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	SERUM	RSV-A NAb (RSV-A Neutralizing Antibody)	NEUT	GSK ** or GSK designated lab
	SERUM	Respiratory Syncytial Virus PreF3 Ab.IgG (RSVPreF3 IgG antibody concentration)	ELISA	GSK ** or GSK designated lab
Molecular Biology	NASMUC (Nasal swab)	Respiratory Syncytial Virus A RNA	QRTPCR	GSK ** or GSK designated lab
	NASMUC (Nasal swab)	Respiratory Syncytial Virus B RNA	QRTPCR	GSK ** or GSK designated lab

*Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.
ELISA = enzyme-linked immunosorbent assay; NEUT = Neutralization;
RSV-A/B quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

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

8.1.3. Immunological read-outs

Table 16 Immunological read-outs *(Amended 23 February 2023)*

Approximately 1533 maternal participants (and their infant participants), in Stage A only, will be assigned to the immunogenicity sub-cohort.

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. Therefore, maternal participants in the immunogenicity subcohort, who have blood samples collected from their respective infants, will have Visit 1 (Day 1), Visit 2 (Day 31), Delivery blood samples and cord blood samples tested for RSV-A NAb. In addition, their delivery and cord blood samples will be tested for RSVPreF3 IgG-specific antibody concentration.

Blood sampling timepoint		**Approximate No. participants – Stage A**	**Approximate No. participants – Stage B**	**Component**
Type of contact and timepoint	**Sampling timepoint**			
Maternal participants*				
V1 (Day 1)	pre vaccination	4600	Up to 5400	RSV-A NAb (neutralizing antibody)
V2 (Day 31)	post vaccination	4600	Up to 5400	RSV-A NAb (neutralizing antibody)
V3 (Delivery)#	post-vaccination	venous blood: 1533 Cord blood: 4600	Venous blood: 0 Cord blood: up to 5400	RSV-A NAb (neutralizing antibody) Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)
Infant participants**				
V1-NB (Birth)	birth (only if cord blood cannot be collected)	Event-driven	Event-driven	RSV-A NAb (neutralizing antibody) Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)
V2-NB (Day 43)***	post birth 1	510	0	RSV-A NAb (neutralizing antibody)
V3-NB (Day 121)***	post birth 2	510	0	RSV-A NAb (neutralizing antibody)
V4-NB (Day 181)***	post birth 3	510	0	RSV-A NAb (neutralizing antibody)

V = Visit; RSV-A/B: respiratory syncytial virus subtype A/B; **NB**: Newborn. **IgG**: immunoglobulin G;

* Refer to Table 12, Table 13

** Refer to Table 14

***Due to the stop on study enrollment and vaccination, blood samples will no longer be collected from the infants at V2-NB, V3-NB or V4-NB.

As from Protocol Amendment 4 - Blood sample at delivery to be collected from all participants. Whenever feasible, placenta sample is expected to be collected from all participants. These samples may be tested to support possible safety assessments, if necessary.

Table 17 Molecular biology tests

Nasal swab sampling timepoint		No. participants	Component***
Type of contact (timepoint)	**Sampling timepoint**		
Maternal MA-RTI * #	Event driven	Event-driven	Respiratory Syncytial Virus A RNA
			Respiratory Syncytial Virus B RNA
Infant RTI**	Event driven	Event-driven	Respiratory Syncytial Virus A RNA
			Respiratory Syncytial Virus B RNA

*Includes maternal RTI hospitalizations
**Includes infant RTI hospitalizations
***Quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4
Due to the stop on study enrollment and vaccination, nasal swabs from maternal participants will not be collected and no MA-RTI assessment visit will be performed.

8.1.4. Immunological correlates of protection

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

8.2. Safety Assessments

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

Surveillance for / evaluation of respiratory tract illness is described in Section 8.4.

8.2.1. Procedures for maternal participants

Additional details are provided in the SPM.

8.2.1.1. Medical/vaccination history

Obtain the maternal participant's medical/vaccination history by interviewing her and/or reviewing her medical records. Record any pre-existing maternal participant conditions, signs and/or symptoms present prior to the study vaccination in the eCRF.

- Record outcome of the fetal anomaly ultrasound (also known as a Level 2 ultrasound scan or fetal morphology assessment). Please see Section 10.7.2 for a description. If results are not available at screening, then the ultrasound can be performed as a study procedure under certain conditions and results confirming no significant abnormalities/congenital malformations should be available prior to participant's study randomization and vaccination. Refer to the SPM for further details. If abnormal, participants will be referred, as/if applicable, per local standard of care.
- Information from additional routine standard of care antenatal / medical evaluations (external to study visits/procedures) are not to be reported in the CRF. If an unscheduled visit is performed *post study vaccination*, for safety reasons, results of

procedures performed, per investigators discretion (eg. hematology/biochemistry testing, urinalysis, etc) will be recorded in the "Unscheduled Safety visit" eCRF.

- Record number of past pregnancies, their outcome(s) and any pregnancy-related complications.
- For the current pregnancy, record:
  - the participant's pre-pregnancy BMI (i.e., BMI during the months before the participant became pregnant or at the very first maternal visit [if occurred early in the 1st pregnancy trimester]). This information can be obtained either via medical record review or participant interview. If BMI is not directly available, investigators will obtain participant's pre-pregnancy weight (i.e. weight during the months before the participant became pregnant or are the very first maternal visit [if occurred early in the 1st trimester]) and calculate pre-pregnancy BMI from it, in order to report it in the eCRF.

    NOTE: in the exceptional circumstance where the pre-pregnancy weight/BMI is unknown and there is no maternal visit performed during the 1st trimester, the BMI calculated based on the weight at screening may be used for eligibility. In those cases, the investigator should carefully assess the nutritional status of the potential participant to exclude any signs of malnutrition, in conjunction with the other eligibility criteria.
  - gestational age, along with GAIA level of certainty as defined in Section 10.8
  - date of Last menstrual period date (LMP) or Embryo Transfer (ET) or Intrauterine insemination (IUI), as applicable
  - expected date of delivery (EDD) and method of estimation
  - number of prenatal visits attended up to the date of the study Screening visit,
  - approximate date and gestational age of first prenatal visit,
  - results of any clinically significant, abnormal pregnancy screening laboratory tests,
  - any pregnancy-related complications
  - results of any procedures intended to screen for congenital anomalies.
  - Record all vaccination received by the maternal participant since the month prior to the estimated date of conception and before study vaccination

8.2.1.2. Physical examination (General and obstetric examination)

Screening and Visits 1 through 3

- Height (only at screening)
- Weight (at screening and Visits 1-2),
- Temperature at screening and Visits 1-3. At Visit 1, temperature need only be measured once, pre-vaccination. At visit 3 (delivery) temperature should be measured if/as per standard of care (SoC).

- Systolic/diastolic blood pressure, heart rate and respiratory rate (after at least 10 minutes rest) at screening and at Visits 1 and 2; and on admission for delivery at Visit 3. Respiratory rate should be measured at Visit 3 (delivery) if/as per SoC.
- Pulmonary examination including measurement of blood oxygen saturation and chest auscultation (at Visit 1).

Obstetric examination should include:

- Fetal heart tones,
- Fetal movement and fundal height (at screening and visits 1 – 2). No specific test required for fetal movement, unless part of standard of care, information reported by the maternal participant while at the visit will be acceptable)
- Presence of edema (at screening and visits 1 – 2)
- Vaginal examination (manual and/or speculum) will be performed ONLY if warranted by participant's symptoms or as per investigator's clinical discretion. If done, results will be recorded (normal or abnormal; if abnormal, specify).

If the Screening Visit and Visit 1/vaccination are performed on the same day:

- Physical examination (general and obstetrical) procedures required both at screening and at Visit 1/vaccination should be performed once; they do not need to be repeated.
- Temperature will only be measured once, but will need to be recorded twice in the eCRF.
- The Pulmonary examination foreseen at Visit 1 should be performed.

Visit 4

- Vital signs **(**systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest)
- History and/or symptom directed physical and obstetrical exam as per standard of care (eg. check of c-section scar / episiotomy scar, any specific checks based on eventual complaints raised by the mother, etc. as applicable). Clinically significant abnormalities will be recorded

All unscheduled visits

General and obstetric examination should be symptom-directed.

Any unscheduled visit for a medically attended respiratory tract illness **must** include the maternal participant assessments listed in Section 8.4.4.

8.2.1.2.1. Pulse oximetry

Measurement of blood oxygen saturation by trained site personnel, using pulse oximeters provided by GSK, is strongly preferred. The SPM presents additional information about GSK-provided pulse oximeters and their use.

8.2.1.2.2. Monthly contacts

At least 3 attempts should be made within the week of a scheduled contact. If these attempts are unsuccessful, that monthly contact is considered a missed contact. The next scheduled contact will be made the following month.

To ensure safety monitoring, in addition to the monthly contact 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.

8.2.2. Procedures for infant participants

Additional details are provided in the SPM.

8.2.2.1. Physical examination at Visits 1-NB through 5-NB

A physical examination will be performed at each protocol-specified visit (Visits 1-NB through 5-NB).

The examination will include assessment of the following:

- Weight, length, head circumference
- Temperature, heart rate and respiratory rate
- Age-appropriate organ system examination including: eyes, ears, musculoskeletal, reflexes (motor/visual/sound), pulmonary (chest auscultation), cardiovascular, neurological, skin and genitourinary.
- Presence of congenital anomalies.

8.2.3. Safety monitoring

Safety evaluations will include those performed by investigators, by a blinded SRT* composed of GSK RSV team members, and by an unblinded, independent data monitoring committee external to GSK (IDMC). Details regarding IDMC safety evaluations are provided in a separate IDMC charter.

If the IDMC's decision(s) after a safety evaluation require(s) them to take some action (e.g., to suspend, modify, or continue the conduct of the study for all groups or for selected groups), the IDMC Chair (or his/her representative) will notify the study CRDL. The study CRDL will be accountable for notifying investigators in writing of the IDMC's decision(s).

*Note: Due to the safety signal observed, the study has been fully unblinded to ensure safety monitoring for the participants.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other events of interest

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 18 Timeframes for collecting and reporting safety (and RTI) information

Applies to Stage A and Stage B unless otherwise noted below

		Before Delivery*				Delivery/Birth	Post-Delivery/Birth*					
Timepoint		**D-28**	**D1**	**D7**	**D31**		**D 43**	**D91**	**D121**	**D181**	**M9**	**M12**
	Maternal participant visits	Pre-**	V1		V2	V3	V4			C1		
	Infant visits					V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB
Event	**Administration site and systemic solicited events - Stage A ONLY**		M									
	Unsolicited AEs that are neither SAEs, MAEs or AESIs		M									
	Subsequent Pregnancies* **					M						
	AEs/SAEs leading to Withdrawal from the study		M									
						I						
	SAEs		M									
						I						
	MAEs		M									
						I						
	AESIs**		M									
						I						
	Medically attended RTIs (mothers)#; RTI/LRTI (infants)		M									
						I						

Applies to Stage A and Stage B unless otherwise noted below

		Before Delivery*				Delivery/Birth	Post-Delivery/Birth*					
Timepoint		**D-28**	**D1**	**D7**	**D31**		**D 43**	**D91**	**D121**	**D181**	**M9**	**M12**
	Maternal participant visits	Pre-**	V1		V2	V3	V4			C1		
	Infant visits					V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB
	SAEs related to study participation or concurrent GSK medication or vaccine	M										

Pre = pre-vaccination; V=visit; D: Day; M = Maternal participants; I= Infant participants. * Approximately monthly contacts pre- delivery also occur within the timeframes described above and are described in Section 1.2. **i.e. consent obtained. *** If subsequent pregnancy occurs during the study, follow-up may extend up to 8 weeks post birth of the infant from that subsequent pregnancy. ****AESIs include adverse pregnancy outcomes, pregnancy related AEs of special interest and neonatal AEs of special interest (for details refer to Section 10.3.5). Neonatal AEs of special interest identified after V2-NB (e.g., congenital anomalies) will continue to be reported as such.
[#]Due to the stop on study enrollment and vaccination, MA-RTI surveillance of the maternal participants will no longer be performed.

The investigator or designee will record and immediately report all SAEs (including RTIs associated with hospitalization of a maternal or infant participant and all adverse pregnancy outcomes), as well as all pregnancy related AESIs and neonatal AESIs to the sponsor or designee via the Expedited AE Reporting Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE/AESI, as indicated in Section 10.3.10. and Table 19. The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

A post-study SAE is defined as any event that occurs after the end of the study. Investigators are not obligated to actively seek SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in the Table 20.

8.3.2. Method of detecting AEs and SAEs, subsequent pregnancies and other events

Methods of detecting and recording AE/SAE/AESI/subsequent pregnancies are detailed in the Section 10.3.8. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.9.

Open-ended and non-leading verbal questioning of the maternal participants/infant participants' parent(s)/LAR(s) is the preferred method of acquiring information related to an AE/SAE/AESI/subsequent pregnancy.

8.3.3. Regulatory reporting requirements for SAEs, subsequent pregnancies, and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI/subsequent pregnancy, he/she must report it to GSK using the required documentation, and within the timeframes, mentioned in the Table 19. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for the preparation of an investigator safety report for Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has a legal responsibility to notify local authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/AESIs/subsequent pregnancies.

Table 19 Timeframes for submitting serious adverse event, subsequent pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs (including adverse outcomes for the study pregnancy)	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
AESIs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Maternal participants: MA-RTIs **Infant participants: RTIs/LRTIs**	3 days*	eCRF	1 week	eCRF
Subsequent Pregnancies	24 hours *	electronic pregnancy report	24 hours *	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once investigator determines event meets protocol definition of an AESI.
‡ The investigator will be required to confirm review of SAE/AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AESI

8.3.3.1. Contact information for reporting of SAEs, AESIs, subsequent pregnancies and study holding rules

Table 20 Contact information for reporting of SAEs, AESIs, subsequent pregnancies

Study contact for questions regarding SAEs, AESIs, subsequent pregnancies Refer to the local study contact information document
Back-up study contact for reporting SAEs, AESIs, subsequent pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com US sites only: Fax: 1-610-787-7053 Canadian sites only: Fax: 1-866-903-4718

8.3.4. Additional Reporting Guidance for the Study Pregnancy

8.3.4.1. Labor and Delivery

- An *uncomplicated* vaginal delivery or planned cesarean section *expected* to occur in a hospital setting should NOT be reported as an AE, MAE or SAE.
- A medical *complication* that requires a cesarean section or an emergency induction may be reported as an SAE/AESI (as applicable), using the corresponding Expedited AE report form.

8.3.4.2. Pregnancy outcomes

Table 21 summarizes the requirements for AESI/ SAE reporting of adverse pregnancy outcomes when congenital anomalies are / are not present

Table 21 Reporting pregnancy outcomes with or without congenital anomalies as AESIs and/or SAEs

	Live birth		Fetal death /stillbirth		Elective / Therapeutic Termination	
Congenital anomalies*	**AESI**	**SAE**	**AESI**	**SAE**	**AESI**	**SAE**
None	-	-	-	X	-	X
Major[1]	X	if reportable per MACDP[3]	-	X	-	X
Minor[2]	-	if reportable per MACDP[3]	-	X	-	X

* In the event of infant's participation in the study, congenital anomalies are to be reported in the infant's eCRF. However, when there is no live birth, or no signed informed consent for the infant or the congenital anomaly is being reported for a subsequent pregnancy, it will be encoded in the maternal participant's eCRF.
[1]Structural or functional defects that require surgical and/or medical treatment and that have serious adverse effects on health or development (functional) or have significant cosmetic impact.
[2]Anatomic variants or defects that do not have serious medical, functional or cosmetic consequences for the child.
[3] Metropolitan Atlanta Congenital Defects Program (MACDP) 6-Digit Code Defect List

Additional guidance when congenital anomalies are present follows:

The term "congenital anomaly" is broad. GSK uses the case definitions provided in the Centers for disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program guidelines, with specific reference to the MACDP 6-Digit Code Defect List [MACDP, 2021] to ensure that the collection and recording of these data is complete and consistent across studies and projects.

To report a pregnancy outcome of live birth with congenital anomaly as an SAE per these guidelines, an infant must have a birth defect that is *included in MACDP surveillance data* per the MACDP 6-Digit Code Defect List. (Congenital anomalies that are not included in MACDP surveillance data may be reported as medically attended or serious adverse events, if appropriate).

The characterization of major and minor congenital anomalies will follow CDC definitions [CDC, 2019]. Major congenital anomalies are structural or functional defects that require surgical and/or medical treatment and that have serious adverse effects on health or development (functional) or have significant cosmetic impact. They are always reported as AESIs, even if they are not reportable as SAEs.

Minor congenital anomalies are anatomic variants or defects that do not have serious medical, functional or cosmetic consequences for the child. Minor congenital anomalies are not to be reported as AESIs, even if they are reportable as SAEs.

If minor congenital anomalies are not reportable either as SAEs or MAEs, they may be recorded in the infant physical examination eCRF.

For example:

- Cleft palate is a major congenital anomaly and should be reported as an AESI. Per the MACDP 6 Digit Code Defect list, cleft palate is always included in MACDP surveillance data and should therefore also be reported as an SAE.
- If congenital aortic valve insufficiency or regurgitation meets the criteria for a major congenital anomaly, it is an AESI. Per the MACDP 6-digit code list, congenital aortic valve insufficiency or regurgitation is only included in MACDP surveillance data and should only be reported as an SAE if designated as moderate or severe, or (if the degree is not specified) if another heart defect is present. Other cases could be reported as medically attended or serious adverse events if the infant meets any other protocol criterion for a medically attended or serious AE because of the condition.
- Mongolian spots, in the absence of any associated findings represent a minor congenital anomaly. Per the MACDP 6-digit code list, they are never included in MACDP surveillance data. They are neither an AESI nor an SAE. They do not typically satisfy the criteria for a medically attended AE and so, in general, would only be recorded in the infant physical examination eCRF.

Refer to the SPM for additional information and guidance.

8.3.5. Treatment of adverse events

Any medication administered for the treatment of an SAE/AESI should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.10.1).

8.3.6. Participant cards

The investigator (or designee) must provide the maternal participant/infant participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. One card will be provided to each maternal participant who enters the study. Another card will be provided for each infant participant who enters the study.

Maternal participants/infant participant's parent(s)/LAR(s) must be instructed to keep these participant cards in their possession at all times throughout the study. In an emergency, the cards serve to inform the responsible attending physician/LAR/care giver/family member that the maternal / infant participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4. Respiratory tract illnesses (RTIs)

The definitions provided in Sections 8.4.1.1 and 8.4.1.2 are for use by site personnel. They are designed to provide GSK with the information needed to apply case definitions during data analyses. They are related but not identical to the case definitions themselves (Section 4.2.6). For additional details regarding maternal MA-RTI and infant RTI surveillance and assessment, refer to the SPM.

8.4.1. Definitions

8.4.1.1. Medically attended respiratory tract illnesses (MA-RTIs) in maternal participants *(Amended 23 February 2023)*

A maternal MA-RTI occurs when the maternal participant visits a healthcare professional (e.g., a General Practitioner) for any respiratory symptom, including (but not limited to) cough, sore throat, sputum production and difficulty breathing.

* *Due to the stop on study enrollment and vaccination, MA-RTI surveillance of the maternal participants will no longer be performed.* ***No nasal swab will be collected and no RTI assessment visit will be performed. However, any MAE related to RTI will still be reported (as applicable).***

8.4.1.2. Respiratory tract illnesses (RTIs) in infant participants

RTI symptoms include:

- Nasal discharge running freely out of the infant's nose (runny nose),
- Breathing through the mouth because the infant's nose is blocked (blocked nose),
- Regular bursts of cough,
- Difficulty in breathing (fast breathing, poor feeding, working hard to breathe, or making unusual sounds when breathing), and
- Wheezing (a whistling sound when the infant breathes out, and thus another sign of potential difficulty in breathing).

Worsening means any clinically observed/diagnosed symptoms and signs that are reported during the same respiratory tract illness and reflect a deterioration in the infant's respiratory tract functions.

A *potential* lower respiratory tract ***illness*** (LRTI) is one in which the infant's RTI symptoms include at least one of the following:

- Difficulty in breathing (fast breathing, poor feeding, working hard to breathe, or making unusual sounds when breathing);
- Wheezing (a whistling sound when the infant breathes out);
- Parental concern (the parent(s)/LAR(s) or their designate(s) are concerned about the infant's respiratory tract illness, or general health in the context of the respiratory tract illness and intend to seek medical care).

8.4.2. Surveillance

8.4.2.1. Maternal participants

MA-RTI surveillance begins when a maternal participant enters the study and ends 6 months after delivery (Contact 1). It will be accomplished via contacts **initiated by** maternal **participants**.

At study entry, each **maternal participant** will be instructed to contact the site should she

- Visit (or plan to visit) a healthcare professional for any respiratory symptoms;
- Be hospitalized because of her respiratory symptoms.

If the study site is the primary treating facility for the maternal participant, a "contact" may also be made by going directly to the study site.

Site personnel will use a script to guide data collection once a contact has been made.

Due to the stop on study enrollment and vaccination, MA-RTI surveillance for the maternal participants will no longer be performed.

8.4.2.2. Infant participants

RTI surveillance in infant participants begins at birth (Visit 1-NB) and ends 12 months after birth (Visit 5-NB).

It will be accomplished via two types of contact and completion of diary cards

8.4.2.2.1. RTI surveillance contacts

- In a **Passive** contact, the participant's parent(s) / LAR(s) contact site personnel. Site personnel will use a script to guide data collection once a passive contact has been made.
- In an **Active** contact, site personnel contact the participant's parent(s) / LAR(s). Active contacts will also be scripted.
  - *In regions where RSV transmission is seasonal, contacts should occur* every week during the RSV season and every month outside the RSV season.
  - *In regions with year-round RSV transmission,* contacts will occur every 2 weeks.
  - At least 3 attempts should be made within the week of a scheduled contact. If these attempts are unsuccessful, that active contact is considered a missed contact. The next active contact will be made according to schedule.

In special circumstances, such as for example, in the event of a pandemic, social distancing and confinement measures may considerably impact the region's usual RSV

seasonality. Hence, frequency of active contacts may be temporarily adapted (in agreement with GSK and subject to IEC/IRB approval, as needed) to avoid unnecessary burden (Refer to Section 8).

Further details are provided in the SPM.

Site staff will use information gathered during each active or passive surveillance contact to determine whether a visit to assess a potential LRTI (Section 8.4.4) should be scheduled.

8.4.2.2.2. RTI Diary cards

Infant RTI diary cards will be provided to the infant participant's Parent(s)/LAR(s) as soon as possible after the infant's birth (ideally, at Visit 1 NB). Parents will use the diary card to document symptoms of the RTI.

Parent(s)/LAR(s) will be asked to bring any completed or partly completed diary cards with them to the infant participant's study visits (including any RTI assessment visits).

At each study visit/contact (including any assessment visits), RTI symptoms may have ended or may be ongoing. This will be evaluated in order to determine whether to retrieve the Diary Card and replenish the parent(s)/LAR(s)/designate(s) supply of blank cards as needed or, instruct them to continue collecting information until the corresponding symptom(s) have ended

- Completed RTI diary cards may be collected by study staff during a site visit, home visit, or via postal mail, whichever is most effective based on local practice.

Refer to the SPM for additional details.

8.4.2.3. Maternal and infant participants

If the maternal participant visited / the infant participant was taken to a healthcare provider not affiliated with the study, site personnel should (if permitted by local regulation) contact that healthcare provider to obtain the medical record(s) for the visit.

8.4.3. When to conduct an assessment visit

8.4.3.1. For a maternal MA-RTI

Due to the stop on study enrollment and vaccination, MA-RTI surveillance for the maternal participants will no longer be performed.

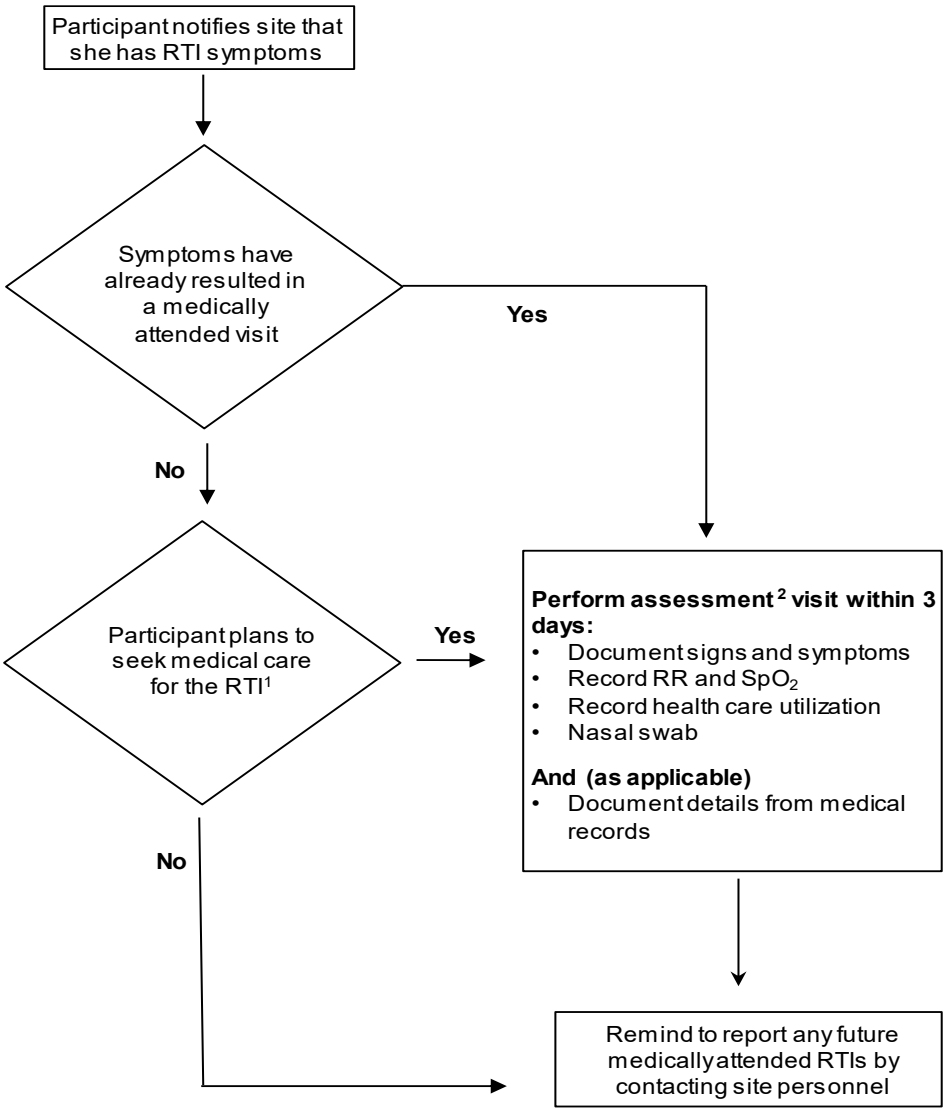
Conduct an assessment visit (Section 8.4.4), ideally within 3 calendar days after a medically attended visit due to RTI symptoms occurs during the surveillance period. However, a visit may be conducted *even beyond this window if* symptoms are ongoing.

If a maternal participant informs the site that she has RTI symptoms and (a) would seek / have sought medical advice for them and (b) is already scheduled for a study visit within the timeframes described above, then the site should perform the MA-RTI assessment visit procedures (including nasal swab) during the already scheduled study visit.

A decision tree is provided in Figure 6.

Refer to the SPM for additional details regarding maternal MA-RTI surveillance.

Figure 6 Decision Tree for site personnel – maternal surveillance and assessment



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation by pulse oximetry.
[1]Includes cases where symptoms would have resulted in a medically attended visit if participant were not already scheduled for a study visit
[2]Details regarding the RTI assessment visit are provided in Section 8.4.4 and the SPM.

8.4.3.2. For an infant RTI

Conduct an assessment visit, as described in Section 8.4.4, as soon as possible after at least one of the following has been reported during the surveillance period:

- Difficulty in breathing,
- Wheezing
- The maternal participant/LAR intends to seek medical care because of concern about the infant's respiratory tract illness, or general health in the context of the infant's respiratory tract illness.

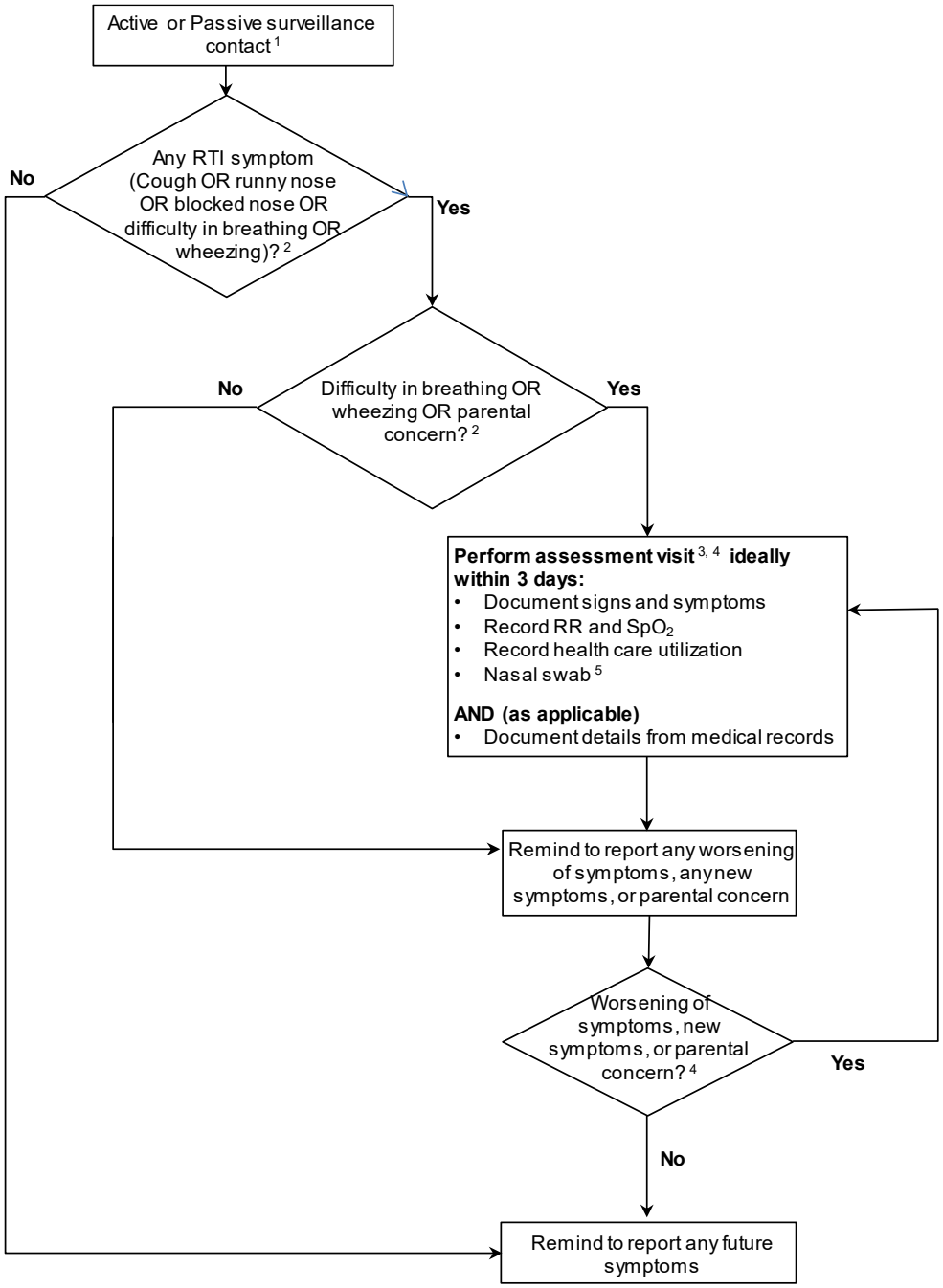
The visit should take place as soon as possible; ideally within 3 calendar days. However, a visit may be conducted *even beyond the specified ideal window* if symptoms are ongoing.

- After the first assessment visit, site personnel should use results of additional contacts to assess the development of new and worsening of previously reported symptoms.
- Site personnel should conduct a **follow-up** assessment **visit** as soon as possible after learning:
  - that any symptom present at the first assessment visit has worsened, OR
  - that there are new symptoms of difficulty in breathing or wheezing, OR
  - that there is new or increased parental concern in the context of the respiratory tract illness.

The timing of the follow-up visit should be consistent with the guidance given above.

A decision tree is provided in Figure 7. Refer to the SPM for additional details regarding infant RTI surveillance.

Figure 7 Decision Tree for site personnel - infant surveillance and assessment



RR: Respiratory rate: **SpO_2**: Blood oxygen saturation by pulse oximetry.
[1]Details regarding Surveillance are provided in Section 8.4.2.2 and the SPM.
[2]Cough, runny nose, blocked nose, difficulty in breathing, wheezing are described in Section 8.4.1.2
[3]Details regarding the RTI assessment visit are provided in Section 8.4.4 and the SPM.
[4] Post-visit follow up is described in Sections 8.4.6 and in the SPM.
[5]If a follow-up assessment visit is conducted, collection of additional nasal swabs is as described in Table 14.
[6]Parental concern *in the context of an RTI*

8.4.4. Assessment visit procedures

The purpose of each assessment visit is to objectively document signs and symptoms of a respiratory tract illness by an appropriately qualified person (i.e. medical or nursing), provide medical advice or referral as appropriate, and collect specimens for detection of RSV infection.

An assessment visit may take place at the investigator's clinical facility or another medical facility, or via a home visit by qualified site staff (or a designated third party), as appropriate per the judgment of the investigator (and as allowed by local law).

Note that if the reported symptoms are severe enough to warrant urgent care, the participant / parent(s)/LAR(s) should be advised to seek such care (e.g. Emergency Room).

8.4.4.1. Clinical evaluation

At every assessment visit, the investigator/study staff/designated third party will evaluate the clinical signs and symptoms of the RTI. Data to be collected and recorded include (but are not limited to):

For maternal participants: Due to the stop on MA-RTI surveillance for maternal participants, these checks will no longer be performed.

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (in room air, if feasible), see further details in Section 8.2.1.2.1
- Results of chest auscultation
- Signs of difficulty in breathing (wheezing and tachypnoea in maternal participants)

For infant participants:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (in room air, if feasible), see further details in Section 8.2.1.2.1
- Results of chest auscultation
- Presence of cough, runny nose or blocked nose
- Signs of difficulty in breathing (wheezing, tachypnoea, nasal flaring, chest in-drawing and apnea)
- Irritability/agitation
- Lethargy/excessive sleepiness
- Cyanosis
- Feeding poorly

8.4.4.2. Nasal swab collection

Refer to Table 12 (maternal participants) and Table 14 (infant participants). Additional details are provided in the SPM.

8.4.4.3. Missed assessment visit

If the criteria for an assessment visit have been met but the visit cannot take place while symptoms are ongoing, it is a missed assessment visit.

If it is truly not possible to perform an assessment visit (for example, if the participant develops a MA-RTI* or potential RTI/LRTI while the family is travelling, and all symptoms have resolved by the time the family returns), then the corresponding assessment visit page of the eCRF should be filled in as completely as possible using available medical history and medical records.

* *Due to the stop on study enrollment and vaccination, MA-RTI surveillance for the maternal participants will no longer be performed.*

8.4.5. RTI hospitalization during the surveillance interval

Whenever a participant is admitted to hospital for observation or treatment of an acute respiratory illness during the surveillance interval for that participant, a nasal swab should be collected using GSK-provided supplies and sent to GSK for analysis. as described in Table 12 and Table 14**.**

8.4.6. Follow-up of infant respiratory tract illnesses

Any infant RTI documented as ongoing at a previous visit/contact will be reviewed at subsequent visits/contacts during the surveillance interval until (a) all symptoms have resolved (except runny nose, often chronic in infants), or (b) the participant completes Visit 5-NB or (c) the participant is lost to follow up.

8.4.7. Covid-19 Infection

Maternal and infant COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE, medically-attended AE or SAE criteria, as outlined in Section 10.3.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [WHO, 2020] using one of the following terms:

- Suspected COVID-19 infection
- Probable COVID-19 infection
- Confirmed COVID-19 infection

8.5. Treatment of overdose

Not applicable.

8.6. Pharmacokinetics

Not applicable.

8.7. Pharmacodynamics

Not applicable.

8.8. Genetics

Not applicable.

8.9. Biomarkers

Not applicable.

8.10. Health outcomes

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

There are no hypotheses test for vaccine efficacy endpoints.

9.2. Sample size determination

Note: A total of 5328 participants have been enrolled and vaccinated in the study so far, and there will be no new maternal participants vaccinated. Please refer to Section 2.3 for details. However, monitoring will continue for rest of the study period. All planned objectives will be assessed for the participants enrolled so far.

9.3. Populations for analyses *(Amended 23 February 2023)*

Table 22 Maternal participants

	Description
Analysis Set	**Maternal participants**
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 23 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.

9.3.1. Criteria for elimination from analysis

The Statistical Analysis Plan (SAP) will provide a complete list of criteria for elimination from the analysis sets. Criteria may include, but are not limited to, those in Sections 9.3.1.1 and 9.3.1.2.

9.3.1.1. Intercurrent medical conditions and concomitant medications / products / vaccines that may lead to elimination of a participant (maternal/infant) from per-protocol analyses (efficacy/immunogenicity)

9.3.1.1.1. Maternal participants

– Any of the medications listed in Section 5.2.1.2 if administered up to Delivery (Visit 3), except corticosteroids for fetal lung maturation administered after study vaccination.

9.3.1.1.2. Infant participants

- **For the efficacy analyses**:
  - Systemic immunosuppressants or other immune-modifying drugs administered chronically (i.e. for more than 14 consecutive days).
    - For corticosteroids, this will mean prednisone or equivalent, ≥ 0.5 mg/kg/day.
    - Topical steroids are allowed.
    - Inhaled steroids are allowed if used in accordance with local labelling information (e.g. for budesonide).
  - RSV-specific immunoglobulins at any time during the study
- **For the immunogenicity analyses**: Immunoglobulins and/or any blood or plasma derivatives administered up to Day 43 post birth (Visit 2-NB), or Day 121 post birth (Visit 3-NB), or Day 181 post-birth (Visit 4-NB), depending on the infant's assigned sub-cohort for blood sampling.

9.3.1.1.3. Maternal and Infant participants

- Diagnosis during the study with an immunological disorder or occurrence during the study of a condition (other than the study pregnancy) capable of altering immune response. For evaluation of immunogenicity endpoints in maternal and infant participants, this includes RSV infection confirmed either locally or by GSK Biologicals during the specified analysis interval.
- Any investigational or non-registered product (drug or vaccine) other than the study vaccine/product administered during the specified analysis interval.

9.3.1.2. Other situations that may lead to elimination of a participant (maternal / infant) from per-protocol analyses (efficacy/immunogenicity)

- Protocol violation(s) linked to the inclusion/ exclusion criteria, including maternal age at Visit 1 (study intervention).
- Study intervention not administered as specified by the protocol.
- Failure to comply with the post-dose immunogenicity blood sampling schedule at a given time-point (Table 3).

9.4. Statistical analyses

9.4.1. General considerations *(Amended 23 February 2023)*

The statistical analysis plan (SAP) will be finalized before database lock and will include a more technical and detailed description of the statistical analyses to be performed. This section summarizes planned statistical analyses of primary and secondary endpoints.

If, during the trial, changes need to be made on primary objectives and statistical methods related to those objectives, the protocol will be amended. Changes on ***secondary/***tertiary

objectives, along with the reason(s) for the changes, will be documented in the SAP and the Clinical Study Report.

9.4.2. Participants disposition

Number of screened, randomised, vaccinated and withdrawn maternal participants in each group and overall will be described.

Number of infant participants enrolled and withdrawn (by group and sub-cohort, and overall) will be described.

9.4.3. Primary endpoints *(Amended 23 February 2023)*

The primary analysis of vaccine efficacy 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.

Analyses of primary safety endpoint will be performed on the Exposed set.

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]
Primary Safety Endpoint – Infant Participants	**Statistical Analysis Methods**
Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 12 months after birth.	CCI [redacted]

9.4.3.1. Detailed Statistical Analysis Methods

CCI

[redacted]

9.4.4. Secondary endpoints

9.4.4.1. Efficacy *(Amended 23 February 2023)*

The primary analysis of vaccine efficacy on secondary efficacy endpoints ***in infants*** will be based on the modified full analysis set for efficacy (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.	CCI [redacted]
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTIs.	
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 (Visit 5-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	

Secondary Efficacy Endpoints	Statistical Analysis Methods
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.	CCI [redacted]
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.	
From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definition.	
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.	

9.4.4.2. Detailed Statistical Analysis Methods

CCI [redacted]

9.4.4.3. Immunogenicity *(Amended 23 February 2023)*

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.

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	Statistical Analysis Methods
• 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 ***birth*** 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.	CCI [redacted]

9.4.4.4. Safety

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

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]

Secondary Safety Endpoints – Maternal Participants	Statistical Analysis Methods
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	Statistical Analysis Methods
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.	CCI [redacted]
Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 6 months after birth.	

9.4.5. Tertiary/exploratory endpoint(s)

CCI [redacted]

9.4.6. Other analyses

9.4.6.1. Demography and baseline characteristics analyses

These analyses will be performed on the Exposed set and on the modified full analysis set for efficacy (modified FAS-E).

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 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 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, standard deviation and range will be provided for continuous data such as age.

9.4.6.2. Case accruals

Rules for MA-RTI and RTI case accountability will be described in the Statistical Analysis Plan.

9.5. Interim analyses

Interim analyses may be performed, if deemed required.

9.5.1. Sequence of analyses

When all infant participants have completed Visit 5-NB (month 12, LSLV), a final analysis (for all maternal and infant participants in both Stage A and Stage B) will be performed. Analyses of any evaluated tertiary endpoints may also be performed.

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

9.5.2. Statistical considerations for interim analysis

Not applicable.

9.6. Data Monitoring Committee (DMC)

An unblinded, independent data monitoring committee external to GSK (IDMC) will review the data for this study. **Details** concerning the IDMC's structure and processes **are provided in a separate IDMC charter**.

The analysis plan for IDMC reviews will be detailed in a separate SAP. These unblinded analyses will all be done by an independent statistician from an Independent Data Analysis Center (IDAC) outside GSK to maintain the study blind, and will be documented in a statistical analysis report.

Only the outcomes of the IDMC reviews will be communicated to the study team (No individual listings or data with information that could unblind the study team to the intervention administered to a study participant will be disseminated).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

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

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the participant/participants' parent(s) or his/her LAR(s) and answer all questions regarding the study.

Participants/participants' parent(s)/LAR(s) must be informed that their participation is voluntary.

Freely given and written/ witnessed/thumb printed informed consent must be obtained from each participant and/or each participant's parent(s)/LAR(s)/witness, as appropriate, prior to participation in the study.

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

The medical record must include a statement that written or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

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

A copy of the ICF(s) must be provided to the participants/participants' parent(s)/LAR(s).

Participants who are re-screened (because, for example, they could not meet the protocol allowed window between initial screening and V1/randomization/vaccination) are not required to sign a new ICF, unless the ICF was amended in the meantime. However, the investigator or his/her representative should ensure that there is documentation that the participant is still in agreement to participate in the study and be re-screened. This can be done on the initially signed ICF or, if applicable, on other study source/documentation (as per local practice/ regulations).

10.1.4. Data protection

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

The participants/participants' parent(s)/LAR(s) must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The participants/participants' parent(s)/LAR(s) must be informed of their rights regarding the use of their personal data in accordance with the data privacy Section of the ICF.

The participants/participants' parent(s)/LAR(s) must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised

personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Committees structure

A firewall will be established to ensure that data are not inadvertently unblinded. Details are provided in a separate Firewall charter.

Safety oversight will be provided by a blinded SRT* composed of GSK RSV team members, and by an unblinded, independent data monitoring committee external to GSK (IDMC). Details regarding IDMC safety evaluations are provided in a separate IDMC charter.

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

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study register in compliance with the applicable regulations/GSK policy. GSK will aim to register the protocol summary prior to study start and target results summaries submission(s) within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

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

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

* *Due to the safety signal observed, the study was fully unblinded to ensure the safety of the participants. Please refer to Section 2.3 for details.*

GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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

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

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

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants [see Section 10.7.2 for the exact definition of source documents] that supports information entered in the eCRF.

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

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

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

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

10.1.8. Source documents

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

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

Definition of what constitutes source data and source documents can be found in Section 10.7.2.

10.1.9. Study and site start and closure

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

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

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

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

10.1.10. Publication policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from Last Subject Last Visit (LSLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

10.2. Appendix 2: Clinical laboratory tests

There is one assessment, hematocrit, which will be tested at Visits 1, 2 and 3, for all maternal participants in Stage A who are assigned to the immunogenicity sub-cohort, until the protocol amendment 2 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 2 being approved) in the respective study country(ies). Testing will be performed by a central laboratory. Results will be used to help evaluate changes over time in antibody titers / concentrations that may be related to volumetric changes during pregnancy, if deemed necessary.

Note that no clinical safety laboratory testing is mandated per protocol; thus, abnormal laboratory findings (if any) would be identified during tests performed per local standard of care.

Laboratory assessments (pathology) may be performed on the placenta tissue samples collected from maternal participants at delivery visit to support possible safety assessments, if necessary. Additional assessments on the placental sample may be performed depending on local standard of practice, site capability and the investigator's medical judgment.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting Definition of AE

10.3.1. Definition of an Adverse Event (AE)

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

10.3.1.1. Events Meeting the AE Definition

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

- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.
- "Lack of efficacy" or "vaccination failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant prior to the study vaccination. These events will be recorded in the medical history Section of the eCRF .
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline.
- Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.
- Disease-related events (DRE), typically associated with the disease under study. These events will be recorded in the participant's eCRF and will be monitored by the IDMC on a routine basis.

However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 10.3.8):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to the administration of the study vaccine/product

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:
a. Results in death
b. Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c. Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered as AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred, or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant Refer to Section 8.3.4.2 for additional information.
f. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies*, ectopic pregnancy) *Refer to Section 8.3.4.2 for additional information.
g. Other situations Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited for maternal participants in Stage A:

Table 24 Solicited administration site events

All age groups
Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited for maternal participants in Stage A:

Table 25 Solicited systemic events

Adult
Fatigue
Fever
Nausea
Vomiting
Diarrhea
Abdominal pain
Headache

Note: maternal participants in Stage A will be instructed to measure and record the (preferably) oral temperature at least once each day, at approximately the same time each day. Should additional temperature measurements be performed at other times of day, participants will be instructed to record the highest temperature in the diary.

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was *not* solicited using a Participant Diary and that was spontaneously communicated by a maternal participant/infant participant's parent(s)/LAR(s) who has /have signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/ parental /LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during interview with the

participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest (AESIs)

AESIs include:

- The following pregnancy-related adverse events of special interest (newly occurring):
  - 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, and
  - chorioamnionitis.
- The following neonatal adverse events of special interest:
  - small for gestational age,
  - low birth weight including very low and extremely low birth weight (<2500 g, <1500 g, <1000 g),
  - 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,

  and
  - preterm birth.

Refer to Section 8.3.4 for additional information about categorizing and reporting congenital anomalies.

Note: Worsening, post study vaccine administration, of pre-existing conditions already present at the time of enrolment. (eg. controlled gestational hypertension or controlled gestational diabetes) will be collected as (S)AEs and indicated as “worsening” or “aggravated” . These are not to be considered as AESIs.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as AESI. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as AESI until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments the investigator considers clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to the Sections 10.3.1 and 10.3.2).

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

Note that no clinical safety laboratory testing is mandated per protocol; thus, abnormal laboratory findings (if any) would be identified during tests performed per local standard of care. Follow-up of such findings should be consistent with local standard of care and the Investigator’s judgement

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Subsequent Pregnancy

All maternal participants will be in the second or third trimester of pregnancy at enrolment and are expected to deliver while participating in the study. Maternal participants who become pregnant again after completing the study pregnancy may continue the study at the discretion of the investigator.

While subsequent pregnancy itself is not considered an AE or SAE, any abnormal subsequent pregnancy outcome or complication or elective termination of a subsequent pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to the Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, AESIs and subsequent pregnancies

The maternal participants/infant participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the maternal or infant participants manifest any signs or symptoms they perceive as serious.

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

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

An electronic Diary, hereafter referred to as the Participant Diary will be used in this study to capture solicited administration site or systemic events for participants in Stage A. The maternal participant should be trained on how and when to complete each field of the Participant Diary.

Any individual(s) who performs the measurements of administration site or systemic events and who will enter the information into the Participant Diary should be trained on the use of the Diary. This training must be documented in the maternal participant's source record. If any individual other than the maternal participant is making entries in the Participant Diary, their identity should be documented in the Participant Diary/maternal participant's source record

Refer to the SPM for more information regarding the use of the Diary.

10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs and subsequent pregnancies

Refer to Section 8.3.1.

10.3.8.2. Where to record AEs, SAEs, AESIs, subsequent pregnancies and other events of interest

All solicited events that occur during the 7 days following administration of the dose of study vaccine/product (Day 1 to Day 7) must be recorded into the electronic Diary, irrespective of intensity or whether or not they are considered vaccination-related.

Details regarding all other AEs should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

10.3.8.3. Follow-up of AEs, SAEs, AESIs, subsequent pregnancies or any other events of interest

10.3.8.3.1. Follow-up during the study

After the initial AE/SAE/AESI/subsequent pregnancy or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts.

The investigator will follow participants with SAEs/AESIs (serious or non-serious), participants withdrawn from the study because of an AE, until the event has resolved, stabilised, disappeared (if applicable), or until the event is otherwise explained, or the participant is lost to follow-up. The investigator will follow maternal participants with subsequent pregnancies as described in Section 10.3.8.3.3.

Non-serious medically attended AEs must be followed until recovered / resolved, or until the participant's last study visit, or until the participant is lost to follow-up.

Other non-serious AEs (maternal participants) must be followed until 30 days after study vaccine/product administration or until the participant is lost to follow-up (if this occurs before Visit 3 (Day 31)).

If a maternal or infant participant dies during participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology. Please refer to the SPM for more details.

10.3.8.3.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information on previously reported SAEs, AESIs, participants withdrawn from the study because of an AE and subsequent pregnancies to GSK using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

10.3.8.3.3. Follow-up of subsequent pregnancies

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

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

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND this is considered by the investigator to be reasonably related to the study vaccine/product , he/she has to report this information to GSK as described in Section 10.3.10.

10.3.8.4. Updating of SAE, AESI and subsequent pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI or subsequent pregnancy information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Section 8.3.3.1) or to GSK Clinical Safety and Pharmacovigilance department, within the defined reporting time frames specified in the Table 19.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 26 Intensity scales for solicited events 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 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 Nausea Vomiting Diarrhea Abdominal pain	0 1 2 3	Normal Mild: Easily tolerated Moderate: Interferes with normal activity Severe: Prevents normal activity

* Refer to the SoA for the definition of fever and the preferred location for temperature 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

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

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

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice. In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the Section 10.3.2.

10.3.9.2. Assessment of causality

All solicited administration-site and systemic events will be considered causally related to vaccination. The complete list of these events is provided in the Table 24 and Table 25.

The investigator must assess the relationship between study vaccine/product and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine/product cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine/product will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

Causality should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined as 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

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

10.3.9.4. Assessment of outcomes

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

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

10.3.10. Reporting of SAEs, AESIs, subsequent pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event.

Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 19 for the details on timeframes for reporting of SAEs / AESIs / subsequent pregnancies.

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

Refer to the Section 10.3.10.2 for the back-up system in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case facsimile or electronic reporting system does not work

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax completed, dated and signed paper Expedited Adverse Events Report to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours upon electronic reporting system is resumed. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of subsequent pregnancy information

Contraceptive guidance does not apply in this study. Refer to Sections 10.3.7, 10.3.8 and 10.3.10 for further information on detection, recording, reporting and follow-up of subsequent pregnancies.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Country-specific requirements *(Amended 23 February 2023)*

10.6.1. France

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

- Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.
- According to French Public Health Code law (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):
  - Healthy volunteer;
  - Subjects if the aim of the study is not linked to their disease;
  - Subjects on request of the Ethics Committee regarding study risks and constraints.
  - The following details will be described:
    - Reference of the study
    - Surname and first name
    - Date and place of birth
    - Gender
    - Dates of beginning and termination of the study
    - Exclusion period during which the subject cannot participate to another study (French Public Health Code law L.1121-12)
    - The total amount of compensation
- The subjects' registration in National File ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.
- The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.
- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study if authorised by the Ethics Committee).

- It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:
  - is either affiliated to or beneficiary of a social security category;
  - has got an authorisation by the Ethics Committee.

Concerning the "STATISTICAL CONSIDERATIONS AND DATA ANALYSES" and specially in the "SAMPLE SIZE ASSUMPTIONS"

The expected number of subjects to be recruited in France is declared to the French regulatory authority.

Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

In section "Regulatory and Ethical Considerations, including the Informed Consent Process"

- Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

- Concerning **the process for obtaining** subject informed consent:
  - **if the subject is minor,** the following text is added:

    The informed consent of the holders of parental authority must be obtained before the beginning of the study. The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If there is only one holder of parental authority, the investigator will ask the present person to file, date and sign the parental certificate indicating their situation regarding the parental authority. A copy of this parental certificate is joined to each consent form.

    If these directives are not followed, the subject inclusion could be considered as a protocol violation and the data of this case won't be taken into account.
- Concerning the management of the Patient Informed Consent Forms, the following text is added:

  French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

  The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

NOTIFICATION TO THE HOSPITAL DIRECTOR

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

INFORMATION TO THE HOSPITAL PHARMACIST

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

Concerning the " DATA MANAGEMENT " the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GlaxoSmithKline data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Data Protection French Law n° 78-17 of 6th January 1978 updated, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

Ethnic Origin

In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 updated – article 4-3°, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

TESTING OF BIOLOGICAL SAMPLES

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

Monitoring visits

- The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health

Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
6. To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

CTR publication

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registered (CTR) including the registration of all the clinical trials conducted by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

Data Protection French Law of 6th January 1978 updated (CNIL)

- In accordance with the Data Protection French Law of 6 January 1978 updated, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions.

10.6.2. South Korea

Concerning the "STUDY POPULATION – Exclusion criteria for enrolment – maternal participants", the following will constitute an exclusion criterion in South Korea:

- Participation in a clinical trial targeting healthy people within the 6 months prior to enrolment/study vaccination.

Concerning the "CRITERIA LEADING TO PAUSE OR EARLY TERMINATION OF THE STUDY", the following clarification is made:

- No safety "holding rules" or criteria for pausing or early termination have been defined for this study.
- An Independent Data Monitoring Committee (IDMC) has been put in place and will be in charge of reviewing unblinded safety data on a regular basis (bi-monthly reviews are foreseen, but frequency may be adapted as the study progresses). It will be the IDMC discretion to recommend, if they deemed necessary, that the study recruitment is paused or terminated based on their unblinded data reviews.
- In addition to the IDMC reviews, GSK's Safety Review Team (SRT) will perform regular reviews of blinded data and may request IDMC to perform ad-hoc unblinded reviews if any potential safety concern is suspected based on blinded data.

10.6.3. *Spain*

With regards to the "COMPENSATION" offered to the infant participants enrolled in the study, infant parents/LAR's were offered the possibility to have the infant vaccinated with a commercially approved vaccine being part of the National Pediatric Immunization Calendar but, which costs are not financially covered by the health system in the corresponding Region/Autonomous Community:

- ***Meningococcus B vaccine (Bexsero®)***

Or

- ***Rotavirus vaccine (Rotarix®)***

This compensation was put in place considering the recommendations laid out in ICH-E11 (Clinical Investigation of Medicinal Products in the pediatric population) as well as in the "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population", developed by the ad-hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.

Compensation was approved by the Spanish regulatory authority and Ethics Committee, and included in the country-specific Informed Consent.

10.6.4. *Argentina*

Concerning the "STUDY POPULATION – Exclusion criteria for enrolment – maternal participants" and, as per request from the Argentinean regulatory authorities (A.N.M.A.T - Administración Nacional de Alimentos, Medicamentos y Tecnología Médica), study recruitment in Argentina was limited to pregnant women aged 18 to 40 years (inclusive), instead of 18 to 49 years (inclusive).

This age limitation was initially expected to be temporal, and dependent on the availability of safety data coming from other countries on pregnant women > 40 years old, which was to be submitted to A.N.M.A.T for evaluation. However, further enrollment and vaccination in the study was stopped on 25th February 2022, before such safety data was submitted.

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CoP:	Correlate of Protection
COVID-19	Corona Virus Disease 2019
eCRF	electronic Case Report Form
EoS	End of Study
FDA:	Food and Drug Administration, United States of America
FU	Follow-Up
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LAR	Legally Acceptable Representative

LLOQ	Lower Limit of Quantification
LML	Local Medical lead
LMP	Last Menstrual Period
LRTI	Lower Respiratory Tract illness
LSLV	Last Participant Last Visit
MAE	Medically attended adverse event
MedDRA:	Medical Dictionary for Regulatory Activities
NAb	Neutralising antibody
NB	Newborn
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PP:	Per protocol
PRO:	Patient Related Outcomes
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Illness
SAE	Serious Adverse Event
SARS-COV-2	The corona virus that is the causative agent of COVID-19.
SBIR:	Source data Base for Internet Randomisation
SDV:	Source Document Verification
SPM	Study Procedures Manual
SpO2	Blood oxygen saturation as measured by pulse oximetry
SRT	***Safety Review Team***
VE	Vaccine efficacy
WHO	World Health Organization

10.7.2. Glossary of terms

Adverse event: Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Blinding: A procedure in which 1 or more parties to the trial are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.

In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.

In a double-blind study, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.

In a single-blind study, the investigator and/or his staff are aware of the intervention assignment but the participant is not.

Body Mass Index A key index for relating weight to height. Calculated as follows: Weight (kg) / (Height (m))^2

Caregiver A ‘caregiver’ is someone who

- lives in the close surroundings of a participant and has a continuous caring role or
- has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g. a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).

In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.

Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child	A young human being below the legal age of majority (generally < 18 years of age).
Child in care:	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biologicals samples, EoS is defined as the date of LSLV or the last testing/reading released of the human biological samples related to primary and secondary endpoints, whichever comes last. EoS must be achieved no later than 8 months after LSLV.
Enrolled	'Enrolled' means a participant's/parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to Section 9.3 for the definition of 'enrolled' applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 9.3 for details on criteria for evaluability).
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy. A project that aims to improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in low to middle income countries.

Gestational age:	A measure of the age of a pregnancy where the origin is the first day of the woman's last normal menstrual period, or the corresponding age as estimated by other methods. Gestational age will be described in weeks of pregnancy completed + number of days completed of the following week. For example: 28 $^{0/7}$ means completed 28 weeks of pregnancy + 0 days of the 29th week and 28 $^{6/7}$ means completed 28 weeks of pregnancy + 6 days of the 29th week.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Infant	A child younger than 1 year of age
Intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Investigational vaccine/product:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Legally acceptable representative	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical trial. The terms legal representative or legally authorized representative are used in some settings.
Level 2 ultrasound (also known as a fetal anomaly ultrasound scan or fetal morphology assessment)	Comprehensive, detailed evaluation of fetal anatomy and development that is usually performed at approximately 20 weeks of gestational age. In addition to standard ultrasound parameters such as fetal heart activity and gestational age estimation, a Level 2 ultrasound usually includes assessment of amniotic fluid levels; assessment of the condition of the placenta, cervix, and uterus; and detection of fetal anomalies.

Local healthcare provider	A healthcare provider who provides participants with medical care per local standards. This individual may or may not be a member of the study staff.
Neonate (or Newborn)	An infant 28 days old or younger.
Neonatal adverse events of special interest	Adverse events that occur from birth through 28 days of age and are to be reported as neonatal AESIs are listed in Table 4 and Section 10.3.5. It is anticipated that most neonatal AESIs will be identified (and thus may be reported in the eCRF) by or before the Day 43 visit (V2-NB). However, as indicated in Table 18, any neonatal AESIs identified *after* V2-NB should *also* be reported in the eCRF.
Parental concern	The parent(s) / Legally Acceptable Representative(s) are concerned about the infant's respiratory tract illness (or general health in the context of the respiratory tract illness) and intend to seek medical care
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine/product or as a control. Synonym: subject
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Pregnancy related adverse events of special interest	Pregnancy related events that occur up to 42 days after delivery and are to be reported as AESIs are listed in Table 4 and Section 10.3.5.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial/ pharmaco-epidemiological study was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of study intervention to participants to reduce selection bias.

Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Study population:	Sample of population of interest.
Sub-cohort:	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.8. Appendix 8: Gestational Age Assessment

10.8.1. GAIA gestational age assessment form

Based on Quinn, JA, Munoz FM, Gonik B et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016; 34: 6047 – 6056.

LEVELS OF CERTAINTY OF GESTATIONAL AGE ASSESSMENT

Level	Description
Level 1 Highest level of certainty	**Certain LMP or IUI date or ET WITH confirmatory 1st trimester U/S** [1] or **1st trimester U/S**
Level 2A	**Certain LMP WITH 2nd trimester U/S** [1] or Certain LMP WITH 1st trimester physical examination[2]
Level 2B	**Uncertain LMP WITH 2nd trimester U/S** [1]
Level 3A	**Certain LMP WITH 3rd trimester U/S**[3], or Certain LMP WITH confirmatory 2nd trimester FH, or Certain LMP WITH birth weight, or Uncertain LMP WITH 1st trimester physical examination
Level 3B Lowest level of certainty	Uncertain LMP WITH FH, or Uncertain LMP WITH neonatal physical assessment (New Ballard score), or Uncertain LMP WITH birth weight

1st trimester U/S: ≤13$^{6/7}$ weeks, 2nd trimester U/S: 14$^{0/7}$ to 27$^{6/7}$ weeks, 3rd trimester U/S: ≥28$^{0/7}$ weeks.
GA: gestational age; U/S: ultrasound examination; LMP: last menstrual period; IUI: intrauterine insemination; ET: embryo transfer, FH: fundal height;
Boldface = Applicable for enrollment in this study.
[1] If LMP and U/S do not correlate, default to U/S GA assessment
[2] For singleton pregnancies only. Unreliable if obesity, or uterine anomalies.
[3] May be enrolled provided gestational age is within the limits specified for eligibility Refer to Section 5.1.1 for further details

10.8.2. Methods of gestational age assessment and estimation of due date

Adapted from: The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice, American Institute of Ultrasound in Medicine and Society for Maternal-Fetal. Committee Opinions: Method for estimating Due Date. Number 700, May 2017 (accessed on-line on 05/Mar/2020 at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/05/methods-for-estimating-the-due-date).

Gestational age range*	Method of measurement	Discrepancy between U/S dating and LMP (or IUI or ET dating) prompting re-dating of EDD considering U/S
1st trimester ≤13$^{6/7}$ weeks		
≤8$^{6/7}$ weeks 9$^{0/7}$ to 13$^{6/7}$ weeks	CRL	> 5 days > 7 days
2nd trimester 14$^{0/7}$ to 27$^{6/7}$ weeks		
14$^{0/7}$ to 15$^{6/7}$ weeks	BPD, HC, AC, FL	> 7 days
16$^{0/7}$ to 21$^{6/7}$ weeks		> 10 days
22$^{0/7}$ to 27$^{6/7}$ weeks		> 14 days
3rd trimester		
28$^{0//7}$ weeks and beyond	BPD, HC, AC, FL	> 21 days

U/S: ultrasound examination; LMP: last menstrual period; IUI: intrauterine insemination; ET: embryo transfer; CRL: crown-rump length; BPD: biparietal diameter; HC: head circumference; AC: abdominal circumference; FL: femur length; , EDD: estimated date of delivery
* Based on LMP (or, if applicable, IUI/ET date)

Refer to the SPM for further details.

10.9. Appendix 9: Definitions of maternal, fetal and neonatal events of interest as per GAIA

- **IMPORTANT:** NOT all the events that are listed below are AESIs for this study. Sections 3, 9.4.4 and 10.3.5 list events of interest per GAIA that must be reported as AESIs in this study.
- Other GAIA events of interest that meet the SAE definition (Section 10.3.2) should be reported with enough detail in the SAE narrative to permit level of diagnostic certainty assessment by GAIA criteria.
- Articles that discuss GAIA events of interest in detail can be found in the following issues of *Vaccine*:
  - Bauwens J, Bonhoeffer J, Chen RT, editors. Harmonising Immunisation Safety Assessment in Pregnancy. Vaccine. 2016. 34 (49): 5991 – 6110.
  - Kochhar S, Bauwens J, Bonhoeffer J, editors. Harmonising Immunization Safety Assessment in Pregnancy – Part II. Vaccine. 2017. 35 (48): 6469-6582.
- Definitions and Levels of Diagnostic Certainty are presented in the following Tables. References specific to each event of interest are given at the end of the relevant Table.

Pregnancy Outcomes	
Fetal Death / Stillbirth	Table 27
Maternal Events of Interest	
Maternal Death – **study defined pregnancy related AESI**	Table 28
Hypertensive Disorders of Pregnancy – **study defined pregnancy related AESIs**	Table 29
Antenatal bleeding	Table 30
Postpartum hemorrhage	Table 31
Fetal Growth restriction – **study defined pregnancy related AESI**	Table 32
Gestational Diabetes Mellitus – **study defined pregnancy related AESI**	Table 33
Non-reassuring fetal status	Table 34
Pathways to Preterm Birth – **study defined pregnancy related AESIs**	Table 35
Chorioamnionitis - **study defined pregnancy related AESI**	Table 36
Standard definitions for events of interest not defined as such in GAIA (Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis)	Table 37
Neonatal Events of Interest	
Small for Gestational Age – **study defined neonatal AESI**	Table 38
Low Birth Weight – **study defined neonatal AESI**	Table 39
Neonatal encephalopathy	Table 40
Congenital Microcephaly	Table 41
Congenital Anomalies – **study defined neonatal AESIs**	Table 42
Neonatal Death – **study defined neonatal AESI**	Table 43
Neonatal Infections	Table 44
Respiratory Distress in the Neonate	Table 45
Preterm Birth – **study defined neonatal AESI**	Table 46
Failure to thrive	Table 47
Standard definitions for events of interest not defined as such in GAIA (large for gestational age, macrosomia)	Table 48

Table 27 Fetal death / Stillbirth

Fetal death occurring before birth after 20 to 28 weeks of gestation (variation due to country definitions).

Antepartum Stillbirth (Fetal death occurs prior to the evidence of labor.)	
Level	**Description**
1	Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined by physical examination after delivery (with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry). AND 1. Prenatal ultrasound examination documenting lack of fetal cardiac activity or movement before the onset of labor. OR 2. Auscultation for fetal heart tones (using electronic devices or non-electronic devices) documenting lack of fetal heartbeat. AND 3. Maternal report of lack of fetal movement for 24 h or more. OR 4. Maternal physical examination confirming lack of fetal movement. OR 5. Radiology findings consistent with intrauterine fetal death. AND 6. Attended delivery followed by fetal physical examination afterbirth consistent with antepartum death, by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, or pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, mid-wife, nurse practitioner, a physician's assistant or other qualified trained practitioner). OR 7. Fetal/placental pathology report consistent with antepartum death. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1 or 2 in GA assessment algorithm).
2	Delivery of an infant with no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, Apgar score of 0 at 1 and 5 min) determined physical examination after delivery. AND 1. Maternal report of lack of fetal movement for 24 h or more. OR 2. Maternal physical examination confirming lack of fetal movement. OR 3. Auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND 4. Attended delivery followed by physical examination after birth consistent with antepartum death, by specialist or qualified trained practitioner appropriate to the health care setting. OR 5. Fetal/placental pathology report consistent with antepartum death. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm).

Antepartum Stillbirth (Fetal death occurs prior to the evidence of labor.) (continued)	
Level	**Description**
3	Delivery of an infant reported to have no of signs of life at birth (No spontaneous movements, no umbilical cord pulse, no heart-beat, no cry or spontaneous respirations, no chest movement, and whole body cyanosis). AND 1. Maternal report of lack of fetal movement for 24 h or more prior to delivery. OR 2. Report of auscultation for fetal heart tones (using electronic or non-electronic devices) documenting lack of fetal heartbeat. AND 3. Non-attended delivery followed by physical examination of the fetus after birth consistent with antepartum death by a healthcare professional appropriate to the level of standard of care in the health care setting. OR 4. Verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth and with physical features consistent with antepartum death. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm).
4	Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made) Maternal information insufficient to assess gestational age
Intrapartum stillbirth (Fetal death occurs during labor and before delivery)	
Level	Description
1	Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry. AND Evidence of live fetus prior to onset of labor (documentation of fetal movement and of fetal heart tones by ultrasound prior to onset of labor) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND Attended delivery followed by physical examination afterbirth consistent with intrapartum death by obstetrician, neonatologist, pediatrician, maternal-fetal medicine specialist, pathologist. In the setting where access to a specialist is not feasible, diagnosis by a health care provider trained or experienced to make the diagnosis is acceptable (e.g. general practice physician, midwife, or other qualified trained practitioner). AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal-neonatal parameters (Level 1 in GA assessment algorithm)

Intrapartum stillbirth (Fetal death occurs during labor and before delivery) (continued)	
Level	Description
2	Delivery of an infant with no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no respirations, and Apgar score of 0 at 1 and 5 min. Determination of the absence of signs of life is made by physical examination after delivery, with or without electronic monitoring of heart rate, respiratory rate, and pulse oximetry OR documentation of lack of response to resuscitation efforts. AND Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor and documentation of fetal heart tones by auscultation or hand held Doppler) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND Attended delivery followed by physical examination after birth consistent with intrapartum death by a health care professional appropriate to the level of standard of care in the health care setting. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level1–2 in GA assessment algorithm).
3	Delivery of an infant reported to have no of signs of life at birth, including: No spontaneous movements, no umbilical cord pulse, no heartbeat, no cry, no spontaneous respirations or chest movement, and whole body cyanosis. AND Evidence of live fetus prior to onset of labor (maternal report of fetal movement prior to onset of labor OR auscultation of fetal heart tones) (Note: in the absence of evidence of a live fetus prior to the onset of labor, the fetal death should be reported as a stillbirth or an antepartum stillbirth). AND Non-attended delivery followed by physical examination of the fetus after birth consistent with intrapartum death by a healthcare professional appropriate to the level of standard of care in the health care setting OR verbal history by a trained health care provider, non-medical witness or the mother of a fetus born with no signs of life or unresponsive to resuscitation efforts immediately after birth. AND Gestational age within pre-defined range for selected stillbirth definition as assessed by maternal and/or fetal parameters (Level2–3 in GA assessment algorithm).
4	Report of stillbirth but fetus is not available for physical examination after birth (no objective assessment can be made). Maternal information insufficient to assess gestational age.

Reference: DaSilva FT, Gonik B, McMillan M, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2016; 34(49):6057-6068.

Table 28 Maternal Death

The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. (As ICD-10 terminology).

In the context of immunization: "Death of a woman during pregnancy, childbirth and the puerperium that is closely related temporally to an immunization event of the mother which is likely the single or contributory cause

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Diagnosis of pregnancy established by any of the following documented criteria: 1. Ultrasound examination 2. Fetal heart tones 3. Positive serum or urine human chorionic gonadotropin pregnancy test 4. Delivery of a neonate or other products of conception (abortus, stillborn) AND 5. Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy AND Documentation of Cause of death as: 6. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications 7. Indirect: non obstetric complications 8. Death during pregnancy, childbirth and the puerperium: other or coincidental
2	Diagnosis of pregnancy established by any of the following criteria in the absence of Level 1 criteria: 1. LMP date 2. Serial Symphysio Fundal Height examinations AND Death of the mother while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy And Documentation of Cause of death as: 3. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric complications, unanticipated complications 4. Indirect: non-obstetric complications 5. Death during pregnancy, childbirth and the puerperium: other or coincidental 6. Unspecified: unknown or undetermined
3	Absence of Level 1 or 2 criteria for establishing diagnosis of pregnancy and: 1. Unsure LMP 2. No clinical examination documented AND Death of the mother temporal to pregnancy, childbirth or the postpartum period when exact timing of death is unknown AND Documentation of cause of death as: 3. Direct: abortive outcome, hypertensive disorder, obstetric hemorrhage, pregnancy related infection, other obstetric com-plications, unanticipated complications 4. Indirect: non-obstetric complications 5. Death during pregnancy, childbirth and the puerperium: other or coincidental 6. Unspecified: unknown or undetermined.

Reference: Patwardhan M, Eckert LO, Spiegel H, et al. Maternal death: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6077-6083.

Table 29 Hypertensive disorders of pregnancy (Gestational hypertension, Pre-eclampsia, Pre-eclampsia with severe features including eclampsia)

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Gestational Hypertension	
Level	**Description**
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h WITHOUT severe features (see preeclampsia with severe features category) and WITHOUT proteinuria
1	No proteinuria (as defined by 24 h urine collection < 300 mg, spot protein:creatinine ratio <0.3)
2	No proteinuria (as defined by urine dipstick negative or trace)
In Ev	Blood pressure cannot be measured OR No proteinuria evaluation is available
Preeclampsia has conventionally been defined as the development of gestational hypertension and proteinuria after 20 weeks gestation. Proteinuria can be quantified by: - 24 h urine collection, - a spot protein:creatinine ratio, or - with urinary dipstick. Proteinuria of ≥300 mg in a 24 h urine specimen (the gold standard for measurement of proteinuria), or ≥0.30 on a spot protein:creatinine ratio, or ≥1+ on a dipstick meets the criteria for preeclampsia.	
Level	**Description**
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND New onset proteinuria
1	Proteinuria diagnosed with ≥300 mg of protein on 24 h urine collection OR ≥0.3 on spot protein:creatinine ratio
2	Proteinuria diagnosed with ≥1+ protein on urine dipstick
In Ev.	Blood pressure cannot be measured OR no proteinuria evaluation is available (note diagnosis of preeclampsia with severe features does not require proteinuria, see definition below)

In Ev = Insufficient Evidence

Hypertensive Disorders of Pregnancy Continued

Preeclampsia with severe features *NOTE :can be diagnosed in the presence or absence of proteinuria*.
Vascular:
Severely elevated blood pressures, with systolic blood pressure≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes (to facilitate timely anti-hypertensive treatment)
Neurologic:
Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol)
Eclampsia
Development of visual changes (including photopsia, scotomata, cortical blindness)
Hematologic:
New onset thrombocytopenia, with platelet count <100,000/L
Gastrointestinal:
New onset of nausea, vomiting, epigastric pain
Transaminitis (AST and ALT elevated to twice the upper limit of normal)
Liver capsular hemorrhage or liver rupture
Renal:
Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease)
Oliguria (urine output <500 mL/24 h)
Respiratory:
Pulmonary edema (confirmed on clinical exam or imaging)

Level	Description
All	Clinical syndrome characterized by pregnancy ≥20 weeks AND New onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND At least one of the criteria for severe disease:
1	At least one of the following: 1. Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110mmHg, which is confirmed after only minutes OR 2. Development of severe, persistent headache OR 3. Development of visual changes OR 4. Eclampsia* OR 5. New onset thrombocytopenia (platelets <100,000/L) OR 6. New onset unremitting epigastric pain OR 7. AST and ALT elevated to twice upper limit of normal OR 8. Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR 9. Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) or oliguria (<500 cc/24 h) OR Pulmonary edema (confirmed on imaging with chest X-ray, or on clinical exam)
2	New onset nausea and vomiting
In Ev	Blood pressure cannot be measured

◦* ECLAMPSIA, or new-onset grand mal seizures in a patient with pre-eclampsia, without other provoking factors (such as evidence of cerebral malaria or pre-existing seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status:
In Ev = Insufficient Evidence
Reference: Rouse CE, Eckert LO, Wylie BJ, et al. Hypertensive disorders of pregnancy: Case definitions & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6069-6076

Table 30 Antenatal Bleeding

Antenatal bleeding is a clinical syndrome characterized by bleeding in the second or third trimester of pregnancy. Pathologic etiologies attributable to the pregnant state include placenta previa, vasa previa and intra-abdominal pregnancy (categories that are not applicable in this study, as women with these conditions are ineligible), and morbidly adherent placentation, placental abruption, cesarean scar pregnancy and uterine rupture.

For both levels of diagnostic certainty for each etiology of antenatal bleeding:

Bleeding is either documented vaginally or suspected to be occurring intrauterine, intraperitoneally, or (rarely) retroperitoneally, based on clinical signs and symptoms.

In the case of ultrasound-based diagnosis, transvaginal ultrasound is more specific than transabdominal ultrasound, and transvaginal ultrasound is recommended where available.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Morbidly adherent placenta	
Level	Description
1	There are two definitions of equal specificity. 1. Second- or third-trimester ultrasound or MRI evidence of placenta previa, AND One of the following ultrasound features: • Greyscale: loss of the retroplacental sonolucent zone, irregular retroplacental sonolucent zone, thinning or disruption of the hyperechoic serosa–bladder interface, presence of focal exophytic masses invading the urinary bladder, abnormal placental lacunae • Color Doppler: diffuse or focal lacunar flow, vascular lakes with turbulent flow (peak systolic velocity over 15 cm/s), hypervascularity of serosa–bladder interface, markedly dilated vessels over peripheral sub placental zone • 3D Power Doppler: numerous coherent vessels involving the whole uterine serosa–bladder junction (basal view), hypervascularity (lateral view), inseparable cotyledonal and intervillous circulations, chaotic branching, detour vessels (lateral view) AND One of the risk factors: prior cesarean delivery, prior uterine surgery (including endometrial ablation or dilation and curettage) or cesarean scar pregnancy OR 2. Morbidly adherent placentation found on histology in a hysterectomy or partial wedge resection specimen.
2	There are two definitions of equal specificity. Ultrasound evidence of placenta previa, AND hypervascularity at the site of the uteroplacental interface, diagnosed at laparotomy. OR 1. Difficulty with placental separation after delivery of the infant, at either a vaginal or cesarean delivery with resultant hemorrhage due to partial separation.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Antenatal Bleeding continued	
Placental abruption	
Level	Description
1	There are two definitions of equal specificity. 1. In the absence of placenta previa on ultrasound, vaginal bleeding in the second or third trimester, AND one of the following: Either uterine irritability or labor, Or clinical signs of hypovolemic shock or coagulopathy. OR 2. Placental pathology with histologic findings of a chronic abruption.
2	There are two definitions of equal specificity. 1. Vaginal bleeding in the second or third trimester, AND uterine irritability or labor, without clinical signs of hypovolemic shock or coagulopathy OR 2. Vaginal bleeding in the second or third trimester, AND Clinical evidence of retroplacental clot or visually evident placental infarcts at the time of delivery.
Cesarean Scar Pregnancy	
Level	Description
1	**There are two definitions of equal specificity.** 1. Transvaginal ultrasound with the following characteristics: empty uterine cavity, AND Empty cervical canal, without contact with the gestational sac, AND Presence of gestational sac, +/- fetal pole, +/- cardiac activity, in the anterior uterine segment adjacent to the cesarean scar, AND Absence or defect in myometrium between bladder and gestational sac, AND Gestational sac well perfused on Doppler ultrasound (to differentiate from an expulsing, avascular gestational sac). OR 2. Hysterectomy specimen with evidence of pregnancy implanted into the cesarean scar.
2	**There is no Level 2 definition for this event.**
Uterine Rupture	
Level	Description
1	Complete uterine disruption at the time of laparotomy in the context of vaginal or intra-abdominal bleeding.
2	There is no Level 2 definition for this event.

Reference: Prabhu M, Eckert LO, Belfort M et al. Antenatal bleeding: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35: 6529-6537.

Table 31 Postpartum hemorrhage

Genital tract bleeding after delivery (up to 42 days) of a fetus or infant that leads to an adverse clinical outcome, such as hypovolemia or anemia e.g. exertional dyspnea, postural presyncope, tiredness or reduced consciousness. At the furthest extreme uncorrected hypovolemic shock can lead to organ-dysfunction and maternal death.

ICD-10 definition: “hemorrhage after delivery of a fetus or infant”

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Genital bleeding after delivery leading to severe maternal out-come (maternal death or maternal near miss) as defined by WHO[1].
2	Genital bleeding after delivery with at least one of the following: measured abnormal bleeding (1000 ml or more), or any bleeding leading to hypotension or blood transfusion.
3	Genital bleeding after delivery estimated at 1000 ml or more

Reference: Kerr R, Eckert LO, Winikoff B, et al. Postpartum hemorrhage: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6102-6109.

[1] Can be found in Kerr (*op cit*), Table 1.

Table 32 Fetal growth restriction

A fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age with increasing specificity for adverse perinatal outcomes below the third percentile.

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
	Fetal growth restriction is a sonographic finding characterized by:
1a	Level 1* evidence of pregnancy dating AND • Estimated fetal weight below 3% using locally-accepted growth curve OR • Estimated fetal weight below 10% using locally-accepted growth curve AND • Absent or reversed end-diastolic flow of the umbilical artery Doppler OR • Oligohydramnios as defined as amniotic fluid index (AFI) < 8 cm or deepest vertical pocket (DVP) < 2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology
1b	Level 1* evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND Lack of absent or reversed end-diastolic flow of the umbilical artery or oligohydramnios (as defined above, cfr. Level 1a)
2a	Level 2 evidence of pregnancy dating AND • Estimated fetal weight below 3% using locally-accepted growth curve OR • Estimated fetal below 10% using locally-accepted growth curve AND • Absent or reversed end-diastolic flow of the umbilical artery Doppler. OR • Oligohydramnios (as defined above, cfr. Level 1a).
2b	• Level 2 evidence of pregnancy dating AND Estimated fetal weight below 10%ile using locally-accepted growth curve AND No findings of absent or reversed end-diastolic flow of the umbilical artery or oligohydramnios (as defined above, cfr Level 1a). OR • Level 1* evidence of pregnancy dating AND Estimated fetal weight below 10% using locally-accepted growth curve with no findings of oligohydramnios (as defined above, cfr. Level 1a) with inability to assess umbilical artery Doppler.
In Ev	Absence of ultrasound for use in assessment of estimated fetal weight.

*Level 1 evidence of pregnancy dating as defined by the Preterm Birth Working Group of the Brighton Collaboration. Level 1 pregnancy dating depends on a confirmatory ultrasound performed ≤13 $^{6/7}$ weeks gestation
In Ev = Insufficient Evidence
Reference: Easter SR, Eckert LO, Boghossian N, et al. Fetal growth restriction: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35: 6546-6554.

Table 33 Gestational diabetes mellitus (pregnancy induced hyperglycemia)

Gestational diabetes mellitus (GDM) is a clinical syndrome characterized by the absence of pre-gestational diabetes diagnosis, defined by

- Previous diagnosis of diabetes while not pregnant

OR

- First trimester hemoglobin A1c level of ≥ 6.5% (47.5 mmol/mol)

OR

- First trimester fasting blood glucose 126 mg/dL / ≥ 7mmol/L

AND

Identification of sustained hyperglycemia during pregnancy not due to other known causes (i.e. corticosteroids, beta-mimetics, etc.)

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with level 1-2 certainty for gestational age using GAIA definition for gestational age (Section 10.8) AND Diagnosis of gestational diabetes based on a positive internationally recognized oral glucose tolerance test ("major criteria" [1,2]) using venous blood sample/samples
2	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 1-2 certainty for gestational age using GAIA definition for gestational age (Section 10.8) AND Diagnosis of gestational diabetes based on positive internationally recognized oral glucose tolerance test ("major criteria" [1,2]) using capillary blood sample/samples
3	Absence of pre-gestational diabetes mellitus diagnosis in the first trimester as defined above with at least level 3 certainty for gestational age using GAIA definition for gestational age AND Diagnosis of gestational diabetes based on positive internationally recognized oral glucose tolerance test (see below "major criteria"[1,2]) using venous blood or capillary blood sample/samples OR Diagnosis of gestational diabetes based on fasting plasma glucose of 5.1-6.9 mmol/l (92-125 mg/dL) using venous or capillary blood samples.
In Ev	Blood glucose cannot be measured OR Elevated postprandial blood glucose level without confirmatory fasting venous blood or capillary glucose level OR Use of Hemoglobin A1c alone for the diagnosis of GDM without a diagnostic oral glucose tolerance test (OGTT) or elevated fasting plasma glucose level. OR Clinical and laboratory findings such as glucosuria, fundal height greater than dates, obesity, prior history of GDM or family history for the diagnosis of gestational diabetes mellitus without a diagnostic test.

In Ev = Insufficient Evidence

Reference(s): Kachikis A, Eckert LO, Walker C, et al. Gestational diabetes mellitus: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017; 35:6555-6562.

[1] Major criteria (presented in Kachikis op cit)

Major criteria	
Endocrine	
Oral glucose Tolerance tests	75 g OGTT IADPSG WHO NICE 100 g OGTT Carpenter-coustan NDDG
Fasting plasma glucose level	Based on WHO criteria (1)
[Absence of] pregestational diabetes mellitus criteria	See above

[2] Further details regarding oral glucose tolerance tests presented in footnote 1 (Major Criteria); also presented in Kachikis (op cit)

Table 1
Diagnostic oral glucose tolerance tests based on organization or country guidelines.

Test	Guidelines	Number of abnormal values necessary for diagnosis	Fasting plasma glucose mmol/l (mg/dl)	1-h plasma glucose mmol/l (mg/dl)	2-h plasma glucose mmol/l (mg/dl)	3-h plasma glucose mmol/l (mg/dl)	Timing
75 g OGTT							
	WHO 2013 [1]	1	⩾5.1–6.9 (92–125)	⩾10.0 (180)	⩾8.5–11.0 (153–199)	N/A	24–28 wks
	IADPSG [25]	1	⩾5.1 (92)	⩾10.0 (180)	⩾8.5 (153)	N/A	
	NICE (UK) [26]	1	⩾5.6 (101)	Not required	⩾7.8 (140)	N/A	24–28 wks
100 g OGTT							
	Carpenter Coustan [27]	2	⩾5.3 (95)	⩾10.0 (180)	⩾8.6 (155)	⩾7.8 (140)	24–28 wks
	NDDG [27]	2	⩾5.8 (105)	⩾10.6 (190)	⩾9.2 (165)	⩾ 8.0 (145)	

OGTT (Oral glucose tolerance test); IADPSG (International Association of Diabetes and Pregnancy Study Groups); WHO (World Health Organization); NICE (The National Institute for Health and Care Excellence, UK); NDDG (National Diabetes Data Group).

Table 34 Non-reassuring fetal status

Indicator of underlying event resulting in temporary or permanent oxygen deprivation to the fetus which may lead to fetal hypoxia and metabolic acidosis

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Level	**Description**
1	• Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD – Absent baseline fetal heart rate variability AND any of the following: recurrent late decelerations recurrent variable deceleration bradycardia (<110 bpm) OR – Sinusoidal pattern AND • Umbilical cord blood analysis consistent with metabolic acidosis (pH < 7.0 and Base deficit >12 mmol/L)
2	• Category III fetal heart rate tracings detected via continuous cardiotocography as defined by NICHD – Absent baseline fetal heart rate variability AND any of the following: recurrent late decelerations recurrent variable deceleration bradycardia (<110 bpm) OR – Sinusoidal pattern
3	• Fetal heart pattern detected via intermittent auscultation suggestive of fetal hypoxia – Baseline Fetal Heart rate (FHR) <110 bpm or >160 bpm – Presence of repetitive or prolonged (>3 min) decelerations More than 5 contractions in a 10 min period

Reference: Gravett C, Eckert LO, Gravett MG, et al. Non-reassuring fetal status: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6084-6092.

Table 35 Pathways to preterm birth

Premature preterm rupture of membranes; Preterm labor; Insufficient cervix (not applicable to this study, as women with insufficient cervix are ineligible); Provider-initiated preterm birth

Preterm = Birth at less than 37 gestation-completed weeks (less than 259 days).

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
Preterm rupture of membranes	
Level	**Description**
All	Patient is determined to be preterm as defined above. • On presentation, patient is determined to not be in preterm labor, having ≤4 contractions per hour documented clinically or on tocodynometer, with <2 cm cervical dilation (greater than 4 contractions per hour would qualify the patient as having preterm labor) • Fluid can be noted to be clear, blood-tinged, meconium-tinged (fetal stool), purulent-tinged (yellowish, suggesting infection)
1	• Clinical history of rupture of membranes AND • Visible leakage of fluid on vaginal speculum exam AND • Visible arborization (ferning) on microscopy of amniotic fluid OR • Ultrasound with oligohydramnios (AFI <5 or MVP <2) AND • Documented membrane rupture by a diagnostic test (one of the below options): 1. Positive intra-amniotic dye-injection method 2. Positive result on amniotic fluid alpha-fetoprotein test kit 3. Amniotic fluid pH measurement (nitrazine paper test) 4. Amniotic fluid placental alpha macroglobulin-1 protein assay (PAMG-1) test (AmniSure test) 5. Amniotic fluid insulin-like growth factor binding protein (IGFBP-1) test (Actim PROM test)
2	• Clinical history of rupture of membranes AND • Visible leakage of fluid on vaginal speculum examination AND • Visible arborization (ferning) on microscopy of amniotic fluid OR • Documented membrane rupture by a diagnostic test (one of those listed above) OR • Ultrasound with oligohydramnios (AFI <5 or MVP <2)
3	• Clinical history of rupture of membranes AND • Visible leakage of presumed amniotic fluid; this may be on vaginal speculum examination (pooling in vagina), on inspection of the perineum (wet perineum due to leakage of fluid from the vagina), or fluid soaked cloth/clothes/sanitary pad.
Preterm labor	
Level	**Description**
All	Patient is determined to be have delivered preterm (at less than 37 gestation-completed weeks (less than 259 days)).
1	• On presentation, >4 documented uterine contractions per hour as determined by a tocodynometer AND • Documented change in length or dilation of cervix by physical examination or transvaginal ultrasound over a two hour period, with clinical criteria for documenting cervical change by exam including:

Levels of Diagnostic Certainty (Highest level (1) to lowest level of certainty)	
	– Cervical dilation 2 cm or greater at the internal os by digital examination – Cervical length of 1 cm or less by digital examination – 50% or greater effacement by digital examination
2	• Greater than 4 uterine contractions per hour as determined by a tocodynometer or clinical assessment AND • Documented change in length or dilation of cervix by physical examination, with clinical criteria including: – Cervical dilation 2 cm or greater at the internal os by digital examination – Cervical length of 1 cm or less by digital examination – 50% or greater effacement by digital examination
3	• Greater than 4 documented uterine contractions per hour determined by clinical assessment AND • Documented change in cervical examination (change in dilation or effacement) over a two hour period
Provider-initiated preterm birth	
Level	**Description**
All	Patient is determined to be preterm (birth at less than 37 gestation-completed weeks (less than 259 days).
1	• Documentation in the healthcare record by a patient's delivering provider that there were no signs or symptoms of the spontaneous onset of preterm labor AND • Documentation in the healthcare record by a patient's delivering provider that the patient needed to undergo induction of labor or cesarean delivery which led to the preterm delivery
2	• From recall, delivering provider confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND • Delivering provider reports from recall that he or she decided that the patient needed to undergo induction of labor or cesarean delivery
3	• From recall, patient confirms that there was an absence of any signs or symptoms of the spontaneous onset of preterm labor AND • Patient reports from recall that the healthcare provider indicated that she needed to undergo induction of labor or cesarean delivery

Reference: Harrison MS, Eckert LO, Cutland C, et al. Pathways to preterm birth: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6093-6101.

Table 36 Chorioamnionitis

Chorioamnionitis encompasses a broad spectrum of disease during pregnancy that is characterized by inflammation and/or infection of intrauterine structures such as the placenta, the chorion and amnion.

This case definition focusses on the infectious manifestation of chorioamnionitis, intra-amniotic infection. Four definitions of chorioamnionitis have been developed based on systematic literature review, are summarized below, and must be considered when applying the case definitions.

It is important to rule out other obvious sources of acute systemic infection (i.e. pyelonephritis) prior to chorioamnionitis diagnosis.

Level	Description
All levels	**Clinical Definition A:** Maternal fever ≥ 38 degrees Celsius on one occasion *plus one or more of*: • Baseline fetal tachycardia (FHR > 160 bpm for 10 min or longer, excluding accelerations, decelerations and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least three consecutive contractions) • Maternal WBC ≥ 15 000 per mm^3 in the absence of corticosteroids. • Definite purulent fluid from the cervical os. **Clinical Definition B** Maternal fever ≥ 38 degrees Celsius on one occasion *plus two of*: • Maternal tachycardia (HR > 100 bpm) • Baseline fetal tachycardia (FHR > 160 bpm for 10 min or longer, excluding accelerations, decelerations and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least three consecutive contractions • Purulent fluid from the cervical os. • Uterine tenderness • Maternal WBC ≥ 15 000 per mm^3 in the absence of corticosteroids **Histologic diagnosis:** • Positive finding of invasion of maternal polymorphonuclear leukocytes into the placental plate, the chorion and/or amnion which meets criteria based on a widely accepted histopathologic staging and grading system [such as Blanc[1] Redline[2], or Salafia[3] criteria]. **Culture criteria:** • Positive culture of amniotic fluid (via amniocentesis), and/or • Positive culture of placental membranes (between chorion/amnion) **GAIA gestational age** level 1–2 criteria denote higher gestational age certainty including a combination of certain last menstrual period (LMP), first or second trimester ultrasound or first trimester exam confirmation. Level 3 diagnostic certainty for gestational age has a lower accuracy compared to levels 1–2. (see Section 10.8)
1a	Clinical Definition A AND Confirmation via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
1b	Clinical Definition A AND Confirmation via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by ANY GAIA gestational age criteria

Level	Description
2a	Clinical Definition A OR Chorioamnionitis via histopathology or culture AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
2b	Clinical Definition B AND Gestational age ≥ 22–0/7 weeks by GAIA gestational age level 1–2 criteria
2c	Clinical Definition A or B OR Chorioamnionitis via histopathology or culture AND Gestational age ≥22–0/7 weeks by any GAIA gestational age criteria
3a	Clinical definition A or B with report of fever or maternal feeling of "feverishness." AND Gestational age ≥ 22–0/7 weeks by any GAIA gestational age criteria
3b	Clinical definition B without fever (documented or reported) AND Gestational age ≥ 22–0/7 weeks by any GAIA gestational age criteria

[1]W.A. Blanc Pathology of the placenta, membranes, and umbilical cord in bacterial, fungal, and viral infections in man. Monogr Pathol, 22 (1981), pp. 67-132

[2]R.W. Redline, O. Faye-Petersen, D. Heller, F. Qureshi, V. Savell, C. Vogler Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatric Dev Pathol: Off J Soc Pediatric Pathol Paediatric Pathol Soc, 6 (5) (2003), pp. 435-448

[3]C.M. Salafia, C. Weigl, L. Silberman The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. Obstet Gynecol, 73 (3 Pt 1) (1989), pp. 383-389

Reference: Kachikis, A, Eckart L, Walker C et al. Chorioamnionitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2019; 7610–7622

Table 37 Standard Definitions for Maternal Events of interest not defined as events in GAIA

Event of Interest	Definition
Oligohydramnios	Amniotic fluid index (AFI) < 8 cm or deepest vertical pocket (DVP) < 2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology
Polyhydramnios	Polyhydramnios is the presence of excess amniotic fluid in the uterus. By definition, polyhydramnios is diagnosed if the deepest vertical pocket is more than 8 cm or amniotic fluid index (AFI) is more than 95th percentile for the corresponding gestational age
Gestational liver disease (Intrahepatic Cholestasis of Pregnancy or ICP)[1]	Intrahepatic cholestasis also called obstetric cholestasis should be suspected when pruritis develops during pregnancy in the absence of a rash. Lab evidence of cholestasis includes elevated bile acids (Glyco and Taurochenodeoxycholic Acid) (> 10 umol/L). Up to 60% of patients will have elevated transaminases and 20% of patients will have increased direct bilirubin levels. Jaundice may or may not be present. ICP typically is transient and resolves after delivery. Women that had ICP in previous pregnancy have higher risk to developing ICP in the following pregnancies or other hepatobiliary disorders in later life. ICP is associated with adverse fetal outcome like meconium-stained liquor, fetal asphyxia, spontaneous preterm delivery and intrauterine death.
Gestational liver disease (Acute Fatty Liver of Pregnancy)[2]	Acute fatty liver of pregnancy (AFLP) is a rare, potentially fatal complication that occurs in the third trimester or early postpartum period. AFLP is characterized by microvesicular fatty infiltration of hepatocytes without any inflammation or necrosis. Most frequent signs and symptoms are the following: • Jaundice • Abdominal Pain (usually right upper quadrat, midepigastric or radiating to back) • Central nervous system (altered sensorium, confusion, disorientation, psychosis, restlessness, seizures or even coma) • Disseminated intravascular coagulation • Nausea and vomiting • Gastrointestinal bleeding • Acute renal failure • Oliguria • Tachycardia • Late onset pyrexia • Hypoglycemia • ALT<500 U/L • Hyperbilirubinemia, elevated ammonia, leukocytosis, hypofibrinogenemia Ultrasound examination and computed tomography may demonstrate fatty infiltration of the liver but are not sufficient for diagnosis

<table>
<tr><th>Event of Interest</th><th>Definition</th></tr>
<tr><td>Maternal Sepsis[3]</td><td>Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, child-birth, post-abortion, or post-partum period.
Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

<table><tr><th></th><th colspan="5">Score</th></tr><tr><th>System</th><th>0</th><th>1</th><th>2</th><th>3</th><th>4</th></tr><tr><td>Respiration</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Pao_2/Fio_2, mm Hg (kPa)</td><td>≥400 (53.3)</td><td><400 (53.3)</td><td><300 (40)</td><td><200 (26.7) with respiratory support</td><td><100 (13.3) with respiratory support</td></tr><tr><td>Coagulation</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Platelets, $\times 10^3/\mu L$</td><td>≥150</td><td><150</td><td><100</td><td><50</td><td><20</td></tr><tr><td>Liver</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Bilirubin, mg/dL (μmol/L)</td><td><1.2 (20)</td><td>1.2-1.9 (20-32)</td><td>2.0-5.9 (33-101)</td><td>6.0-11.9 (102-204)</td><td>>12.0 (204)</td></tr><tr><td>Cardiovascular</td><td>MAP ≥70 mm Hg</td><td>MAP <70 mm Hg</td><td>Dopamine <5 or dobutamine (any dose)[b]</td><td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]</td><td>Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]</td></tr><tr><td>Central nervous system</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Glasgow Coma Scale score[c]</td><td>15</td><td>13-14</td><td>10-12</td><td>6-9</td><td><6</td></tr><tr><td>Renal</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Creatinine, mg/dL (μmol/L)</td><td><1.2 (110)</td><td>1.2-1.9 (110-170)</td><td>2.0-3.4 (171-299)</td><td>3.5-4.9 (300-440)</td><td>>5.0 (440)</td></tr><tr><td>Urine output, mL/d</td><td></td><td></td><td></td><td><500</td><td><200</td></tr></table>
Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.
[a] Adapted from Vincent et al.[27]
[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.
[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [Sepsis-related] Organ Failure Assessment</td></tr>
</table>

References:
[1] Geenes V. Williamson C, Chappell L. Intrahepatic cholestasis of pregnancy. The Obstetrician and Gynecologist. 2016; 18:273-81.
[2] Ko H, Yoshida E. Acute Fatty Liver of Pregnancy. Can J Gastroenterol. 2006; 20:25-30.
[3] Bonet M, Pileggi V, Rijken M et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health. 2017; 14:67.

Table 38 Small for Gestational Age

Weight below 10th percentile for gestational age as assessed against a validated global, regional or local standard.

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Newborn weighed within 24 hours of birth – Weight assessed using a calibrated electronic scale with 10 g resolution AND • The following for assessment of gestational age: – Certain LMP or IUI or embryo transfer date AND confirmatory ultrasound in first trimester OR – First trimester ultrasound
2a	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following for assessment of gestational age: – Certain LMP with first or second trimester ultrasound OR – Certain LMP with first trimester physical exam
2b	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Newborn weighed within 24 hours of birth on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following assessment of gestational age: – Uncertain LMP with second trimester ultrasound
3a	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Infant weighed within the first 48 hours of life – Newborn weighed on any scale with a < 50 g resolution, tared to zero and calibrated AND • The following assessment of gestational age: – Certain LMP with third trimester ultrasound OR – Certain LMP with confirmatory 2nd trimester fundal height OR – Certain LMP with birthweight OR – Uncertain LMP with first trimester physical exam

Small for Gestational Age (continued)	
Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
3b	• Weight below 10th percentile for gestational age AND • The following used in assessment of weight: – Infant weighed within the first 48 hours of life – Newborn weight assessed by measuring the difference between an adult holding the infant and the adult being weighed alone on any scale AND • The following assessment of gestational age: – Uncertain LMP with fundal height OR – Uncertain LMP with newborn physical assessment OR – Uncertain LMP with birthweight
4	• Baby noted to be small, but no actual weight • Baby with GA assessed only by infant examination • Diagnosis extracted from billing codes or chart, with no documentation of actual birth weight or GA

Reference: Schlaudecker EP, Munoz FM, Bardají A, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017; 35:6518-6528.

Table 39 Low Birth Weight (LBW)

Regardless of gestational age:

- Low birth weight (LBW): <2500 grams.
- Very low birth weight (VLBW): <1500 grams
- Extremely low birth weight (ELBW): <1000grams

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	Newborn infant weighed within 24 hours of birth AND Use electronic scale which is graduated to 10 grams AND Scale is calibrated at least once a year AND Scale placed on level, hard surface AND Scale tared to zero grams AND Weight recorded as <2500 grams OR Birth weight recorded as <2500 grams AND Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 5 above.
2	Newborn infant weighed within 24 hours of birth AND Scale (electronic/spring) is graduated to at least 50 grams AND Scale is calibrated at least once a year, or more often if moved AND Scale tared to zero grams or 0.00kg AND Weight recorded as <2500 grams OR Birth weight recorded as <2500 grams AND Birth weight assessed as per health care facility's standard operating procedure, which fulfills criteria 1 to 4 above. (Scale used could be electronic or spring scale, including color-coded scale)
3	Newborn infant weighed on day 1 or 2 of life (first 48 hours of life) AND Weight measured using dial/spring/color-coded scale AND Weight assessed as <2500 grams
4	Newborn weight assessed between day 1 and 2 of life (first 48 hours) AND Proxy measure (newborn foot length, chest circumference, mid upper arm circumference) of birth weight used AND Weight CATEGORY assessed as <2500 grams

Reference: Cutland CL, Lackritz EM, Mallett-Moore T, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35:6492-6500.

Table 40 Neonatal encephalopathy

Disease, malfunction of damage of the brain in a newborn (1–28 days) born at or beyond 35 weeks of gestation, that may be due to a variety of etiologies including but not limited to hypoxia/ischemia, metabolic disturbance, infection and traumatic processes

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Level	**Description**
1	(Definite) Abnormal level of alertness or seizures AND Difficulty with initiating and maintaining respiration AND Depression of tone
2	(Probable) Abnormal level of alertness or seizures AND Difficulty with initiating and maintaining respiration OR Depression of tone
3	(Possible) Abnormal level of alertness or seizures without difficulty with initiating and maintaining respiration nor depression of tone

Reference: Sell E, Munoz FM, Soe A, et al. Neonatal encephalopathy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017; 35: 6501-6505.

Table 41 Congenital Microcephaly

Congenital microcephaly, also referred to as primary microcephaly due to its presence in utero or at birth, is a descriptive term for a structural defect in which a fetus or infant's head (cranium) circumference is smaller than expected when compared to other fetuses or infants of the same gestational age, sex and ethnic background

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Postnatally Diagnosed Microcephaly	
Level	**Description**
1	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of Gestational Age (GA)~ AND Head Circumference (HC) 2 Standard Deviations (SD) below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured between 24–36 hours after birth or end of pregnancy. *~GA assessed based on certain Last Menstrual Period (LMP) with confirmatory 1st trimester or 2nd trimester ultrasound (US) scan, intrauterine insemination (IUI), or embryo transfer date*
2a	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured • within the first 24 hours§ OR • >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA assessed based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, IUI, or embryo transfer date* *§Take into account the variability in this period based on molding of the head*
2b	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND • within the first 24 hours§ OR • >36 hours and up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA assessed based on uncertain LMP with 2nd trimester US scan* *§Take into account the variability in this period based on molding of the head*

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Postnatally Diagnosed Microcephaly (continued)	
Level	**Description**
3a	Live birth, stillbirth, or spontaneous or therapeutic abortion of at least 24 weeks of GA~_ AND HC 2 SD below mean or <3rd percentile according to GA and gender, using appropriate standardized reference charts for the population (e.g., WHO growth reference charts if GA P37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Measured up to 6 weeks after birth or end of pregnancy with no apparent post-natal insult resulting in microcephaly *~GA based on LMP without confirmatory 1st or 2nd trimester Ultrasound*
3b	Live birth, stillbirth, or spontaneous or therapeutic abortion AND Case meets criteria for microcephaly using a validated algorithm: 1 inpatient diagnosis OR 2 outpatient diagnoses OR 1 outpatient diagnosis AND death in first year using the following diagnostic codes ICD-9-CM code 742.1 or ICD-10-CM code Q02
4	Live birth, stillbirth, or spontaneous or therapeutic abortion AND Diagnosis of congenital microcephaly based on: • physical inspection without HC measurement OR • ICD-9-CM or ICD-10-CM code that does not meet validated algorithm criteria above.
Prenatally Diagnosed Microcephaly	
Level	**Description**
1a	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester (<14 weeks) or 2nd trimester US scan IUI, or embryo transfer date AND HC 2 SD below mean or <3rd percentile according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (e.g. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3rd percentile) by: • at least one additional US after 24 weeks and at least one week after first US OR • HC measurement with standard tape measure at birth or autopsy
1b	Fetus of at least 24 weeks GA based on uncertain LMP with 2nd trimester US AND HC 2 SD below mean or <3rd percentile according to fetal ultrasound (US) examination using appropriate standardized reference charts according to GA and gender for the population (e.g. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) by: • at least one additional US after 24 weeks and at least one week after first US OR • HC measurement with standard tape measure at birth or autopsy

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Prenatally Diagnosed Microcephaly (continued)	
Level	**Description**
2	Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US scan AND HC 2 SD below mean or <3rd percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (e.g. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND Confirmation of microcephaly (i.e., HC 2 SD below mean or <3%) by: • at least one additional US scan after 24 weeks and at least one week after first US OR • HC measurement with standard tape measure at birth or autopsy
3a	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, uncertain LMP with 2nd trimester US, IUI, or embryo transfer date AND HC 2 SD below mean or <3rd percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (e.g. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND No additional data to confirm microcephaly (i.e., No additional prenatal US scan or confirmation of microcephaly with any additional US or by HC measurement at birth or autopsy at birth or autopsy)
3b	Fetus of at least 24 weeks GA based on certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US AND HC 2 SD below mean or <3 percentile according to fetal US scan using appropriate standardized reference charts according to GA and gender for the population (e.g., WHO growth reference charts if GA P37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) with femur length and abdominal circumference concordant with GA assessment AND No additional data to confirm microcephaly (i.e., No additional prenatal US scan or confirmation of microcephaly by HC measurement at birth or autopsy)
4	Fetus of at least 24 weeks GA based on certain LMP with confirmatory 1st trimester or 2nd trimester US scan, uncertain LMP with 2nd trimester US, IUI, embryo transfer date, or certain or uncertain LMP with fundal height and no confirmatory 1st or 2nd trimester US scan AND HC 2 SD below mean or <3% according to fetal US examination using appropriate standardized reference charts according to GA and gender for the population (e.g. WHO growth reference charts if GA ≥37 weeks and Intergrowth-21st reference charts for GA 24–36 weeks) AND HC at birth or autopsy is in the normal range using appropriate standardized reference charts according to GA and gender for the population, which means that this is NOT a case of prenatally diagnosed congenital microcephaly

Reference: DeSilva M, Munoz FM, Sell E, et al. Congenital microcephaly: Case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation. Vaccine. 35; 6472 – 6482.

Table 42 Major Congenital anomalies

Congenital anomalies, also commonly referred to as birth defects, congenital disorders, congenital malformations, or con-genital abnormalities. Major congenital anomalies are events of prenatal origin that a represent at birth, potentially impacting an infant's health, development and/or survival.

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Major External Structural Defects	
Level	**Description**
1	Alterations in external anatomy visible: • at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR • in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting
2	Alterations in external anatomy visible: • at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR • in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies
3	Alterations in external anatomy visible: • at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR • in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed: • by documentation of a diagnosis made by a trained maternal or child health care provider with at least minimal experience diagnosing congenital anomalies OR • For live births, by using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) Alterations in external anatomy visible: • at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR • in a stillbirth or in the products of conception of a spontaneous or therapeutic abortion AND Confirmed: • by medical record review OR • in claims data (ICD-9/ICD-10 diagnoses)

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Internal Structural Defects	
Level	**Description**
1	Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND Confirmed by definitive imaging study or intraoperative diagnosis OR Alterations in internal anatomy detected during autopsy for a stillbirth, spontaneous or therapeutic abortion confirmed by documentation by a pathologist or other relevant subspecialist
2	Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of morphology training for the specific setting without definitive imaging or intraoperative evaluation OR For stillbirth, spontaneous or therapeutic abortion, internal structural defect is visible by ultrasound or other imaging modality prenatally
3	Alterations in internal anatomy present at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired AND Confirmed: • by documentation of a diagnosis made by a clinician with some experience diagnosing congenital anomalies OR • using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) Alterations in internal anatomy present: • at the time of live birth and persistent beyond the immediate peripartum period unless surgically repaired OR • at time of stillbirth, spontaneous abortion, or induced abortion AND Confirmed: • through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child health care provider with minimal experience diagnosing congenital anomalies OR • by claims data (ICD-9/ICD-10 diagnoses)

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Functional Defects	
Level	**Description**
1	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of birth (or propensity to develop alteration present at live birth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND Confirmed by definitive diagnostic study
2	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND Confirmed by documentation of a diagnosis made by a clinician experienced in diagnosing congenital anomalies and with the highest level of training in the diagnosis of functional defects for the specific setting
3	For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at livebirth (or propensity to develop alteration present at live birth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND Confirmed: • by documentation of a diagnosis made by a clinician with some experience diagnosing functional defects OR • using individual (ICD-9/ICD-10) codes or as part of an ICD-9/ICD-10 code based algorithm, where the outcome (individual code or algorithm) has been validated
4	(Insufficient evidence to confirm) For live births, alterations in functioning of one or more organs or body parts not due to a structural defect, present at the time of live birth (or propensity to develop alteration present at livebirth), and persistent beyond the immediate peripartum period, unless treated through gene therapy or stem cell transplantation OR For stillbirths, spontaneous or therapeutic abortions, alterations in functioning of one or more organs or body parts, not due to a structural defect AND Confirmed: • through medical record review, with the medical record demonstrating that the anomaly was present at the time of live birth or time of fetal demise, and that the anomaly was diagnosed by a trained maternal or child healthcare provider who is not a qualified geneticist, neonatologist, pathologist, subspecialist, pediatrician, obstetrician, or family medicine practitioner OR • by claims data (ICD-9/ICD-10 diagnoses)

Reference: DeSilva M, Munoz FM, Mcmillan M, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6015-6026.

Table 43 Neonatal Death

Death of a live born infant regardless of gestational age at birth, within the first 28 completed days of life

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Neonatal death in a non-viable live birth	
Level	**Description**
1	Live born infant AND • Gestational age <22 weeks (GA level of certainty = 1) OR • Birth weight <500 g AND Death of infant in first 28 days of life AND Medically-confirmed death
2	Live born infant AND Gestational age/size of newborn assessed as at least one of: • Gestational age <22 weeks (GA Level of Certainty = 1 OR 2) • Birth weight <500 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
3	Live born infant AND Gestational age <5 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
Neonatal death in an extremely preterm live birth	
Level	**Description**
1	Live born infant AND • Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1) OR • Birth weight ≥500 g but <1000 g AND Death of infant in first 28 days of life AND Medically-confirmed death
2	Live born infant AND Gestational age/size of newborn assesses as one or more of: • Gestational age ≥22 and <28 weeks (GA Level of Certainty = 1 OR 2) • Birth weight ≥500 g but <1000 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Neonatal death in an extremely preterm live birth (continued)	
Level	**Description**
3	Live born infant AND Gestational age ≥5 months but <7 months according to neonate's parent (mother/father)/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
Neonatal death in a preterm live birth (gestational age ≥28to <37 weeks)	
Level	**Description**
1	Live born infant AND • Gestational age ≥28 and <37 weeks (Level of Certainty = 1) OR • Birth weight ≥1000 g but <2500 g AND Death of infant in first 28 days of life AND Medically-confirmed death
2	Live born infant AND Gestational age/size of newborn assesses as one or more of: • Gestational age ≥28 and <37 weeks (GA Level of Certainty = 1 OR 2) • Birth weight ≥1000 g but <2500 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
3	(MAY apply to LMIC- or may be non-viable in LMIC) Live born infant AND Gestational age ≥7 months but <9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death
Neonatal death in a term live birth	
Level	**Description**
1	Live born infant AND Gestational age ≥37 weeks (GA Level of Certainty = 1) AND • Birth weight >2500 g OR • Documented intra-uterine growth retardation if ≤2500 g AND Death of infant in first 28 days of life AND Medically-confirmed death

Levels of Diagnostic Certainty (1 highest level to 4 lowest level of certainty	
Neonatal death in a term live birth (continued)	
Level	**Description**
2	Live born infant AND Gestational age/size of newborn assesses as one or more of: • Gestational age ≥37 weeks (GA Level of Certainty = 1 OR 2) • Birth weight ≥2500 g AND Death of infant in first 28 days of life AND Medically-confirmed death OR non-medically-confirmed death which is confirmed by examination by (by at least) non-medically-trained attendant (e.g. undertaker, community member)
3	(apply to Lower Middle Income Countries) Live born infant AND 2. Gestational age ≥9 months according to parent/family member/delivery attendant (GA Level of Certainty = 2 OR 3) AND 3. Death of infant in first 28 days of life AND 4. Medically-confirmed death OR non-medically-confirmed death

Reference: Pathirana J, Muñoz FM, Abbing-Karahagopian V, et al. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6027-6037.

Table 44 Neonatal Infections

Neonatal bacteremia and sepsis (of early or late onset), meningitis, pneumonia and other respiratory infections such as bronchiolitis, caused by bacteria, parasites, viruses or fungi. Localized eye and ear infections, encephalitis, urinary tract infections and intestinal infections were excluded from these guidelines

Neonatal invasive blood stream infections: bacterial/fungal/viral	
Level	**Description**
1	Recognized pathogen identified using a validated method and from a normally sterile site.
2	Not meeting Level 1 of evidence AND Meeting 3 or more of the following criteria: Temperature ≥37.5 ◦C or <35.5 ◦C Tachycardia or new or more frequent episodes of bradycardia New or more frequent episodes of apnea or increased oxygen requirement or increased requirement for ventilatory support Lethargy or moving only when stimulated or hypotonia or irritability Difficulty in feeding or abdominal distention Pallor or poor perfusion or hypotension Abnormal White Cell Count or I/T ratio >0.2 Abnormal platelet count Increased inflammatory markers (CRP, procalcitonin) Metabolic acidosis as defined by a base excess
3	Not meeting Level 1 or 2 of evidence AND Meeting 2 or more of the following criteria: Temperature ≥37.5 ◦C or <35.5 ◦C Tachypnea or severe chest in drawing or grunting or cyanosis Change in level of activity History of feeding difficulty History of convulsions

Bacterial/fungal/viral meningitis	
Level	**Description**
1	Recognized pathogen identified using a validated method from cerebrospinal fluid (CSF)
2	CSF pleocytosis OR positive IgM antibodies to a specific pathogen in the CSF AND Recognized pathogen identified using a validated method from a normally sterile site (other than CSF) AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 1 or more criteria below: History of convulsions Lethargy or irritability Coma Apnea Bulging fontanel Neck stiffness
3a	CSF pleocytosis AND No pathogen identified using a validated method from a normally sterile site AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 3 or more criteria below: History of convulsions Lethargy or irritability Coma Apnea Bulging fontanel Neck stiffness
3b	No lumbar puncture done or no sample available AND Temperature ≥37.5 ◦C or <35.5 ◦C AND 4 or more criteria below: History of convulsions Lethargy or irritability Coma Apnea Bulging fontanel Neck stiffness

Respiratory bacterial/fungal/viral infection	
Level	**Description**
1	New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND • Recognized virus identified using a validated assay from an upper respiratory sample OR • Recognized pathogen identified using a validated method and from a normally sterile site AND 3 or more criteria below: Temperature ≥37.5 ◦C or <35.5 ◦C Tachypnea or Nasal flaring or Chest in-drawing or Grunting Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% Apneas Increased respiratory secretions or Increased suctioning requirements Cough or wheeze or crepitations Increased CRP or procalcitonin
2	New or progressive or persistent infiltrate or shadowing or fluid in the intrapleural cavity or interlobar fissure on chest X-ray AND 4 or more criteria below: Temperature ≥37.5 ◦C or <35.5 ◦C Tachypnea or Nasal flaring or Chest in-drawing or Grunting Desaturations or increased oxygen requirements or increased ventilator requirements or oxygen saturation <95% Apneas Increased respiratory secretions or Increased suctioning requirements Cough or wheeze or crepitations Increased CRP or procalcitonin
3	2 or more criteria below: Difficulty in breathing/Tachypnea Severe chest in-drawing Nasal flaring Grunting Wheezing Stridor Fever

Reference: Vergnano S, Buttery J, Cailes B, et al. Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34 (49):6038-6046

Table 45 Respiratory Distress in the Neonate

Constellation of clinical findings that support the presence of breathing difficulty in the neonate (0-28 days of life), independent from etiology or severity, and independent from the infant's gestational age or circumstances at the time of delivery

Level	Description
1	Newborn 0 to 28 days of life AND Abnormal respiratory rate: Measurement of number of breaths per minute consistent with: • Tachypnea = respiratory rate of more than 60 breaths per minute OR • Bradypnea = respiratory rate of less than 30 breaths per minute OR • Apnea = cessation of respiratory effort (no breaths) for at least 20 seconds AND Clinical symptoms consistent with labored breathing: • Nasal flaring (dilatation of alae nasi) OR • Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR • Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) OR • Central cyanosis (whole body, including lips and tongue) on room air OR • Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND Examination and documentation by qualified, trained, health care provider appropriate for the clinical setting.
2	Newborn 0 to 28 days of life AND Abnormal respiratory rate: Not measured, but reported as "rapid breathing", "slow breathing", having periods of "no breathing", or "abnormal breathing" AND Clinical symptoms consistent with labored breathing: • Nasal flaring (dilatation of alae nasi) OR • Noisy respirations in the form of expiratory grunting, stridor, or wheeze OR • Retractions or increased chest in-drawings on respiration (subcostal, intercostal, sternal, suprasternal notch) or seesaw respirations OR • Central cyanosis (whole body, including lips and tongue) on room air OR • Low Apgar Score (< 7 points) at 10 min, with respiration score <2 AND • No medical record documentation, but reporting through either a non-medical observer (e.g. mother, father, community worker) or via standard census mechanisms (e.g. Demographic and Health Surveillance System) OR • Collection of information from medical record review or billing codes.
3	No need for a level 3 per working group.
4	Not enough information to ascertain case of respiratory distress.
5	Not a case of respiratory distress in the neonate.

Reference: Leigh R. Sweet, Cheryl Keech, Nicola P. Klein, et al. Respiratory distress in the neonate: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35: 6506-6517.

Table 46 Preterm Birth

Birth in less than 37 gestation-completed weeks (less than 259 days).

Prematurity and assessment of gestational age	
Level	**Description**
1	Certain last menstrual period date (LMP) LMP or intrauterine insemination (IUI) date or embryo transfer (ET) date with confirmatory 1st trimester scan (≤13 $^{6/7}$ weeks). OR 1st trimester scan (≤13 $^{6/7}$ weeks)
2a	Certain LMP* with 2nd trimester scan (14 $^{0/7}$ weeks to 27 $^{6/7}$weeks). *Note: If LMP and U/S do not correlate, default to U/S GA assessment.* OR Certain LMP* with 1st trimester physical examination.
2b	Uncertain LMP with 2nd trimester scan (14 $^{0/7}$ weeks to 27 $^{6/7}$ weeks).
3a	Certain LMP with 3rd trimester scan ≥ 28 $^{0/7}$ weeks OR Certain LMP with confirmatory 2nd trimester Fundal Height (FH) OR Certain LMP with birth weight OR Uncertain LMP with 1st trimester physical examination.
3b	Uncertain LMP with FH. OR Uncertain LMP with newborn physical assessment. OR Uncertain LMP with Birth weight
*	Definitions of LMP, birth weight and physical assessment in referenced article.

Reference: Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6047-6056.

Table 47 Failure to Thrive

Failure to Thrive (FTT) can be broadly defined as a faltering of growth from a previously established pattern of growth. It is universally established that a diagnosis of failure to thrive should be based on anthropometric data. However no consensus exits as to which measurements achieve the highest specificity and sensitivity. Weight is generally regarded is the indicator of choice, particularly a change in growth velocity, and as such has been selected as the standard for this case definition with a weight for age deceleration as the primary indicator of failure to thrive. The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Level	Description
1	Infant age[1] determined by a documented birth date AND Bare weights obtained using an appropriate electronic baby scale AND At least 2 such weights, measured at least 4 weeks apart AND Weight for age or weight for length/height falling by two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time [2,3,4]
2a	Infant age determined by a documented birth date AND Weights obtained using a beam balance scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart OR Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month AND Weights obtained using electronic scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time
2b	Infant age determined by a documented birth date AND Weights obtained using a spring balance scale AND At least 2 weights, measured at least 4 weeks apart AND Weight for age deceleration through at least 2 centile spaces on growth chart OR Weight measured using electronic scale or beam balance scale AND Length taken using Infantometer AND Weight for length less than or equal to the 3rd centile on the appropriate growth chart

Level	Description
3a	Infants with an undocumented birth date, where age is determined based on Mothers recall to nearest month AND Weight obtain using either beam balance or spring balance scale AND At least 2 weights, measured as least 4 weeks apart AND Weight for age deceleration through at least two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time
3b	Infants with no weight available AND Physical examination consistent with FTT[5] AND MUAC[6] indicative of severe wasting

[1]This case definition is limited to infants up to 12 months of age.
[2]Homan GJ, Failure to Thrive: A Practical Guide. Am Fam Physician. 2016; 94(4):295-9
[3] Weight should be documented on the appropriate growth chart at the time of assessment. A fall through 2 centile spaces may be demonstrated at any point in the first 12 months of life, using any two weights as long as they are taken at least 4 weeks apart. Details of use of the weight balances allowable under this case definition and use of the Infantometer for length assessment are presented in the reference given below.
[4] For infants born at 37 weeks gestation or above, the WHO growth charts should be applied. When using weight for age use the growth chart most accurate for the infants age. The birth to 6 months age range should be used where data is available for this range only, the birth to 2 years chart should be used where data is available beyond 6 months of life. When using weight for length, use the chart for birth to 2 years. For infants born less than 37 completed weeks gestation, the Intergrowth charts for postnatal growth standards in preterm infant should be used. All infants should be plotted on their respective growth chart using their corrected age. Links to relevant growth charts are presented in the reference given below.
[5] Physical examination with signs of Failure to Thrive (must include at least 2 findings, with at least one major finding) Major findings: Reduced subcutaneous fat stores; poor muscle mass; loose skin folds; prominent ribs; thin limbs. Other less specific signs include: sparse hair; rashes; pallor; miserable; lethargy/fatigue.
[6] Mid Upper Arm Circumference (MUAC): For infants 0–6 months, a MUAC of 6 110 mm is indicative of severe wasting. For infants 6–12 months, a MUAC of 6 115 mm is indicative of severe wasting. Instructions on performing MUAC are presented in the reference given below.
Reference: Ross E, Munoz F, Edem B et al. Failure to thrive: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017; 35:6483-6491.

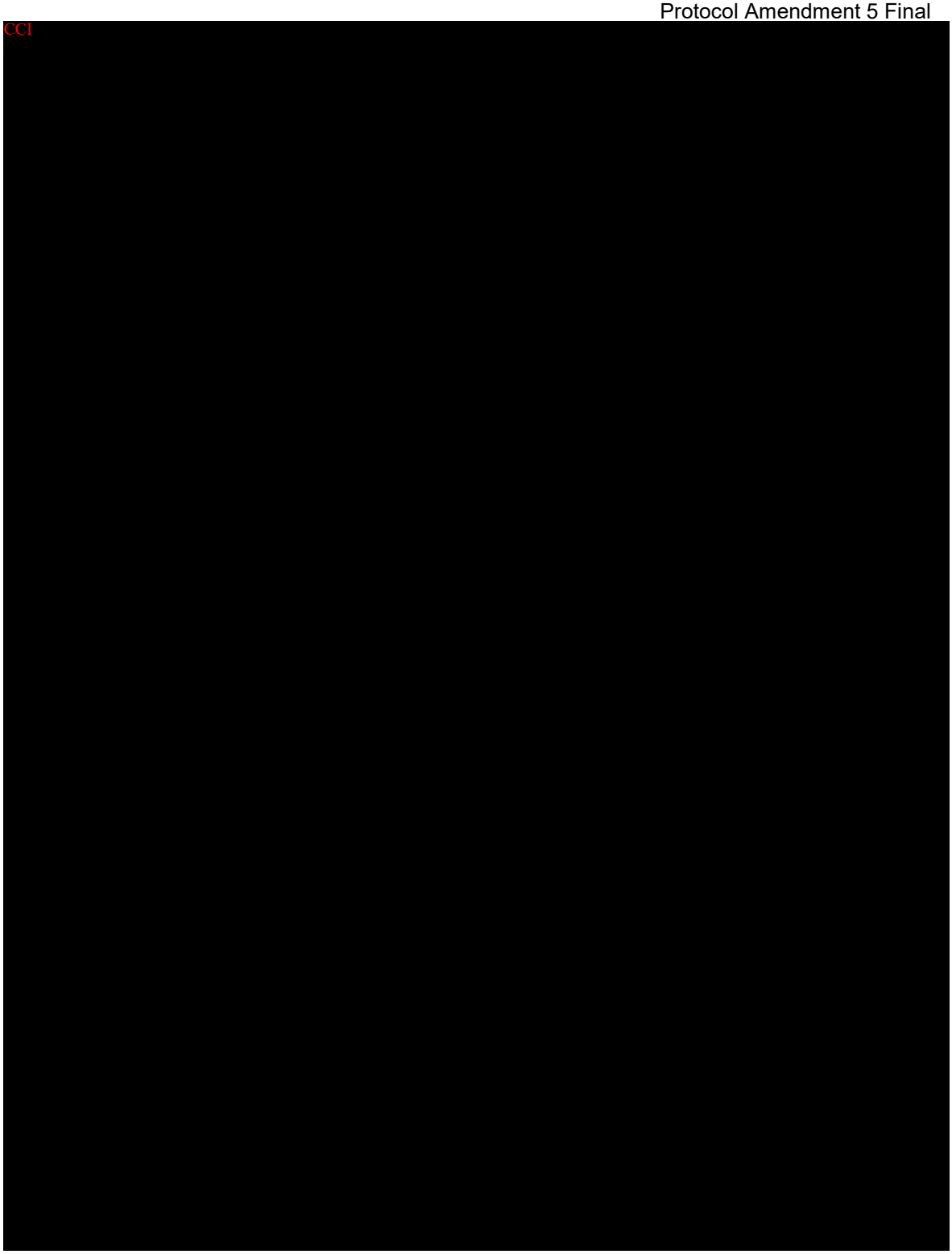
Table 48 Standard Definitions for Neonatal Events of interest not defined as events in GAIA

Event of Interest	Definition
Large for gestational age	Birth weight > 90% for newborns of same gestational age in same population (>4000g at term).
Macrosomia	BW >4000 g (8 lb, 13 oz).

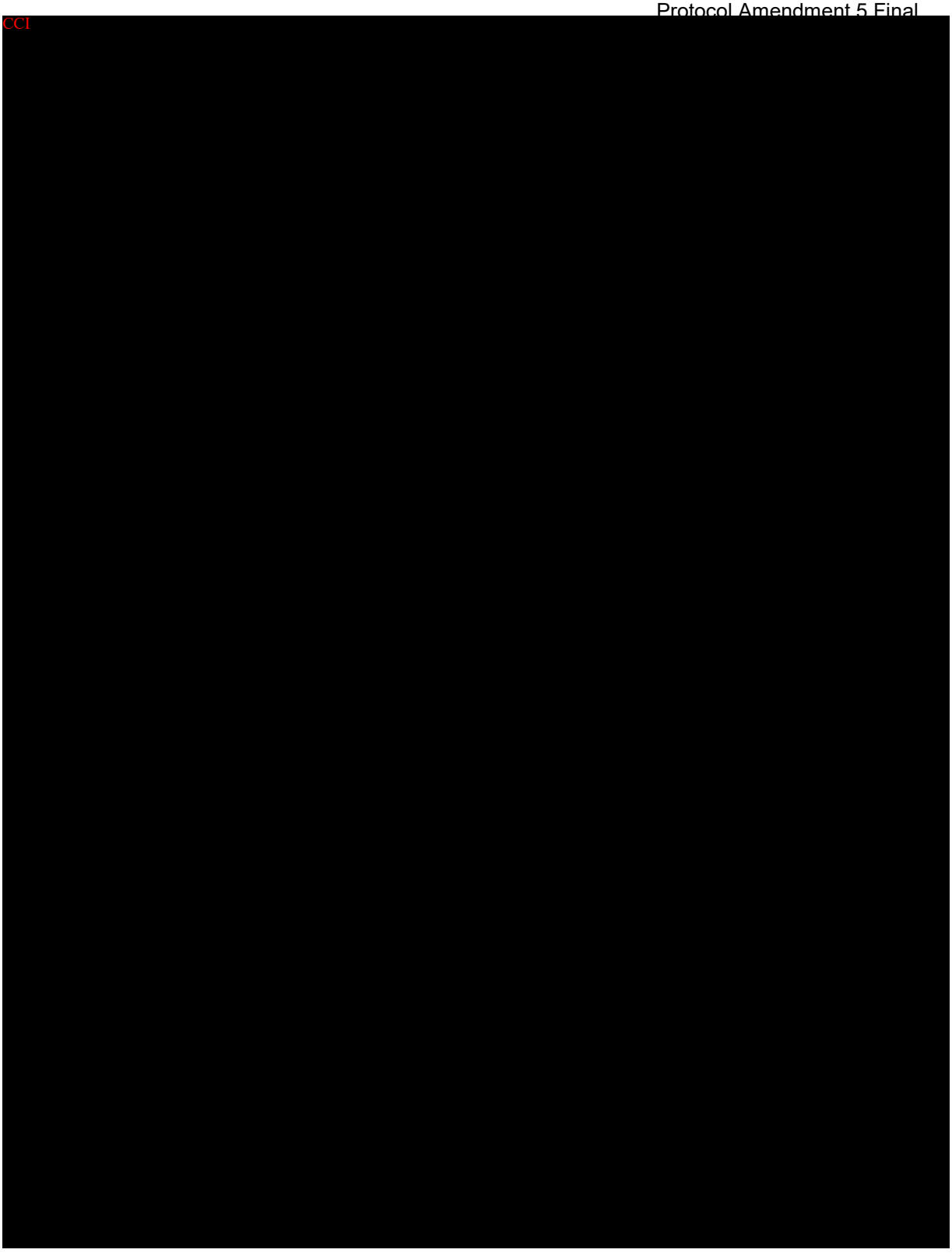
10.10. Appendix 10: CCI [redacted]

CCI [redacted]

CCI



CCI



10.11. Appendix 11: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	Date of Issue
Protocol	26 June 2020
Protocol Amendment 1	5 October 2020
Protocol Amendment 2	23 June 2021
Protocol Amendment 3	10 February 2022
Protocol Amendment 4	15 March 2022
Protocol Amendment 5	23 February 2023

Overall Rationale for the Protocol Amendment 5:

This protocol has been amended to reflect the following:

- The Benefit/Risk assessment has been updated to clarify that:
  - The observed numerical imbalance in neonatal deaths is not an independent safety signal but a consequence of the validated signal of preterm births.
  - Based on the evaluation of the Study Day 43 post-birth interim analysis, GSK concluded that preterm birth is an identified risk for the pregnant women population, for the RSV Maternal vaccine candidate.
  - GSK has discontinued the work on this RSV Maternal vaccine candidate and is closing out all ongoing vaccine trials. GSK will continue to monitor and follow-up the immunized participants in the trials for the duration specified in the respective protocols.
- For vaccine efficacy (VE) related objectives, the sensitivity and supportive analyses will be only conducted for primary efficacy endpoints, but the sensitivity analysis using the negative binomial model has been removed.
- The following changes have been made to the secondary efficacy endpoints:
  - For efficacy endpoint from birth to 7 months and above, only the efficacy endpoints of “From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of severe medically assessed, RSV-associated LRTIs” and “From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed, RSV-associated LRTIs” will be kept, and the analyses

will be conducted by using Kaplan-Meier curves from birth to 12 month, so that the VE changes across time can be observed.

  - "From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed, RSV-associated LRTIs by alternative case definitions" has been removed.
  - "From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of severe medically assessed, RSV-associated LRTIs according to the case definition" has been removed.
  - "From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition" has been removed.

- Secondary efficacy endpoints on infant participants will only be assessed in the Modified Full Efficacy set (FAS) and Secondary efficacy endpoints on maternal participants will only be assessed in the Exposed Set (ES).
- Secondary immunogenicity endpoints will be assessed in a sub-cohort of maternal-infant pairs including only those maternal-infant pairs from the per protocol set whose babies had blood collected for immunogenicity assessments at the allocated time-point.
- RSVPreF3 IgG antibody concentrations will be assessed only in maternal blood samples collected at delivery, and cord blood (or blood samples collected from their respective infants within 72 hours after birth, if no cord blood available).
- RSV-B neutralizing antibody titers will no longer be assessed as part of the secondary immunogenicity endpoints.
- CCI [redacted]
- CCI [redacted]
- The following populations for analyses have been removed:
  - Maternal participants :- Full Analysis – Immunogenicity, Full Analysis – Efficacy
  - Infant participants:- Full analysis – Immunogenicity
- Country-specific requirements have been added in Appendix 10.6 for Spain and Argentina.

Also, this amendment includes editorial changes to improve the consistency and typographical error corrections.

Detailed description of <u>current</u> Protocol Amendment (# 5) changes:

In this section, deleted text is indicated in strikethrough and changed text in ***bold italics***.

- **Section 1.1:**

Note: Based on all available safety information following vaccination with the RSV MAT vaccine, there will be no further enrollment and vaccination of maternal participants. However, monitoring will continue for rest of the study. All planned objectives ***described in the latest protocol amendment*** will be assessed for the participants enrolled so far.

- **Section 1.2**

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, since sample collection in infants was discontinued following stop of enrollment.

- **Section 2.1**

Note: Due to the stop on study enrollment and vaccination, nasal swabs from maternal participants will not be collected and no MA-RTI assessment visit will be performed. Assessment of incidence of MA-RTI in maternal participants and RTI/LRTI in infant participants will be limited to cases where a nasal swab was collected before study stop.

- **Section 2.3**

In February 2022, the Independent Data Monitoring Committee (IDMC) for the RSV MAT-009 study observed an imbalance in the proportion of preterm births in the active versus the placebo group and recommended that study enrollment be paused. As a result, GSK voluntarily paused the enrollment, randomization, and vaccination of participants in its active pregnant women studies to investigate this safety signal.

Following a review of additional unblinded data from the RSV MAT-009 study, the imbalance in preterm births was noted to persist across a range of risk factors. A higher proportion of neonatal deaths reported in the active group compared to the placebo group was also observed. GSK then decided to stop enrollment and vaccination in all ongoing trials of RSV Maternal Vaccine (RSVPreF3) as a precautionary measure.

The observed numerical imbalance in neonatal deaths is not an independent safety signal but a consequence of the validated signal of preterm birth. No numerical imbalance in neonatal deaths was observed in the cohort of infants born at term. An in-depth qualitative review of the clinical information available for each neonatal death concluded that the events leading to neonatal death (e.g., very low or low birth weight, sepsis, necrotizing colitis, pneumonia, respiratory distress syndrome, hypoxic-

ischemic injury) are commonly observed in preterm-born infants, particularly those who are extremely and very preterm, and there is no consistent temporal pattern of events from birth or from maternal vaccination.

In January 2023, following assessment of the Study Day 43 post-birth interim analysis (DLP 04 October 2022) with data from 5328 maternal participants (3557 in the active group) and 5235 infant participants (3496 in the active group), the imbalance in preterm birth remains statistically significant (RR 1.38 (95% CI 1.08, 1.75); p value: 0.0090) and persists across a range of risk factors. The overall incidence of preterm birth in the study is low in both groups and remains below the preterm birth background rates for the majority of the participating countries. The imbalance in preterm births was observed more with low and middle-income countries (RR: 1.57, 95% CI: 1.17–2.10) than high-income countries (RR: 1.04, 95% CI: 0.68–1.58). In low and middle-income countries, the preterm birth imbalance peaked from August to December 2021 and was not observed consistently from January 2022 onward.

GSK concluded that preterm birth is an identified risk for the pregnant women population, for the RSV Maternal vaccine candidate. GSK has discontinued the work on this RSV maternal candidate vaccine and is closing out all ongoing trials. Additionally, GSK continues to monitor and follow up those participants immunized in the trials. Another study (RSV MAT-015) has been initiated to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or control in previous RSV MAT studies, including the RSV MAT-009 study, during any pregnancy conceived post-vaccination or post-control.

~~Following a recommendation from the IDMC, the Sponsor made the decision to pause the enrollment, randomization and vaccination of participants in our active pregnant women studies, including RSV MAT-009, based on an observation of imbalance in the proportion of preterm births between the vaccine group and the placebo group in the RSV MAT-009 study. This pause was to allow for an evaluation of the available data in RSV MAT-009 to better understand the safety signal observed. Following a review of additional unblinded data from this study in which a higher proportion of neonatal deaths reported in the treatment group compared to the placebo group was also observed, the Sponsor decided to STOP enrollment and vaccination in these studies.~~

~~The safety signals are being investigated and, although at this time a cause has not been determined, GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling pregnant women on February 25, 2022 as a precautionary measure. The study remains ongoing for safety follow-up. Participants already vaccinated and their infants will continue to be monitored until the end of the study.~~

- **Section 3: Objectives and endpoints**

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 medically assessed[1],	From birth (Visit 1-NB) ~~to 7 months, birth to 8 months,birth to 9 months (C2-NB), birth to 10 months, birth to 11 months, and birth~~ to 12 months (Visit 5-NB), occurrences of medically

RSV-associated severe LRTIs in their infant[43] participants up to ~~7, 8, 9, 10, 11 and~~ 12 months of age.	assessed, RSV-associated 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[43] participants up to ~~7, 8, 9, 10, 11 and~~ 12 months of age.	From birth (Visit 1-NB) ~~to 7 months, birth to 8 months,birth to 9 months (C2-NB), birth to 10 months, birth to 11 months, and birth~~ 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, in their infant[4] participants up to 6 months of age, medically assessed[1] RSV LRTI by alternative case definitions[2].~~	~~From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of medically assessed[1] RSV LRTI by alternative 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[43] 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 effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any severe medically assessed[1], RSV-associated LRTIs, in their infant[4] participants up to 12 months of age, according to the case definition[2].~~	~~From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of severe medically assessed[1], RSV-associated LRTIs according to the case definition[2].~~
~~To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any medically assessed, RSV-associated LRTIs in their infant[4] participants up to 12 months of age, according to the case definition[2].~~	~~From birth (Visit 1-NB) to *12 months (Visit 5-NB),* time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition[2].~~
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	• ~~RSVPreF3 IgG-specific antibody concentration, and~~ • Neutralizing antibody titers against RSV-A ~~and RSV-B~~

participants 30 days after the study intervention, and at delivery.	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.	~~• RSVPreF3 IgG-specific antibody concentration, and~~ • Neutralizing antibody titers against RSV-A ~~and RSV-B~~ 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 pre-term 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]	

[2]Case definitions for ***RSV-associated medically attended RTIs (RSV-MA-RTIs),*** RSV associated LRTIs and surveillance for potential LRTIs are briefly summarized in Section 4.2.6.

- **Section 4.1**

Figure 1

Footnote modified to add: ***Due to the stop on study enrollment 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.***

- **Section 4.2.4.2**

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.

- **Section 6.3.2.1.1**

~~Samples collected from maternal and infant participants in the immunogenicity sub-cohort will be used to evaluate secondary immunogenicity objectives and to assess antibody persistence in the infants.~~

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.

Note: As per Amendment 4, blood samples were collected from all maternal participants at Delivery (Visit 3).

- **Section 8.1.2**

Table 15

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	SERUM	RSV-A NAb (RSV-A Neutralizing Antibody)	NEUT	GSK ** or GSK designated lab
	~~SERUM~~	~~RSV-B NAb (RSV-B Neutralizing Antibody)~~	~~NEUT~~	~~GSK ** or GSK designated lab~~
	SERUM	Respiratory Syncytial Virus PreF3 Ab.IgG (RSVPreF3 IgG antibody concentration)	ELISA	GSK ** or GSK designated lab
Molecular Biology	NASMUC (Nasal swab)	Respiratory Syncytial Virus A RNA	QRTPCR	GSK ** or GSK designated lab
	NASMUC (Nasal swab)	Respiratory Syncytial Virus B RNA	QRTPCR	GSK ** or GSK designated lab

*Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.
ELISA = enzyme-linked immunosorbent assay; NEUT = Neutralization;

RSV-A/B quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4. CCI [redacted] CCI [redacted]

- **Section 8.1.3**

Table 16

~~All participating maternal participants will have Visit 1 (Day 1) and Visit 2 (Day 31) blood samples tested. All cord blood samples will also be tested~~.

Approximately 1533 maternal participants (and their infant participants), in Stage A only, will be assigned to the immunogenicity sub-cohort.

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. Therefore, maternal participants in the immunogenicity subcohort, who have blood samples collected from their respective infants, will have Visit 1 (Day 1), Visit 2 (Day 31), Delivery blood samples and cord blood samples tested for RSV-A NAb. In addition, their delivery and cord blood samples will be tested for RSVPreF3 IgG-specific antibody concentration.

Blood sampling timepoint		**Approximate No. participants – Stage A**	**Approximate No. participants – Stage B**	**Component**
Type of contact and timepoint	**Sampling timepoint**			
Maternal participants*				
V1 (Day 1)	pre vaccination	4600	Up to 5400	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~ ~~Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)~~
V2 (Day 31)	post vaccination	4600	Up to 5400	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~ ~~Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)~~
V3 (Delivery)#	post-vaccination	venous blood: 1533 Cord blood: 4600	Venous blood: 0 Cord blood: up to 5400	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~ Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)
Infant participants**				
V1-NB (Birth)	birth (only if cord blood cannot be collected)	Event-driven	Event-driven	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~ Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)
V2-NB (Day 43)***	post birth 1	510	0	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~ ~~Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)~~
V3-NB (Day 121)***	post birth 2	510	0	RSV-A NAb (neutralizing antibody) ~~RSV-B NAb (neutralizing antibody)~~

Blood sampling timepoint		Approximate No. participants – Stage A	Approximate No. participants – Stage B	Component
Type of contact and timepoint	Sampling timepoint			
				~~Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)~~
V4-NB (Day 181)* **	post birth 3	510	0	RSV-A NAb (neutralizing antibody)
				~~RSV-B NAb (neutralizing antibody)~~
				~~Respiratory Syncytial Virus PreF3 Ab.IgG (concentration)~~

Table 17

Footnote modified: Quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4.~~CCI [redacted] CCI [redacted]~~

- **Section 8.4.1.1**

* *Due to the stop on study enrollment and vaccination, MA-RTI surveillance of the maternal participants will no longer be performed.* ***No nasal swab will be collected and no RTI assessment visit will be performed. However, any MAE related to RTI will still be reported (as applicable).***

- **Section 9.3**

Table 22

	Description
Analysis Set	**Maternal participants**
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.
~~Full Analysis – Immunogenicity~~	~~All maternal participants in the Exposed set who have post-vaccination immunogenicity data.~~
Per Protocol – Immunogenicity	All maternal participants who received the study intervention to which they were randomised and have post-vaccination data ~~(Full Analysis Set)~~ minus participants with protocol deviations that lead to exclusion.
Full Analysis – Efficacy	All maternal participants in the Exposed set.
Solicited Safety – Stage A only	All maternal participants in the Exposed Set who have solicited safety data

Table 23

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
~~Full Analysis – Immunogenicity~~	~~All infant participants in the Exposed set who have post-delivery/birth immunogenicity data.~~
Per Protocol – Immunogenicity	All infant participants in the ~~Full Analysis (Immunogenicity)~~ ***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.

- **Section 9.4.1**

If, during the trial, changes need to be made on primary ~~or secondary~~ objectives and statistical methods related to those objectives, the protocol will be amended. Changes on ***secondary/***tertiary objectives, along with the reason(s) for the changes, will be documented in the SAP and the Clinical Study Report.

- **Section 9.4.3.1.2**

~~To evaluate how missing efficacy data (PCR confirmed RSV LRTI results) can impact on the estimated VE from primary analysis, a tipping point analysis for binary data may be conducted. Sub-group analyses by regions and key demographic characteristics will also be explored, and the details will be included in the SAP.~~

- **Section 9.4.4.1**

~~In general,~~ The primary analysis of vaccine efficacy on secondary efficacy endpoints ***in infants*** will be based on the modified full analysis set for efficacy (modified FAS-E). ~~A secondary analysis based on the full analysis set for efficacy and the per protocol set for efficacy will be performed to complement the modified FAS-E analysis. all secondary or tertiary efficacy analyses will be performed on the final data containing all participants enrolled and their follow up.~~

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.	CCI [redacted]
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTIs.	
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTIs with hospitalization.	
~~From birth (Visit 1-NB) to 7 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 7 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 8 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 8 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.~~	

Secondary Efficacy Endpoints	Statistical Analysis Methods
~~From birth (Visit 1-NB) to 9 months (C2-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.~~	CCI [redacted]
~~From birth (Visit 1-NB) to 9 months (C2-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 10 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 10 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 11 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.~~	
~~From birth (Visit 1-NB) to 11 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.~~	

Secondary Efficacy Endpoints	Statistical Analysis Methods
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 12 months (Visit 5-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 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.	
From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definition.	

Secondary Efficacy Endpoints	Statistical Analysis Methods
From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	CCI [redacted]
~~From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed, RSV-associated LRTIs by alternative 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), time to the first occurrence of severe medically assessed, RSV-associated LRTIs according to the case definition.~~	
~~From birth (Visit 1-NB) to 12 months (Visit 5-NB), time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition.~~	

Secondary Efficacy Endpoints	Statistical Analysis Methods
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of RSV-associated hospitalizations according to the case definitions.	CCI [redacted]

- **Section 9.4.4.3**

All immunogenicity analyses in stage A will be based on the Per Protocol Immunogenicity set. ~~If, in any study group and at any timepoint, the percentage of study intervention recipients with serological results excluded from the Per Protocol set for analysis of immunogenicity is 5% or more, a second analysis based on the Full Analysis Immunogenicity Set will be performed to complement the Per Protocol analysis.~~

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.

Secondary Immunogenicity Endpoints – Maternal Participants	Statistical Analysis Methods
~~• RSVPreF3 IgG-specific antibody concentration, and~~ • 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	
• ***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)	CC1 [redacted]
Secondary Immunogenicity Endpoints – Infant Participants	
~~• RSVPreF3 IgG-specific antibody concentration, and~~ • Neutralizing antibody titers against RSV-A ~~Measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 72 hours after birth (if no cord blood sample can be obtained).~~ Measured ~~on a blood sample collected~~ ***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~~ ***birth*** 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.	

- **Section 10.6**

10.6.3. Spain

With regards to the "COMPENSATION" offered to the infant participants enrolled in the study, infant parents/LAR's were offered the possibility to have the infant vaccinated with a commercially approved vaccine being part of the National Pediatric Immunization Calendar but, which costs are not financially covered by the health system in the corresponding Region/Autonomous Community:

- ***Meningococcus B vaccine (Bexsero®)***

Or

- ***Rotavirus vaccine (Rotarix®)***

This compensation was put in place considering the recommendations laid out in ICH-E11 (Clinical Investigation of Medicinal Products in the pediatric population) as well as in the "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population", developed by the ad-hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.

Compensation was approved by the Spanish regulatory authority and Ethics Committee, and included in the country-specific Informed Consent.

10.6.4. Argentina

Concerning the "STUDY POPULATION – Exclusion criteria for enrolment – maternal participants" and, as per request from the Argentinean regulatory authorities (A.N.M.A.T Administración Nacional de Alimentos, Medicamentos y Tecnología Médica), study recruitment in Argentina was limited to pregnant women aged 18 to 40 years (inclusive), instead of 18 to 49 years (inclusive).

This age limitation was initially expected to be temporal, and dependent on the availability of safety data coming from other countries on pregnant women > 40 years old, which was to be submitted to A.N.M.A.T for evaluation. However, further enrollment and vaccination in the study was stopped on 25th February 2022, before such safety data was submitted.

- **Section 10.7.1**

The following abbreviation was added: ***SRT – Safety Review Team***

<u>Overall Rationale for the Protocol Amendment 4</u>:

This protocol has been amended to reflect the following:

- Following review of data collected so far from the study, safety signals have been identified: an imbalance in the proportion of preterm births and neonatal deaths has been observed in infants born to vaccinated mothers who received RSV maternal vaccine versus those who received a placebo. It is not known at this time whether this imbalance is related to the study participation or study vaccine. Based on the above observation, GSK has decided to stop enrolment and vaccination for all actively enrolling RSV MAT studies .
- There will be no new participants included in the ongoing studies.
- However, safety monitoring will continue, with additional monitoring measures implemented, for both maternal and infant participants during the rest of the study period.
- Blood samples from all maternal participants at delivery will be collected.

- Placental sample from all maternal participants at delivery will be collected, whenever feasible.
- No blood sample from the infants will be collected at V2-NB, V3-NB and V5-NB.
- Additional monitoring contact/s or visit/s for the maternal participants and infants have been included.
- Respiratory tract illness surveillance for maternal participants will not be performed.
- All planned objectives will be assessed for the participants enrolled so far.

Also, this amendment includes editorial changes to improve the consistency and typographical error corrections.

Detailed description of Protocol Amendment (# 4) changes:

In this section, deleted text is indicated in strikethrough and changed text in ***bold italics***.

- **Section 1.1:**

Note: Based on all available safety information following vaccination with the RSV MAT vaccine, there will be no further enrollment and vaccination of maternal participants. However, monitoring will continue for rest of the study. All planned objectives will be assessed for the participants enrolled so far.

- **Section 1.2**

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

- **Section 1.3**

Table 1: Schedule of activities for maternal participants

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
Informed consent	●										Section 10.1.3
Check Inclusion/exclusion criteria	●	O									Sections 5.1.1, 5.1.2
Assign maternal participant study number	●										Section 6.3.1

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
Register maternal participant in SBIR	O										Section 6.3.1
Assign infant participant study number		O									Section 6.3.1
Record Demographic data	●										Section 5.3
Record lifestyle characteristics	●										
Review & collect Medical and vaccination history	O	●									Section 8.2.1.1
Record outcome of fetal morphology ultrasound scan	●										
Record obstetric history from past and current pregnancies	● (current pregnancy)	● (past pregnancy/ies)									
Record Travel history to or living in Zika virus endemic countries/regions	●	●	●	●	●			●			During the current pregnancy only

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
General and/or obstetrical examination	●	●	●		●	●			If needed	If needed	General and/or Obstetrical exam is symptom directed at V4, & event-driven visits. Vaginal exams are symptom directed. See Section 8.2.1.2
Pre-vaccination body temperature		●									Preferred location for measurement will be the oral cavity. "Fever" = temperature ≥38.0°C/100.4° F regardless of the location of measurement.
Blood sample (immunogenicity ~ 10 ml)		●	●		Sub-cohort ●						At V1 and V2, collected from all participants in both Stage A and Stage B. At V3, collected only from a sub-cohort in Stage A. See Table 12 and Sections 8.1.1 and 8.1.3 ***Blood sample at delivery to***

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
											be collected from all participants.
Cord blood (~ 5 to 10 ml)					•						Collected from all participants in both Stage A and Stage B. See Table 13 and Sections 8.1.1 and 8.1.3.
Placenta sample					•						Collected from all participants in both Stage A and Stage B. See Table 13 and Sections 8.1.1 and 8.1.3. ***Collect from all participants, if feasible.***
Nasal swab										•	See Table 12 and Sections 8.1.1, 8.1.3, and 8.4.4. ***Note: nasal swab from maternal participants will no longer be collected and MA-RTI visit is no longer required.***

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
Check contraindications to and criteria for temporary delay for vaccination		O									Section 7.1
Allocate maternal study group, intervention number		O									Sections 6.3.2, 6.3.3 Recording will be done at Visit 1, upon maternal participant randomization but the eCRF entry will be done on the demography screen
Record maternal sub-cohort for immunogenicity assessment		●									
Allocate infant sub-cohorts for immunogenicity assessment		O									
Administer Study Intervention (study vaccine / placebo)		●									Sections 6.1, 6.2
Record administered intervention number		●									
Observe for 30 minutes post-dose		O									

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
Distribute maternal participant card	O	O									At screening or at Visit 1 as per local practice. Section 8.3.6
Record Labor / Delivery information					●						
Record pregnancy / delivery outcomes					●						Submit Expedited AE report for an adverse pregnancy outcome (Section 8.3.3)
Train maternal participant /LAR on use of electronic diary		O Stage A									Section 10.3.8
Distribute electronic diary to maternal participant / LAR.		O Stage A									Section 8.3.1
Review electronic diary entries			O Stage A								
Return electronic diary			O Stage A								
Concomitant medications / vaccinations		●	●	●	●	●	●	●	●	●	Sections 6.5.1 and 6.5.3

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
All unsolicited AEs (Days 1 to 30)		●	●						●	●	Sections 8.3.1, 10.3.4 and 10.3.8
Pregnancy-related AESIs		●	●	●	●	●		●	●		Table 4, Sections 8.3.1, 8.3.3, 8.3.4, and 10.3.5. Must submit an Expedited AE report.
MAEs other than MA-RTIs		●	●	●	●	●		●	●		Medically attended RTIs to be reported up to C1.
MA-RTI signs										●	Sections 8.3.1, 8.3.3, 8.4 ***Note: nasal swab from maternal participants will no longer be collected and MA-RTI visit is no longer required.***
SAEs, MA-RTI associated AEs and AEs leading to study withdrawal		●	●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1 and 10.3.8
SAEs related to study participation or	●	●									Sections 8.3.1 and 10.3.8

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven			
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery[1]	Delivery			***Additional contact(s)[1]***	Safety visit	MA-RTI visit	For monthly contacts: Section ~~8.4.2~~ 8.2.1.2.2. ***Additional contact(s) and/or safety visit(s) can be made between Visit-2 and the Delivery visit, if deemed necessary.***
Visit Day	D-28 – D1 before randomization	D1	D31		D1 PD	D43 PD	D181 PD	***V2-Delivery***			Table 3
concurrent GSK medication/vaccine											
Subsequent pregnancies						●	●		●	●	Section 8.3.1 and 10.3.8
Record interest in joining future extension study	O						●				Section 6.7
Screening conclusion	●										
Study conclusion							●				Section 4.4
Investigator sign-off at study conclusion							●				

The timing of an event-driven site visit (e.g., to further evaluate a potential AE or MA-RTI) cannot be defined with precision in the protocol. Event-driven visits may occur throughout the study. ● is used to indicate a study procedure that requires documentation in the individual eCRF. ○ is used to indicate a study procedure that does not require documentation in the individual eCRF. V = visit; D = day; GA = gestational age; MA-RTI = medically attended respiratory tract illness; PD = post delivery.

* V2 may be replaced by V3, depending on delivery date.

[1] 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.

Table 2 Schedule of activities for infant participants

Visit / Contact	V1-NB[1]	***Safety contact (recommended)[1]***	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	Birth	***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months	Contacts	Visits	
Visit Day	D 1-21	***D8 (7 days post-birth)***	D43	D91	D121	D181	D271	D366	Birth – *D366*		See Table 3 for intervals between visits, contacts. Sections 5.1.2 and 5.2.2
Check Inclusion / exclusion criteria	●										
Re-consent / Consent for infant participation *if required by local regulations*	●										
Record infant participant study number	●										
Record sub-cohort for immunogenicity assessment, if applicable	●										Section 6.3.2.1.2
Distribute infant's participant card	O										Section 8.3.6
Distribute infant RTI-diary card	O	**O**	O	O	O	O	O			O	Distribute at V1-NB: Distribute additional RTI-diary cards as needed. Section

Visit / Contact	V1-NB[1]	***Safety contact (recommended)[1]***	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	Birth	***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months	Contacts	Visits	
Visit Day	D 1-21	***D8 (7 days post-birth)***	D43	D91	D121	D181	D271	D366	Birth – *D366*		See Table 3 for intervals between visits, contacts.
											8.4.2.2 and SPM
Review infant RTI-diary card		**O**	O	O	O	O	O	O		O	
Collect infant RTI-diary card			O	O	O	O	O	O		O	Collect RTI-diary cards that are fully filled out. Section 8.4.2.2 and SPM
Transcribe applicable infant RTI-diary card data to eCRF			●	●	●	●	●	●		●	
Demographic data	●										Section 5.3 Record at Visit 1-NB and if changes in lifestyle characteristics thereafter At 1, 5 and (if available/performed) at 10 minutes,
Lifestyle characteristics	●		●	●	●	●	●	●			
Apgar score	●										
Weight, length, head circumference, physical examination	●		●		●	●		●			Section 8.2.2
Blood sample if no cord	●										Adjust volume if weight ≤ 2.5 Kg. Refer to Table 14

Visit / Contact	V1-NB[1]	***Safety contact (recommended)[1]***	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	Birth	***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months	Contacts	Visits	
Visit Day	D 1-21	***D8 (7 days post-birth)***	D43	D91	D121	D181	D271	D366	Birth – *D366*		See Table 3 for intervals between visits, contacts.
blood ~2.5 ml											
Blood sample (immunology, infants) ~2.5 ml			● Subcohort 1		● Subcohort 2	● Subcohort 3					1 sample at one of these visits, as per infant's assigned sub-cohort. Adjust volume if weight ≤ 2.5 Kg. Refer to Table 14 ***Blood samples will no longer be collected at V2-NB, V3-NB or V4-NB.***
Concomitant vaccinations	●	●	●	●	●	●					
Concomitant medications	●	●	●	●	●	●	●	●	●	●	Sections 6.5.2 and 6.5.3
Neonatal AESIs	●	●	●								Table 4, Section 8.3.1, 8.3.3, 8.3.4, and 10.3.5. Must submit an Expedited AE report. ***An additional recommended safety contact may be performed ~8 days post-birth if***

Visit / Contact	V1 - NB [1]	***Safety contact (recommended)[1]***	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	Birth	***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months	Contacts	Visits	
Visit Day	D 1-21	***D8 (7 days post-birth)***	D43	D91	D121	D181	D271	D366	Birth – *D366*		See Table 3 for intervals between visits, contacts.
											deemed necessary to closely monitor the newborn and support collection and reporting of any neonatal AESI(s).
SAEs, MAEs and AEs leading to study withdrawal	●	●	●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1, and 10.3.8
Symptom-directed physical examination (includes RTI signs, symptoms)										●	Section 8.4.4
Nasal swab										●	Sections 8.1.1 , 8.4.4.2, Table 14
Study conclusion								●			Section 4.4
Investigator sign-off at study conclusion								●			

The timing of an event-driven visit cannot be defined with precision in the protocol. ● indicates a study procedure that requires documentation in the individual eCRF. ○ indicates a study procedure that does not require documentation in the individual eCRF. LAR = legally acceptable representative; V=visit; D=day; NB = newborn.

[1] An additional optional but recommended safety contact may be performed on ~Day 8 (7 days post-birth) if deemed necessary by the investigator or by the parent/LAR(s).

- **Table 3**

Maternal participants

Monthly contacts	~ every 25 – 35	Monthly beginning after Visit 2 until Delivery. Contacts are additional to and do not replace protocol specified Visits. ***Additional contact(s)/visit(s) can be made more often if deemed necessary by the investigator or the maternal participant.***

Infant participants			
Birth to recommended safety contact	***8***		***Safety contact (recommended, in interval between Day 7 to Day 10)***

- **Section 2.3**

~~Detailed information about the known and expected benefits and risks and reasonably expected adverse events of the RSV Maternal (RSVPreF3) vaccine can be found in the IB.~~

GSK has included provisions in this trial to ensure participant's safety. ~~Maternal participants will remain under observation for 30 minutes after administration of the study intervention to ensure that immediate treatment may be provided in the event of a hypersensitivity reaction, or syncope.~~ Safety monitoring ***has been and*** will be conducted throughout this study by an unblinded Independent Data Monitoring Committee (IDMC) and by ~~blinded Safety Review Team.~~***the Sponsor***. The study includes the establishment of a surveillance system which may facilitate detection of respiratory tract infections, in particular lower respiratory tract infections (LRTIs) in ~~women and~~ infants enrolled in the study. Measures to suspend the study should a potential safety issue be identified are described in Section 8.2.3.

~~Taking into account the measures to minimize potential risks for participants participating in this study, the potential or identified risks are justified by the potential benefits of enhanced surveillance for the participants, and by the potential future benefits an RSV vaccine for maternal immunization may provide in preventing LRTIs in the infants of vaccinated mothers.~~

~~Based on ongoing systematic review of the safety data, the benefit-risk profile of the RSV Maternal Vaccine (RSVPreF3) continues to be favourable and justifies unaltered continuation of the development programme.~~

Following a recommendation from the IDMC, the Sponsor made the decision to pause the enrollment, randomization and vaccination of subjects in our active pregnant women studies, including RSV MAT-009, based on an observation of imbalance in the proportion of preterm births between the vaccine group and the placebo group in the RSV MAT-009 study. This pause was to allow for an evaluation of the available data in RSV MAT-009 to better understand the safety signal observed. Following a review of additional unblinded data from this study in which a higher proportion of neonatal deaths reported in the treatment group compared to the placebo group was also observed, the Sponsor decided to STOP enrollment and vaccination in these studies.

The safety signals are being investigated and, although at this time a cause has not been determined, GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling pregnant women on February 25, 2022 as a precautionary measure. The study remains ongoing for safety follow-up. Participants already vaccinated and their infants will continue to be monitored until the end of the study.

- **Section 3: Objectives and endpoints**

A secondary safety endpoint has been re-categorized as primary endpoint.

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[4] 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[4] 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].***

Mention of 'confirmatory' and 'descriptive' been deleted from this section.

Footnote deleted: ~~For analysis of secondary confirmatory efficacy objectives, overall type 1 error is controlled~~

- **Figure 1**

Footnote added:

In addition to the monthy 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.
Blood samples will be collected at delivery from all maternal participants. Placental samples will be collected at delivery from all maternal participants, if feasible.

- **Figure 2: Study design overview- infant participants**

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 enrollment and vaccination, blood samples will no longer be collected.

- Across the document note included (in sections 4.1, 4.2.3, 10.1.5)

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

- Across the document note included (in Sections 6.3.6)

**** Following the decision to stop enrollment and vaccination, the study/site staff and maternal participants no longer stay blinded. Refer to Section 2.3 for details.***

- **Table 18, Section 8.4.1.1, Section 8.4.2.1, Section 8.4.3.1, Section 8.4.4.3**

Note added: ***Due to the stop on study enrollment and vaccination, MA-RTI surveillance of the maternal participants will no longer be performed.***

- **Table 12**

Footnote added:

**** Due to the stop on study enrollment and vaccination, nasal swab samples will no longer be collected from any maternal participant and no MA-RTI assessment visit will be performed.***
 # Blood samples will be collected at delivery from all maternal participants. Hence, even if not assigned to the immunogenicity sub-cohort, the estimated total volume of blood for all maternal participants wil be ~30mL. In addition placental samples will also be collected at delivery, whenever feasible.

- **Table 14**

Footnote added:

Due to the stop on study enrollment and vaccination, there will no longer be collection of blood samples from the infants at Visit-2-NB, Visit-3-NB and Visit-4-NB.

- **Table 16**

Footnote added:

******Due to the stop on study enrollment and vaccination, blood samples will no longer be collected from the infants at V2-NB, V3-NB or V4-NB.***

 # Blood sample at delivery to be collected from all participants. Whenever feasible, placenta sample is expected to be collected from all participants. These samples may be tested to support possible safety assessments, if necessary.

- **Table 17**

Footnote added:

 # Due to the stop on study enrollment and vaccination, nasal swabs from maternal participants will not be collected and no MA-RTI assessment visit will be performed.

- **Section 8.2.1.2.2**

To ensure safety monitoring, in addition to the monthly contact 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.

- **Section 8.2.3**

Safety evaluations will include those performed by investigators, by a blinded ~~safety review team (~~SRT~~)~~ composed of GSK RSV team members, and by an unblinded, independent data monitoring committee external to GSK (IDMC). Details regarding IDMC safety evaluations are provided in a separate IDMC charter.

If the IDMC's decision(s) after a safety evaluation require(s) them to take some action (e.g., to suspend, modify, or continue the conduct of the study for all groups or for selected groups), the IDMC Chair (or his/her representative) will notify the study CRDL. The study CRDL will be accountable for notifying investigators in writing of the IDMC's decision(s).

~~In addition, a firewall will be established to ensure that data are not inadvertently unblinded. Details are provided in a separate Firewall charter.~~

Note: Due to the safety signal observed, the study has been fully unblinded to ensure safety monitoring for the participants.

- **Section 6.7**

~~It is likely that the RSV antibodies elicited by the vaccine may wane during the period between pregnancies, therefore there may be a need to administer the vaccine during each pregnancy to achieve optimal anti-RSV antibody levels in the neonate. In order to assess whether a booster dose might induce a higher reactogenicity or immune-tolerance, RSV MAT-009 participants may be invited to take part in a booster study.~~

~~The investigator will ask each participant, at the time of informed consent, if she is interested in taking part in a booster study and will document this in the source documents only. During the study conclusion visit/contact, the investigator will confirm the participant's interest and report it in the eCRF.~~***There will be no access to study intervention after the end of the study, because of the safety signal identified, leading to stopping of further enrolment and vaccination.***

- **Section 4.2.4**

Note however that blood samples for assessment of immune response at Day 1 (Visit 1~~)~~ ~~and~~, Day 31 (Visit 2~~)~~), ***and delivery (Visit 3)*** will be collected from *all* maternal participants. Cord blood will also be collected from all participants. ~~Analyses of these~~***T***hese samples ~~will~~***may*** be ~~used~~***tested*** to support possible ~~future bridging studies.~~***safety assessments, if necessary.***

- **Section 6.3.2.1.1**

All maternal participants in Stage A will:

- provide reactogenicity (solicited event) data for the first 7 days post-vaccination.
- have blood samples collected at Day 1 (Visit 1) and Day 31 (Visit 2) ***and Delivery (Visit 3)***.

~~The Day 1, Day 31 and cord blood (or neonatal blood) samples may be tested to support development of a sero-correlate for life cycle bridging.~~

All these samples may also be tested to support possible safety assessments, if necessary.

[….]

For the ~ 1533 infant participants in the immunogenicity sub-cohort:

- Randomization will identify a single timepoint post-birth (Day 43 (Visit 2-NB), or Day 121 (Visit 3-NB), or Day 181 (Visit 4-NB)) at which each (as yet unborn) infant will have a blood sample collected. Thus, at each of the 3 post-birth immunogenicity timepoints, a sample will be collected from approximately one third of the infants in the sub-cohort (N ~510).

Note that due to the stop on study enrollment and vaccination, there will no longer be collection of blood samples from the infants at V2-NB, V3-NB and V4-NB.

- **Section 6.3.2.1,2**

All maternal participants in Stage B will have blood samples collected at Day 1 (Visit 1) ~~and~~ Day 31 (Visit 2~~).~~) ***and Delivery (Visit 3)***. Cord blood (or if not possible, neonatal blood within 72 hours from birth) will also be collected from all participants. These samples may ***also*** be tested to support ~~development of a sero-correlate for life cycle bridging~~***possible safety assessments, if necessary***.

- **Section 8.4.4**

~~Unless otherwise specified, assessment visit procedures will be the same for maternal participants with MA-RTIs and for infant participants with RTIs.~~

- **Section 8.4.4.1**

For maternal participants: ***Due to the stop on MA-RTI surveillance for maternal participants, these checks will no longer be performed.***

- **Section 9.1: Statistical hypotheses**

~~The RSV vaccine arm will be compared to the control (placebo) arm in terms of the vaccine efficacy against any medically assessed RSV associated LRTI (VE_{any}) and severe LRTI (VE_{severe}) in infants followed for 6 months after birth. The null hypothesis on any medically assessed RSV associated LRTI is that vaccine efficacy is less than or equal to 20%. The null hypothesis on severe LRTI is that the vaccine efficacy is less than or equal~~

~~to 20%. The alternative hypothesis of interest is that either vaccine efficacy on any severity LRTI is above 20% or vaccine efficacy on severe LRTI is above 20%. That is:~~

~~H_{10}: $VE_{any} \leq 20\%$ vs H_{1a}: $VE_{any} > 20\%$, and, H_{20}: $VE_{severe} \leq 20\%$ vs H_{2a}: $VE_{severe} > 20\%$~~

~~The study is considered a success if at least one null hypothesis is rejected.~~

There are no hypotheses test for vaccine efficacy endpoints.

- **Section 9.2: Sample size determination**

CCI

[redacted]

CCI

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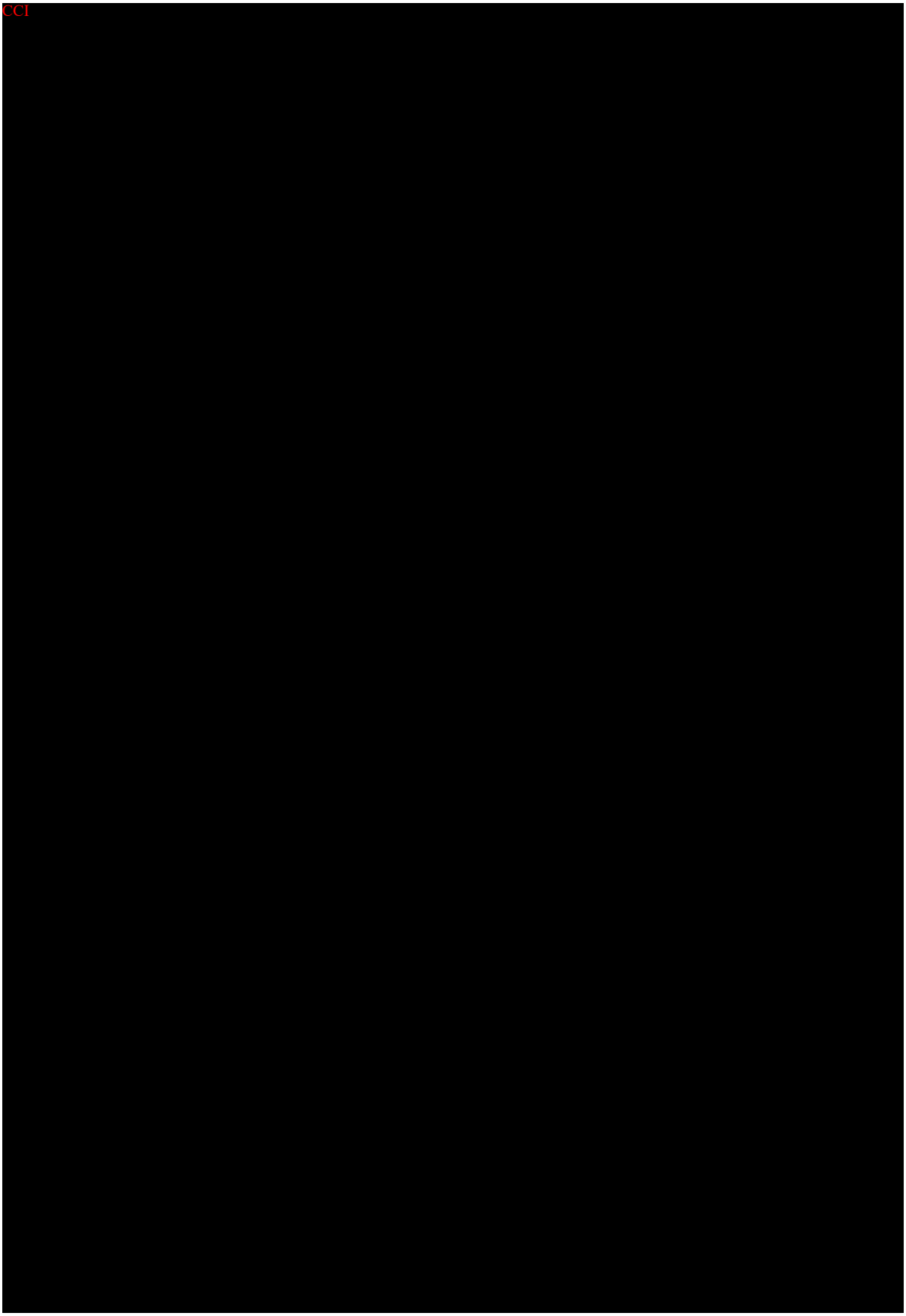

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- **Section 9.4.3: Primary endpoints**

The primary analysis of vaccine efficacy 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.

Analyses of primary safety endpoipoint will be performed on the Exposed set.

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]
Primary Safety Endpoint – Infant Participants	***Statistical Analysis Methods***
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 – Infant Participants	**Statistical Analysis Methods**
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	CCI [redacted]

Secondary Safety Endpoints – Infant Participants	Statistical Analysis Methods
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.	CCI
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.~~	

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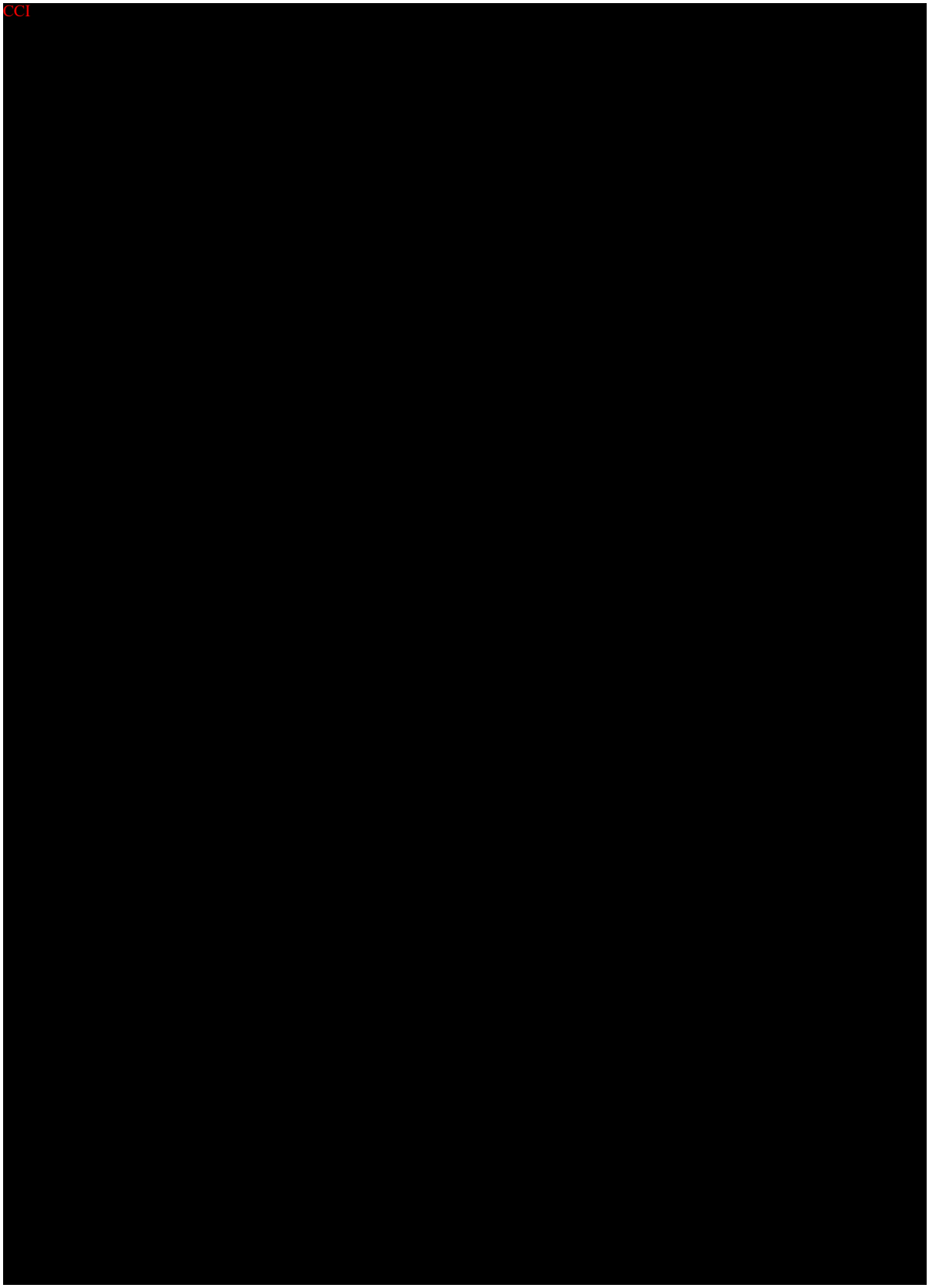

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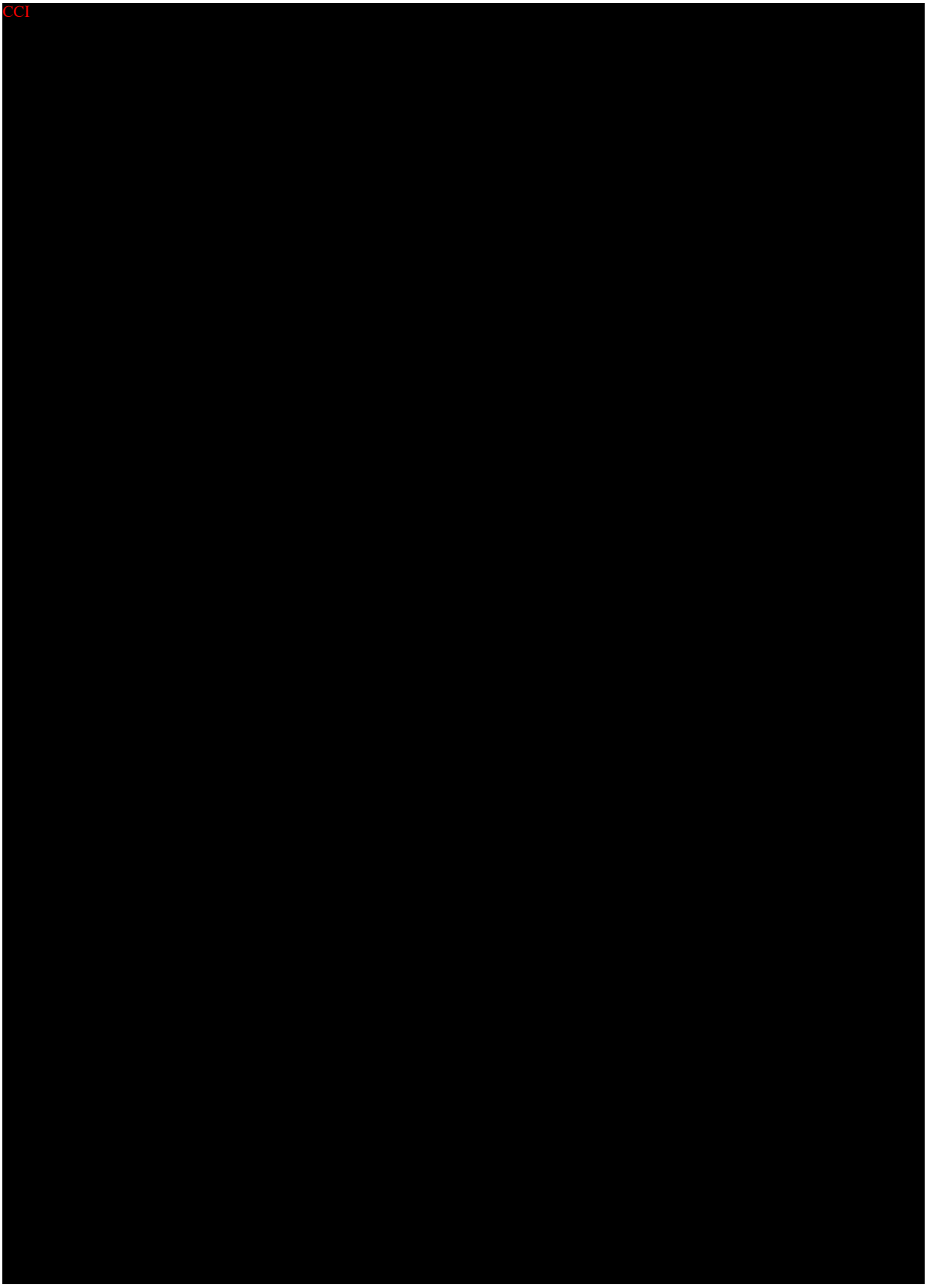

- **Section9.4.4.2: Detailed Statistical Analysis Methods**

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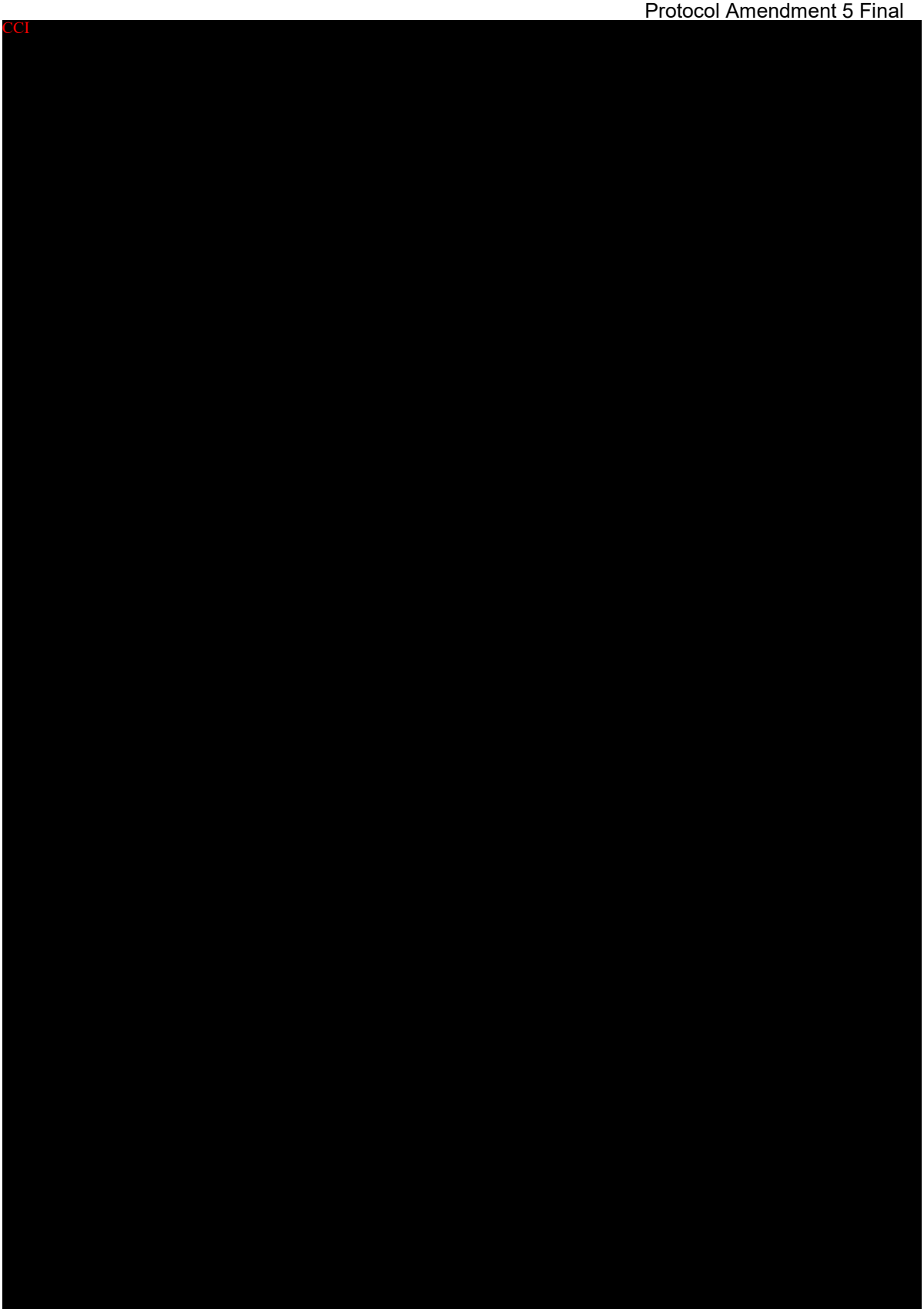

Overall Rationale for the Protocol Amendment 3:

This protocol has been amended to:

- Change the trigger point for interim analyses which could lead to claim VE(2, 3 and 4) as there is a high chance of claiming VE earlier than initially anticipated.
- Add 2 new secondary descriptive efficacy objectives to assess VE against severe medically assessed LRTIs and any medically assessed LRTIs associated to RSV subtypes A and B separately in the infant participants from birth up to 6 months of age.
- Acquire further information on how the VE can be sustained up to 12 months post-birth.
- Remove the distribution of antibody titers/concentrations and the scatter plots showing the individual post-vaccination versus pre-vaccination results, as well as scatter plots showing relationship between maternal and infant antibody titers. These analyses have been already described as part of previous completed RSV MAT studies and performing them in RSV MAT-009 (i.e. a larger sample size), is not expected to provide any additional critical information with regards to the study vaccine immunogenicity.
- Remove the section about predicted VE based on a surrogate endpoint due to the limitation of data from internal epidemological studies. Hence, the surrogate endpoint model cannot be robustly established and validated.

Also, this amendment includes clarifications, editorial changes to improve the consistency and typographical error corrections.

Detailed description of Protocol Amendment (# 3) changes:

In this section, deleted text is indicated in strikethrough and changed text in *bold italics*.

- **Section 3, Objectives and endpoints**

Table 4 Study objectives and endpoints

Secondary descriptive efficacy objectives	Secondary descriptive efficacy endpoints
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 subtype (A and B) separately in their infant[4] participants up to 6 months of age.	***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.***
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, for each RSV subtype (A and B)	***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.***

separately in their infant[4] 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 medically assessed[1], RSV-associated severe LRTIs in their infant[4] 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[4] 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[4] participants up to 6 months of age, medically assessed[1] RSV LRTI by alternative case definitions[2].	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of medically assessed[1] RSV LRTI by alternative 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[4] 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.
Secondary descriptive efficacy objectives	Secondary descriptive efficacy endpoints
To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any severe medically assessed[1], RSV-associated LRTIs, in their infant[4] participants up to ***12*** ~~6~~ months of age, according to the case definition[2].	From birth (Visit 1-NB) to ~~6 months (Visit 4-NB)~~***12 months (Visit 5-NB)***, time to the first occurrence of severe medically assessed[1], RSV-associated LRTIs according to the case definition[2].
To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any medically assessed, RSV-associated LRTIs in their infant[4] participants up to ~~6~~ ***12*** months of age, according to the case definition[2].	From birth (Visit 1-NB) to ~~6 months (Visit 4-NB)~~***12 months (Visit 5-NB)***, time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition[2].

- **Section 4.1, Overall design**

[…]

The study design is adaptive, with recruitment and randomization occurring in 2 sequential stages, A and B. ~~Decisions regarding progression to Stage B are described in detail in Sections 9.2 and 9.5. If progression to~~ Stage B ~~occurs, it~~ may begin immediately after the last participant is randomized in Stage A.

Table 6 Study groups, sub-cohorts, interventions, and blinding foreseen in the study: Stage B

Stage B will only start after the last participant is randomized in Stage A. ~~Decisions regarding progression to Stage B are described in detail in Sections 9.2 and 9.5.~~

- **Section 4.2.4.2, Blood sampling and immune response assessment**

[…]

Note however that blood samples for assessment of immune response at Day 1 (Visit 1) and Day 31 (Visit 2) will be collected from *all* maternal participants. Cord blood will also be collected from all participants. Analyses of these samples will be used to support possible ~~surrogate endpoint assessment as well as~~ future bridging studies.

- **Section 4.2.5, Adaptive Design**

This adaptive trial design will provide evidence for the efficacy of the RSV maternal vaccine in the prevention of medically assessed, RSV-associated LRTI of any severity and medically assessed, RSV-associated severe LRTI. The design has ~~over~~ 90% power to detect the target vaccine efficacies of 70% and 50% on severe and any-severity LRTI, respectively. If the vaccine meets these target VE estimates, this design offers the opportunity to identify this benefit with an expected sample size of approximately ***7,598*** ~~8,500~~ maternal participants, which may obviate the need to enroll the maximum sample size of 10,000. ~~In addition to the analysis of observed vaccine efficacy, as described above, the study may also assess predicted vaccine efficacy through a surrogate endpoint (namely RSV neutralizing antibody) reasonably likely to predict clinical benefit.~~

- **Section 5.2.1.1, Medical conditions**
  - […]
  - Any intervention to prevent preterm delivery or medical treatment for suspected preterm delivery, including administration of systemic corticosteroids for fetal lung maturation.

    Note: pregnant women under progesterone treatment beyond the 1st trimester of pregnancy, exclusively based on a prior pregnancy which resulted in preterm delivery/birth, but <u>without</u> any medical/clinical finding(s) which would lead to suspecting that there is a risk of preterm delivery in the current pregnancy (e.g. shortened cervical length, etc), would not be considered as meeting this exclusion criterion.

- **Section 6.3.2.1.1, Stage A**

[…]

~~The Day 1 and cord blood (or neonatal blood) samples will be tested to support surrogate endpoint analysis.~~ The Day 1, Day 31 and cord blood (or neonatal blood) samples may ~~also~~ be tested to support development of a sero-correlate for life cycle bridging.

- **Section 6.3.2.1.2, Stage B**

Stage B will only start after the last participant is randomized in Stage A. ~~Decisions regarding progression to Stage B are described in detail in Sections 9.2 and 9.5.~~

- **Section 7.1.1, Criteria for temporary delay for enrolment and/or vaccination**

Vaccination ~~may~~ ***must*** be postponed ~~within the permitted time interval~~ until transient circumstances cited below are resolved:

- Acute disease and/or fever within 48 hours before study vaccination. Fever is defined as temperature ≥38ºC by any age appropriate route (oral route preferred). Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.
- Use of systemic antibiotic or antiviral treatment within 48 hours before study vaccination.

Note: vaccination must be completed within the permitted time interval. If a participant is screened but not vaccinated within the allowed interval, a re-screening should be done to establish the participant's eligibility. Please make sure the participant's gestational age is still within the allowed range.

- **Section 8.1, Efficacy and/or immunogenicity assessments**

[…]

Sample testing will be done in accordance with the recorded consent of the individual maternal participant/infant participant's parent(s)/LAR(s).

~~If additional testing is performed, the marker priority ranking given in the Section 8.1.3 may be changed.~~

- **Section 8.2.1.1, Medical/vaccination history**
- For the current pregnancy, record:
  - […]
  - number of prenatal visits attended up to the date of the study Screening visit,
  - approximate date ***and gestational age*** of first prenatal visit,

- **Section 8.4.4.1, Clinical evaluation**

For maternal participants:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (~~Section 8.2.1.2.1),~~ in room air, if feasible***), see further details in Section 8.2.1.2.1***
- […]

For infant participants:

- Temperature
- Respiratory rate

- Blood oxygen saturation ~~(~~measured by pulse oximetry ***(in room air, if feasible), see further details in Section 8.2.1.2.1*** ~~(Section 8.2.1.2.1), in room air, if feasible~~

- **Section 9.2, Sample size determination**

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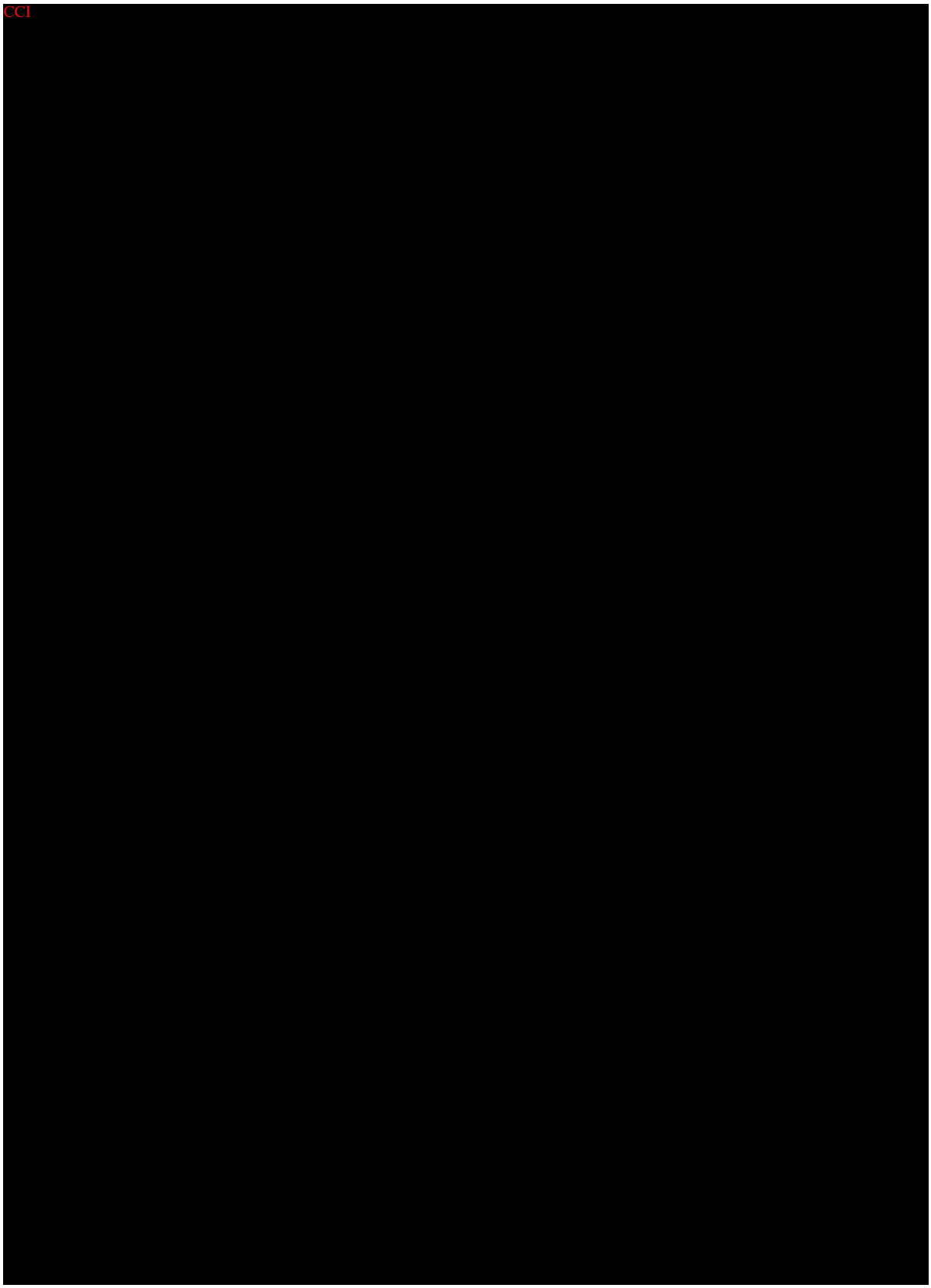

- **Section 9.3, Populations for analyses**

Table 24 Maternal Participants

	Description
Analysis Set	**Maternal participants**
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.
Full Analysis – Immunogenicity	All maternal participants in the Exposed set who have post-vaccination immunogenicity data.
Per Protocol – Immunogenicity	All maternal participants who received the study intervention to which they were randomised and have post-vaccination data (Full Analysis Set) minus participants with protocol deviations that lead to exclusion.
Full Analysis – Efficacy	All maternal participants in the Exposed set~~who either complete 6 months of follow-up after delivery or have a medically attended RTI (MA-RTI) case before completing the 6-month Contact.~~
Solicited Safety – Stage A only	All maternal participants in the Exposed Set who have solicited safety data

Table 25 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
Full Analysis – Immunogenicity	All infant participants in the Exposed set who have post-delivery/birth immunogenicity data.
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 vaccination and/ or (b) have protocol deviations that lead to exclusion.
Full Analysis - Efficacy	All infant participants in the Exposed set.~~ who either complete 6 months of follow-up or have a medically assessed RSV-associated LRTI case before completing the 6-month Visit (Visit 4-NB).~~
Modified Full Analysis - Efficacy	All infant participants in the Exposed set who were born after at least 4 weeks of vaccination.~~ AND either complete 6 months of follow-up or have a medically assessed RSV-associated LRTI case before completing the 6-month Visit (Visit 4-NB)~~
Per Protocol – Efficacy	All infant participants in the ***Modified Full Analysis – Efficacy set*** ~~Full analysis (efficacy) set~~ minus those who have protocol deviations that lead to exclusion.

- **Section 9.3.1.1.1, Maternal participants**

  – Any of the medications listed in Section 5.2.1.2 ***if administered up to Delivery (Visit 3), except corticosteroids for fetal lung maturation administered after study vaccination.***~~if administered up to Delivery (Visit 3).~~

- **Section 9.4.3, Primary endpoints**

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]

- **Section 9.4.3.1, Detailed Statistical Analysis Methods**

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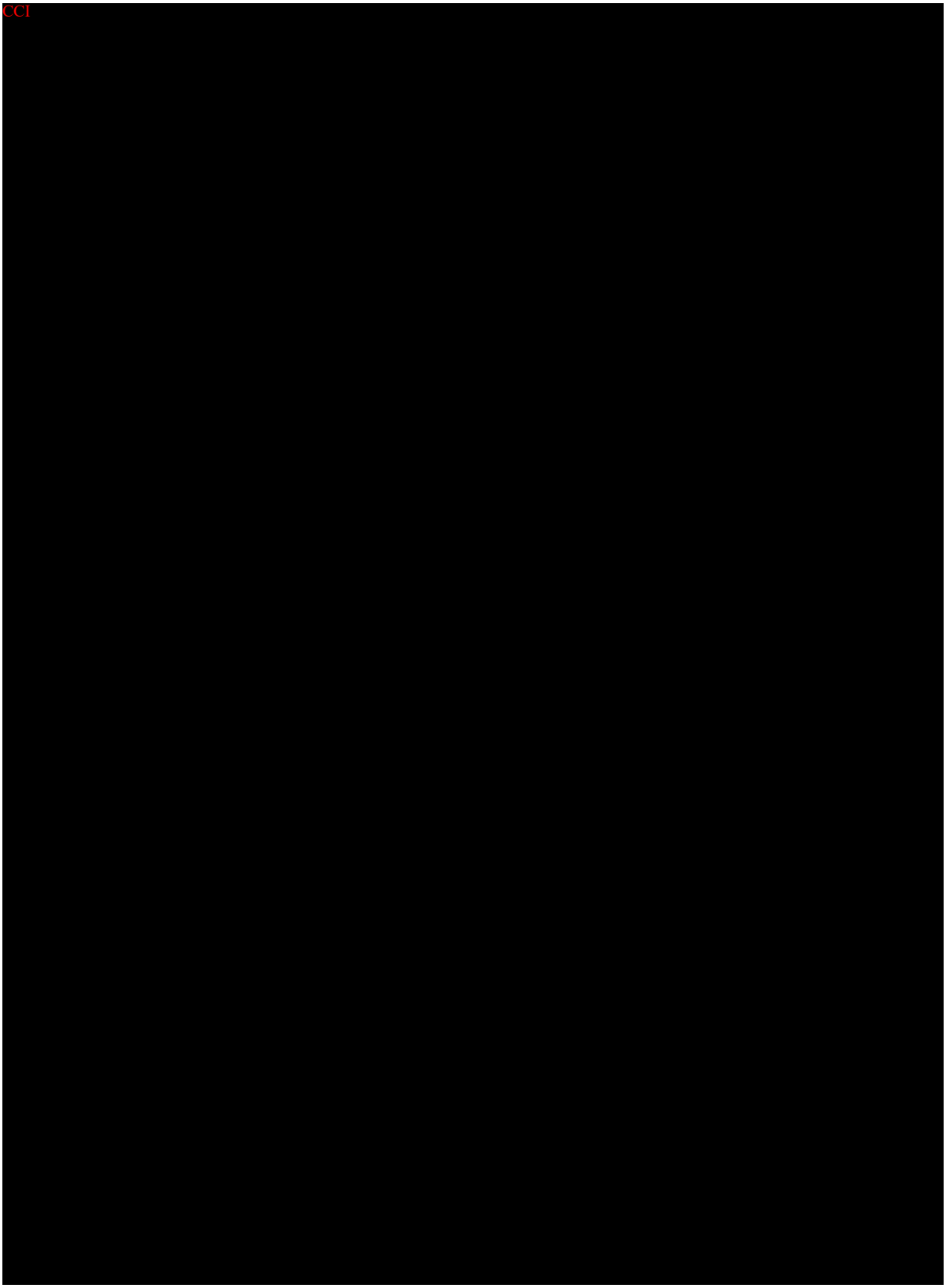

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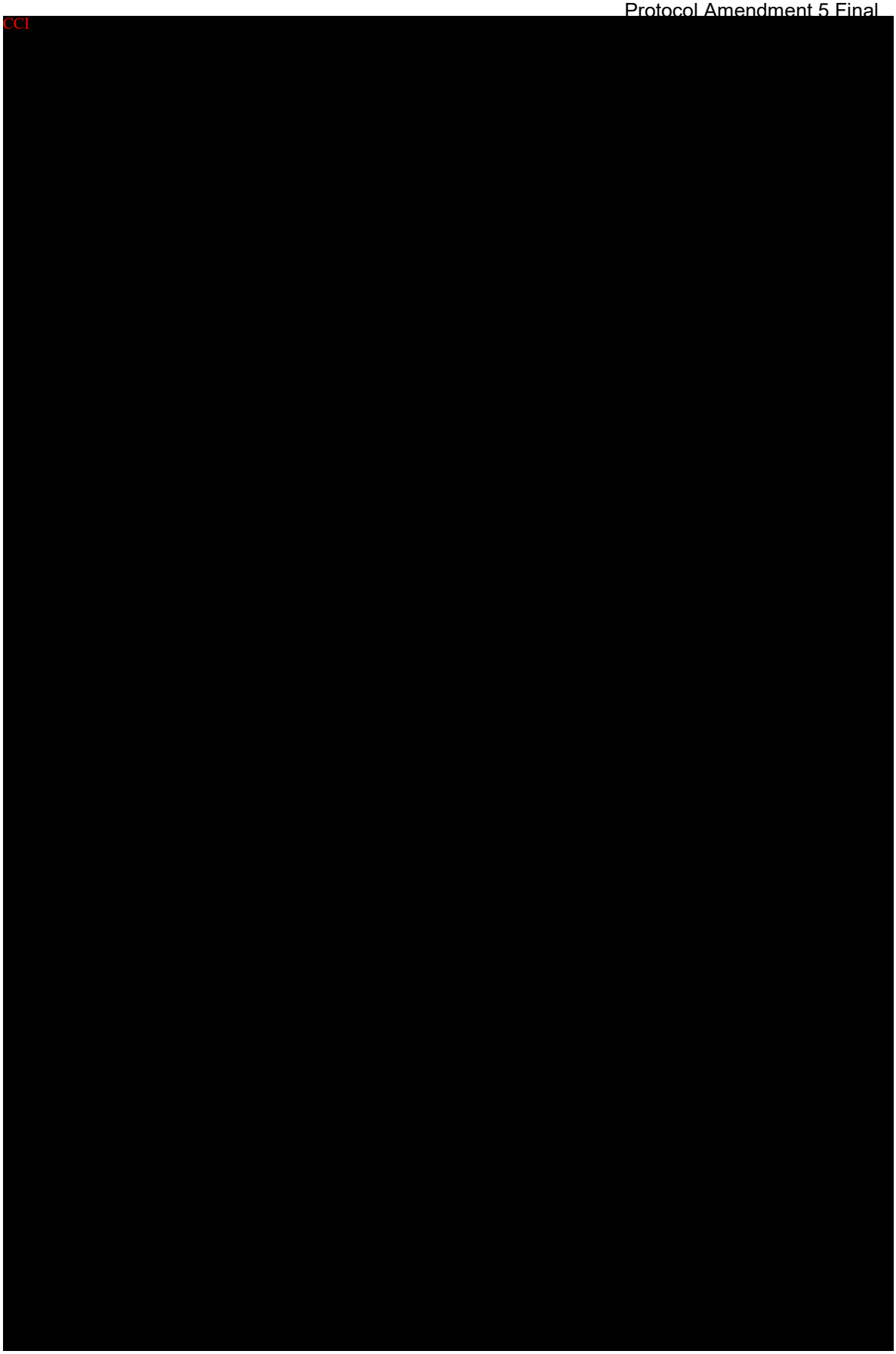

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- **Section 9.4.4.1, Efficacy**

Secondary Descriptive Efficacy Endpoints	Statistical Analysis Methods
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.	CCI [redacted]
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.	
[...]	
From birth (Visit 1-NB) to ***12 months (Visit 5-NB)*** ~~6 months (Visit 4-NB)~~, time to the first occurrence of severe medically assessed, RSV-associated LRTIs according to the case definition.	
From birth (Visit 1-NB) to ***12 months (Visit 5-NB)***~~6 months (Visit 4-NB)~~, time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition.	

Figure 8 Secondary confirmatory endpoint hierarchy

Block 1: RSV vaccine group versus placebo

H_{21}: From birth to 6 months, occurrences of RSV-associated hospitalizations
H_{22}: From birth to 6 months, occurrences of all-cause LRTI
H_{23}: From birth to 6 months, occurrences of all-cause LRTI with hospitalization

Block 2: RSV vaccine group versus placebo

H31: From birth to 7 months, occurrences of severe RSV-associated LRTIs
H32: From birth to 8 months, occurrences of severe RSV-associated LRTIs
H33: From birth to 9 months, occurrences of severe RSV-associated LRTIs
H34: From birth to 10 months, occurrences of severe RSV-associated LRTIs
H35: From birth to 11 months, occurrences of severe RSV-associated LRTIs
H36: From birth to 12 months, occurrences of severe RSV-associated LRTIs

H41: From birth to 7 months, occurrences of any RSV-associated LRTIs
H42: From birth to 8 months, occurrences of any RSV-associated LRTIs
H43: From birth to 9 months, occurrences of any RSV-associated LRTIs
H44: From birth to 10 months, occurrences of any RSV-associated LRTIs
H45: From birth to 11 months, occurrences of any RSV-associated LRTIs
H46: From birth to 12 months, occurrences of any RSV-associated LRTIs

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- **Section 9.4.4.2, Detailed Statistical Analysis Methods:**

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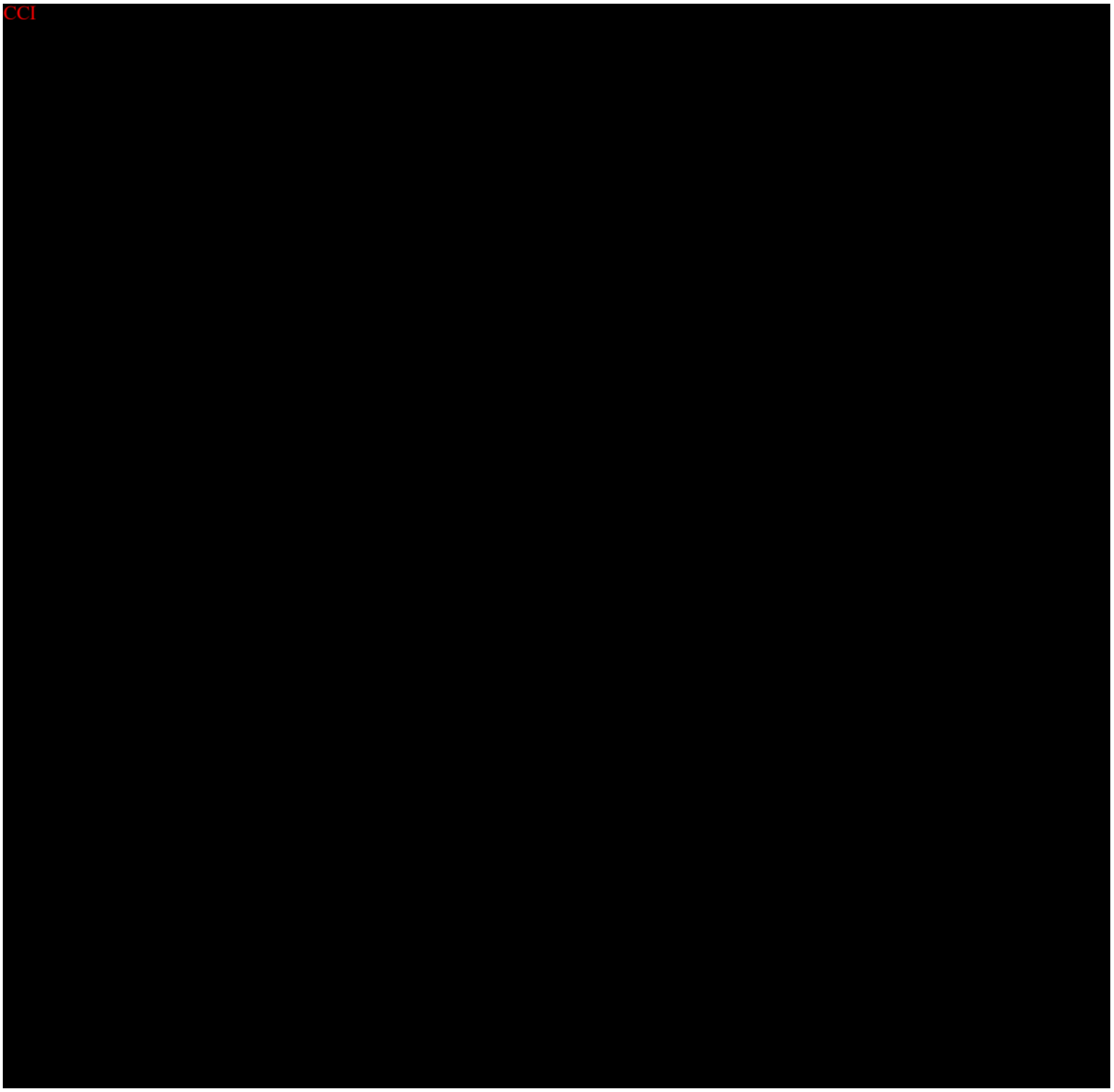

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- **Section 9.4.4.3, Immunogenicity**

Secondary Immunogenicity Endpoints – Maternal Participants	Statistical Analysis Methods
• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and RSV-B 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 – Infant Participants	Statistical Analysis Methods
• RSVPreF3 IgG-specific antibody concentration, and • Neutralizing antibody titers against RSV-A and RSV-B. 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)	CCI [redacted]

• Measured on a blood sample collected 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.	

- **Section 9.4.6.1, Demography and baseline characteristics analyses**

[…]

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 summarized by group, and for each immunogenicity sub-cohort within each group, using descriptive statistics.

- **Section 9.4.6.3, Predicted VE based on surrogate endpoint (deleted)**

~~Surrogate endpoint analyses will be conducted at the same time as interim analysis #2 when there are approximately 4,600 maternal participants with the opportunity to complete 6 months follow up post-delivery. If the lower bounds of the credible interval for the observed vaccine efficacy (VE) on either primary objective meet the pre-specified criteria, then the company will claim success based on the VE. However, if the pre-specified lower bounds for the observed VE are not met for either primary objective, then the company plans to evaluate VE predicted by the surrogate endpoint model:~~

~~The strategy can be summarized in 3 steps:~~

1. ~~Estimate the surrogate endpoint model using data from one or more GSK epidemiology studies. The model will be created based on the GSK RSV neutralizing antibody assay before the analysis of RSV MAT-009.~~
2. ~~Validate the model at interim analysis #2 (that is, validate whether the observed VE (when 4600 participants have had the opportunity to complete 6 months post-delivery) is "similar to" the predicted VE). The validation of the model is done using an equivalence test (H_0: $\delta < -\Delta$ or $\delta > \Delta$) if feasible, where δ is the difference between the predicted VE and the observed VE, and Δ is an appropriate equivalence margin, or other methods for the validation of surrogate endpoints such as Principal stratification [Frangakis, 2002; Follmann, 2006; Gilbert, 2008].~~
3. ~~Claim success based on predicted VE at the end of interim analysis #2. This will occur if the predicted VE for either primary endpoint meets the pre-specified success criteria based on a successfully validated surrogate endpoint model. RSV MAT-009 will continue as designed. It is expected that the observed VE will meet the success criteria as trial continues (during Stage B).~~

~~4. For more details, please refer to the separate statistical analysis plan "RSV Maternal Serocorrelate SAP."~~

- **Section 9.5, Interim analyses**

Interim analyses of vaccine efficacy for the two primary endpoints will be performed.

~~In Stage A, t~~***T***he ***1st*** interim analysis will be conducted when 4600 maternal participants are randomized, and the purpose of this analysis is to decide if further enrollment is needed and if the study can be stopped for futility. The number of completed participants and events at this interim will be based on the accrual rate and attack rate in the trial. Based on a blinded assessment of the overall accrual rate and attack rate in the trial, GSK may decide if this interim will be performed. If the accrual rate is faster than expected or the attack rate is lower than expected, GSK may decide to skip this interim.

Interim analyses of vaccine efficacy for the two primary endpoints will be conducted when ***3000,*** 4600, ~~6500,~~ and ***7000***~~8000~~ maternal participants have had the opportunity to complete 6 months follow-up post-delivery. The trial can claim success if either of the two primary endpoints meet success criteria at any of those three interim analyses. ***If there is a small number of events when interim analyses for efficacy are conducted, GSK may decide (blinded to treatment group) to skip those interim analyses. The alpha at skipped interim analyses will be considered not spent and the remaining alpha will be distributed according to the alpha spending function at the remaining interim and final analyses.***

Table 26 summarizes the interim analysis schedule and the decisions that may be made at each analysis. Decision rules are summarized in Section 9.2 and described in detail in the SAP and related documents.

Table 26 Interim Analysis Schedule and Possible Decisions Made at each Analysis

Interim #	Timing of analysis			Can decide to stop accrual?	Can stop for futility?	Can claim success?
	~~Stage~~	# Participants	Participants triggering analysis			
1	~~A~~	4600	Maternal participants randomized	Yes	Yes	No
2	~~B~~	***3000***~~4600~~	Maternal participants with the opportunity to complete 6 months follow-up post-delivery	-	Yes	Yes
3	~~B~~	***4600***~~6500~~		-	Yes	Yes
4	~~B~~	***7000***~~8000~~		-	Yes	Yes

- **Section 9.5.1, Sequence of analyses**

In addition to the interim analyses of efficacy described above, full analyses will occur as described below:

- ***When an interim analysis of vaccine efficacy for the two primary endpoints shows that the trial can claim success (to evaluate primary efficacy endpoints, immunogenicity, reactogenicity and safety).***

- ~~When 4600 maternal participants have had the opportunity to complete 6 months follow up post-delivery/birth (to evaluate primary and surrogate efficacy endpoints, immunogenicity, reactogenicity and safety if either primary (observed), or surrogate (predicted) vaccine efficacy endpoints meet success criteria).~~
- When all maternal and infant participants enrolled ~~in both Stage A and Stage B~~ complete 6 months follow-up post-delivery/birth (to evaluate primary and secondary efficacy endpoints, immunogenicity, reactogenicity and safety).

- **Section 9.5.2, Statistical considerations for interim analysis**

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[redacted]

- **Section 10.2, Appendix 2: Clinical laboratory tests**

There is one assessment, hematocrit, which will be tested at Visits 1, 2 and 3, for all maternal participants in Stage A who are assigned to the immunogenicity sub-cohort, until the ~~current~~ protocol amendment 2 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 2 being approved) in the respective study country(ies). Testing will be performed by a central laboratory. Results will be used to help evaluate changes over time in antibody titers / concentrations that may be related to volumetric changes during pregnancy, if deemed necessary.

- **Section 10.7.1, List of abbreviations**

[…]

VE	***Vaccine efficacy***
WHO	World Health Organization

- **Section 10.10.1,** CCI [redacted]

CCI [redacted]

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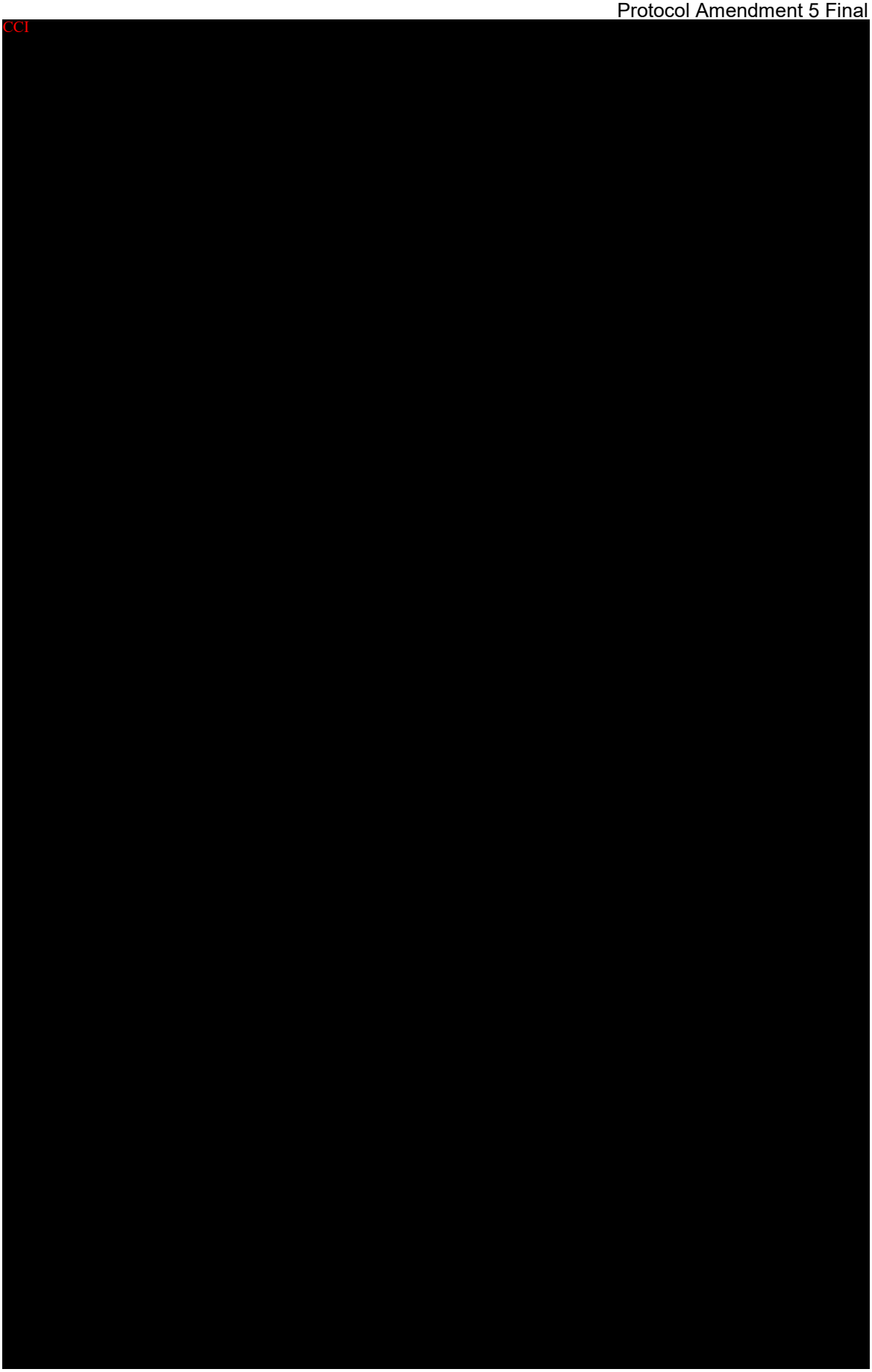

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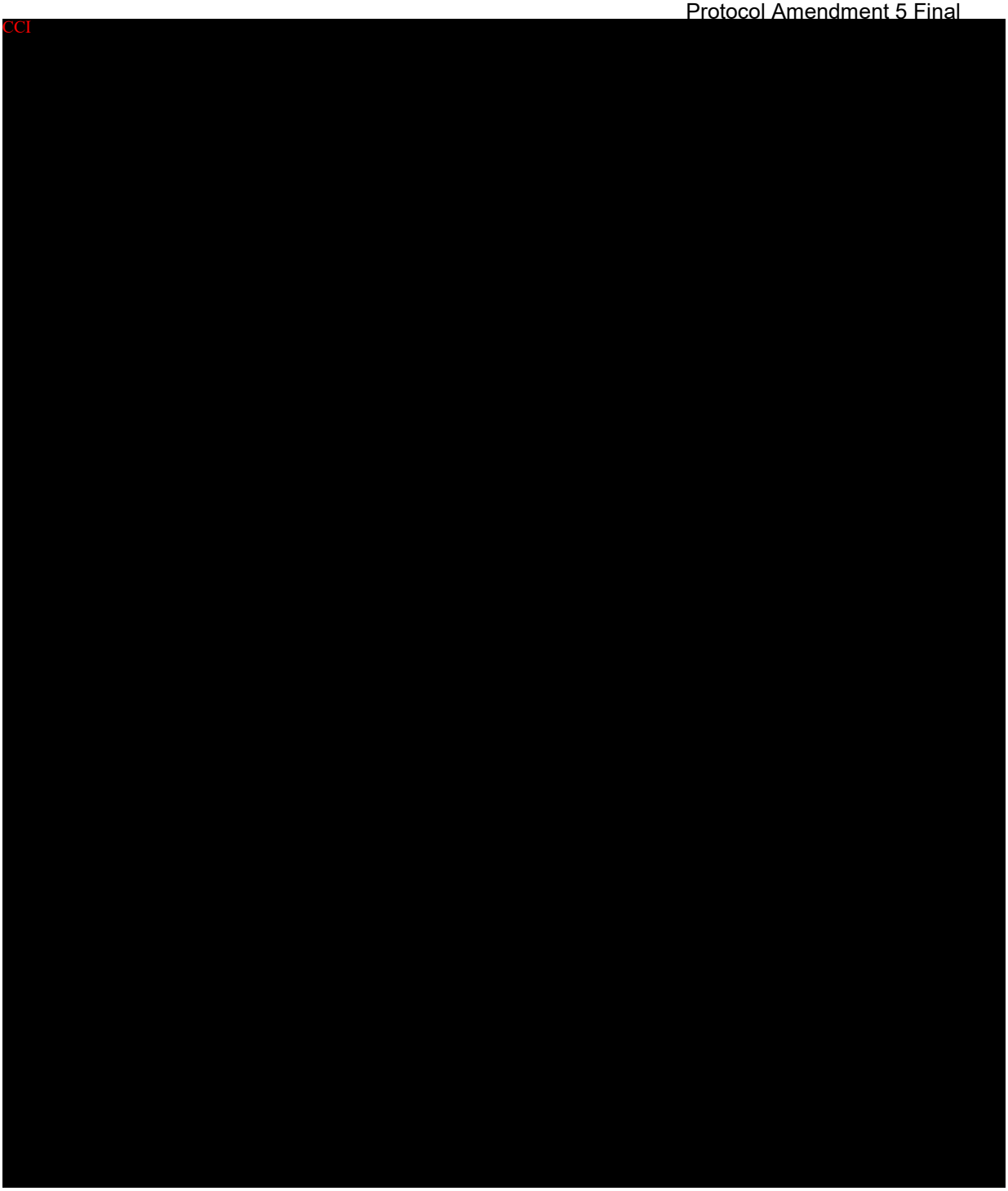

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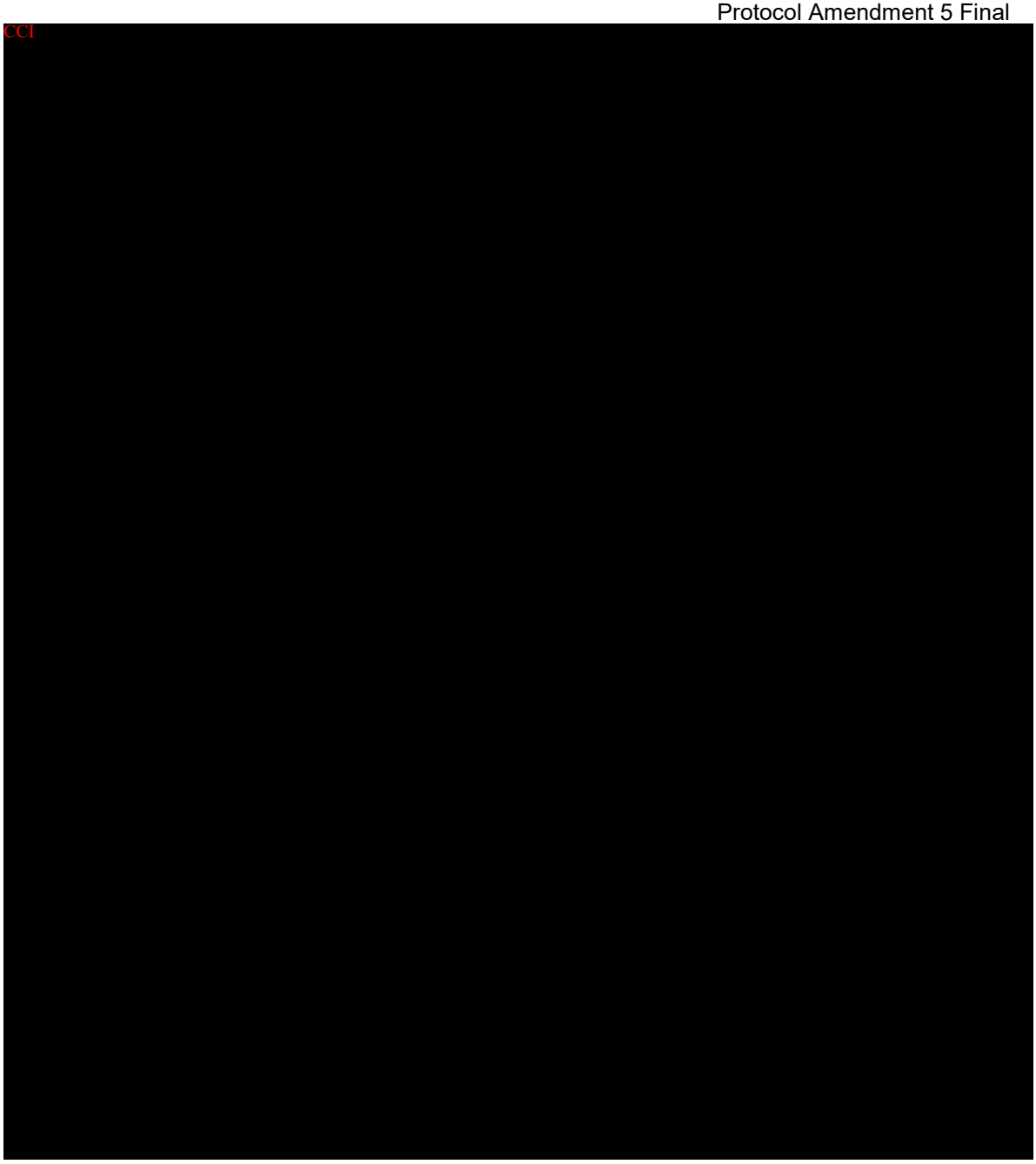


Overall Rationale for the Protocol Amendment 2:

This protocol has been amended to:

- implement the changes discussed and agreed with Center for Biologics Evaluation and Research (CBER).
- extend the infant respiratory tract illness (RTI) surveillance to 12 months to ensure that this period will cover at least 1 full RSV season.
- remove the collection of hematocrit samples due to challenges (mostly due to the COVID-19 pandemic) faced in several countries preventing the samples from reaching the central lab in adequate time for testing.
- define an additional population for analysis: Modified Full Analysis- Efficacy Set.

Also, this amendment includes editorial changes to improve the consistency and applicable administrative changes. Typographical errors have been corrected.

List of main changes:

Section # and title	Description of change	Brief rationale
Section 1.2 Schema, Section 1.3 Schedules of Activities (Table 2, Table 3), Section 2 Schedule of activities for infant participants, Section 2.1 Study rationale, Section 3 Objective(s) and Endpoint(s), Section 4.1 Overall design (Figure 2), Section 4.4 End of study definition, Section 8.3.1 Time period and frequency for collecting AE, SAE and other safety information (Table 18), Section 8.4.2.2 Infant participants, Section 8.4.6 Follow-up of infant respiratory tract illnesses, Section 9.4.4.1 Efficacy (Figure 8, Figure 9), Section 9.5.1 Sequence of analyses, Section 10.7.2 Glossary of terms	Updated to extend the infant RTI surveillance to 12 months.	Extended to ensure that infant RTI surveillance will cover at least 1 full RSV season.
Section 1.3 Schedule of activities (Table 1), Section 4.1 Overall design (Figure 1), Section 4.2.4.2, Section 6.3.2.1.1 Stage A (Figure 4), Section 8 Study assessments and	Updated to remove the collection of hematocrit samples	Removed due to challenges (mostly due to the COVID-19 pandemic) faced in several countries preventing the samples from reaching the central lab in adequate time for testing. Samples collected until the current protocol amendment 2 is approved (unless IEC/IRB allows for immediate

Section # and title	Description of change	Brief rationale
procedures, Section 8.1.1 Biological samples (Table 12), Section 8.1.2 Laboratory assays (Table 15, Table 17), Section 10.2 Appendix 2: Clinical laboratory tests		implementation of this measure to reduce participant's burden, prior to full Amendment 2 being approved) will be still used, if required, as described in Section 10.2.
Section 1.3 Schedule of activities (Table 3)	The interval between screening to Day 1 visit has been updated from 0-29 days to 0-28 days.	The interval between screening and Day 1 has been updated to ensure consistency (between Table 1 and Table 3).
Section 4.2.6 Case defintions	The case definitions for data analysis in infants have been updated to merge the severe and very severe LRTI case definitions. Therefore, across the document, mention of 'including very severe' has been deleted.	The case definition has been updated based on the feedback received from CBER.
CCI [redacted]		
Section 5.1.1 Inclusion criteria for enrolment-Maternal participants	Change has been made to the allowed pre-pregnancy BMI range for enrolment (17.0-39.9 kg/m^2 instead of 18.5-39.9 kg/m^2)	The pre-pregnancy BMI range has been modified to allow enrolment of participants considered as mild underweight. Also, the BMI ranges may differ depending on the race and ethnicity (e.g. the average values in the Asian population are about 1-2 points lower than the standard international chart).
Section 5.2.1.1 Medical conditions	Included a note to clarify that- still births, pre-terms births and spontaneous abortions will be counted per pregnancy (regardless of the number of fetuses in the concerned pregnancy) .	The note is added to further clarify that the exclusion criteria on history of 2 or more prior stillbirths/preterm births ≤34 weeks or consecutive spontaneous abortions are to be counted/considered "per pregnancy" Thus, when any of those events occurs on multiple pregnancies (twin/triplet, etc.), it will be considered as a single case.
Section 5.2.1.2 Prior/concomitant therapy	Addition of the specific allowed window for COVID-vaccines	Following the implementation of Covid-19 mass vaccination strategies in the different countries, incuding vaccination of pregnant women, the allowed window for the administration of these vaccines has been added.
Section 6.5.1 Maternal participants	Included "antivirals" to the list of concomitant medications to be recorded (in addition to antibiotics, analgesics and anti-pyretics).	Text added to record all infection-related medications taken within 7 days- prior to the study vaccination.
Section 8 Study assessment and procedures	Text added to allow flexibility towards the conduct of RTI surveillance contact in the event of special circumstances.	For the ease of study conduct in the event of a pandemic, social distancing, confinement measurements and considering the impact on the region's usual RSV seasonality, the frequency of

Section # and title	Description of change	Brief rationale
		active contacts may be temporarily adapted.
Section 8.2.1.1 Medical/vaccination history	Added guidance with regards to the pre-pregnancy BMI in the exceptional circumstance when a pre-pregnancy weight/BMI (or weight/BMI in the 1st trimester of pregnancy) is not available.	Addition made since there might be instances were the first maternal visit does not take place at the 1st pregnancy trimester but later.
Section 8.3.3 Regulatory reporting requirements for SAE, subsequent pregnancies, and other events (Table 19)	Timeframe for reporting subsequent pregnancy by the investigator/site staff after receipt or awareness, changed from 2 weeks to 24 hours.	This change is being made to correct inconsistencies between pregnancy reporting form and protocol template.
Section 8.3.3.1 Contact information for reporting SAES, AESIs, subsequent pregnancies and other events	Contact information updated for SAE reporting email address.	The email address is changed to align to the most recent GSK template related recommendation.
Section 8.3.4.2 Pregnancy outcomes (Table 21), Section 10.3.2 Definition of SAE	Footnote added to clarify the reporting plan for congenital anomalies in the event of infant's participation in the study, versus in the event that there is no live birth, or no signed informed consent for the infant or the congenital anomaly is being reported for a subsequent pregnancy	Clarification made in order to prevent double reporting in both maternal participant and infant's eCRF. Clarification has been added to the table as a footnote.
Section 8.3.4.2 Pregnancy outcomes, Section 11 References	The reference of Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines has been updated.	To refer to the most updated version of MACDP guidelines.
Section 9.3 Populations for analyses(Table 25)	An additional analysis set for infant participants- 'Modified Full Analysis-Efficacy Set' has been added that excludes the infants born less than 4 weeks post maternal participant's vaccination	The elimination of infants born less than 4 weeks after the maternal participant's vaccination from this population for analyses has been made to ensure that the analysis set takes into account the optimal timeframe for elicitation of immune response in the maternal participants and for antibody transfer to the babies prior to delivery.
Section 9.4 Statistical analyses	The analysis plan has been updated to include details about modified full analysis- efficacy set	For consistency, the statistical analysis plan section has been updated.
Section 10.3.5 Adverse events of special interest	All AESIs are presented in list format. Also, the mention of 'worsening of existing conditions' has been deleted. A note has been added that worsening of existing AESI conditions are to be collected as (S)AEs (aggravated) but not as study-AESIs.	For the ease of reading and presentation, all AESIs are presented in list format. As per the GAIA guidelines, AESIs to be reported will include only the new diagnoses made post study vaccine administration, and not the worsening of pre-existing events.
Section 10.6 Appendix 6: Country specific requirements	Section 10.6.2 has been added to include South Korea specific regulatory requirements for the study.	The details have been added under country specific requirements, following consultation with South Korea regulatory authorities.

Section # and title	Description of change	Brief rationale
Section 10.8 Appendix 8: Gestational age assessment	A note is added to refer to SPM for details on estimation of the date of delivery/due date.	Additional details and clarifications are added in SPM on accurate estimation of due date. Hence the note is added in the protocol.
Section 10.9 Appendix 9: Definitions of maternal, fetal and neonatal events of interest as per GAIA	Clarification note added in Appendix 9, that not all events listed in this section are AESIs in the RSV MAT-009 (GRACE) study and to refer to Section 10.3.5 for the list of AESIs. Also, all the events that are AESIs, have been flagged.	As Appendix 9 contains all maternal, fetal and neonatal events of interest per GAIA definition as well as definitions for those events not (yet) defined per GAIA, of which only specific events are considered as AESIs in this study, The note is added to help in accurate categorization.

Detailed description of Protocol Amendment (# 2) changes:

In this section, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***.

- Across the document mention of 'very severe/including very severe' has been deleted.
- **Section 1.2, Schema**

During both stages, maternal participants who receive the study intervention will be followed for safety for up to approximately 10 to 11 months (from screening until 6 months after delivery). Infant participants will be evaluated for the occurrence of medically assessed, RSV-associated lower respiratory tract infections ***and safety*** for ***12***~~9~~ months after birth ~~and followed for safety for 12 months after birth~~.

- **Section 1.3 Schedules of Activities (SoAs)**

Table 1 Schedule of activities for maternal participants

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven		
Gestational Age (GA)	≤ 28 days before V1	$24^{0/7}$ – $34^{0/7}$		Until Delivery	Delivery			Safety visit	MA-RTI visit	For monthly contacts: Section 8.4.2.
Visit Day	D-28 – D1 before randomization	D1	D31		D1PD	D43 PD	D181 PD			Table 3
~~Blood sample (hematocrit: ~ 3.0 ml)~~		~~Sub-cohort ●~~	~~Sub-cohort ●~~		~~Sub-cohort ●~~					~~Collected only from a sub-cohort in Stage A. See Table 12 and Sections 8.1.1 and 8.1.3.~~

The timing of an event-driven site visit (e.g., to further evaluate a potential AE or MA-RTI) cannot be defined with precision in the protocol. Event-driven visits may occur throughout the study. ● is used to indicate a study procedure that requires documentation in the individual eCRF. ○ is used to indicate a study procedure that does not require documentation in the individual eCRF. V = visit; D = day; GA = gestational age; MA-RTI = medically attended respiratory tract illness; PD = post delivery~~; Hct = hematocrit~~.
* V2 may be replaced by V3, depending on delivery date.

Table 2 Schedule of activities for infant participants

Visit / Contact	V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		RTI Surveillance: Section 8.4.2 RTI Visit: Sections 8.4.3 and 8.4.4
Age of infant	Birth	6 weeks	3 months	4 months	6 months	9 months	12 months	Contacts	Visits	
Visit Day	D 1-21	D43	D91	D121	D181	D271	D366	Birth – ***D366***		See Table 3 for intervals between visits, contacts.
Distribute infant RTI-diary card	O	O	O	O	O	***O***			O	Distribute at V1-NB: Distribute additional RTI-diary cards as needed. ***Section 8.4.2.2 and SPM***
Review infant RTI-diary card		O	O	O	O	O	***O***		O	
Collect infant RTI-diary card		O	O	O	O	O	***O***		O	Collect RTI-diary cards that are fully filled out. ***Section 8.4.2.2 and SPM***
Transcribe applicable infant RTI-diary card data to eCRF		●	●	●	●	●	●		●	

Table 3 Intervals between study visits and contacts

Interval	Optimal interval in Days	Allowed interval in Days	Additional Information
Maternal participants			
Screening to V1	0	0–***28***~~29~~	The screening interval extends from Day -28 to Day 1 before randomization. If all eligibility criteria can be confirmed on the day of screening and all required procedures can be performed, then, "Screening" and "Visit 1" may occur on the same day (refer to Section 8.2.1.2). Data from all screening procedures must be available and eligibility must be confirmed before the participant is randomized. If a participant is screened but not vaccinated within the allowed interval, a re-screening should be done to establish the participant's eligibility. Please make sure the participant's gestational age is still within the allowed range, refer to Section 10.8 for guidance on gestational age assessment.
V3 (delivery)	0	1 day before to 3 days after delivery	For maternal participants in the Stage A immunogenicity sub-cohort: collect maternal blood sample at any point from the start of labour up to delivery. ***(NOTE: For participants for which a cesarean section is planned, the sample may be collected as soon as the participant arrives at the clinic and the intravenous line is inserted to prepare them for the cesarean section).*** If blood is not collected during delivery, collect maternal blood sample no later than 72 hours after delivery. For all participants in both Stage A and Stage B: A cord blood sample should be collected at the time of delivery. If cord blood cannot be collected at delivery, a blood sample should be collected from the infant participant as soon as possible and no later than 72 hours after birth.
Infant participants			
RTI surveillance contacts (Birth to ***V5-NB*** ~~Contact 2-NB~~)*			

**** In special circumstances, the frequency of active contacts may be temporarily adapted, refer to Section 8.4.2.2.1 for guidance***

- **Section 2, Study Rationale**

The study will also evaluate the incidence of medically attended RSV-associated respiratory tract illnesses (MA-RTI) in maternal participants for up to 6 months after delivery, and the incidence of medically assessed, RSV-associated respiratory tract / lower respiratory tract illnesses (RTI/LRTI) in infants for up to ***12***~~9~~-months after birth.

- **Section 3, Objectives and endpoints**

Secondary confirmatory[3] efficacy objectives	Secondary confirmatory[3] efficacy endpoints
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed1, RSV-associated severe LRTIs in their infant[4] participants up to 7, 8***,*** ~~and~~ 9***, 10, 11 and 12*** months of age.	From birth (Visit 1-NB) to 7 months, birth to 8 months, ~~and~~ birth to 9 months (C2-NB), ***birth to 10 months, birth to 11 months, and birth to 12 months (Visit 5-NB),*** occurrences of medically assessed, RSV-associated severe LRTIs according to the case definitions2.
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing medically assessed1, RSV-associated LRTIs of any severity in their	From birth (Visit 1-NB) to 7 months, birth to 8 months, ~~and~~ birth to 9 months (C2-NB), ***birth to 10 months, birth to 11 months, and birth to 12 months (Visit 5-NB),*** occurrences of

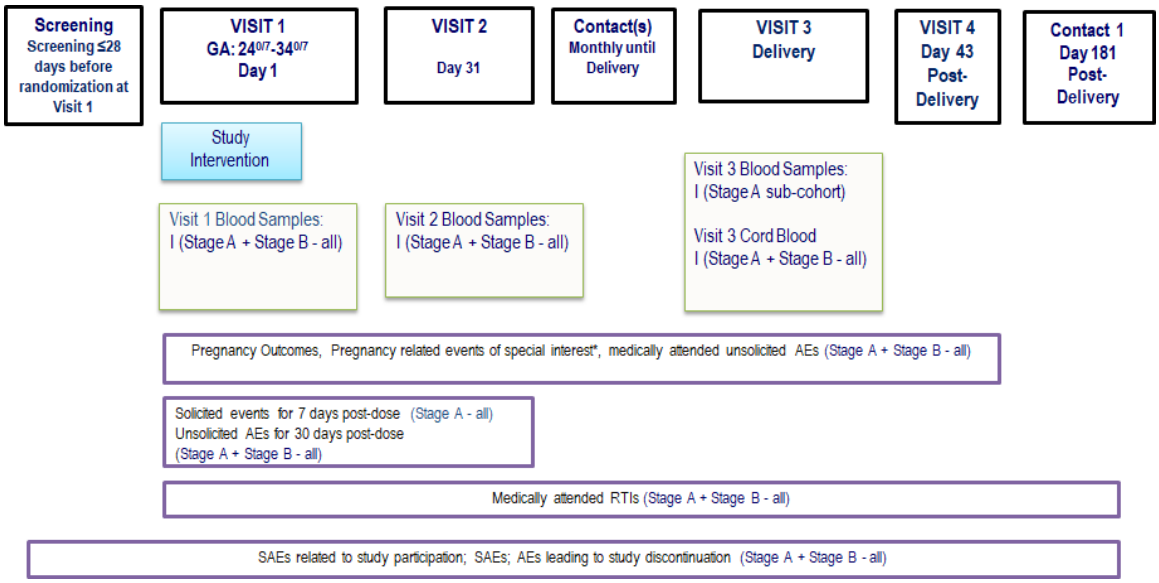
Secondary confirmatory[3] efficacy objectives	Secondary confirmatory[3] efficacy endpoints
infant***[4]*** participants [4] up to 7, 8~~, and 9~~***, 10, 11 and 12*** months of age.	any medically assessed, RSV-associated LRTIs according to the case definitions2.
Secondary descriptive efficacy objectives	Secondary descriptive efficacy endpoints
To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any severe medically assessed1, RSV-associated LRTIs, in their infant4 participants ***up to 6 months of age***, according to the case definition2.	From birth ***(Visit 1-NB)*** to 6 months ***(Visit 4-NB)***, time to the first occurrence of severe medically assessed1, RSV-associated LRTIs according to the case definition2
To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any medically assessed, RSV-associated LRTIs in their infant4 participants ***up to 6 months of age***, according to the case definition2.	From birth ***(Visit 1-NB)*** to 6 months ***(Visit 4-NB)***, time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition2
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[4] 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].***

A footnote as not applicable has been deleted. Therefore, all the footnote numbers have been revised.

[3]~~Note that as per the case definitions outlined in Table 8, which are based on the WHO case definitions, RSV-associated very severe LRTIs are a subset of RSV-associated LRTIs but not necessarily a subset of RSV-associated severe LRTIs. As such, an infant participant may meet the criteria for RSV-associated very severe LRTI without meeting that of RSV-associated severe LRTI. In this protocol, the primary endpoint related to medically assessed RSV-associated severe LRTI will include medically assessed RSV-associated very severe LRTI. Similarly, medically assessed, RSV-associated LRTI endpoints will include RSV LRTI of any severity including cases that meet severe and very severe LRTI case definitions.~~

- **Section 4.1, Overall design**

Figure 1 Study design overview – maternal participants



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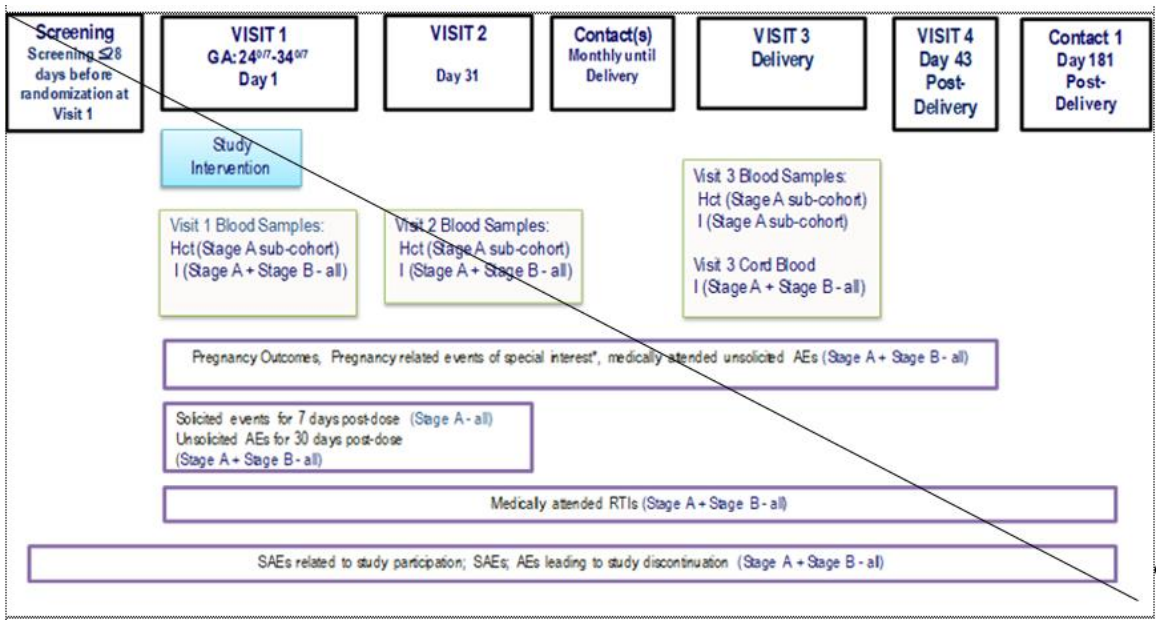
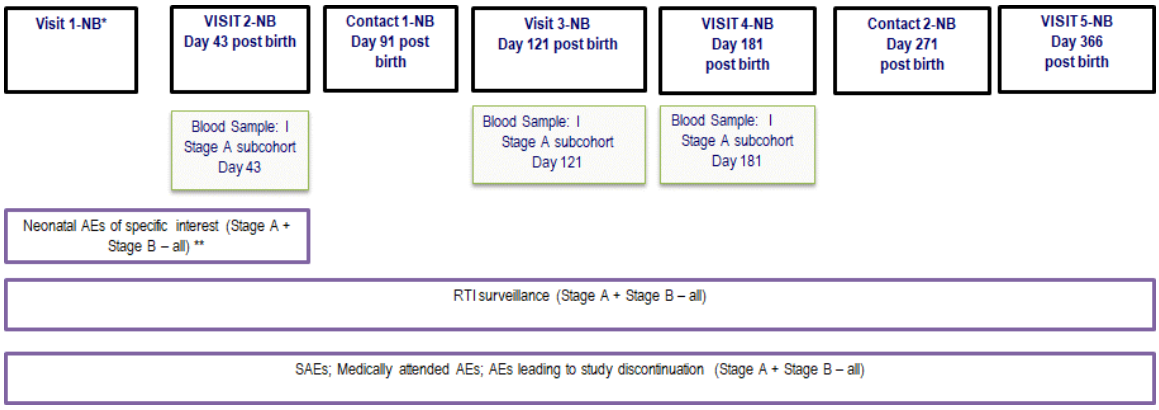


GA = Gestational age~~; Hct = hematocrit~~; I = immune response; (S)AE = (serious) adverse event; RTI = respiratory tract illness

Figure 2 Study design overview – infant participants



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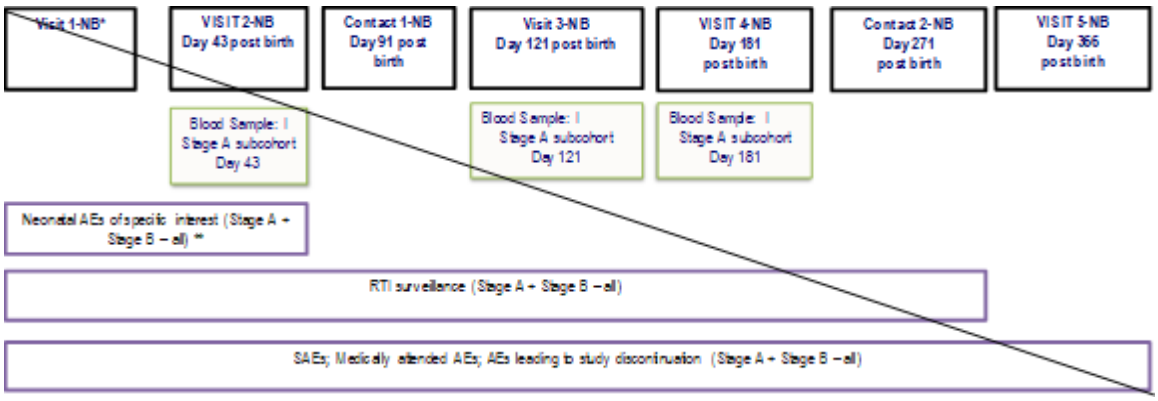


- **Section 4.2.4.2 Blood sampling and immune response assessment**

A sub-cohort for maternal blood sampling and assessment (~~haematocrit plus~~ immune response at Day 1 (Visit 1), Day 31 (Visit 2), and Delivery) has been defined to limit discomfort and risk while ensuring enough observations to support robust evaluation of secondary maternal immunogenicity objectives ***(see also Table 3)***.

- **Section 4.2.5, Adaptive design**

Typographical error corrected:

This adaptive trial design will provide evidence for the efficacy of the RSV maternal vaccine in the prevention of medically assessed, RSV-associated LRTI of any severity and medically assessed, RSV-associated severe LRTI. The design has over 90% power to detect the target vaccine efficacies of 70% and 50% on severe and any-severity LRTI, respectively. If the vaccine meets these target VE estimates, this design offers the opportunity to identify this benefit with an expected sample size of approximately ***8,500***~~7,000~~ maternal participants, which may obviate the need to enroll the maximum sample size of 10,000. In addition to the analysis of observed vaccine efficacy, as described above, the study may also assess predicted vaccine efficacy through a surrogate endpoint (namely RSV neutralizing antibody) reasonably likely to predict clinical benefit.

- **Section 4.2.6, Case definitions**

Table 8 RTI/LRTI case definitions for data analysis in infants

RSV-RTI	Runny nose, OR Blocked nose, OR Cough AND Confirmed RSV infection ~~5,6~~ ***4,5***
RSV-LRTI	History of cough OR difficulty in breathing ***1*** ~~2~~ AND SpO_2 < 95%***2***~~3~~, OR RR increase ***3*** ~~4~~ AND Confirmed RSV infection ***4,5*** ~~5,6~~
RSV-severe LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93%***2***~~3~~, OR lower chest wall in-drawing *OR inability to feed OR failure to respond / unconscious*
~~RSV-very severe LRTI~~	~~Meeting the case definition of RSV-LRTI~~ ~~AND~~ ~~SpO2 < 90%[3], OR inability to feed OR failure to respond / unconscious~~
RSV hospitalization	Confirmed RSV infection *4,5* ~~5,6~~ AND Hospitalized for acute medical condition *6* ~~7~~
All-cause RTI	Runny nose, OR Blocked nose, OR Cough
All-cause LRTI	History of cough OR difficulty in breathing *1* ~~2~~ AND SpO2 < 95% *2* ~~3~~, OR RR increase *3* 4
All-cause LRTI hospitalization	Hospitalized due to all cause LRTI as defined above

Definitions based on [Modjarrad, 2016], ***except that severe and very severe (SpO2 < 90% OR inability to feed OR failure to respond/unconscious) RSV LRTI cases will be presented together.*** **RTI** = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.

~~1~~ ***~~Please note that per the above case definitions which are based on the WHO case definitions, "RSV-very severe LRTIs" are a subset of "RSV-LRTIs" but not necessarily a subset of the "RSV-severe LRTIs". As such, an infant participant may meet the criteria for very severe LRTI without meeting that of severe LRTI~~***

1 ~~2~~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 ~~3~~ For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI~~, <87% for very severe LRTI.~~

3 ~~4~~ 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 ~~5~~ Confirmed RSV infection defined in Section 4.2.6.3

5 ~~6~~ RSV (nasal swab) sampling and testing as specified in Table 14.

6 ~~7~~ Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

CCI

[redacted]

- **Section 4.4, End of Study definition**

End of Study (EoS) occurs with the ***date of*** last (infant) participant last visit (LSLV) ***or the last testing/reading released of the human biological samples related to primary***

and secondary endpoints, whichever comes last. EoS must be achieved no later than 8 months after LSLV*.*

- **Section 5.1.1, Maternal participants inclusion criteria**

  Pre-pregnancy BMI (based on participant's report) ***17.0*** ~~18.5~~ to 39.9 kg/m^2, inclusive.

- **Section 5.2.1.1, Maternal participants exclusion criteria, Medical conditions**

  History of 2 or more prior stillbirths or neonatal deaths, or history of multiple (2 or more) preterm births at ≤ 34 weeks gestation, or multiple (3 or more) *consecutive* spontaneous abortions.

  Note: Still births, pre-terms births and spontaneous abortions will be counted per pregnancy (i.e. regardless of the number of fetuses in the concerned pregnancy).

- **Section 5.2.1.2, Maternal participants exclusion criteria, Prior/Concomitant therapy**

Note that if public health authorities organize an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) outside the routine immunisation program, then the intervals described above can be reduced if necessary for that mass vaccination vaccine, provided the vaccine is licensed and used according to its Product Information. ***In that sense, COVID-19 vaccines will be allowed, when administered ≥ 15 days before or after study vaccination.***

- **Section 6.3.2.1.1, Stage A**

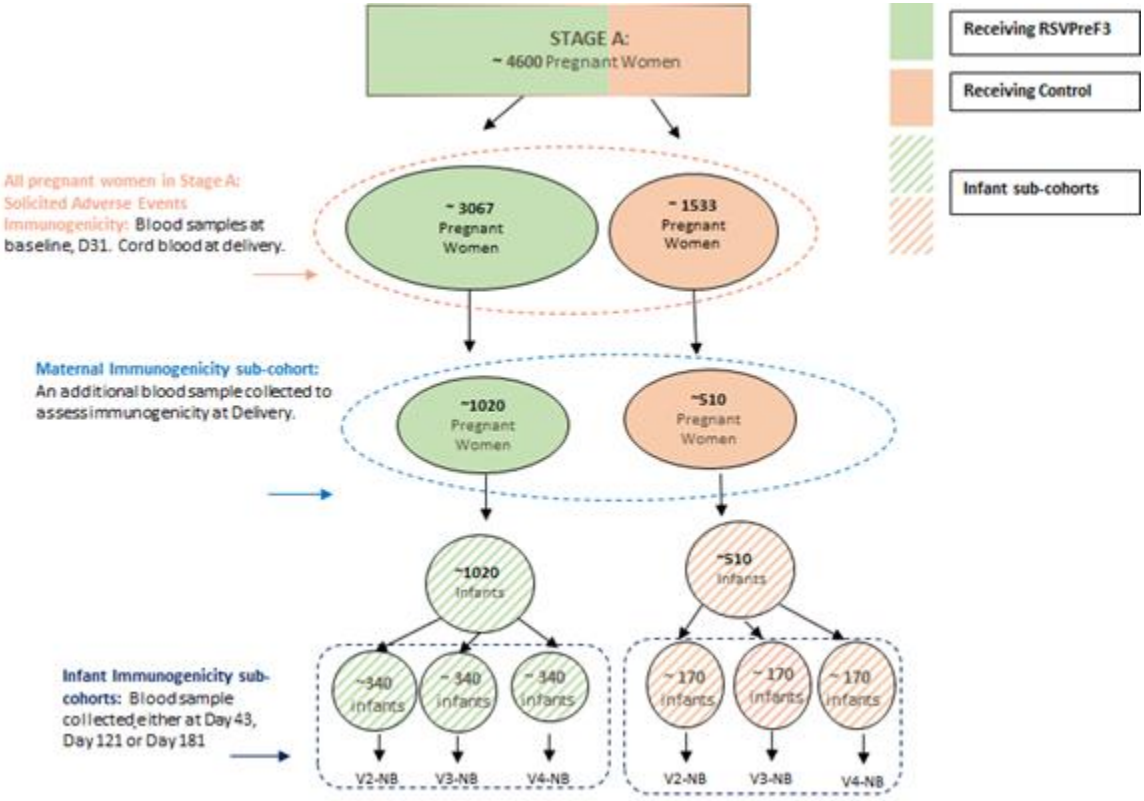
Randomization to the immunogenicity subcohort:

For the ~ 1533 maternal participants in the immunogenicity sub-cohort**,** ~~:~~

a~~A~~n additional blood sample will be collected at delivery**.**

- ~~In order to assess the impact of fluid shifts on the antibody concentration/titer, hematocrit will be evaluated at all 3 blood sampling timepoints (Day 1, Day 31, and delivery).~~

Figure 4 Stage A Sub-Cohort Distributions



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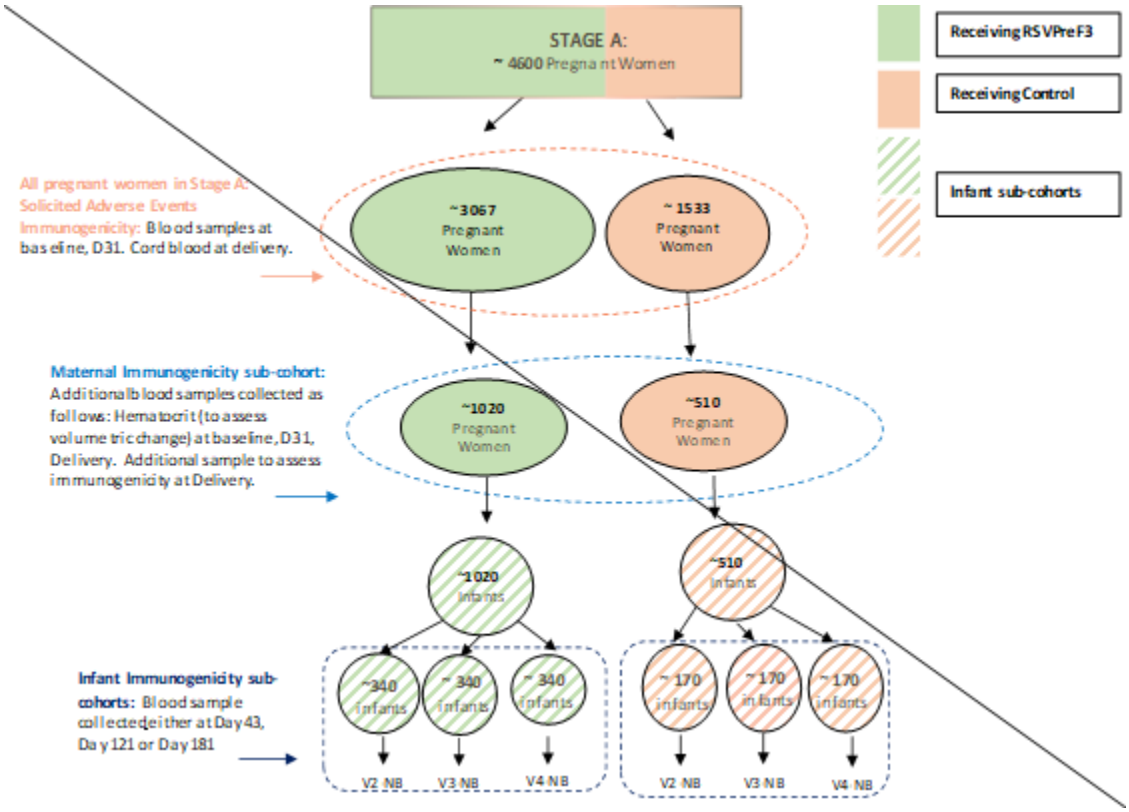


- **Section 6.5.1, Maternal participants**

  All antibiotics, ***antivirals,*** analgesics and anti-pyretics taken within 7 days before dose administration.

- **Section 6.7, Intervention after the end of the study**

The investigator will ask each participant, at the time of informed consent, if she is interested in taking part in a booster study and will document this in the source documents only. During the study conclusion visit***/contact***, the investigator will confirm the participant's interest and report it in the eCRF.

- **Section 7.1.1, Criteria for temporary delay for enrolment and/or vaccination**

  Use of systemic antibiotic or antiviral treatment within 48 hours before study vaccination.

Refer to SPM for further guidance.

- **Section 8, Study assessment and procedures**

Study Procedures During Special Circumstances

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

For guidance regarding the temporary delay of study intervention administration because of exposure to COVID-19, please refer to the SPM for details.

For the duration of such special circumstances:

- Nasal swabs for central testing must be collected using GSK-provided supplies. (note: if collection at either the study site, participant's home or an alternate location is not possible, participants may be instructed to collect nasal swab samples by themselves/for their infant. Collection will be done using GSK-provided supplies and all the corresponding detailed instructions to allow such collection will be provided along with the nasal swab sampling kit)
- ~~Blood samples for central assessment of hematocrit must be collected using GSK provided supplies.~~
- Blood / cord blood samples for assessment of immune response must be retrieved, processed and stored in accordance with the Investigator Laboratory Manual.

The frequency of RTI surveillance contacts by site personnel may be temporarily adapted.

Impact on the analysis sets for efficacy and immunogenicity will be determined on a case by case basis.

*It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic ~~(version 2, 27 March, 2020)~~ for more details.

- **Section 8.1.1, Biological samples**

Table 12, Biolgical samples- maternal participants

Maternal Sample type	Collected to Evaluate	Minimum Quantity per participant	Unit	Time point	Additional Information
Whole blood	~~Hematocrit~~	~~~3~~	~~ml~~	~~Visit 1 (Day 1) pre dose~~ ~~Visit 2 (Day 31)~~ ~~Visit 3 (Delivery)~~	~~*Applies to Stage A Immunogenicity sub-cohort only*~~
	Immune response	~10	ml	Visit 1 (Day 1) pre dose Visit 2 (Day 31) Visit 3 (Delivery)	*Visit 1 and Visit 2: Applies to all participants, Stages A & B* *Visit 3: Applies to Stage A Immunogenicity sub-cohort only*
		~***30***~~39~~ ~20	ml ml	Estimated TOTAL if assigned to the immunogenicity sub-cohort Estimated TOTAL if NOT assigned to the immunogenicity sub-cohort	

Table 14, Biolgical samples- infant participants

Additional text to refer to SPM, added for clarification on blood collection volume.

Infant Sample type	**Collected to Evaluate**	**Minimum Quantity per participant**	**Unit**	**Time point**	**Additional Information**
Whole Blood	Immune response - IF cord blood not collected	~2.5 - Stages A and B	ml	Visit 1-NB (Within 3 days after birth)	Volume must be reduced if weight ≤ 2.5 kg. [Trial-related blood loss for infant participants should be ≤ 1 % at each timepoint. Total blood volume is estimated at 80 to 90 ml/kg body weight, and venipuncture should not exceed ~ 1.6 ml for a 2kg baby or 2.0 ml for a 2.5 kg baby.] Refer to the Laboratory Manual ***and/or SPM*** for additional information. All minimum totals given below assume a body weight > 2.5 kg.
	Immune response – sub-cohort*	~2.5* - Stage A immunogenicity sub-cohort only	ml	Either Visit 2-NB (Day 43) or Visit 3-NB (Month 4) or Visit 4-NB (Month 6)	
		~2.5	ml	Estimated TOTAL if cord blood NOT collected	
		~2.5	ml	Estimated TOTAL if assigned to one of the three blood sampling sub-cohorts in Stage A	
		~5.0	ml	Estimated TOTAL if assigned to a blood sampling sub-cohort in Stage A AND cord blood NOT collected	
Nasal swab	Presence of RSV A / B	-	-	LRTI Assessment Visit	Collect at least one nasal swab for each potential LRTI reported. If more than one follow-up assessment visit is conducted, additional nasal swabs may be collected at the Investigator's discretion..
		-	-	RTI hospitalization	Collect (if possible) from any participant hospitalized with a RTI (or soon after release, as long as symptoms are ongoing).

- **Section 8.1.2, Laboratory assays**

Table 15, Laboratory assays

Assay type	System	Component	Method	Laboratory*
~~Hematocrit~~	~~Whole Blood~~	~~Hematocrit~~	~~Per Central Laboratory SOP~~	~~Central Laboratory~~

*Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium~~; Marburg, Germany~~. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.

- **Section 8.1.2, Immunological read-outs**

Table 16, Immunological read-outs

Infant participants**	

Footnote updated to refer to correcponding tables: **V = Visit; RSV-A/B**: respiratory syncytial virus subtype A/B; **NB**: Newborn. **IgG**: immunoglobulin G;
* Refer to Table 12, Table 13
** ***Refer to*** ~~and~~ Table 14

Table 17, Hematocrit readouts – Stage A (deleted and subsequent tables have been renumbered accordingly)

~~Hematocrit will only be performed for maternal participants in the Stage A immunogenicity subcohort. Data will be used exclusively to support evaluation of secondary immunogenicity objectives.~~

~~Blood sampling timepoint~~		~~Approximate No. participants~~	~~Component~~
~~Type of contact and timepoint~~	~~Sampling timepoint~~		
~~Maternal participants~~			
~~V1 (Day 1)~~	~~pre vaccination~~	~~1,533~~	~~Hematocrit~~
~~V2 (Day 31)~~	~~post vaccination~~	~~1,533~~	~~Hematocrit~~
~~V3 (Delivery)~~	~~delivery~~	~~1,533~~	~~Hematocrit~~

- **Section 8.2.1.1, Medical/vaccination history**

  – the participant's pre-pregnancy BMI (i.e., BMI during the months before the participant became pregnant or at the very first maternal visit [if occurred early in the 1st pregnancy trimester]). This information can be obtained either via medical record review or participant interview. If BMI is not directly available, investigators will obtain participant's pre-pregnancy weight (i.e. weight during the months before the participant became pregnant or are the very first maternal visit [if occurred early in the 1st trimester]) and calculate pre-pregnancy BMI from it, in order to report it in the eCRF.

  NOTE: in the exceptional circumstance where the pre-pregnancy weight/BMI is unknown and there is no maternal visit performed during the 1st trimester. The BMI calculated based on the weight at screening may be used for eligibility. In those cases, the investigator should carefully assess the

nutritional status of the potential participant to exclude any signs of malnutrition, in conjunction with the other eligibility criteria.

- **Section 8.3.1, Time period and frequency for collecting AE, SAE and other safety information**

Table 18, Timeframes for collecting and reporting safety (and RTI) information

RTI/LRTI surveillance follow-up period (infant participants) extended to 12 months.

Footnote added to add further clarification and to refer to relevant section for details:

Pre = pre-vaccination; V=visit; D: Day; M = Maternal participants; I= Infant participants. * Approximately monthly contacts pre- delivery also occur within the timeframes described above and are described in Section 1.2. **i.e. consent obtained. *** If subsequent pregnancy occurs during the study, follow-up may extend up to 8 weeks post birth of the infant from that subsequent pregnancy. ****AESIs include adverse pregnancy outcomes, pregnancy related AEs of special interest and neonatal AEs of special interest ***(for details refer to Section 10.3.5)***. Neonatal AEs of special interest identified after V2-NB (e.g., congenital anomalies) will continue to be reported as such.

A post-study SAE is defined as any event that occurs after the end of the study. Investigators are not obligated to actively seek SAEs from former study participants. ~~A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 18. Investigators are not obligated to actively seek AEs or SAEs in former study participants.~~

- **Section 8.3.3, Regulatory reporting requirements for SAEs, subsequent pregnancies, and other events**

Table 19, Timeframes for submitting serious adverse event, subsequent pregnancy and other events reports to GSK

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

Table 20, Contact information for reporting of SAEs, AESIs, subsequent pregnancies

GSK Clinical Safety & Pharmacovigilance
Outside US & Canada sites:
Fax: +32 2 656 51 16 or +32 2 656 80 09
Email address: ~~PV.ICSRManagement~~***ogm28723***@gsk.com

- **Section 8.3.4.1, Labor and Delivery**

Spelling modified to align across the document.

- An *uncomplicated* vaginal delivery or planned ***cesarean*** ~~caesarian~~ section *expected* to occur in a hospital setting should NOT be reported as an AE, MAE or SAE.
- A medical *complication* that requires a ***cesarean*** ~~caesarian~~ section or an emergency induction may be reported as an SAE/AESI (as applicable), using the corresponding Expedited AE report form.

- **Section 8.3.4.2, Pregnancy outcomes**

Table 21, Reporting pregnancy outcomes with or without congenital anomalies as AESIs and/or SAEs

	Live birth		Fetal death /stillbirth		Elective / Therapeutic Termination	
Congenital anomalies*	AESI	SAE	AESI	SAE	AESI	SAE
None	-	-	-	X	-	X
Major[1]	X	if reportable per MACDP[3]	-	X	-	X
Minor[2]	-	if reportable per MACDP[3]	-	X	-	X

**** In the event of infant's participation in the study, congenital anomalies are to be reported in the infant's eCRF. However, when there is no live birth, or no signed informed consent for the infant or the congenital anomaly is being reported for a subsequent pregnancy, it will be encoded in the maternal participant's eCRF.***

The term "congenital anomaly" is broad. GSK uses the case definitions provided in the Centers for disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program guidelines, with specific reference to the MACDP 6-Digit Code Defect List [MACDP, ***2021***~~2019~~] to ensure that the collection and recording of these data is complete and consistent across studies and projects.

- **Section 8.4.2.2, Infant participants**

RTI surveillance in infant participants begins at birth (Visit 1-NB) and ends ***12***~~9~~ months after birth (***Visit 5***~~Contact 1~~-NB).

- **Section 8.4.2.2.1, RTI surveillance contacts**

Additional text added to allow modifiications to the frequency of planned RTI surveillance contacts.

In special circumstances, such as for example, in the event of a pandemic, social distancing and confinement measures may considerably impact the region's usual RSV seasonality. Hence, frequency of active contacts may be temporarily adapted (in agreement with GSK and subject to IEC/IRB approval, as needed) to avoid unnecessary burden (Refer to Section 8).

- **Section 8.4.2.2.2, RTI Diary cards**

At each study visit/***contact*** (including any assessment visits), RTI symptoms may have ended or may be ongoing. This will be evaluated in order to determine whether to retrieve the Diary Card and replenish the parent(s)/LAR(s)/designate(s) supply of blank cards as needed or, instruct them to continue collecting information until the corresponding symptom(s) have ended

- **Section 8.4.6, Follow-up of infant respiratory tract illnesses**

Any infant RTI documented as ongoing at a previous visit/contact will be reviewed at subsequent visits/contacts during the surveillance interval until (a) all symptoms have resolved (except runny nose, often chronic in infants), or (b) the participant completes ***Visit 5***~~Contact 2~~-NB or (c) the participant is lost to follow up.

- **Section 9.3, Populations for analyses**

Table 25, Infant participants

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
Full Analysis – Immunogenicity	All infant participants in the Exposed set who have post-delivery/birth immunogenicity data.
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 vaccination and/ or (b) have protocol deviations that lead to exclusion.
Full Analysis - Efficacy	All infant participants in the Exposed set who either complete 6 months of follow-up or have a ***medically assessed RSV-associated LRTI*** case before completing the 6 month Visit (Visit 4-NB).
Modified Full Analysis - Efficacy	***All infant participants in the Exposed set who were born after at least 4 weeks of vaccination AND either complete 6 months of follow-up or have a medically assessed RSV-associated LRTI case before completing the 6 month Visit (Visit 4-NB)***
Per Protocol – Efficacy	All infant participants in the Full analysis (efficacy) set minus those ~~a) were born less than 4 weeks post- maternal participant vaccination and/ or (b)~~ who have protocol deviations that lead to exclusion.

- **Section 9.4.3, Primary endpoints**

The primary analysis of vaccine efficacy 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.

CCI

CCI [redacted]

- **Section 9.4.4.1, Secondary endpoints/Efficacy**

In general, the primary analysis of vaccine efficacy on secondary efficacy endpoints will be based on the ***modified*** full analysis set for efficacy (***modified*** FAS-E). A secondary analysis based on the ***full analysis set for efficacy and the*** per protocol set for efficacy will be performed to complement the ***modified*** FAS-E analysis. However, if the trial is stopped for efficacy for primary endpoints at an interim analysis, all secondary or tertiary efficacy analyses will be performed on the final data containing all participants enrolled and their follow up.

Secondary confirmatory Efficacy Endpoints – Block 2	Statistical Analysis Methods
From birth (Visit 1-NB) to 9 months (C2-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 10 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 10 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 11 months, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 11 months, occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	

From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of severe medically assessed, RSV-associated LRTIs according to the case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed, RSV-associated LRTIs according to the case definitions.	
Secondary Descriptive Efficacy Endpoints	
From birth ***(Visit 1-NB)*** to 4 months ***(Visit 3-NB)***, occurrences of severe medically assessed, RSV-associated LRTIs according to the case definition.	
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 any medically assessed, RSV-associated LRTIs by alternative case definitions.	
From study intervention administration (Visit 1) to 6 months post-delivery (Contact 1), o~~O~~ccurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) ~~from vaccination up to 6 months post-delivery (Visit 4)~~	

From birth ***(Visit 1-NB)*** to 6 months ***(Visit 4-NB)***, time to the first occurrence of severe medically assessed, RSV-associated LRTIs according to the case definition	CCI [redacted]
From birth ***(Visit 1-NB)*** to 6 months ***(Visit 4-NB)***, time to the first occurrence of any medically assessed, RSV-associated LRTIs according to the case definition	
From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of RSV-associated hospitalizations according to the case definitions.	

Strong control of type I error is applied for secondary confirmatory endpoints, and multiplicity will be controlled using a hierarchical, closed testing procedure. The secondary confirmatory endpoints will be grouped sequentially in two blocks. Block 1 includes three endpoints: RSV-associated hospitalization, all cause LRTI, and all cause LRTI hospitalization from birth to 6 months. Block 2 includes ***12*** ~~six~~ endpoints: severe medically assessed, RSV-associated LRTI and medically assessed, RSV-associated LRTI of any severity from birth to 7, 8, ***9, 10, 11*** and ~~9~~***12*** months respectively (see Figure 8).

Figure 8, Secondary confirmatory endpoint hierarchy

Block 1: RSV vaccine group versus placebo

H_{21}: From birth to 6 months, occurrences of RSV-associated hospitalizations
H_{22}: From birth to 6 months, occurrences of all-cause LRTI
H_{23}: From birth to 6 months, occurrences of all-cause LRTI with hospitalization

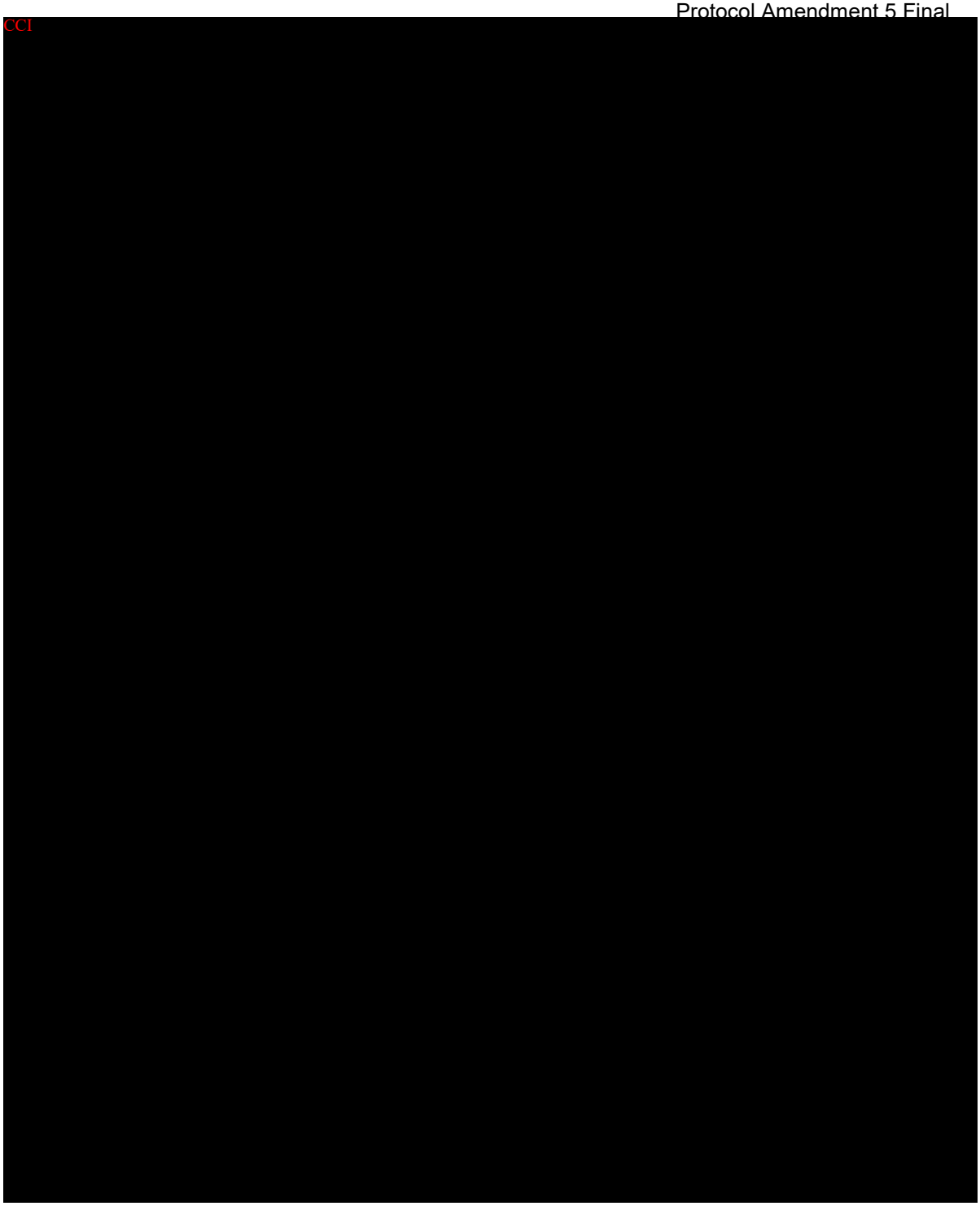
Block 2: RSV vaccine group versus placebo

H31: From birth to 7 months, occurrences of severe or very severe RSV-associated LRTIs
H32: From birth to 8 months, occurrences of severe or very severe RSV-associated LRTIs
H33: From birth to 9 months, occurrences of severe or very severe RSV-associated LRTIs
H34: From birth to 10 months, occurrences of severe or very severe RSV-associated LRTIs
H35: From birth to 11 months, occurrences of severe or very severe RSV-associated LRTIs
H36: From birth to 12 months, occurrences of severe or very severe RSV-associated LRTIs

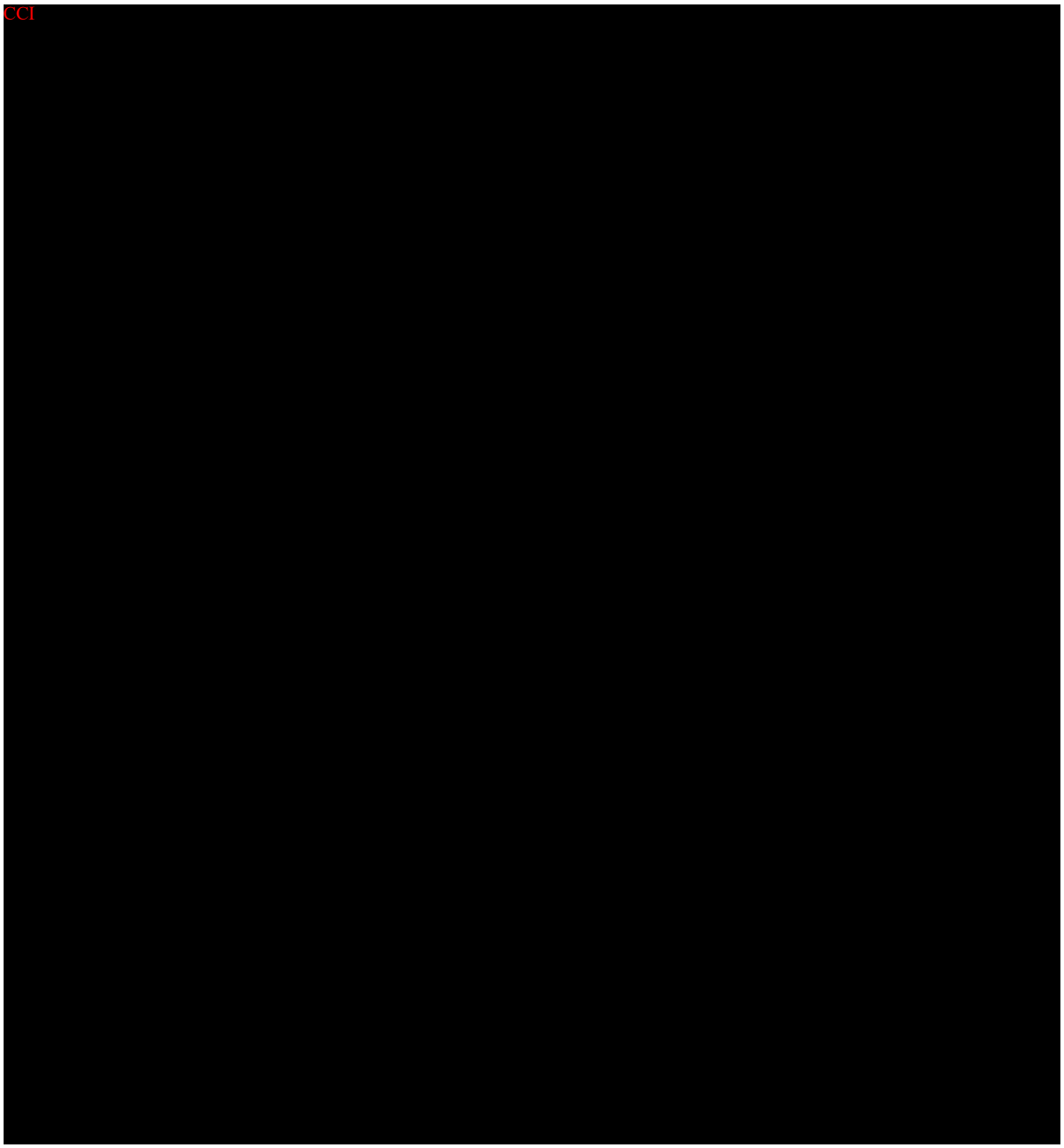
H41: From birth to 7 months, occurrences of any RSV-associated LRTIs
H42: From birth to 8 months, occurrences of any RSV-associated LRTIs
H43: From birth to 9 months, occurrences of any RSV-associated LRTIs
H44: From birth to 10 months, occurrences of any RSV-associated LRTIs
H45: From birth to 11 months, occurrences of any RSV-associated LRTIs
H46: From birth to 12 months, occurrences of any RSV-associated LRTIs

CCI

CCI



CCI



- **Section 10.2, Appendix 2: Clinical laboratory tests**

There is one assessment, hematocrit, which will be tested at Visits 1, 2 and 3, for all maternal ***participants*** in Stage A who are assigned to the immunogenicity sub-cohort, ***until the current protocol amendment 2 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 2 being approved) in the respective study country(ies).*** Testing will be performed by a central laboratory. Results will be used to help evaluate changes over time in antibody titers / concentrations that may be related to volumetric changes during pregnancy***, if deemed necessary***.

- **Section 10.3.2, Definition of a Serious Adverse Event (SAE)**

e.	Is a congenital anomaly/birth defect in the offspring of a study participant Refer to Section ***8.3.4.2***~~8.3.4~~ for additional information.
f.	Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies*******, ectopic pregnancy) ****Refer to Section 8.3.4.2 for additional information.***

- **Section 10.3.5, Adverse events of special interest (AESIs)**

In this section, all AESIs are presented in list format.
AESIs include:

- ~~The adverse pregnancy outcomes indicated in Table 21.~~
- The following pregnancy-related adverse events of special interest (newly occurring ~~or worsening of existing conditions~~):
  - 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, and
  - chorioamnionitis.
- The following neonatal adverse events of special interest:
  - small for gestational age,
  - low birth weight including very low and extremely low birth weight (<2500 g, <1500 g, <1000 g),
  - 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),

and

– preterm birth.

Refer to Section 8.3.4 for additional information about categorizing and reporting congenital anomalies.

Note: Worsening, post study vaccine administration, of pre-existingconditions already present at the time of enrolment. (eg. controlled gestational hypertension or controlled gestational diabetes) will be collected as (S)AEs and indicated as "worsening" or "aggravated" . These are not to be considered as AESIs.

- **Section 10.3.8.2, Where to record AEs, SAEs, AESIs, subsequent pregnancies and other events of interest**

All solicited events that occur during the 7 days following administration of the dose of study vaccine/product (Day 1 to Day 7) must be recorded into the ***electronic*** Diary, irrespective of intensity or whether or not they are considered vaccination-related.

- **Section 10.6, Appendix 6: Country specific requirements**

Section 10.6.2, South Korea

Concerning the "STUDY POPULATION – Exclusion criteria for enrolment – maternal participants", the following will constitute and exclusion criterion in South Korea:

- ***Participation in a clinical trial targeting healthy people within the 6 months prior to enrolment/study vaccination.***

Concerning the "CRITERIA LEADING TO PAUSE OR EARLY TERMINATION OF THE STUDY", the following clarification is made:

- ***No safety "holding rules" or criteria for pausing or early termination have been defined for this study.***
- ***An Independent Data Monitoring Committee (IDMC) has been put in place and will be in charge of reviewing unblinded safety data on a regular basis (bi-monthly reviews are foreseen, but frequency may be adapted as the study progresses). It will be the IDMC discretion to recommend, if they deemed necessary, that the study recruitment is paused or terminated based on their unblinded data reviews.***
- ***In addition to the IDMC reviews, GSK's Safety Review Team (SRT) will perform regular reviews of blinded data and may request IDMC to perform ad-hoc unblinded reviews if any potential safety concern is suspected based on blinded data.***

- **Section 10.7.2, Glossary of terms**

End of Study (EoS) (Synonym of End of Trial)	***For studies with collection of human biologicals samples,*** EoS ~~occurs with~~***is defined as*** the ***date of*** ~~last infant participant last visit (~~LSLV~~; Visit 5 NB)~~ ***or the last testing/reading released of the human biological samples related to primary and secondary endpoints, whichever comes last. EoS must be achieved no later than 8 months after LSLV***.

- **Section 10.8, Appendix 8: Gestational age assessment**

A note has been added to Section 10.8.2: ***Refer to the SPM for further details.***

- **Section 10.8.2, METHODS OF GESTATIONAL AGE ASSESSMENT AND ESTIMATION OF DUE DATE**

Missing Asterix added against gestational age range:

Gestational age range*	Method of measurement	Discrepancy between U/S dating and LMP (or IUI or ET dating) prompting re-dating of EDD considering U/S
1st trimester ≤13$^{6/7}$ weeks		
≤8$^{6/7}$ weeks 9$^{0/7}$ to 13$^{6/7}$ weeks	CRL	> 5 days > 7 days
2nd trimester 14$^{0/7}$ to 27$^{6/7}$ weeks		
14$^{0/7}$ to 15$^{6/7}$ weeks	BPD, HC, AC, FL	> 7 days
16$^{0/7}$ to 21$^{6/7}$ weeks		> 10 days
22$^{0/7}$ to 27$^{6/7}$ weeks		> 14 days
3rd trimester		
28$^{0//7}$ weeks and beyond	BPD, HC, AC, FL	> 21 days

Text added: ***Refer to the SPM for further details.***

- **Section 10.9, Appendix 9: Definitions of maternal, fetal and neonatal events of interest as per GAIA**
- ***IMPORTANT: NOT all the events that are listed below are AESIs for this study.*** Sections 3, 9.4.4 and 10.3.5 list events of interest per GAIA that must be reported as AESIs ***in this study***.

Pregnancy Outcomes	
Fetal Death / Stillbirth	Table 30
Maternal Events of Interest	
Maternal Death ***– study defined pregnancy-related AESI***	Table 31
Hypertensive Disorders of Pregnancy ***– study defined pregnancy related AESIs***	Table 32
Antenatal bleeding	Table 33
Postpartum hemorrhage	Table 34
Fetal Growth restriction ***– study defined pregnancy related AESI***	Table 35
Gestational Diabetes Mellitus ***– study defined pregnancy related AESI***	Table 36
Non-reassuring fetal status	Table 37
Pathways to Preterm Birth ***– study defined pregnancy related AESIs***	Table 38
Chorioamnionitis ***- study defined pregnancy related AESI***	Table 39
Standard definitions for events of interest not defined as such in GAIA (Oligohydramnios, Polyhydramnios, Intrahepatic Cholestasis of Pregnancy (ICP), Acute Fatty Liver of Pregnancy, Maternal Sepsis)	Table 40
Neonatal Events of Interest	
Small for Gestational Age ***– study defined neonatal AESI***	Table 41
Low Birth Weight ***– study defined neonatal AESI***	Table 42
Neonatal encephalopathy	Table 43
Congenital Microcephaly	Table 44
Congenital Anomalies ***– study defined neonatal AESIs***	Table 45
Neonatal Death ***– study defined neonatal AESI***	Table 46
Neonatal Infections	Table 47
Respiratory Distress in the Neonate	Table 48
Preterm Birth ***– study defined neonatal AESI***	Table 49
Failure to thrive	Table 50
Standard definitions for events of interest not defined as such in GAIA (large for gestational age, macrosomia)	Table 51

- **Section 11, References**

~~Morgan WJ, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172(10):1253-8.~~

Carbonell-Estrany X, Pérez-Yarza G E, Laura García Sanchez L, et al. Long-Term Burden and Respiratory Effects of Respiratory Syncytial Virus Hospitalization in Preterm Infants-The SPRING Study. PLoS One 2015; May 8;10(5):e0125422

Fauroux B, Simo˜es A. F.E, Checchia A. P, et.alThe Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. Infect Dis Ther 2017; 6:173–197

Metropolitan Atlanta Congenital Defects Program (MACDP). ***2021***~~2019~~. ***https://www.cdc.gov/ncbddd/birthdefects/documents/bpa-codes-rev2021-508c.xls***x~~https://www.cdc.gov/ncbddd/birthdefects/macdp.html~~. Accessed ***8***~~5~~ ***June***~~March~~ ***2021***~~2020~~.

Overall Rationale for the Protocol Amendment 1:

Case definitions for lower respiratory tract illness have been modified to include the phrase “medically assessed." In addition, the success criteria for the primary objective on any RSV-associated lower respiratory tract infection has been changed. Previously the lower bound of this primary endpoint was 10%; it has been increased to 20%. The timing of interim analyses have been modfied to make overall interim analyses operationally pragmatic. In addition, the corresponding study design operational characteristics have been updated. Editorial changes to improve internal consistency have been made. Typographical errors have been corrected.

List of main changes:

Section # and title	Description of change	Brief rationale
Sections 1.2 (Schema), 2.1 (Study rationale), 3 (Endpoints and Objectives), 4.2.5 (Adaptive design), 4.2.6 (Case definitions), 9.4.3 (Primary Endpoints), 9.4.4.1 (Secondary efficacy endpoints), 9.4.4.2 (Detailed statistical methods)	The phrase “medically assessed” has been added to the phrase “RSV-associated lower respiratory tract infection.”	To clarify that medical assessment is required to meet the case definition.
Sections 3 (Endpoints and Objectives), 4.2.5 (Adaptive design), 4.2.6 (Case definitions), 9 (Statistical considerations), 10.10 (Operating characteristics)	The phrases “severe / very severe” and “severe or very severe” LRTI have been replaced by the phrase “severe LRTI.	To clarify that in this protocol, the primary endpoint related to medically assessed RSV-associated severe LRTI will not include medically assessed RSV-associated very severe LRTI. Similarly, medically assessed, RSV-associated LRTI endpoints will not include RSV LRTI of very severe LRTI case definitions.
Section 2.1 (study rationale)	Infant participants are to be evaluated for medically assessed RSV-associated lower respiratory tract infection for 9 months post birth.	Evaluation of the infant occurs for 9 months post-birth. An incorrect reference to “6 months” has been adjusted.
Section 1.3 (Schedules of Activities), Table 1; row 35; Section 8.3.1 (Time period and frequency for collecting AE, SAE and other safety information), Table 19, column 9	References to maternal “Visit 5” have been replaced with references to maternal “contact 1.”	Evaluation of the mother 6 months post-delivery occurs via contact. A “visit” was referenced in these 2 locations in error.
Section 2.3 (Benefit/risk assessment)	Language in the previous version of the protocol that presented risks information has been removed.	More current and complete information is now available in Edition 3 of the Investigator’s Brochure.
Sections 1.2 (Schema) and 4.1 (Overall design)	Language has been added to indicate that at least 20% of participants will be enrolled at centers in the U.S.	Addresses a regulatory request.
Section 4.2.2 (Use of Placebo)	The phrase “and efficacy” has been added	The placebo serves as a control for safety, reactogenicity, immunogenicity and efficacy assessments.

Section # and title	Description of change	Brief rationale
Section 5.2.1.2 (Prior / Concomitant Therapy)	Has been re-written to remove a redundant reference to the phrase "planned use during the study period."	To improve clarity, a redundant reference to "planned use during the study period" has been removed.
Sections 9.1 (Statistical hypotheses), 9.2 (Sample size determination), 9.4.3.1 CCI [redacted], Section 10.10 (Operating characteristics)	The success criterion on lower bound of medically assessed RSV associated LRTI (VE_{any}) has been changed to 20% and all the relevant design charicterristics have been updated	Section 9 has been updated following changes to the success criteria for the primary objectives and in response to regulatory comments.
CCI [redacted]		
Section 9.4.4.1 (Efficacy)	Text describing the methods of type I error control on the analyses of the secondary confirmatory endpoints was updated.	
Section 9.4.6.3 (Predicted VE based on surrogate endpoint)	The strategy for surrogate endpoint analyses was simplified.	
Section 9.5 (Interim analyses)	The number of interim analyses has been reduced; the text was updated to reflect this and to further clarify the sequence of full analyses.	
Section 10.1.3 (Informed consent process)	The discussion of consent for participants who are re-screened has been modified.	For consistency with electronic data capture and study procedures.

Detailed description of *previous* Protocol Amendment (#1) changes:

In this section, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***.

Section 1.2, Schema

Up to approximately 10,000 participants will be enrolled; it is expected that at least 20% of these participants will be enrolled at centers located in the U.S.

Infant participants will be evaluated for the occurrence of ~~RSV-associated~~ ***medically assessed,*** RSV-associated lower respiratory tract infections for ~~6~~ ***9*** months after birth and followed for safety for 12 months after birth.

Table 1, Schedule of activities for maternal participants

Visit / Contact	Screening	V1	V2*	Contacts (Monthly)	V3	V4	C1	Event Driven		
MAEs other than MA-RTIs		●	●	●	●	●				Medically attended RTIs to be reported up to ~~V5 or~~ C1.
Pregnancy-related AESIs		●	●	●	●	●	~~●~~	●	~~●~~	Table 4, Sections 8.3.1, 8.3.3, 8.3.4, and 10.3.5. Must submit an Expedited AE report.
MAEs other than MA-RTIs		●	●	●	●	●		●		Medically attended RTIs to be reported up to ~~V5 or~~ C1.
SAEs, MA-RTI associated AEs, ~~AESIs~~ and AEs leading to study withdrawal		●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1 and 10.3.8

Table 3, Intervals between study visits and contacts

Interval	Optimal interval in Days	Allowed interval in Days	Additional Information
Maternal participants			
Screening to V1	0	0– 29	…Data from all screening procedures must be available and eligibility must be confirmed before the ~~subject~~***participant*** is randomized….

Section 2.1, Study rationale

GSK is developing an investigational Respiratory Syncytial Virus (RSV) vaccine for administration to pregnant women, with the aim of preventing ~~RSV-associated~~ ***medically assessed***, RSV-associated lower respiratory tract illnesses (LRTIs) in their infants …

~~Safety~~***Reactogenicity*** and ~~reactogenicity~~***safety*** of the candidate vaccine will be evaluated in maternal participants for up to 6 months after delivery~~; and~~. ***Safety*** in infants ***will be evaluated*** for up to 12 months after birth. Safety evaluation will include assessment of ***medically attended adverse events, serious adverse events***, pregnancy outcomes, and pregnancy-related and neonatal adverse events of special interest (AESIs).

The study will also evaluate the incidence of medically attended RSV-associated respiratory tract illnesses (MA-RTI) in maternal participants ***for up to 6 months after delivery, and*** the incidence of ***medically assessed,*** RSV-associated respiratory tract / lower respiratory tract illnesses (RTI/LRTI) in infants for up to ~~6~~***9*** months after ~~delivery/~~birth~~, and the incidence of medically attended and serious adverse events for up to 12 months, in infants born to vaccinated mothers~~.

Section 2.3, Benefit/Risk assessment

~~One phase 1 clinical trial of the RSV investigational vaccine in non-pregnant women has been completed. Two phase 2 clinical trials – one in non-pregnant and one in pregnant women – are ongoing.As of the date of this protocol:~~

- ~~The most commonly reported adverse events have been pain at the injection site, headache, and fatigue.~~
- ~~Fever post-vaccination has been infrequent (about 1% of participants).~~
- ~~Most adverse events have caused only limited discomfort, have not lasted long and have not prevented normal everyday activities.~~
- No serious adverse events attributed by the Investigator or by GSK to study vaccine administration have been reported in non-pregnant women, pregnant women, or their infants.

Taking into account the measures to minimize potential risks for ~~subjects~~ ***participant***s participating in this study, the potential or identified risks are justified by the potential benefits of enhanced surveillance for the ~~subjects~~ ***participant***s…….

Section 3, Objectives and Endpoints, Table 4

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 ~~or~~ ***(including very severe)*** LRTIs in their ~~infant participants~~[2] infant[5] 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 ~~or~~ ***(including very severe***~~RSV-associated~~ ***)*** LRTIs according to the case ~~definitions~~[3] definitions[2,3].
	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~~ infant[5] 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~~[3] definitions[2,3].
Secondary ~~confirmatory~~[4] confirmatory[4] efficacy objectives	**Secondary ~~confirmatory~~[4] confirmatory[4] 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~~ infant[5] 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~~[3] definitions[2,3].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their ~~infant~~ infant[5] 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[3].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their ~~infant~~ infant[5]	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTI with hospitalization[3].

participants up to 6 months of age, 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 (including very severe)*** LRTIs in their ~~infant~~ infant[5] participants up to 7, 8 and 9 months of age.	From birth (Visit 1-NB) to 7 months, birth to 8 months, and birth to 9 months (C2-NB), occurrences of ***medically assessed,*** RSV-associated ***severe (including very severe~~RSV~~)*** LRTIs according to the case ~~definitions[3]~~ definitions[2,3]
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 ***participants*** [5] up to 7, 8 and 9 months of age.	From birth (Visit 1-NB) to 7 months, birth to 8 months, and birth to 9 months (C2-NB), occurrences of any ***medically assessed,*** RSV-associated LRTIs according to the case ~~definitions[3]~~ definitions[2,3].
Secondary descriptive efficacy objectives	**Secondary descriptive efficacy 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 (including very severe)*** LRTIs in their ~~infant~~ infant[5] participants up to 4 months of age	From birth (Visit 1-NB) to 4 months (Visit 3-NB), occurrences of ***severe (including very severe) medically assessed[1],*** RSV-associated LRTIs according to the case ~~definitions[3]~~ definitions[2,3].
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~~ infant[5] 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[3]~~ definitions[2,3]
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their ~~infant~~infant[5] participants up to 6 months of age, ***medically assessed[1]*** RSV LRTI by alternative case definitions[2].	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of ***medically assessed[1]*** RSV LRTI by alternative case ~~definitions[3]~~definitions[2].
To assess the efficacy of a single dose of the RSV Maternal vaccine administered to maternal participants in preventing, in their ~~infant~~infant[5] 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 effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any severe ~~or~~ ***(including very severe) medically assessed[1],*** RSV-associated LRTIs, in their ~~infants~~ infant[5] ***participant***s, according to the case ~~definition~~ definition[2,3].	From birth to 6 months, time to the first occurrence of severe ~~or~~ ***(including very severe) medically assessed[1],*** RSV-associated LRTIs according to the case ~~definitions[3]~~ definitions[2,3]
To assess the effect of administering a single dose of the RSV Maternal vaccine administered to maternal participants on time to first occurrence of any ***medically assessed,*** RSV-associated LRTIs in their ~~infants~~ infant[5] ***participant***s, according to the case ~~definition~~ definition[2].	From birth to 6 months, time to the first occurrence of any ***medically assessed,*** RSV-associated LRTIs according to the case ~~definition[3]~~definition[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) [3] [2].
Secondary safety objectives	**Secondary safety endpoints**
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) [4] [6], 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~~ outcomes[6] 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]~~ [6,7]
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 pre-term birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth), preterm birth. ~~[4, 5]~~ [6,7]
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. [4] [6] Occurrence of SAEs, AEs leading to study termination and medically attended AEs from birth up to 12 months after birth. [4] [6]

Tertiary objectives:
CCI [redacted]

[1]~~For analysis of secondary confirmatory efficacy objectives, overall type 1 error is controlled~~
[2]~~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.~~
[3]~~Case~~[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 LRTIs and surveillance for potential LRTIs are briefly summarized in Section 4.2.6. Alternative case definitions are briefly summarized in Section 4.2.6.2.
[3]~~Maternal~~***Note that as per the case definitions outlined in Table 8, which are based on the WHO case definitions, RSV-associated very severe LRTIs are a subset of RSV-associated LRTIs but not necessarily a subset of RSV-associated severe LRTIs. As such, an infant participant may meet the criteria for RSV-associated very severe LRTI without meeting that of RSV-associated severe LRTI. In this protocol, the primary endpoint related to medically assessed RSV-associated severe LRTI will include medically assessed RSV-associated very severe LRTI. Similarly, medically assessed, RSV-associated LRTI endpoints will include RSV LRTI of any severity including cases that meet severe and very severe LRTI case definitions.***
[4]For analysis of secondary confirmatory efficacy objectives, overall type 1 error is controlled
[5]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.
[6]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 disorders of pregnancy is an event with three subcategories that include: 1) gestational hypertension; 2) pre-eclampsia; and 3) pre-eclampsia with severe features (including eclampsia). For each event, the investigator should identify the event and select the applicable sub-category.
[5]~~The~~[7]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.

Section 4.1, Overall Design

The study is a Phase III, double-blind, randomized, placebo controlled, multi-centric, multi-country study with 2 parallel groups. ***At least 20% of participants will be enrolled at centers in the U.S.***

Section 4.2.2, Use of placebo

The placebo group serves as a control for safety, reactogenicity, ~~and~~ immunogenicity ***and efficacy*** assessments. No licensed vaccine against RSV is currently available.

Section 4.2.3, Randomization ratio

GSK plans to mitigate the potential risk associated with the increased randomization of vaccinated to placebo ~~subject~~***participant***s by…

Section 4.2.4.2, Blood sampling and immune response assessment

Note however that blood samples for assessment of immune response at Day 1 (Visit 1) and Day 31 (Visit 2) will be collected from *all* maternal participants. Cord blood will also be collected from all participants. Analyses of these samples will be used to support possible surrogate endpoint ~~filing~~ ***assessment*** as well as future bridging studies.

Section 4.2.5, Adaptive Design

This adaptive trial design will provide evidence for the efficacy of the RSV maternal vaccine in the prevention of ***medically assessed,*** RSV-associated LRTI of any severity and ***medically assessed,*** RSV-associated severe ***(including*** very severe***)*** LRTI. The design has ~~93.7~~ ***over 90***% power to detect the target vaccine efficacies of 70% and 50% on severe ***(including*** very severe***)*** and any-severity LRTI, respectively. If the vaccine meets these target VE ~~rates~~ ***estimates***, this design offers the opportunity to identify this benefit with an expected sample size of approximately 7,000 maternal ***participant***s, ~~obviating~~ ***which may obviate*** the need to enroll the maximum sample size of 10,000.

Section 4.2.6.2, Table 8, RTI/LRTI case definitions for data analysis in infants, Footnotes:

Definitions based on [Modjarrad, 2016]; **RTI** = respiratory tract illness; **LRTI** = lower respiratory tract illness; **RR** = respiratory rate; **SpO_2** = blood oxygen saturation by pulse oximetry.
[1] ~~Based~~[1] ***Please note that per the above case definitions which are based on the WHO case definitions, "RSV-very severe LRTIs" are a subset of "RSV-LRTIs" but not necessarily a subset of the "RSV-severe LRTIs". As such, an infant participant may meet the criteria for very severe LRTI without meeting that of severe LRTI***
[2] 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).
[3] For blood oxygen saturation (SpO_2), the lowest value monitored will be used. In high altitudes (>2500m), SpO_2 <92% for LRTI, <90% for severe LRTI, <87% for very severe LRTI.
[4] 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)
[5] Confirmed RSV infection defined in Section 4.2.6.3
[6] RSV (nasal swab) sampling and testing as specified in Table 14.
[7] Hospitalization is defined as admission for observation or treatment based on the judgement of a health care provider.

Section 4.3, Justification for dose:

A single formulation of the investigational RSV maternal vaccine (containing 120µg of the RSVPreF3 antigen) is planned. Currently available data suggest that the 120 µg formulation has an acceptable safety profile and tends to elicit stronger immune responses in non-pregnant women ***(RSV MAT-001 and RSV MAT-011) and pregnant women (RSV MAT-004)***, which is likely to result in higher placental transfer of antibodies to the fetus than formulations containing 30 or 60 µg of the RSVPreF3 antigen~~However, this will be confirmed after review of additional safety and immune response data from RSV MAT-011, and RSV MAT-004.~~ Available results from these studies ~~will be~~ ***are*** included in the Investigator Brochure~~to support RSV MAT-009~~.

Section 5.2.1.2, Prior/Concomitant therapy

- Use of any investigational or non-registered product other than the study vaccine/product ~~during the period beginning~~ ***as described below, or planned use during the study period):***
  - **For a drug, vaccine or medical device:** 29 days before the dose of study vaccine/product (Day -28 to Day 1) ~~or planned use during the study period~~.
  - **For immunoglobulins:** 3 months before the dose of study vaccine/product,

  ~~Or planned use during the study period.~~

Section 6.3.2.1.1, randomization to maternal study intervention group, Stage A

The Day 1 and cord blood (or neonatal blood) samples will be tested to support surrogate endpoint ~~filing~~ ***analysis***. The Day 1, Day 31 and cord blood (or neonatal blood) samples may also be tested to support development of a sero-correlate for life cycle bridging.

Section 6.3.3, Intervention allocation to the participant

Verify eligibility of the maternal ~~subject~~***participant***

Section 8.0, Study procedures during special circumstances

- Enrolment of ADDITIONAL maternal ~~subject~~***participant***s may be placed on hold.
- "Medically attended visits" will include instances where, due to the special circumstances, the ~~subject~~ ***participant*** cannot seek medical advice for…….

Section 8.1.1, Biological samples, Table 12:

Nasal Swab	Presence of:RSV A / B	-	-	MA RTI Assessment Visit	Collect a nasal swab from any maternal participant who reports a medically attended (MA) RTI
		-	-	RTI hospitalization	Collect a nasal swab (if possible) from any ***maternal*** participant hospitalized with a RTI (or soon after discharge, as long as symptoms are ongoing).

Section 8.1.2, Laboratory Assays, Table 15, Laboratory Assays, Footnote only

The panel may include testing for SARS-COV-2 Please note that SARS-COV-2 testing is not intended to be diagnostic and results will not be provided to the investigator. Testing for SARS-COV-2 in any suspected infected ~~subject~~ ***participant*** should be performed as per the standard of care.

Section 8.1.3, Immunological Readouts, Table 18, Molecular Biology Tests, Footnote only

Testing for Covid-19 in any suspected infected ~~subject~~ ***participant*** should be performed as the standard of care.

Section 8.2.1.2, Physical Examination (General and obstetric examination)

Obstetric examinations should include:

- Vaginal examination (manual and/or speculum) will be performed ONLY if warranted by ~~subject~~***participant***'s symptoms or as per investigator's clinical discretion. If done, results will be recorded (normal or abnormal; if abnormal, specify).

Section 8.3.1, Table 19, Timeframes for collecting and reporting safety (and RTI) information

Applies to Stage A and Stage B unless otherwise noted below

	Before Delivery*				Delivery/Birth	Post-Delivery/Birth*					
Timepoint	**D-28**	**D1**	**D7**	**D31**		**D 43**	**D91**	**D121**	**D181**	**M9**	**M12**
Maternal participant visits	Pre-**	V1		V2	V3	V4			~~V5~~ ***C1***		
Infant visits					V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB

Section 9.1, Statistical hypotheses

CCI

[redacted]

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[redacted]

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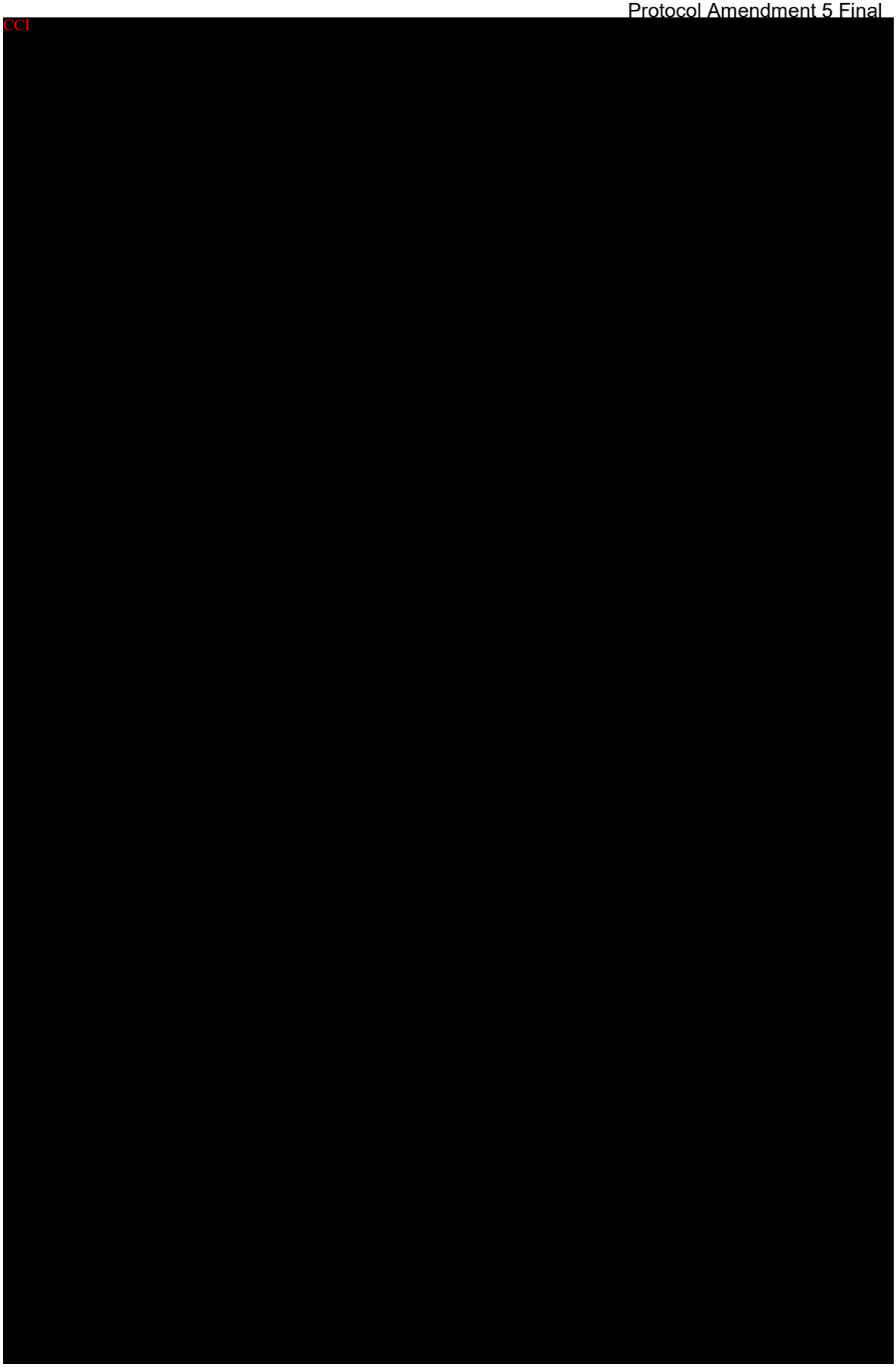


CCI

[redacted]

CCI [redacted]

Section 9.4.1, Statistical analysis, general considerations:

~~The SAP describes how missing data will be handled during analyses.~~

If, during the trial, changes need to be made on primary or confirmatory secondary objectives and statistical methods related to those objectives prior to any unblinding, the protocol will be amended. Changes on other secondary objectives/tertiary objectives, along with the reason(s) for the changes, will be documented in the SAP and the Clinical Study Report.

Section 9.4.2, Participants disposition

Number of infant participants enrolled and withdrawn (by group and sub-cohort, and overall) will be described~~. Additional analyses by country and/or by site may be performed.~~

Section 9.4.3, Primary ~~objectives~~ *endpoints*

Primary Efficacy Endpoints – Infant participants	**Statistical Analysis Methods**
From birth to 6 months, occurrences of ***medically assessed***, RSV-associated severe ~~or~~ *(**including very severe**~~RSV-associated~~)* 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]

Section 9.4.3.1, Detailed statistical analysis methods

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

Section 9.4.4.1 Secondary endpoints, efficacy

……However, if the trial is stopped for efficacy for primary endpoints at an interim analysis, all secondary or tertiary efficacy analyses will be performed on the final data containing all ~~subject~~***participant***s enrolled and their follow up. **Secondary confirmatory Efficacy Endpoints – Block 2**	**Statistical Analysis Methods**
From birth (Visit 1-NB) to 7 months, occurrences of severe ~~or~~(***including*** very severe) ***medically assessed,*** RSV-associated LRTIs according to the case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 7 months, occurrences of any ***medically assessed,*** RSV-associated LRTIs according to the case definitions.	

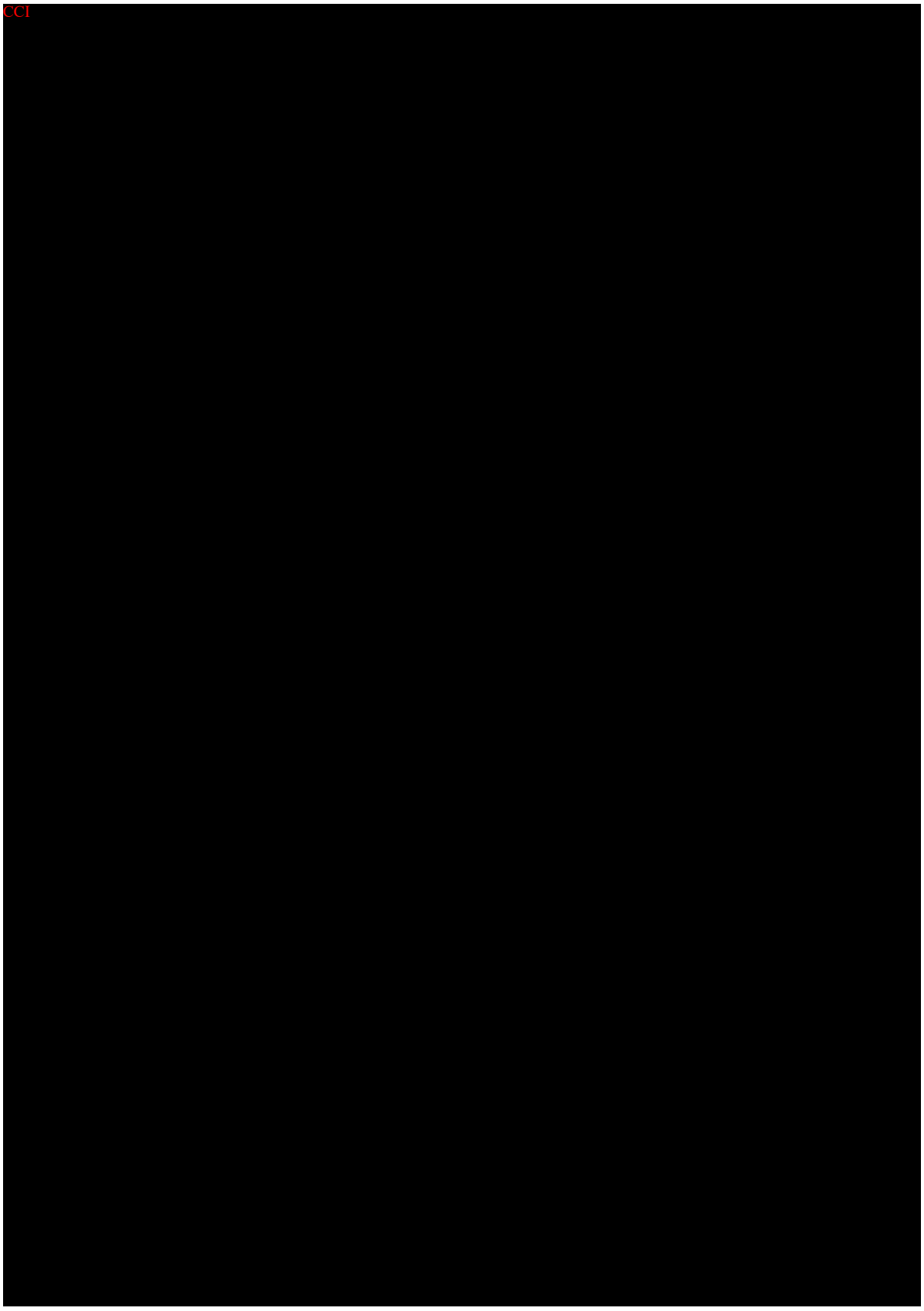
From birth (Visit 1-NB) to 8 months, occurrences of severe ~~or~~(***including*** very severe) ***medically assessed,*** RSV-associated LRTIs according to the case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 8 months, occurrences of any ***medically assessed,*** RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 9 months (C2-NB), occurrences of severe (***including*** very severe) ***medically assessed***, RSV-associated LRTIs according to the case definitions.	
From birth (Visit 1-NB) to 9 months (C2-NB), occurrences of any ***medically assessed,*** RSV-associated LRTIs according to the case definitions.	

Secondary Descriptive Efficacy Endpoints	**Statistical Analysis Methods**
From birth to 4 months, occurrences of severe or very severe ***medically assessed,*** RSV-associated LRTIs according to the case definition.	CCI [redacted]
From birth to 4 months, occurrences of any ***medically assessed, RSV-associated*** LRTIs according to the case definitions	

Secondary Descriptive Efficacy Endpoints	Statistical Analysis Methods
From birth to 6 months, occurrences of any ***medically assessed,*** RSV-associated LRTIs by alternative case definitions.	CCI [redacted]
From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause pneumonia.	
Occurrence of RSV-associated medically attended RTIs (RSV-MA-RTIs) from vaccination up to 6 months post-delivery (Visit 4)	
From birth to 6 months, time to the first occurrence of severe (***including*** very severe) ***medically assessed***, RSV-associated LRTIs according to the case definition	

CCI [redacted]

CCI



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[redacted]

Section 9.4.4.2, Detailed Statistical Analysis Methods

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CCI

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Section 9.4.6.3, Predicted VE based on surrogate endpoint

~~As a part of filing licensure strategy,~~ ***Surrogate*** endpoint analyses will be conducted ~~at the end of Stage A or~~ at ***the same time as*** interim analysis ***#2*** when there are approximately 4,600 ***maternal*** participants ~~completing~~ ***with the opportunity to complete*** 6 months follow up ~~in RSV MAT-009.~~***post-delivery***. If the lower bounds of the credible interval for the observed vaccine efficacy (VE) ***on either primary objective*** meet the pre-specified criteria, ***then the company*** ~~plans to submit a file~~ ***will claim success*** based on the VE. However, if the pre-specified lower bounds for the observed VE are not met for either primary objective, ***then the company plans to*** ~~submit a file based on the~~ ***evaluate*** VE predicted by the surrogate endpoint ~~(predicted VE) based on the following two strategies~~ ***model***:

~~Strategy 1~~ ***The strategy*** can be summarized in 3 steps:

1. ***Estimate the surrogate endpoint model using data from one or more GSK epidemiology studies. The model will be created based on the GSK RSV neutralizing antibody assay before the analysis of RSV MAT-009.***
2. ***Validate the model at*** ~~the end of RSV MAT-009 Stage A~~ ***interim analysis #2 (that is, validate whether the observed VE*** ~~at the end of Stage A~~ ***(when 4600 participants have had the opportunity to complete 6 months post-delivery) is "similar to" the predicted VE). The validation of the model is done using an equivalence test (H_0: $\delta < -\Delta$ or $\delta > \Delta$) if feasible, where δ is the difference between the predicted VE and the observed VE, and Δ is an appropriate equivalence margin, or other methods for the validation of surrogate endpoints such as Principal stratification [Frangakis, 2002; Follmann, 2006; Gilbert, 2008].***
3. ~~File under Accelerated Approval~~ ***Claim success based on predicted VE at the end of*** ~~RSV MAT-009 Stage A~~ ***interim analysis #2. This will occur if the predicted VE for either primary endpoint meets the pre-specified success criteria based on a successfully validated surrogate endpoint model. RSV MAT-009 will continue as designed. It is expected that the observed VE will meet the success criteria as trial continues (during Stage B***~~); The final results would be submitted to convert to traditional approval.~~***).***

For more details~~for strategy 1~~, please refer to the separate statistical analysis plan "RSV Maternal Serocorrelate SAP."

~~Strategy 2 will be implemented due to the impact of COVID 19. If RSV MAT-009 is conducted during COVID 19 and social distancing, the number of RSV cases may be much smaller than needed for the observed VE to meet the success criteria. In addition, the smaller number of RSV cases may make it impossible to validate the surrogate~~

~~endpoint model at the end of Stage A as outlined in step 2 above. As routine prevention of RSV LRTI remains an unmet medical need, Strategy 2 is proposed as an alternative should social distancing result in the number of RSV LRTI cases being too low to estimate observed vaccine efficacy.~~

~~Strategy 2 to license based only on a surrogate endpoint can be summarized in the following steps~~

1. ~~Estimate the surrogate endpoint model using data from one or more GSK epidemiology study(ies).~~
2. ~~Evaluate the surrogate endpoint model based on Novavax study results (immune response and observed VE). A comparison of the Novavax predicted VE using the surrogate endpoint model vs. the actual efficacy observed in the Novavax trial could serve to validate the surrogate endpoint model. This would be done before the analysis of RSV MAT-009.~~
3. ~~File under Accelerated Approval at the end of RSV-MAT-009 Stage A if the predicted VE for either of primary endpoints meets pre-specified success criteria based on the above surrogate endpoint model.~~
4. ~~Demonstration of vaccine effectiveness post licensure.~~

~~A detailed plan for surrogate endpoint licensure strategy due to the impact of COVID-19 will be provided in a separate document.~~

~~In the case of filing based on a surrogate endpoint, RSV MAT-009 will continue as designed and the interim/final analysis on observed vaccine efficacy will be included as supplemental evidence.~~

Section 9.5, Interim analyses

Interim analyses of vaccine efficacy ***for the two primary endpoints*** will be performed.

~~In Stage A, these interim analyses will be timed according to the number of mother/infant pairs who have completed 6 months of follow-up post-delivery/birth. This coincides with maternal Contact 1 / infant Visit 4-NB (Day 181 Post-Delivery/Birth).~~

~~In Stage B, interim analyses will be timed according to the number of maternal participants randomized in the trial. Interims begin when 6,000 maternal subjects have been randomized and will be conducted every 1,000 maternal subjects randomized thereafter, up to a maximum of 9,000 maternal subjects randomized.~~

In Stage A, the interim analysis will be conducted when 4600 maternal participants are randomized, and the purpose of this analysis is to decide if further enrollment is needed and if the study can be stopped for futility. The number of completed participants and events at this interim will be based on the accrual rate and attack rate in the trial. Based on a blinded assessment of the overall accrual rate and attack rate in the trial, GSK may decide if this interim will be performed. If the accrual rate is faster than expected or the attack rate is lower than expected, GSK may decide to skip this interim.

Interim analyses of vaccine efficacy for the two primary endpoints will be conducted when 4600, 6500, and 8000 maternal participants have had the opportunity to complete 6 months follow-up post-delivery. The trial can claim success if either of the two primary endpoints meet success criteria at any of those three interim analyses.

Table 27, Interim Analysis Schedule and Possible Decisions Made at each Analysis

Prior table:

~~Interim #~~	~~Stage~~	~~Timing of analysis~~		~~Can decide to begin accrual to Stage B?~~	~~Can stop for futility?~~	~~Can claim success?~~
		~~# Participants~~	~~Participants triggering analysis~~			
~~1~~	~~A*~~	~~2,000**~~	~~Maternal subjects with the opportunity to complete 6 months follow-up post-delivery~~	~~Yes~~	~~No~~	~~No~~
~~2~~	~~A*~~	~~2,800~~		~~Yes~~	~~Yes~~	~~Yes, after Stage A follow-up~~
~~3~~	~~B~~	~~6,000~~	~~Maternal subjects randomized~~	~~-~~	~~Yes~~	~~Yes~~
~~4~~	~~B~~	~~7,000~~		~~-~~	~~Yes~~	~~Yes~~
~~5~~	~~B~~	~~8,000~~		~~-~~	~~Yes~~	~~Yes~~
~~6~~	~~B~~	~~9,000~~		~~-~~	~~Yes~~	~~Yes~~

~~* If randomization and dosing in Stage A are completed before the data needed for the first and/or second interim analysis(es) is/are available, GSK may choose to continue to Stage B while remaining blinded to the clinical endpoint data.~~

~~**If *both* the first and second interim analyses in Stage A would occur only after stage B enrolment and randomization has started, then the *first* analysis will not be performed.~~

Replaced by:

Interim #	***Timing of analysis***			***Can decide to stop accrual?***	***Can stop for futility?***	***Can claim success?***
	Stage	***# Participants***	***Participants triggering analysis***			
1	***A***	***4600***	***Maternal participants randomized***	***Yes***	***Yes***	***No***
2	***B***	***4600***	***Maternal participants with the opportunity to complete 6 months follow-up post-delivery***	***-***	***Yes***	***Yes***
3	***B***	***6500***		***-***	***Yes***	***Yes***
4	***B***	***8000***		***-***	***Yes***	***Yes***

~~If accrual to~~ ***If*** the trial is not halted at any interim analysis, then ~~accrual to~~ the trial will continue to 10,000 maternal ***participants with the opportunity to complete 6 months follow-up post-delivery to evaluate vaccine efficacy for the primary endpoint(s)***.

Section 9.5.1, Sequence of analyses

In addition to the interim analyses of efficacy described above, full analyses will occur as described below:

- When ~~all~~ ***4600*** maternal ~~and infant~~ participants ~~enrolled in Stage A~~ complete 6 months follow up post-delivery/birth (to evaluate primary and surrogate efficacy endpoints, immunogenicity, reactogenicity and safety ***if either primary (observed), or surrogate (predicted) vaccine efficacy endpoints meet success criteria***.)
- When all maternal and infant participants enrolled in both Stage A and Stage B ***have the opportunity to*** complete 6 months follow-up post-delivery/birth (to evaluate primary and secondary efficacy endpoints, immunogenicity, reactogenicity and safety)

Section 9.5.2, Statistical considerations for interim analysis

CCI [redacted]

Section 10.1.3, Informed consent process

~~Participants who are rescreened are required to sign a new ICF.~~

Participants who are re-screened (because, for example, they could not meet the protocol allowed window between initial screening and V1/randomization/vaccination) are not required to sign a new ICF, unless the ICF was amended in the meantime. However, the investigator or his/her representative should ensure that there is documentation that the participant is still in agreement to participate in the study and be re-screened. This can be done on the initially signed ICF or, if applicable, on other study source/documentation (as per local practice/ regulations).

Section 10.10, CCI [redacted]

Table 53, CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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TRADEMARKS

The following trademarked products are referenced in the present protocol.

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

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