Protocol Amendment 1

Study ID: 214725

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

NCT ID: NCT04980391

Date of Document: 16 Mar 2022

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention and number	GSK Respiratory Syncytial Virus (RSV) Maternal (RSVPreF3) Vaccine (GSK3888550A)
Other study intervention	Placebo (Lyophilized sucrose reconstituted with saline [NaCl] solution)
eTrack study number and abbreviated title	214725 (RSV MAT-012)
EudraCT number	2021-000994-96
Date of protocol	Final: 12 March 2021
Date of protocol amendment	Amendment 1 Final: 15 March 2022
Title	A Phase III, double-blind, randomized, placebo-controlled study to evaluate the safety, reactogenicity and immune response of a single intramuscular dose of unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.
Brief title	A study on the safety and immune response to an unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	214725 (RSV MAT-012)
EudraCT number	2021-000994-96
Date of protocol amendment	Amendment 1 Final: 15 March 2022
Title	A Phase III, double-blind, randomized, placebo-controlled study to evaluate the safety, reactogenicity and immune response of a single intramuscular dose of unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.
Sponsor signatory	Joon Hyung Kim Clinical and Epidemiology Project Lead, RSV Maternal
Signature	_____
Date	_____

Protocol Amendment 1 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 Biologicals SA (GSK).
- 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 intervention 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 participant and/or the participant's legally acceptable representative (LAR).
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational intervention(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the 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 all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	214725 (RSV MAT-012)
EudraCT number	2021-000994-96
Date of protocol amendment	Amendment 1 Final: 15 March 2022
Title	A Phase III, double-blind, randomized, placebo-controlled study to evaluate the safety, reactogenicity and immune response of a single intramuscular dose of unadjuvanted RSV Maternal vaccine, in high risk pregnant women aged 15 to 49 years and infants born to the vaccinated mothers.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

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 Events (SAEs)

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 Helpdesk for emergency unblinding

Refer to the protocol Section 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (15 March 2022)**:**

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants, conduct of the trial and scientific value of the trial.

Overall rationale for the current amendment:

This protocol has been amended to reflect the following:

- Following review of data collected so far from the RSV MAT-009 (212171) study, safety signals have been identified. An imbalance in the proportion of preterm births and neonatal deaths have been observed in infants born to vaccinated mothers who received RSV maternal vaccine versus those who received a placebo. The safety signals are being investigated and, although at this time a cause has not been determined, based on the above observations, the Sponsor has nevertheless decided to stop enrollment and vaccination for all actively enrolling RSV MAT studies.
  - There will be no additional participants included in the ongoing studies. All planned objectives will be assessed for the participants enrolled so far.
  - Safety monitoring will continue, with additional monitoring measures implemented, for both maternal and infant participants during the rest of the study period.
  - The ongoing studies were unblinded to ensure the safety monitoring of the participants.
  - Additional monitoring contact/s or visit/s for the maternal and infant participants has been included.
  - Respiratory tract illness surveillance for maternal participants will no longer be performed.
  - Placenta samples will be taken from all maternal participants at delivery visit, whenever feasible. These samples may be tested to support possible safety assessments, if necessary.
  - Blood samples for immunogenicity assessment at Visit 2-NB, Visit 3-NB and Visit 4-NB will no longer be collected from infant participants.
- To 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.

Also, this amendment includes clarifications, 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 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall design, Section 4.3 Justification for dose, Section 5.5 Criteria for temporarily delaying study intervention administration, Section 6.1 Study interventions administered, Section 6.3.2 Randomization to study intervention, Section 6.4 Study intervention compliance, Section 8 Study assessments and procedures, Section 8.2.3.2 Independent data monitoring committee (IDMC) evaluation	Updated to revise the overall study design and impacted sections as no further enrollment and vaccination will be performed. Figure 1, Table 5 and Table 6 have been updated to reflect the changes.	To adapt the wording according to the new study requirements.
Section 1.2 Schema, Section 1.3 Schedule of activities (SoA), Section 4.1 Overall design, Section 4.2.5 Case definition, Section 4.2.5.1 Maternal, medically attended respiratory tract illness (MA-RTI), Section 4.2.5.5 RSV infection, Section 8 Study assessments and procedures, Section 8.1.1 Biological samples, Section 8.1.3 Immunological read-outs, Section 8.3.1 Time period and frequency for collecting AE, SAE and other safety information, Section 8.4.1.1 Medically attended respiratory tract illnesses (MA-RTIs) in maternal participants, Section 8.4.2.1 Maternal participants, Section 8.4.2.3 Maternal and infant participants, Section 8.4.3.1 For a maternal MA-RTI, Section 8.4.4 Assessment visit procedures, Section 8.4.4.1 Clinical evaluation, Section 8.4.4.2 Nasal swab collection, Section 8.4.4.3 Missed assessment visit, Section 8.4.5 RTI hospitalization during the surveillance interval	Updated to remove Maternal RTI surveillance. Table 1, Table 6, Table 10, Table 15, Table 17 and Figure 1 have been updated to reflect the changes.	Updated to reduce the burden on the maternal participants.
Section 1.2 Schema, Section 1.3 Schedule of activities (SoA), Section 8.1.1 Biological samples,	Update to remove blood sample collection at Visit 2-NB, Visit 3-NB and Visit 4-NB for the infant partcipants	Updated to decrease the burden on the infant participants.

Section # and title	Description of change	Brief rationale
	Table 2, Table 12, Table 14, and Figure 2 have been updated to reflect the changes.	
Section 1.3 Schedule of activities	Updated to have an allowed window of time to plan the delivery visit. Table 3 has been updated to reflect the changes.	Updated to have an allowed window of time to plan the delivery visit.
Section 1.3 Schedule of activities (SoA), Section 4.1 Overall design, Section 8.2.1.4.2 Monthly contacts, Section 10.2.1	Updated to increase the number of safety contacts/visits to be made for maternal and infant participants and to collect placenta tissue samples from all participants. Table 1, Table 2, Table 3 and Figure 1 have been updated to reflect the changes.	Updated to monitor better any safety event associated with the safety signal observed in RSV MAT-009 study and to further understand the cause of the event.
Section 1.3 Schedule of activities, Section 4.1 Overall design, Section 8 Study assessments and procedures, Section 8.1.1 Biological samples, Section 8.1.2 Laboratory assays, Section 8.1.3 Immunological read-outs, Section 10.2.2 Descriptions of the assays to be performed in the study	Updated to remove the collection of hematocrit samples. Table 1, Table 10, Table 13 and Figure 4 have been updated to reflect the changes. Previous Table 15 about hematocrit readout has been deleted to reflect the changes.	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 1 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 1 being approved), will be still used for hematocrit analysis if required, as described in Section 10.2.
Section 2.3 Benefit/Risk assessment	Updated to provide details on the current status on expected benefits and risks from receiving the RSV MAT (RSVPreF3) vaccine	Updated to reflect potential changes in the benefit-risk profile.
Section 3 Objectives and Endpoints, Section 9.4.4.1 Safety.	Updated the objectives and endpoints plan and categorized the secondary safety objective as a primary one to assess safety of the infants.	Updated to reflect the change to study's safety assessment plan.
Section 1.2 Schema, Section 4.1 Overall design, Section 6.3.5 – Blinding and unblinding, Section 6.3.5.1 Emergency unblinding, Section 8.2.3.1 Safety evaluation by the Safety Review Team (SRT), Section 8.2.3.2 Independent data monitoring committee (IDMC) evaluation, Section 9.4.3.1 Safety, Section 9.4.4.1 Safety, Section 10.1.6 Dissemination of	Updated to provide details on the blinding status of the study. Table 5 has been updated to reflect the changes and sections impacted by this change have been updated accordingly.	Updated as the study team was unblinded while assessing the safety issue; and also to allow investigators to identify and inform the recipients of the potential risk observed with the RSV MAT vaccination.

Section # and title	Description of change	Brief rationale
clinical study data, Section 10.7.2 Glossary of terms		
Section 6.6 Continued access to study intervention after the end of the study	Updated as there will be no access to RSV MAT vaccine after the study end.	Updated because of the safety signal identified, leading to stopping of further enrollment and vaccination.
Section 6.8.1 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 8.2.3 - Study holding rules and safety monitoring, Section 8.2.3.2 - Study holding rules, Section 10.1.5 - Commitees structure, Section 10.7.1 - List of abbreviations	Name of the GSK safety monitoring board changed from “Vaccine Monitoring Board (VSMB)” to “Global Safety Board”.	Updated to include the new name of the GSK safety monitoring board.
Section 8.3.3 Regulatory reporting requirements for SAE, subsequent pregnancies, and other events	Timeframe for reporting subsequent pregnancy by the investigator/site staff after receipt or awareness, changed from 2 weeks to 24 hours. Table 18 has been updated to reflect the changes.	This change was 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. Table 19 has been updated to reflect the changes.	The email address is changed to align to the most recent GSK template related recommendation.
Section 9.3 Analysis sets	Definition of the enrolled set has been updated to exclude screen failures. Table 22 has been updated to reflect the changes.	Updated to remove screen failures from the enrolled set.
Section 9.5 Conduct of analyses, Section 9.5.1 Sequence of analyses	Updated to remove the intermediate analysis to evaluate all maternal and infant data collected up to Day 43 post-delivery/birth visit.	Updated to reflect the change to study’s statistical analysis plan from the decision to stop further enrollment and vaccination.

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1. PROTOCOL SUMMARY

1.1. Synopsis (Amended 15 March 2022)

Rationale:

The objective of the study is to evaluate the safety, reactogenicity, and immunogenicity * of the single intramuscular 120 µg dose of the study RSV maternal vaccine compared to placebo, in women with high risk pregnancies in the late second or third trimester of pregnancy and in the infants born to the vaccinated mothers.

The study will enroll pregnant adult participants with prevalent obstetric complications and risk factors that increase the risk of adverse pregnancy and neonatal outcomes: gestational diabetes, gestational hypertension, pre-eclampsia, fetal growth restriction, history of preterm labor in the current pregnancy, Human Immunodeficiency Virus (HIV) infection or uncomplicated twin pregnancy.[ACOG, 2019; EPI-RSV-015, 2019; Kachikis, 2017]. This study will also enroll pregnant healthy adolescent participants, considered as a potential high risk group.

Objectives and endpoints are presented in Table 4.

**** Based on all available safety information following vaccination with 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.***

1.2. Schema (Amended 15 March 2022)

The study is a Phase III, double-blind*, randomized, placebo-controlled, multi-center, multi-country study.

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

Maternal participants 15 to 49 years of age (YOA) (inclusive, at the time of the study intervention administration) will be enrolled to receive either RSV maternal (RSV MAT) vaccine (120 µg of RSVPreF3) or the placebo control, between the 24 $^{0/7}$ to 36 $^{0/7}$ weeks of gestation (inclusive).

Approximately 378 eligible maternal participants will be enrolled* and randomized (2:1) to receive either RSV MAT vaccine or the placebo control. At least eighteen (5%) of the enrolled and randomized maternal participants will be between 15 and 17 YOA, inclusive. At the same time, infant participants (as yet unborn) will be further randomized (1:1:1) into sub-cohorts for blood sample collection for the assessment of immunogenicity at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

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

An automated internet-based system (SBIR) will be used to randomly allocate a study group and treatment number to each maternal participant and her infant participant (as yet unborn) to a blood sampling sub-cohort. Age at the time of study intervention administration (<18, ≥18 YOA) will be a stratification factor within the randomization algorithm, while:

(a) gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks),

(b) pre-existing HIV infection and obstetric complication status (HIV present and obstetric complication present, HIV present and obstetric complication absent, or HIV absent and obstetric complication present) for participants ≥18 YOA only,

(c) center

will be the minimization factors. Minimization factors will have equal weight in the algorithm.

Study duration for maternal participants will be approximately 10 to 11 months (including screening visit, from informed consent/assent until 180 days post-delivery), and will be evaluated for safety, reactogenicity and immune responses.

Blood samples for humoral immunogenicity will be collected from all maternal participants at Day 1 (pre-study intervention), Day 31 (only if the delivery occurs after Day 31 post-study intervention) and on delivery day. Cord blood samples to evaluate the transfer of RSV-specific antibodies from maternal participants to their infants will be collected from all maternal participants on delivery day. The primary immunogenicity analysis will be based on the per protocol set (PPS) for immunogenicity. A second analysis of immunogenicity based on the full analysis set (FAS) may be performed to complement the PPS analysis (Refer to Sections 9.3 and 9.4.1.2 for details).

All maternal participants who receive the study intervention (exposed set [ES]) will be followed for safety and reactogenicity and evaluated for: solicited administration site and systemic adverse events (AEs) within 7 days of study intervention, unsolicited AEs within 30 days of study intervention, pregnancy outcomes and pregnancy-related adverse events of special interest (AESIs) within 42 days of delivery, serious adverse events (SAEs), medically attended respiratory tract illnesses (MA-RTIs)***** and medically attended adverse events (MAEs) throughout the study period and up to the time of the last contact.

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

Study duration for infant participants will be approximately 12 months (from birth until 365 days post-birth) which is expected to cover at least 1 complete RSV season and will be evaluated for safety and immune responses.

Blood samples for humoral immunogenicity will be collected from sub-cohorts of infant participants at Day 43, Day 121 and Day 181 post-birth*****. The primary immunogenicity analysis will be based on the PPS for immunogenicity. A second analysis of

immunogenicity based on the FAS may be performed to complement the PPS analysis (Refer to Sections 9.3 and 9.4.1.2 for details).

**** Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.***

All infant participants born to exposed maternal participants (ES) will be followed for safety and evaluated for: neonatal/infant related AESIs up to 42 days of birth, medically assessed, RSV-associated lower respiratory tract illnesses (RSV-LRTIs) up to 365 days post-birth which is expected to cover at least 1 complete RSV season, SAEs and MAEs throughout the study period and up to the time of the last visit.

Section 4.1 provides an overview of the study design.

Safety monitoring and safety data review will be performed by an internal Safety Review Team (SRT) and an external Independent Data Monitoring Committee (IDMC).

1.3. Schedule of Activities (SoA) (Amended 15 March 2022)

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

Whenever possible, the investigator should arrange study visits within the allowed visit window. Immunogenicity data from blood samples collected outside an allowed visit window may not be considered in the associated 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 AE / potential AE 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 enrollment of the neonate.
- Maternal participant Visit 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 visit location must have appropriate infrastructure and logistics to complete **all** study procedures if a visit is to be conducted at a different location other than the study site or at participant's home. Blood samples including cord blood samples for immunogenicity collected outside of the study site must be centrifuged between 30 minutes and at most, 24 hours after collection.
- Contact may be via telephone, SMS, email, video-telephone/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.
- Refer to Section 8 for information about special circumstances (e.g., the Covid 19 pandemic) and their impact on study activities.

Table 1 Schedule of Activities (SoA) – Maternal participants (Amended 15 March 2022)

Visit / Contact	**Screening**	**V1**	**C1**	**V2** [1]	**Monthly contacts until delivery** [6]	**V3**	**V4**	**C2**	**Safety Visit - Event-driven**	**RSV-associated MA-RTI Visit - Event-driven** [7]	**Notes**
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Informed consent/assent	●										Section 10.1.3 ***Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
Check inclusion/exclusion criteria	●	O									Sections 5.1.1 and 5.1.2
Assign maternal participant study number	●										Section 6.3.1
Register maternal participant in SBIR	O										
Assign infant participant study number		O									
Record demographic data	●										Section 5.3
Record lifestyle characteristics	●	●	●	●		●	●	●			
Review & collect medical and vaccination history,	O	●									Section 8.2.1.3

Visit / Contact	**Screening**	**V1**	**C1**	**V2** [1]	**Monthly contacts until delivery** [6]	**V3**	**V4**	**C2**	**Safety Visit - Event-driven**	**RSV-associated MA-RTI Visit - Event-driven** [7]	**Notes**
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
including pre-existing medical conditions and/or obstetric complications											
Record outcome of fetal morphology ultrasound scan	●										Section 8.2.1.3
Record the estimated fetal weight by ultrasound or record presence of fetal growth restriction if diagnosed using other ultrasound parameters	●										
Record obstetric history from current pregnancy	●	O									Section 8.2.1.3
Record obstetric history from past pregnancies	O	●									Section 8.2.1.3
Record travel history to or living in Zika virus endemic countries/regions (During the current pregnancy only)	●	●	●	●		●					
General and obstetric examination	●	●		●		●	●		O	O	Section 8.2.1.4

Visit / Contact	**Screening**	**V1**	**C1**	**V2** [1]	**Monthly contacts until delivery** [6]	**V3**	**V4**	**C2**	**Safety Visit - Event-driven**	**RSV-associated MA-RTI Visit - Event-driven** [7]	**Notes**
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Body temperature before study interventions administration [2]		•									
Review of safety lab data required for assessing eligibility criteria **OR** Blood sample (hematology / biochemistry, ~ 5.5 ml) if not performed as part of the routine care.	O										Section 10.2.1
Review of safety lab data required for assessing eligibility criteria **OR** Urine sample (Dipstick) if not performed as part of the routine care	O										
Blood sample (immunogenicity ~ 10 ml)		•		•		•					Sections 8.1.1 and 8.1.3
Cord blood (~ 5 to 10 ml)						•					Sections 8.1.1 and 8.1.3

Visit / Contact	**Screening**	**V1**	**C1**	**V2** [1]	**Monthly contacts until delivery** [6]	**V3**	**V4**	**C2**	**Safety Visit - Event-driven**	**RSV-associated MA-RTI Visit - Event-driven** [7]	**Notes**
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Nasal swab [7]										•	Sections 8.1.1, 8.1.3, and 8.4.4 ***Nasal swab samples will no longer be collected.***
Placental tissue sample [8]						•					***Section 10.2.1 Samples will be collected at delivery from all participants, if feasible.***
Check contraindications, warnings and precautions to study interventions administration		O									Section 8.2.1.5
Check criteria for temporary delay for study interventions administration		O									Section 7.1
Allocate maternal study group, intervention number		O									Sections 6.3.2 and 6.3.3
Allocate infant sub-cohorts for immunogenicity assessment [3]		O									

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 $^{0/7}$ - 36 $^{0/7}$ weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Administer Intervention (study vaccine / placebo)		•									Sections 6.1 and 6.2
Record administered intervention number		•									
Observe for 30 minutes post-dose		O									
Distribute maternal participant card	O	O									Section 8.3.6
Record Labor / delivery information						•					
Record pregnancy / delivery outcomes (Day 1 post-study intervention to Day 42 post-delivery)		O	O		O	•	O				Section 8.3.3. Must submit Expedited AE report for an adverse pregnancy outcome
Train maternal participant/LAR on use of eDiary device		O									Section 10.3.8
Distribute eDiary device to maternal participant / LAR.		O									
Review eDiary entries		O	O	O					O [4]	O [4]	Section 8.3.1
Return eDiary device				O							

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Concomitant medications / vaccinations		●	●	●	●	●	●	●	●	●	Sections 6.8.1 and 6.8.3
All solicited AEs (Day 1 post-study intervention to 7 days post-study intervention)		O	O						O		Sections 8.3.1, 10.3.4 and 10.3.8
All unsolicited AEs (Day 1 post-study intervention to 30 days post-study intervention)		●	●	●					●	●	Sections 8.3.1, 10.3.4 and 10.3.8
Record of worsening of pre-existing medical conditions and/or obstetric complications (Day 1 post-study intervention to 180 days post-delivery)		●	●	●	●	●	●	●	●	●	Section 8.2.1.2
Pregnancy-related AESIs (Day 1 post-study intervention to 42 days post-delivery)		●	●	●	●	●	●		●	●	Sections 8.3.1, 8.3.3, 8.3.4 and 10.3.5. Must submit an Expedited AE report.
Suspected, probable and confirmed cases of COVID-19 infection (depending on		●	●	●	●	●	●	●	●	●	Sections 8.4.7

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 $^{0/7}$ - 36 $^{0/7}$ weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
the epidemiological COVID-19 situation) (Day 1 post-study intervention to 180 days post-delivery)											
MA-RTIs (Day 1 post-study intervention to 180 days post-delivery) [7]		O [5]	O [5]	O [5]	O [5]	O [5]	O [5]	O [5]		●	Sections 8.3.1, 8.3.3, 8.4 and 10.3.8 ***MA-RTIs for the maternal participants will no longer be performed.***
SAEs, (S)AEs leading to study withdrawal, MAEs (Day 1 post-study intervention to 180 days post-delivery)		●	●	●	●	●	●	●	●	●	Sections 7.2, 8.3.1 and 10.3.8
SAEs related to study participation (Screening to Day 1 pre-study intervention)	●	●									Sections 8.3.1 and 10.3.8
Subsequent pregnancies							●	●	●	●	
Record interest in joining future extension study								●			Section 6.6

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Screening conclusion	●										
Study conclusion								●			Sections 4.4 and 10.1.9

V = visit; **C** = Contact; **D** = day; **MA-RTI** = medically attended respiratory tract illness; **LAR** = Legally acceptable representative

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

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

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

[2] Fever is defined as temperature 38.0°C/100.4°F regardless of the location of measurement. The preferred location for measuring temperature in this study is the oral cavity.

[3] Recording will be done at Visit 1, upon maternal participant randomization but the eCRF entry will be done on the demography screen.

[4] For safety visit or RSV-associated MA-RTI visit, eDiary entries should be reviewed only if the visit occurs between Day 1 and Day 31.

[5] RSV-associated MA-RTI unscheduled visit should be planned if the maternal participant has any symptoms or signs as defined in Section 8.4.3.1.

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

[7] Due to the change in the study requirements, RTI surveillance/ assessment for the maternal participants will no longer be performed

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

Note:

Contact may be via telephone, SMS, email, video-telephone/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.

The timing of an event-driven site visit (e.g., to further evaluate a potential (S)AE or RSV-MA-RTIs) cannot be defined with precision in the protocol. Event-driven visits may occur throughout the study.

In times of special circumstances, refer to Section 8 for study procedures.

Table 2 Schedule of activities (SoA) – Infant participants (Amended 15 March 2022)

Visit / Contact	V1-NB	*Safety contact (recommended)* [5]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		Notes
									Contacts (Section 8.4.2.2.1)	**Visit**	
Age of infant		*8 days*	6 weeks	3 months	4 months	6 months	9 months	12 months			
Visit Day	**Birth**	***D8 Post-birth***	**D43 Post-birth**	**D91 Post-birth**	**D121 Post-birth**	**D181 Post-birth**	**D271 Post-birth**	**D366 Post-birth**	**Birth to Day 366 Post-birth**	**Event-Driven**	
Check inclusion / exclusion criteria	●										Sections 5.1.2 and 5.2.2
Re-consent / Consent for infant participation if required by local regulations	●										
Record infant participant study number	●										
Record sub-cohort for immunogenicity assessment	●										Section 6.3.2
Distribute infant's participant card	O										Section 8.3.6
Distribute infant RTI diary card	O		O		O	O		O		O	Distribute at V1-NB: Distribute additional RTI diary cards as needed.
Review infant RTI diary card		***O***	O	O	O	O	O	O	O	O	
Collect infant RTI diary card			O		O	O		O		O	Collect RTI diary cards that are fully filled out.
Transcribe applicable infant RTI diary card data to eCRF		***O***	●	●	●	●	●	●	●	●	

Visit / Contact	**V1-NB**	***Safety contact (recommended)*** [5]	**V2-NB**	**C1-NB**	**V3-NB**	**V4-NB**	**C2-NB**	**V5-NB**	**RTI Surveillance**		**Notes**
									Contacts (Section 8.4.2.2.1)	**Visit**	
Age of infant		***8 days***	**6 weeks**	**3 months**	**4 months**	**6 months**	**9 months**	**12 months**			
Visit Day	**Birth**	***D8 Post-birth***	**D43 Post-birth**	**D91 Post-birth**	**D121 Post-birth**	**D181 Post-birth**	**D271 Post-birth**	**D366 Post-birth**	**Birth to Day 366 Post-birth**	**Event-Driven**	
Demographic data	●										Section 5.3
Lifestyle characteristics [1]	●	***O***	●	●	●	●	●	●			
Apgar score (at 1, 5 and [if available/performed] 10 minutes)	●										
Weight, length, head circumference, physical examination	●		●		●	●		●		●	Section 8.2.2.1
Blood sample **if no cord blood** ~2.5 ml [2]	●										Table 12
Blood sample (immunology, infants) ~2.5 ml [3, 6]			● Sub-cohort 1		● Sub-cohort 2	● Sub-cohort 3					Table 12 ***Samples will no longer be collected at Visit 2-NB, Visit 3-NB and Visit 4-NB***
Concomitant vaccinations	●	***O***	●	●	●	●					Sections 6.8.2 and 6.8.3
Concomitant medications	●	***O***	●	●	●	●	●	●	●	●	
Neonatal / Infant AESIs (Birth to 42 days post-birth)	●		●								Section 8.3.1, 8.3.3, 8.3.4, and 10.3.5. Must submit an Expedited AE report.
Suspected, probable and confirmed cases of COVID-19 infection	●	***O***	●	●	●	●	●	●	●	●	Sections 8.4.7

Visit / Contact	**V1-NB**	***Safety contact (recommended)*** [5]	**V2-NB**	**C1-NB**	**V3-NB**	**V4-NB**	**C2-NB**	**V5-NB**	**RTI Surveillance**		**Notes**
									Contacts (Section 8.4.2.2.1)	**Visit**	
Age of infant		***8 days***	**6 weeks**	**3 months**	**4 months**	**6 months**	**9 months**	**12 months**			
Visit Day	**Birth**	***D8 Post-birth***	**D43 Post-birth**	**D91 Post-birth**	**D121 Post-birth**	**D181 Post-birth**	**D271 Post-birth**	**D366 Post-birth**	**Birth to Day 366 Post-birth**	**Event-Driven**	
(depending on the epidemiological COVID-19 situation) (Birth to 365 days post-birth)											
LRTIs (including medically assessed, RSV-associated LRTIs) (Birth to 365 days post-birth)	O [4]	***O*** [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	●	Sections 8.3.1, 8.3.3, 8.4 and 10.3.8.
Medically assessed, RSV-associated hospitalizations (Birth to 365 days post-birth)	O [4]	***O*** [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	●	Sections 8.3.1, 8.3.3, 8.4 and 10.3.8.
SAEs, (S)AEs leading to study withdrawal, MAEs (Birth to 365 days post-birth)	●	***O***	●	●	●	●	●	●	●	●	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 and 8.4.4.2
Study conclusion								●			Sections 4.4 and 10.1.9

LAR = legally acceptable representative; **V**= visit; **C** = contact; **D**=day; **NB** = newborn.
● indicates a study procedure that requires documentation in the individual eCRF.
○ indicates a study procedure that does not require documentation in the individual eCRF.

[1] Record at Visit 1-NB and if changes in lifestyle characteristics thereafter.
[2] Adjust volume if weight ≤ 2.5 Kg. If no cord blood was collected, an infant blood sample must be collected within 72 hours after birth.
[3] One sample at one of these visits, as per infant's assigned sub-cohort. Adjust volume if weight ≤ 2.5 Kg.
[4] RTI unscheduled visit should be planned in case the infant participant has any symptoms or signs as defined in Section 8.4.3.2.
[5] An additional recommended safety contact may be performed ~7 days post-birth if deemed necessary by the investigator or by the parent/ LAR(s).
[6] Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.
In times of special circumstances, refer to Section 8 for study procedures.
Note:
Contact may be via telephone, SMS, email, video-telephone/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.
The timing of an event-driven visit cannot be defined with precision in the protocol.

Table 3 Allowed windows for study visits (Amended 15 March 2022)

Visit	Study Day [a]	Allowed visit window [b]
Maternal participants		
Screening	Up to 28 days prior to Visit 1	Day (-28) - Day 1
Visit 1	Day 1	Day 1
Contact 1	Day 8	Day 8 – Day 12
Visit 2 [c]	Day 31	Day 21 – Day 46
Monthly contacts until delivery	every 30 days	every 25 – 35 days
Visit 3 (Delivery) [d]	-	***1 day before to 3 days after delivery[G]***
Visit 4	Day 43 after delivery	Day 31 - Day 61 after delivery
Contact 2	Day 181 after delivery	Day 166 - Day 201 after delivery
Infant participants		
Visit 1-NB (Birth) [d, e]	Birth	-
Recommended safefy contact	***Day 8***	***Day 7 - Day 10***
Visit 2-NB	Day 43 after birth	Day 31 – Day 61 after birth
Contact 1-NB	Day 91 after birth	Day 84 - Day 98 after birth
Visit 3-NB [f]	Day 121 after birth	Day 111 – Day 141 after birth
Visit 4-NB [f]	Day 181 after birth	Day 166 – Day 201 after birth
Contact 2-NB	Day 271 after birth	Day 257 – Day 287 after birth
Visit 5-NB	Day 366 after birth	Day 331 – Day 401 after birth

[a] Whenever possible the Investigator should arrange study visits at study days.

[b] The investigator should endeavor to have the participants come in for the visits within this window.

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

[d] If no cord blood was collected, an infant blood sample must be collected within 72 hours after birth.

[e] If consent is not obtained within the allowed interval, but the parent(s) /LAR(s) still wish the infant to participate, consent may be obtained at any time until the Day 43 post-delivery/birth visit.

[f] Visit may coincide with infant participant's routine care visit.

[G] ***For participants in whom a cesarean section is performed, 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.***

Note: In times of special circumstances, refer to Section 8 for study procedures.

2. INTRODUCTION

2.1. Study rationale

GSK is developing an investigational respiratory syncytial virus (RSV) vaccine for administration to pregnant women in their late second and third trimester of pregnancy, with the aim of preventing RSV-associated lower respiratory tract illnesses (LRTIs) in their infants by transfer of maternal antibodies.

The investigational vaccine is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation. The F protein has been selected because it is a major surface antigen of the RSV virus that is well conserved among RSV-A and RSV-B subgroups. The RSV F protein is the main target of the neutralizing antibody response to RSV, which is considered essential for protection against RSV-associated severe disease [Magro, 2012]. Vaccination of pregnant women with the RSV F protein is expected to protect the baby against RSV (subtypes A and B) LRTI from birth up to 6 months of age.

In the RSV maternal program RSV preF3 vaccine safety, reactogenicity and immunogenicity has been studied in healthy non-pregnant women, 18-45 yoa (study RSV MAT-001 [NCT 03674177] tested 30, 60 and 120 µg dose-levels, completed; study RSV MAT-011[NCT 04138056] tested 60 and 120 µg dose-levels in co-administration with dTpa vaccine, ongoing) and in healthy pregnant women 18-40 yoa (study RSV MAT-004 [NCT 04126213], tested 60 and 120 µg dose-levels, ongoing) and in infants born to vaccinated mothers.

The 120 µg dose has demonstrated robust immunogenicity with no safety concerns identified. It was, therefore, selected for evaluation in the Phase ***III*** studies: the RSV MAT-009 confirmatory efficacy trial is ongoing and the RSV MAT-012 trial is planned to assess the safety, reactogenicity and immunogenicity in the high risk obstetric population.

High risk pregnancies represent up to 33% in the overall population of pregnant women [Holness, 2018]; however, women with high risk pregnancies will not be part of the pivotal RSV MAT-009 study, which will enroll healthy pregnant women. In order to collect proper information in this population, RSV MAT-012 study will enroll pregnant adult participants with prevalent obstetric complications or conditions which increase the risk of adverse pregnancy and neonatal outcomes: gestational diabetes, gestational hypertension, pre-eclampsia, fetal growth restriction, history of preterm labor in the current pregnancy, HIV infection or uncomplicated twin gestation.[ACOG, 2019; EPI-RSV-015, 2019; Kachikis, 2017]. This study will also enroll healthy pregnant adolescent participants, considered as a potential high risk group.

The objective of the RSV MAT-012 study is to evaluate the safety, reactogenicity, and immunogenicity of the single intramuscular 120 µg dose of the study RSV maternal vaccine compared to placebo, when administered in the second or third trimester of pregnancy in women with high risk pregnancies and in the infants born to the vaccinated mothers.

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 and epidemiology studies of RSV infection.

2.3. Benefit/Risk assessment (Amended 15 March 2022)

The Sponsor 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 infections (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.

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-012, based on an observation of imbalance of 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 trial 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, the Sponsor 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.

3. OBJECTIVES AND ENDPOINTS (AMENDED 15 MARCH 2022)

Table 4 Study objectives and endpoints (Amended 15 March 2022)

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

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

Objectives	Endpoints
Secondary	
Safety assessment: **Maternal participants:**	
• To evaluate the safety of a single IM dose of study intervention (RSV maternal vaccine and placebo) administered to maternal participants, up to 180 days post-delivery.	• Number and percentage of maternal participants reporting: – SAEs, (S)AEs leading to study withdrawal and MAEs from Day 1 up to 180 days post-delivery.
• To evaluate the worsening of pre-existing medical conditions and/or obstetric complications up to 180 days post-delivery, in maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Number and percentage of maternal participants reporting: – Worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery.
• To evaluate the occurrence of RSV-associated MA-RTIs in maternal participants who received a single IM dose of study intervention (RSV maternal vaccine and placebo) up to 180 days post-delivery.	• Number and percentage of maternal participants reporting: – RSV-associated MA-RTIs from Day 1 up to180 days post-delivery.
Infant participants:	
• To evaluate the occurrence of medically assessed, RSV-associated LRTIs up to 365 days post-birth (12 months of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated LRTIs of any severity and severe RSV-associated LRTIs (according to the cases definitions).
• To evaluate the occurrence of medically assessed, RSV-associated hospitalization up to 365 days post-birth (12 months of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• From birth up to 365 days post-birth (12 months of age), number and percentage of infant participants reporting medically assessed, RSV-associated hospitalizations (according to the cases definitions).
Immunogenicity assessment: **Maternal participants:**	
• To evaluate the immunogenicity of a single IM dose of study intervention (RSV maternal vaccine or placebo) administered to maternal participants up to delivery.	• Humoral immune responses at Day 31 post-dosing: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A • Humoral immune responses at pre-dosing (Day 1), at Day 31 post-dosing and at delivery: – Neutralizing antibody titers against RSV-B
Infant participants:	
• To evaluate neutralizing antibody titers against RSV-B at birth in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).	• Humoral immune responses at delivery*: – Neutralizing antibody titers against RSV-B * Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).
• To evaluate RSV-specific antibodies up to Day 181 post-birth (6 months of age) in infants born to	• Humoral immune responses at Day 43*, at Day 121* and at Day 181*:

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

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

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

4. STUDY DESIGN

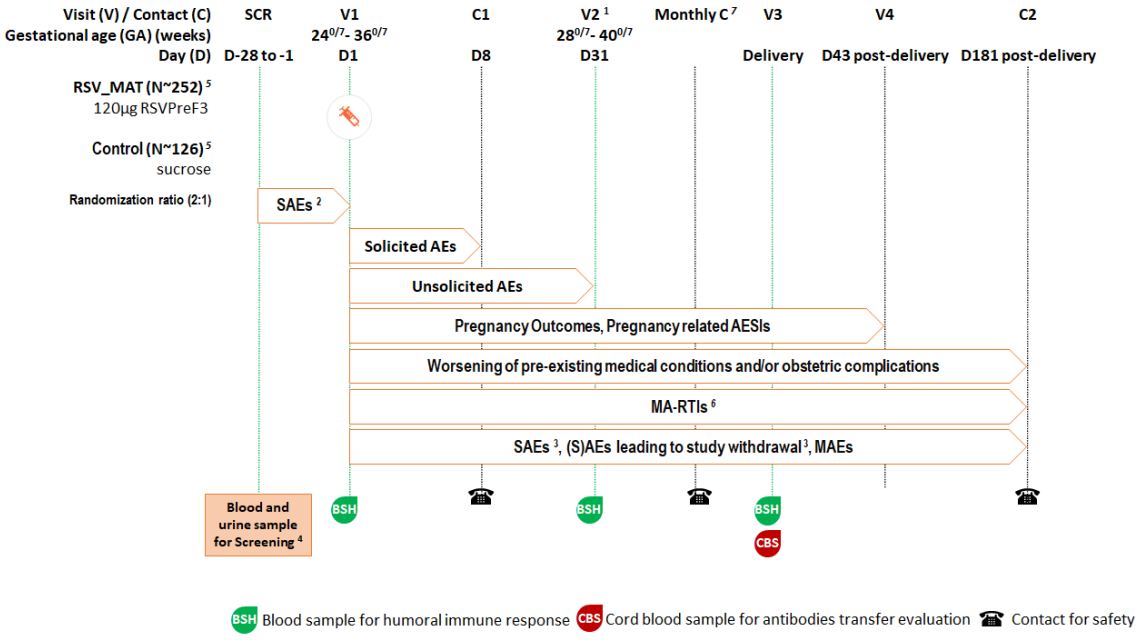
4.1. Overall design

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

Section 1.3 provides SoAs for maternal and infant participants. In times of special circumstances, refer to Section 8 for study procedures.

Section 9.5.1 describes the sequence of analyses for maternal and infant participant data.

Figure 1 Study design overview – Maternal participants (Amended 15 March 2022)



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

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

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

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

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

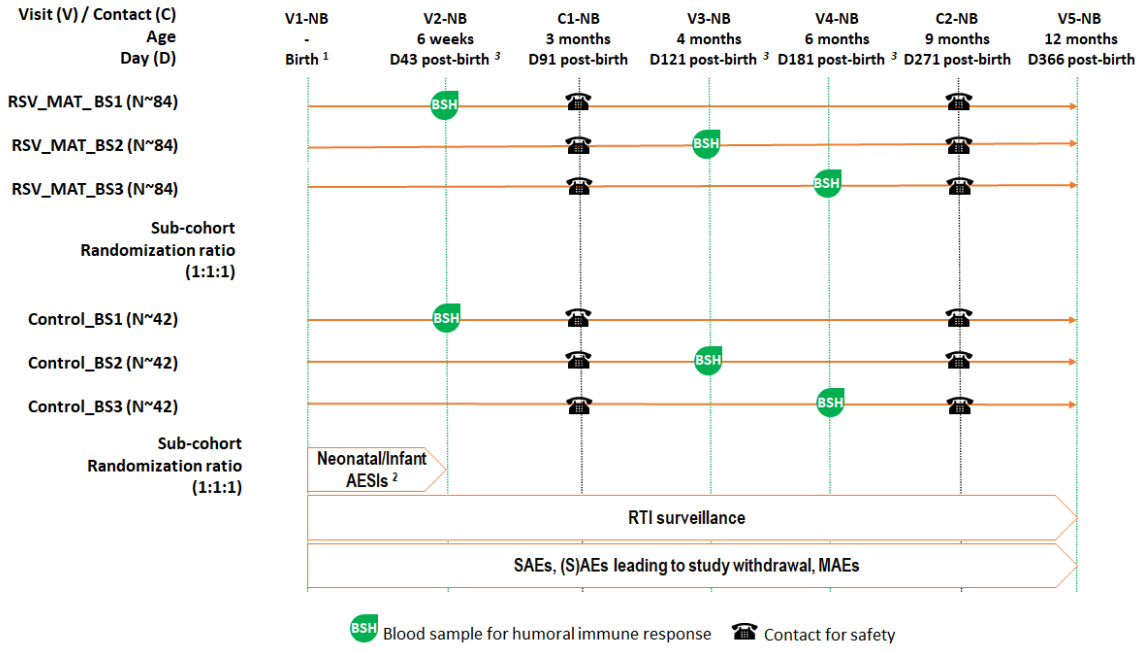
[5] Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants. Refer to section 2.3 for further details.

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

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

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

Figure 2 Study design overview – Infant participants (Amended 15 March 2022)



AESI = adverse event of special interest; **MAE** = medically attended adverse event; **RTI** = respiratory tract illness;**(S)AE** = (serious) adverse event

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

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

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

[1] If cord blood was not collected at delivery/birth, a blood sample should be collected from the infant within 72 hours post-birth.

[2] Any neonatal / infant AESIs identified after 42 days post-birth should also be reported.

[3] ***Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.***

Note:

An additional recommended safety contact may be performed ~7 days post-birth if deemed necessary by the investigator or by the parent/ LAR(s).

- **Study Type:** self-contained.
- **Experimental design**: Phase III, double-blind*, randomized, placebo-controlled, multi-center, multi-country study with 1 investigational RSV MAT vaccine group in a parallel design.

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

- **Duration of the study:** The intended duration of the study for maternal participant is approximately 10 to 11 months (including screening visit, from informed consent/assent until 180 days post-delivery) and approximately 12 months for infant

participants (from birth until 365 days post-birth), which is expected to cover at least 1 complete RSV season.

- **Control**: Placebo control.
- **Blinding:** Double-blind*, as described in Table 5.

  **** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.***
- **Study (intervention) groups** are single 120 µg dose of the investigational RSV vaccine and Placebo control, as described in Table 5.
- **Study intervention schedule***: 1 single dose administered IM between 24 and 36 weeks of gestation (at Visit 1, Day 1) to maternal participants.

  **** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
- **Randomized study intervention allocation*** is 2:1 (investigational vaccine : placebo), as described in Table 5 and Section 6.3.

  **** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
- **Sampling schedule**:
  - Blood and urine samples for **assessing eligibility criteria** will be taken, if not performed locally as per standard of care, from all maternal participants at screening. Refer to section 10.2.1 for details.
  - Blood samples for **immunogenicity** assessment will be taken from all maternal participants at Days 1, 31 and delivery.
  - ***Placenta samples will be taken from all maternal participants at delivery visit, whenever feasible. These samples may be tested to support possible safety assessments, if necessary. Additional details are provided in the study procedures manual (SPM).***
  - Cord blood samples for **immunogenicity** assessment will be taken from all maternal participants at delivery. If no cord blood sample can be obtained, the infant blood sample will be collected within 72 hours days after birth.
  - Blood samples for **immunogenicity*** analysis will be taken from sub-cohorts of infant participants at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

    **** Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.***
  - Nasal swab for confirmation of RSV-A/B infection will be taken from participants* clinically diagnosed as having a suspected case of RSV-associated RTIs at an event-driven timepoint.

    **** Due to the change in the study requirements, nasal swab samples from the maternal participants will no longer be collected.***

- **Primary completion Date (PCD)**: V***isit 5-NB (Day 366 post-birth)***.

  Refer to Section 10.7.2 for the definition of PCD.

- **Data collection:** standardized Electronic Case Report Form (eCRF).

  e-Diaries will be used to collect solicited event data. Unsolicited AEs 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 external IDMC and an internal SRT. Safety precautions such as study holding rules have been pre-defined.

  Refer to Sections 8.2.3 and 10.1.5 for detailed description safety monitoring and holding rules.

Table 5 Study groups, intervention and blinding (Amended 15 March 2022)

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

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

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

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

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

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

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

4.2. Scientific rationale for study design

4.2.1. Study population

The study population will include pregnant women with prevalent obstetric complications and risk factors for adverse pregnancy outcome, including healthy pregnant adolescent participants.

4.2.2. Use of placebo

The placebo group serves as a control for safety, reactogenicity, and immunogenicity 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, reactogenicity and immunogenicity 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 unbalanced randomization by: a) improving standardization of reporting of pre-defined pregnancy-related and neonatal AESI using Global Alignment of Immunization Safety Assessment in pregnancy [GAIA] definitions; b) referring to the background rates for events available in the literature in the epidemiological study [EPI-RSV-008, 2020] and observational natural history studies [EPI-RSV-015, 2019; EPI-RSV-015, 2020]; and c) establishing processes for continuous review of safety data by the SRT and IDMC.

4.2.4. Sub-cohorts for infant blood sampling

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 infants.

4.2.5. Case definition (Amended 15 March 2022)

RTI cases will be classified (during data analyses) according to the definitions provided in Sections 4.2.5.1*, 4.2.5.2 and 4.2.5.3.

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

4.2.5.1. Maternal, medically attended respiratory tract illness (MA-RTI) (Amended 15 March 2022)

Table 6 MA-RTI case definitions for data analysis in maternal participants (Amended 15 March 2022)

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

[1] Confirmed RSV infection defined in Section 4.2.5.3

[2] RSV (nasal swab) sampling and testing as specified in Table 10.

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

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

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

Table 7 RTI/LRTI case definitions for data analysis in infants

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

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

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

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

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

[4] Confirmed RSV infection defined in Section 4.2.5.3

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

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

4.2.5.3. RSV infection (Amended 15 March 2022)

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

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

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

4.3. Justification for dose (Amended 15 March 2022)

A single formulation of the investigational RSV maternal vaccine (containing 120 µg of the RSVPreF3 antigen) ***was*** planned. Available data ***suggested*** that the 120 µg formulation ***had*** an acceptable safety profile and tends to elicit stronger immune responses, 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 RSV MAT-001 and RSV MAT-004 studies are included in the IB to support RSV MAT-012.

Infection with RSV occurs in almost all participants by the time of reproductive age and it is extremely unlikely that a maternal participant would not have been naturally infected with RSV before. Results of study RSV MAT-001 in non-pregnant women ***and RSV MAT-004 in 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 $36^{0/7}$ 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 term 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).

* ***Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants. For details, refer to Section 2.3.***

4.4. End of Study definition

A participant is considered to have completed the study if he/she returns for the last visit or is available for the last scheduled contact as described in the protocol. Refer to Section 10.7.2 for the definition of EoS.

EoS: Last subject last visit (LSLV) of infant participants (Visit 5-NB, Day 366 post-birth)

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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 and legally acceptable representatives (LARs) 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).

  * *Written informed consent obtained from parents/LARs and written informed assent obtained from the maternal participant if she is less than legal age, or written informed consent obtained from the participant if the participant has achieved legal age. The legal age is determined according to local regulations in each participating country.*

  In case the legal age is achieved during the conduct of the study, an additional written informed consent from the maternal participant should be obtained at the time of the legal age.

  - both mother and father should consent if local regulations / guidelines require it.
- Pre-pregnancy Body Mass Index (BMI) (based on participant's report) 18.5 to 39.9 kg/m^2, inclusive.
- Healthy (as established by medical history and clinical examination) adolescent pregnant women, 15 to 17 YOA, inclusive, at the time of study intervention administration.

  OR
- Pregnant women, 18 to 49 YOA, inclusive, at the time of study intervention administration with:

- HIV infection (as confirmed by local standard of care serologic tests)

AND/OR

- Obstetric complications or risk factors during the current pregnancy, where the expectant management of the pregnancy is possible and without evidence of non-reassuring fetal status (only cases for which fetal heart rate can be ascertained) as follows:
  - Gestational diabetes, well-controlled on medications (with or without diet or exercise): i.e. when normoglycemia is maintained (fasting or preprandial blood glucose values <95 mg/dL [5.3 mmol/L], and/or postprandial blood glucose concentration <140 mg/dL [7.8 mmol/L] at 1 hour and/or postprandial blood glucose concentration: <120 mg/dL [6.7 mmol/L] at 2 hours).
  - Gestational hypertension, well-controlled on diet or medications below 160/110 mmHg.
  - Pre-eclampsia without severe features (i.e. eclampsia, severe hypertension [>160/110 mmHg], organ dysfunction, unstable or complicated by Hemolysis, Elevated Liver enzymes, and Low Platelets [HELLP] syndrome).
  - Fetal Growth Restriction in singleton pregnancies, with normal umbilical artery (UA) Doppler and estimated fetal weight 3 to 10th percentile for gestational age.
  - History of threatened preterm labor in the current pregnancy, with no cervical dilation greater than 2 cm or effacement exceeding 50%, and/or no progressive change in cervical dilation or effacement detected by serial examinations, when maternal participant is asymptomatic (i.e. no vaginal bleeding or uterine contractions or amniotic fluid loss).
  - Uncomplicated twin gestation.

- Pregnant females at 24 $^{0/7}$ to 36 $^{0/7}$ weeks of gestation at the time of study intervention administration (Day 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).
  - first or second 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 intrauterine insemination (IUI) or embryo-transfer (ET) date. Refer to Section 10.8 for guidance on gestational age assessment.

  The level of diagnostic certainty of the gestational age should be established by using the GAIA gestation age assessment tool (Section 10.8).

- Participants who are willing to provide cord blood.

- Willing to have their offspring followed-up after delivery for a period of 12 months.
- Participants who do not plan to give their offspring for adoption or place the child in care.

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 infant 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

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 any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention.
- Hypersensitivity to latex.
- Any pre-existing medical conditions or obstetric complications in the current pregnancy that, based on the investigator's clinical judgment, are poorly controlled and/or with clinical evidence of a non-reassuring fetal status and/or are likely to result in delivery within 7 days after study intervention administration and/or when the timing of planned delivery is within 7 days after study intervention administration and/or acute conditions requiring immediate medical attention for maternal stabilization and/or treatment.
- A multiple pregnancy with 3 or more fetuses.

- Complicated twin gestation (e.g twin to twin transfusion syndrome or fetal growth restriction).
- Placenta Accreta Spectrum, including placenta increta, percreta, and accreta.
- Fetal structural defects or genetic abnormalities that affect (or are likely to affect) fetal health or survival during the first year of life.
- Known or suspected impairment of the immune system or immunodeficiency syndrome other than HIV.
- Lymphoproliferative disorder or malignancy within 5 years before study dose administration (excluding effectively treated non-melanoma skin cancer).
- Any illness of the mother or conditions of the fetus that, in the investigator's judgment, may substantially interfere with the maternal participant's ability to comply with study procedures, or could increase the risks to the mother or the fetus, or could preclude the evaluation of the participant's data.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study, as determined by medical history, physical examination or laboratory screening tests.
- Women with any diagnosis, condition, treatment, or other factor that, in the opinion of the investigator, has the potential to affect or confound assessments of immunogenicity or safety
- Any conditions which, in the investigator's opinion, would increase the risks of study participation to the unborn infant.

5.2.1.2. Prior/Concomitant therapy (Amended 15 March 2022)

- Prior receipt of an RSV maternal vaccine.
- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning:
  - *For a drug, vaccine or medical device:* 29 days before the dose of study intervention(s) (Day -28 to Day 1), or their planned use during the study period.
  - *For immunoglobulins:* 90 days before the dose of study intervention(s), or their planned use during the study period.

  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 study intervention administration, but may be allowed following delivery.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 29 days before the study Day 1 and ending at delivery, with the exception of 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 intervention (Day 1).

Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly. ***In that sense, COVID-19 vaccines may be allowed, when administered ≥ 15 days before or after study vaccination.***

- Receipt of blood or plasma products or immunoglobulin, from 90 days before study intervention administration, or planned receipt through delivery, with the exception of Rho(D) immunoglobulin, which can be given at any time. ***In that sense, antibody therapy received against COVID-19 disease should be recorded.***
- Administration of immune-modifying therapy within 6 months before study intervention administration, or planned administration through delivery, except if it is part of management of HIV infection. 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.

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 intervention (drug, vaccine or invasive medical device).

  Note: European Economic Community (EEC) directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.

5.2.1.4. Other exclusions

- Alcoholism or substance use disorder within the past 24 months based on the presence of 2 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 [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 dependants, family, or household members.

5.2.2. Infant participants

- Concurrently participating in another clinical trial, 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 invasive 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 including geographic ancestry (race)*, ethnicity*, month of birth (if allowed per local regulation) and year of birth, will be collected.

*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 that should be collected may include highest level of education, smoking status/exposure, illicit drug use, household environment, and other factors that could place study participants at risk of adverse study outcomes.

5.3.2.2. Infant participants

Lifestyle characteristics that should be collected 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 YOA.

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 due to not meeting all of the eligibility criteria.

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.

5.5. Criteria for temporarily delaying study intervention administration (Amended 15 March 2022)

Study intervention administration may be postponed* within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever within 48 hours before study intervention administration. Refer to Section 1.3 for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be dosed at the discretion of the investigator.
- Use of systemic antibiotic or antiviral (except for HIV+ participants) treatment within 48 hours before study intervention administration.

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to Section 10.7.2 for the definition of study intervention.

Refer to Section 4 for the study intervention administration schedule.

Refer to the SPM for additional details.

6.1. Study interventions administered (Amended 15 March 2022)

Table 8 Study interventions administered (Amended 15 March 2022)

Study Interventions Name:	**RSV MAT**		**Control**	
Vaccine/product name	RSVPreF3	NaCl Solution	Sucrose	NaCl Solution
Study intervention formulation:	RSVPreF3 (120 µg)	Sodium chloride (NaCl) (0.9%); Water for injections**	Sucrose	Sodium chloride (NaCl) (0.9%); Water for injections**
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
Type:	Biologic		Not applicable	
Route of administration	Intramuscular injection		Intramuscular injection	
Administration site: • **Location** • **Laterality ***	 Deltoid Non-dominant		 Deltoid Non-dominant	

Study Interventions Name:	RSV MAT	Control
Number of doses to be administered:	1	1
Volume to be administered**	Whole content	Whole content
Packaging and labeling	Refer to the SPM	Refer to the SPM
Manufacturer	GSK	GSK

SPM = study procedure manual

* The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine / product 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.

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.

Maternal participants must be observed closely for at least 30 minutes after the administration* of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

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

6.2. Preparation/Handling/Storage/Accountability

The study interventions must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study interventions. Storage conditions will be assessed by a sponsor study contact during pre-study activities.

Refer to the SPM for more details on storage and handling of the study interventions.

6.3. Measures to minimize bias: randomization 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/assent 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 (Refer to Section 6.3.3).

The maternal participant's infant (as yet unborn) 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 has received the study intervention at Visit 1.

Maternal and infant identification numbers will be linked.

6.3.2. Randomization to study intervention (Amended 15 March 2022)

Approximately 378 maternal participants will be enrolled* and randomized (2:1) to receive either the RSV maternal vaccine or the placebo control at Day 1 (Visit 1). At the same time, infant participants (as yet unborn) will be further randomized (1:1:1) into sub-cohorts for blood sample collection for the assessment of immunogenicity at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

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

6.3.3. Intervention allocation to the participant (Amended 15 March 2022)

The randomization algorithm will use a stratification procedure accounting for maternal age at the time of study intervention administration (<18, ≥18 YOA) and a minimization procedure accounting for (a) gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), (b) pre-existing HIV infection and obstetric complication status (HIV present and obstetric complication present, HIV present and obstetric complication absent, or HIV absent and obstetric complication present) for participants ≥18 YOA only, and (c) center. Minimization factors will have equal weight in the minimization algorithm.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the dose.

When an 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 the study intervention number allocation.

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants

6.3.4. Allocation of participants to assay subsets

Not applicable.

6.3.5. Blinding and unblinding (Amended 15 March 2022)

To minimize the introduction of bias, this study will be double-blinded* from Day 1 pre-study intervention to Day 43 post-delivery/birth visit after which the first analysis will be conducted and treatment-level unblinded* summaries will be provided to GSK and regulatory agency for review. No individual treatment code will be shared with investigators, site staff and participants until the end of the study. After Day 43 delivery/birth visit, the study will be conducted as a single-blind* study.

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

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention and the identity of the participant.

6.3.5.1. Emergency unblinding (Amended 15 March 2022)

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information 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 site staff who do not need it, in order to ensure that other members of the study team remain blinded.

A physician other than the investigator (e.g. an emergency room physician) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back up option). The subject/participant card provides contact information for the investigator, his/her back up and GSK Helpdesk.

The investigator may contact a GSK Helpdesk (refer to the Table 9) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the automated Internet-based system).

Note: Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.

Table 9 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: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com	
Toll-free numbers are available for the following countries.	
Country	**Toll-free number**
Canada	1 833 541 0263
United States	1 844 446 3133
Spain	00 800 4344 1111
Italy	800 879 197
Finland	999 800 4344 1111
Brazil	0800 891 2906
India	000800 919 0928
South Africa	0800 984 003

6.3.5.2. Unblinding prior to regulatory reporting of SAEs (Amended 15 March 2022)

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined 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 SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

Note: Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.

6.4. Study intervention compliance (Amended 15 March 2022)

Before dosing, a qualified member of the site 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.

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.

6.5. Dose modification

Section is not applicable.

6.6. Continued access to study intervention after the end of the study (Amended 15 March 2022)

There will be no access to RSV MAT vaccine after the end of the study. Please refer to Section 2.3 for details.

6.7. Treatment of overdose

Section is not applicable.

6.8. Concomitant therapy

At the timepoints indicated in the SoA, the investigator or his/her delegate should question the participant and/or the infant participant's parent(s)/LAR(s) about all 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.

6.8.1. Maternal participants (Amended 15 March 2022)

- **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 2).
- **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-study intervention AEs such as headache).
- Any concomitant **medications/products** given for pre-existing medical conditions, beginning at Visit 1 and ending at Contact 2 (Day 1 to Day 181).

- Any concomitant **medications/products** associated with a solicited event or with an unsolicited AE, beginning at Visit 1 and ending at Visit 2 (Day 1 to Day 31).
- Any **corticosteroids for fetal lung maturation** administered prior to/during labor 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 (eg. general/regional/local anesthetics, analgesics, etc) do not need to be reported.
- Any concomitant **medications/products** associated with a 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 2 (Day 1 to Day 181 post-delivery).

6.8.2. Infant participants

- Vaccinations administered from birth (Visit 1-NB) through the Day 181 post-birth visit (Visit 4-NB).
- Medications administered in relation to RTIs/LRTIs from birth (Visit 1-NB) through the Day 366 post-birth visit (Visit 5-NB).
- Medications/products administered in relation to MAEs from birth (Visit 1-NB) through Day 366 post-birth visit (Visit 5-NB).

6.8.3. 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Criteria for discontinuation of study interventions 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 5.5 are met.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

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

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

All data and samples collected up to and including the date of withdrawal of /last contact with the participant will be included in the study analyses.

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

- AEs requiring expedited reporting to GSK (Section 10.3.10.1)
- Unsolicited non-SAEs
- Solicited AE (maternal participants)
- Withdrawal by participant, not due to an AE*
- 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 the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.8.2).

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 cannot 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 actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES (AMENDED 15 MARCH 2022)

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the SoA (Section 1.3).

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

The investigator will maintain a 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/participant's parent(s)/LAR(s) 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 (Section 5.1 and 5.2).

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

Study procedures during special circumstances (Amended 15 March 2022)

During special circumstances (e.g., the COVID-19 pandemic), the resulting limitations may affect the sites' ability to conduct the study procedures.

Enrollment* of ADDITIONAL maternal participants may be placed on hold. Decisions on re-starting enrollment* to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.

For guidance regarding the temporary delay of study intervention administration because of exposure to COVID-19, please refer to the SPM for details.

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

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, video-telephone or telemedicine. In such cases:
  - Protocol-specified clinical data that cannot be collected by site staff during the contact (e.g., physical examination results; SpO_2 results) BUT are available within the allowed visit window (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 judgment of the investigator and as allowed by local law, arrangements should be made for qualified personnel to collect any protocol-specified safety data/safety assessment(s) and/or biological samples at an alternate location* or at participant's home within the allowed visit window (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).

    **** Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant.***
  - 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, video-telephone or telemedicine, or other means.

Additional details of how these visits can be conducted are outlined in the SPM.

Impact on the analysis sets for immunogenicity will be determined on a case by case basis. Any impact of above-mentioned measures on the study results will be described in the clinical study report (CSR).

The specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

*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.

8.1. Immunogenicity assessments

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

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

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

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples (Amended 15 March 2022)

Table 10 Biological samples - Maternal participants (Amended 15 March 2022)

Maternal Sample type	Collected to evaluate	Minimum Quantity per participant	Unit	Time point	Additional information
Whole blood	Hematology, Biochemistry	~5.5	mL	Screening	Blood sample to be collected and analyzed locally only if not performed as per standard of care. [5]
	Immune response [1]	~10	mL	Visit 1 (Day 1) pre-Dose Visit 2 (Day 31) [4] Visit 3 (Delivery)	-
Urine	Protein, Glucose	Dipstick	NA	Screening	Urine sample to be collected and analyzed locally only if not performed as per standard of care. [5]
Nasal Swab [2, 3, 6]	Presence of RSV-A/B	-	-	MA-RTI Visit (Event-Driven)	Collect a nasal swab from any maternal participant who reports a MA-RTI.
				RTI hospitalization (Event-Driven)	Collect a nasal swab (if possible) from any participant hospitalized with RTI (or soon after discharge, as long as symptoms are ongoing).

[1] 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.

[2] 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.

[3] 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 4.2.5.3. 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.

[4]. Blood sample at Visit 2 (Day 31) will not be collected if the delivery occurs prior to Day 31 post-study intervention.

[5] Blood sample for hematology, biochemistry evaluation should be tested and analyzed locally.

[6] Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant for RTI assessment.

Table 11 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 12 Biological samples – Infant participants (Amended 15 March 2022)

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	mL	Visit 1-NB (Within 72 hours 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 2 kg baby or 2.0 ml for a 2.5 kg baby.] Refer to the Laboratory Manual for additional information. All minimum totals given below assume a body weight > 2.5 kg.
	Immune response – sub-cohort [4]	~2.5 [1]	mL	Either Visit 2-NB (Day 43 post-birth) or Visit 3-NB (Day 121 post-birth) or Visit 4-NB (Day 181 post-birth)	
Nasal swab [2, 3]	Presence of RSV-A/B	-	-	RTI Surveillance Visit - LRTIs (Event-Driven)	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 Surveillance Visit - RTI hospitalization (Event-Driven)	Collect (if possible) from any participant hospitalized with a RTI (or soon after release, as long as symptoms are ongoing).

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

[2] 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.

[3] 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 4.2.5.3. 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.

[4] Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.

- An overall blood volume of approximately ***30*** mL will be collected from maternal participants during the entire study period, if blood sample for assessing eligibility criteria should not be taken at screening.
- An overall blood volume of approximately ***35.5*** mL will be collected from maternal participants during the entire study period, if blood sample for assessing eligibility criteria must be taken at screening.
- An overall blood volume of approximately 2.5 mL will be collected from infant participants during the entire study period*. If cord blood sample cannot be collected, then an overall volume of 5 mL will be collected*.

  **** Due to the change in the study requirements, there will no longer be collection of blood samples from infant participants at Visit 2-NB, Visit 3-NB and Visit 4-NB.***
- Refer to Table 10 and SoA (Setion 1.3) for details of volumes collected for different assessments.

8.1.2. Laboratory assays (Amended 15 March 2022)

Following laboratory assays will be performed (Table 13):

- Serological assays for the determination of RSV-A/B neutralizing antibodies (nAbs) will be performed by neutralization assay with wild type virus. Further characterization of the humoral immune response will be performed using enzyme-linked immunosorbent assay (ELISA) based assays for measurement of IgG antibodies binding to the RSV PreF3 protein.
- RSV-A/B qRT-PCR assay is the core assay on nasal swab samples to confirm RSV cases in RSV program. The assay is able to identify, and discriminate RSV-A and RSV-B subtypes extracted from the nasal swabs.

Table 13 Laboratory assays (Amended 15 March 2022)

Assay type	System	Component	Method	Laboratory [1]
Humoral Immunity (Antibody determination)	SERUM	RSV-A NAb	NEUT	GSK [2] or GSK designated lab
	SERUM	RSV-B NAb	NEUT	GSK [2] or GSK designated lab
	SERUM	RSV PreF3 Ab.IgG	ELISA	GSK [2] or GSK designated lab
Molecular Biology [3]	NASMUC (Nasal swab)	Respiratory Syncytial Virus A RNA	qRT-PCR	GSK [2] or GSK designated lab
	NASMUC (Nasal swab)	Respiratory Syncytial Virus B RNA	qRT-PCR	GSK [2] or GSK designated lab

ELISA = enzyme-linked immunosorbent assay; **NEUT** = Neutralization; **qRT-PCR** = Quantitative Reverse Transcription PCR; **RSV-A Nab** = RSV-A neutralizing antibody; **RSV-B Nab** = RSV-B neutralizing antibody; **RSVPreF3 Ab.IgG** = RSV PreF3 antibody.immunoglobulin G; **SOP** = Standard operating procedure

[1] Refer to the list of clinical laboratories for details.

[2] 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.

[3] RSV-A/B quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4. To evaluate tertiary objectives, an Allplex Respiratory Viruses Panel or alternative may

be performed for RSV-A/B-positive samples, and (if deemed necessary) for RSV-A/B-negative samples. 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 participant should be performed as per the standard of care.

Please refer to the Section 10.2 for a detailed description of the assays performed in the study.

Additional exploratory testing on the disease under study and/or other RTIs or infections of relevance to pregnant women and their newborns may be performed within the framework of the study if deemed necessary for accurate interpretation of the data/ should such assay(s) become available at GSK. These assays may not be represented in the objectives/ endpoints of the study protocol.

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 (Amended 15 March 2022)

Table 14 Immunological read-outs (Amended 15 March 2022)

Blood sampling timepoint		Study group	Approximate No. participants	Component
Type of contact and timepoint	**Sampling timepoint**			
Maternal participants*				
Visit 1 (Day 1)	pre-study intervention	All study groups	378	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 2 (Day 31) [1]	post-study intervention	All study groups	378	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 3 (Delivery)	post-study intervention	**Whole blood:** All study groups **Cord blood:** All study groups	378	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Infant participants*				
Visit 1-NB (Birth)	birth (only if cord blood cannot be collected)	Event-driven	Event-driven	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 2-NB (Day 43) [2]	post-birth	RSV_MAT_BS1	84	RSV-A NAb RSV-B NAb
				RSV PreF3 Ab.IgG
		Control_BS1	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 3-NB (Day 121) [2]	post-birth	RSV_MAT_BS2	84	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG

Blood sampling timepoint		Study group	Approximate No. participants	Component
Type of contact and timepoint	Sampling timepoint			
		Control_BS2	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 4-NB (Day 181) [2]	post-birth	RSV_MAT_BS3	84	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
		Control_BS3	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG

RSV-A Nab = RSV-A neutralizing antibody; **RSV-B Nab** = RSV-B neutralizing antibody; **RSVPreF3 Ab.IgG** = RSV PreF3 antibody.immunoglobulin G.

[1] Blood sample at Visit 2 (Day 31) wil not be collected if the delivery occurs prior to Day 31 post-study intervention.

[2] Due to the change in the study requirements, there will no longer be collection of blood samples from infant participants at Visit 2-NB, Visit 3-NB and Visit 4-NB.

* Refer to Table 10, Table 11, and Table 12

Table 15 Molecular biology tests (Amended 15 March 2022)

Nasal swab sampling timepoint		No. participants	Component [3]
Type of contact (timepoint)	Sampling timepoint		
Maternal MA-RTI [1, 4]	Event-driven	Event-driven	RSV-A RNA
			RSV-B RNA
Infant RTI [2]	Event-driven	Event-driven	RSV-A RNA
			RSV-B RNA

[1] Includes maternal RTI hospitalizations

[2] Includes infant RTI hospitalizations

[3] Quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4. To evaluate tertiary objectives, an Allplex Respiratory Viruses Panel or alternative, may be performed for RSV-A/B-positive samples, and (if deemed necessary) for RSV-A/B-negative samples. 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 participant should be performed as the standard of care.

[4] Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant for MA-RTI assessment.

8.1.4. Clinical safety laboratory assessments

Refer to the Section 10.2 for the list of clinical laboratory safety assessments required by the protocol.

These assessments must be conducted according to the clinical laboratory manual and the SoA.

8.1.5. 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 his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study.

Surveillance for evaluation of RTI is described in Section 8.4.

8.2.1. Procedures for maternal participants

Additional details are provided in the SPM.

8.2.1.1. Collection of demographic data

At screening, record demographic data such as date of birth, sex, race and ethnicity in the participant's eCRF.

8.2.1.2. Collection of worsening of the pre-existing medical condition and/or obstetric complication

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

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

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

8.2.1.3. Medical/vaccination history

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

- Record outcome of the comprehensive detailed fetal morphology ultrasound assessment (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 should be available prior to participant's study randomization and study intervention administration. 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 eCRF. If an unscheduled visit is performed post-study intervention, 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.
  - gestational age, along with GAIA level of certainty as defined in Section 5.1.1 and 10.8.
  - date of: LMP or ET or 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 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 intervention administration.

Note: Medical / vaccination history and past pregnancy history will be captured in the source document as part of screening, but recorded in eCRF only at Visit 1 if the maternal participant is eligible.

8.2.1.4. Physical examination (General and obstetric examination)

Screening and Visit 1 to Visit 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-study intervention. At Visit 3 (Delivery) temperature should be measured if/as per standard of care.
- Systolic/diastolic blood pressure, heart rate and respiratory rate (after at least 10 minutes rest) at screening and at Visits 1-2; 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).

Note: At delivery visit, the results of the general and obstetric examination can be obtained from the medical chart as activity performed as part of standard of care and transcribed into the eCRF.

If the screening visit and Visit 1/study intervention are performed on the same day:

- Physical examination (general and obstetric examination) procedures required both at screening and at Visit 1/study intervention 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 RTI **must** include the maternal participant assessments listed in Section 8.4.4.

8.2.1.4.1. 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.

8.2.1.4.2. Monthly contacts (Amended 15 March 2022)

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.

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

8.2.1.5. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at the visit with planned administration of study intervention.

8.2.2. Procedures for infant participants

Additional details are provided in the SPM.

8.2.2.1. Physical examination at Visit 1-NB to Visit 5-NB

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

The examination will include assessment of the following:

- Weight*, length, head circumference.

  * At Visit 1-NB, body weight should be taken within 24 hours after the birth.
- 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. Study holding rules and safety monitoring (Amended 15 March 2022)

An internal SRT and an external IDMC (external to GSK) will review available maternal and infant safety data on a regular basis throughout the study. Any potential safety concern identified will be escalated to the GSK ***Global Safety Board (GSB)***.

8.2.3.1. Safety evaluation by the Safety Review Team (SRT) (Amended 15 March 2022)

The SRT includes as core members the GSK' Central Safety physician, Safety scientist, Clinical Research & Development Lead (CRDL), Epidemiologist, Global Regulatory Lead and Biostatistician of the project. The SRT is responsible for ongoing safety monitoring of the entire study and will review on a regular, ongoing basis the safety data. Continuous monitoring throughout the study will allow for ad-hoc data review meetings if deemed necessary by the SRT.

The SRT will inform the IDMC about any potential safety concern or study holds at any point during the study and may request ad-hoc safety evaluations by the IDMC.

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

8.2.3.2. Independent data monitoring committee (IDMC) evaluation (Amended 15 March 2022)

An unblinded IDMC will be established by GSK. The IDMC will monitor the safety data and the scientific validity of the study.

The IDMC will conduct unblinded reviews of all available safety data on an ongoing basis. The unblinded analyses will 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. No unblinded data***** will be shared with the study team.

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

In addition, there will be at least 3 planned IDMC data review meetings. The first will take place after ~63 active vaccine recipients have completed the Day 43 post-delivery visit (Visit 4 for maternal participants; Visit 2-NB for their enrolled infants). The second planned IDMC meeting will occur after all participants have completed follow-up to the Day 43 post-delivery/birth visit (Visit 4 for maternal participants; Visit 2-NB for their enrolled infants). The third planned IDMC meeting will occur when all data up to study end (Visit 5-NB, 12 months post-birth) are available. For each review, the IDMC will be provided with unblinded safety data as described above. Ad-hoc data reviews or meetings may be organized, if deemed necessary by the IDMC.

As part of ongoing review, the IDMC will monitor the rates of SAEs, pregnancy-related outcomes, pregnancy-related and neonatal /infant AESIs, medically attended RTIs in maternal participants and LRTIs in infants.

Additional details concerning the IDMC's structure and processes will be provided in the IDMC charter.

8.2.3.3. Study holding rules (Amended 15 March 2022)

The safety holding rules are defined in Table 16.

Holding rules 1a-b will be assessed by the investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of study intervention administration and consenting of new participants irrespective of number of participants enrolled and/or timing of the event relative to study dose administration.

Of note, all available safety data will also be reviewed by the SRT/IDMC to allow an overall assessment of the benefit/risk ratio of study intervention administration.

Table 16 Holding rules assessed by the investigator

Holding Rule	Event	Number of mothers/infants
1a	Any **maternal or fetal death** within 30 days from study dose administration that cannot be reasonably attributed to a cause other than vaccination as per Investigator assessment.	≥ 1
1b	Any **life-threatening SAE** in a maternal participant or fetus within 30 days from study dose administration that cannot be reasonably attributed to a cause other than vaccination as per Investigator assessment.	≥ 1

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform GSK immediately (e.g. holding rules 1a-b).Refer to the Table 19 for contact information).

The following communication sequence must be followed:

- Investigator (or a designee) informs their local sponsor contact as soon as possible (no later than within 24 hours). (Table 19).
- The local sponsor contact informs the central sponsor contact (e.g., the Study Delivery Lead [SDL]; the CRDL) as soon as possible (no later than within 24 hours).
- The central sponsor team ensures that SBIR is blocked, all sites administering study vaccine/product are informed, and all country or region- specific regulatory authorities are informed.
- Study sites confirm that they have been notified and have taken appropriate action, providing appropriate documentation to their local sponsor contact.
- The GSK ***GSB*** evaluates the case after receipt of the IDMC's recommendations / and takes the decision to stop or to re-start dose administration.

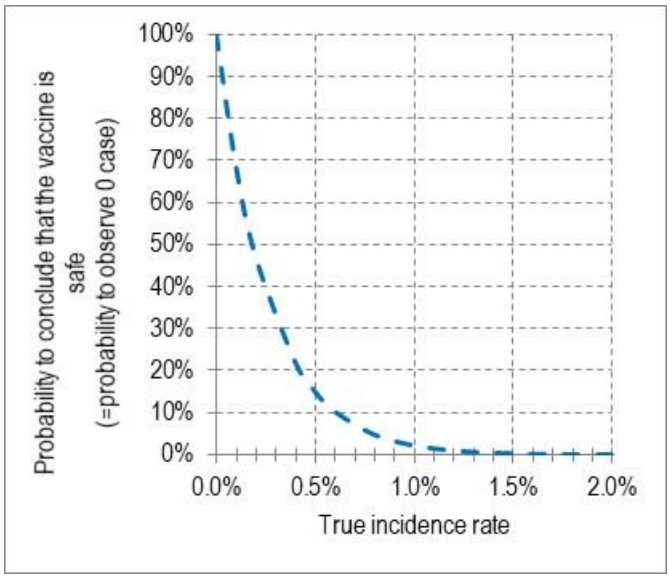
- Where required per local / regional regulation, the central sponsor team submits a substantial amendment to the local/regional authority requesting authorization to re-start the study.
- When all required authorizations to re-start the study in a country / region have been provided, the central sponsor team provides written notification to local sponsor contacts; local sponsor contacts then provide written notification to study sites.

Risk assessment:

Figure 3 presents the probability of not meeting the defined holding rules 1 (a-b) for the entire study population (n = 378 maternal participants).

For holding rules 1 (a-b), using a cut-off of 1/378, there is around 85% chance that the holding rule is met if the corresponding event has a true incidence rate of 0.5% and around 70% chance the holding rule is not met if the corresponding event has a true incidence rate of 0.1%.

Figure 3 Risk assessment curve for the defined safety holding rules



8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information (Amended 15 March 2022)

Table 17 Timeframes for collecting and reporting of safety information (including RTI information) (Amended 15 March 2022)

		Before delivery [1, 5]				Delivery/Birth	Post-delivery/birth					
Timepoint		D-28	D1	D8	D31		D 43	D91	D121	D181	D271	D366
Maternal participant visits/contacts		Pre-[2]	V1	C1	V2	V3	V4			C2		
Infant participant visits/contacts						V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB
Event	Administration site and systemic solicited events		M (Days 1-7)									
	Unsolicited AEs that are neither SAEs, MAEs or AESIs		M (Days 1-30)									
	Worsening of pre-existing medical conditions and/or obstetric complications (reported as AESIs)		M (Day 1 to 180 days post-delivery)									
	Pregnancy-related AESIs		M (Day 1 to 42 days post-delivery)									
	Pregnancy outcomes		M (Day 1 to 42 days post-delivery)									
	Suspected, probable and confirmed cases of COVID-19 infection (depending on the epidemiological COVID-19 situation)		M (Day 1 to 180 days post-delivery)			I (Birth to 365 days post-birth)						
	MA-RTIs [6]		M (Day 1 to 180 days post-delivery)									
	SAEs, AEs/SAEs leading to Withdrawal from the study and MAEs		M (Day 1 to 180 days post-delivery)									

		Before delivery [1, 5]				Delivery/Birth	Post-delivery/birth					
Timepoint		**D-28**	**D1**	**D8**	**D31**		**D 43**	**D91**	**D121**	**D181**	**D271**	**D366**
Maternal participant visits/contacts		Pre-[2]	V1	C1	V2	V3	V4			C2		
Infant participant visits/contacts						V1-NB	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB
						I (Birth to 365 days post-birth)						
	Subsequent Pregnancies [3]					M (Day 1 to 180 days post-delivery)						
	SAEs related to study participation	M (Screening to Day 1 pre-study intervention)										
	Neonatal / Infant AESIs [4]					I (Birth to 42 days post-birth)						
	LRTIs (including medically assessed, RSV-associated LRTIs)					I (Birth to 365 days post-birth)						
	Medically assessed, RSV-associated hospitalizations					I (Birth to 365 days post-birth)						

Pre = pre-study intervention; **V** =visit; **D** = Day; **M** = Maternal participants; **I**= Infant participants; RTI = Respiratory tract infection; LRTI

[1] Approximately monthly contacts pre- delivery also occur within the timeframes described above and are described in Section 1.2.

[2] i.e. consent obtained.

[3] If subsequent pregnancy occurs during the study, follow-up may extend up to 8 weeks post-birth of the infant from that subsequent pregnancy.

[4] Neonatal AEs of special interest identified after Visit 2-NB (e.g., congenital anomalies) will continue to be reported as such.

[5] SAEs and/or AESIs experienced by an infant born to the exposed mother will be reported (if become known to the site staff), even if the re-consent for infant participants is not provided.

[6] Due to the change in the study requirements, 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 serious adverse pregnancy outcomes), as well as all pregnancy-related AESIs and neonatal AESIs to the sponsor or designee via the Adverse Events Form and the corresponding Expedited Adverse Event Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10 and Table 18. 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 intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 19.

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

Detection and recording of AE/SAE/AESI/subsequent pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

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

8.3.2.1. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that he/she did so, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values associated with an AE reported during the study or within 30 days after the study intervention administration should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or LML. Refer to the Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, subsequent pregnancies and other events (Amended 15 March 2022)

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 Table 18. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator must 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 SUSAR must be followed. These reports will be forwarded to investigators as necessary.

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

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

Table 18 Timeframes for submitting SAE, subsequent pregnancy and other events reports to GSK (Amended 15 March 2022)

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 and RSV-associated hospitalizations)	24 hours* ‡	electronic Adverse Events Form and the corresponding Expedited Adverse Event Form	24 hours*¥	electronic Adverse Events Form and the corresponding Expedited Adverse Event Form
Subsequent Pregnancies	***24 hours****	electronic pregnancy report	***24 hours****	electronic pregnancy report
AESIs	24 hours** ‡,	Adverse Events Form and the corresponding Expedited Adverse Event Form	24 hours* ¥	electronic Adverse Events Form and the corresponding Expedited Adverse Event Form
Maternal participants: MA-RTIs Infant participants: Medically assessed, RSV-associated LRTIs	72 hours	eCRF	1 week	eCRF

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
‡ The investigator will be required to confirm review of the SAE/AESI causality within 72 hours of submission of the SAE/AESI.
¥ The assessment of causality should be included in the initial report to be submitted within 24 hours.

8.3.3.1. Contact information for reporting SAEs, AESIs, pregnancies and study holding rules (Amended 15 March 2022)

Table 19 Contact information for reporting SAEs, AESIs, subsequent pregnancies and study holding rules (Amended 15 March 2022)

Study contact for questions regarding SAEs, AESIs, subsequent **pregnancies** Refer to the local study contact information document	**Study contact for reporting of study holding rules** As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the LML.
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	**Back up study contact for escalation of holding rules** Refer to the local study contact information document.

8.3.4. Additional reporting guidance for the study pregnancy

8.3.4.1. Labor and delivery

- An uncomplicated vaginal delivery or planned 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 caesarian section or an emergency induction may be reported as an SAE/AESI (as applicable), using the corresponding Adverse Events Form and the corresponding Expedited Adverse Event Form.

8.3.4.2. Pregnancy outcomes

Pregnancy outcomes include:

- Live birth with no congenital anomalies
- Live birth with minor congenital anomalyies only
- Live birth with at least 1 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
- Elective/therapeutic termination with at least 1 major congenital anomaly

8.3.4.3. Reporting of congenital anomalies in relation to pregnancy outcomes and SAEs and/or AESIs

For characterization and reporting of the congenital anomalies, which will be captured during the study, the following classifications should be used:

- Congenital anomaly as an SAE OR Congenital anomaly as not an SAE
  - The characterization of congenital anomalies as an SAE should be based on the Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines, as oulined in [MACDP].
  - Congenital anomalies that are included in the MACDP 6-Digit Code Defect List should be reported as SAEs.
  - Congenital anomalies that are not included in MACDP 6-Digit Code Defect List should not be reported as SAEs, unless they are fatal, life-threatening, led to hospitalization, prolongation of hospitalization, disability or permanent damage or are other medically significant events.
  - Congenital anomalies that are not included in MACDP 6-Digit Code Defect List may be also reported as MAEs, as appropriate.
  - If minor congenital anomalies are not reportable either as SAEs or MAEs, they should be recorded in the infant physical examination eCRF.
- Major congenital anomaly OR Minor congenital anomaly
  - The characterization of congenital anomalies as major or minor should be based on the Centers for disease Control and Prevention (CDC) definitions, as outlined in [CDC].
  - 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.
  - Minor congenital anomalies are anatomic variants or defects that do not have serious medical, functional or cosmetic consequences for the child.
- Congenital anomaly as an AESI OR Congenital anomaly as not an AESI
  - All major congenital anomalies should be reported as AESIs. Minor congenital anomalies should not be reported as AESIs.

Refer to the SPM for additional information and guidance.

8.3.5. Treatment of adverse events (AEs)

Any medication administered for the treatment of an SAE/AESI should be recorded in the eCRF and linked to the corresponding electronic Expedited Adverse Event Form (refer to the Section 10.3.10.1).

8.3.6. Participant card

At screening or at Visit 1, 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.

The maternal participant/infant participant's parent(s)/LAR(s) must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves 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 or his/her back up.

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 4.2.5). 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 15 March 2022)

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

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 RTI and reflect a deterioration in the infant's respiratory tract functions.

A ***potential*** **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 RTI, or general health in the context of the RTI and intend to seek medical care).

8.4.2. Surveillance

8.4.2.1. Maternal participants (Amended 15 March 2022)

MA-RTI surveillance***** begins at Day 1 post-study intervention and ends 180 days after delivery (Contact 2). It will be accomplished via 2 types of contact.

- For a **Passive** contact, each maternal participant will be instructed at study entry 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.

- For an **Active** contact, site personnel contact the maternal participant monthly in addition to the scheduled visits/contacts as per Table 1. Active contacts will be scripted.

**** Due to the change in the study requirements, RTI surveillance of 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 366 days after birth (Visit 5-NB) which is expected to cover at least 1 complete RSV season (i.e. the majority of the infant participants).

It will be accomplished via 2 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 if:
  - they observe cold-like respiratory tract symptoms such as cough, runny nose, blocked nose, difficulty in breathing and wheezing.
  - they intend to seek medical care because of concern about the infant's RTI, or general health in the context of the infant's RTI.

  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 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.

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) at Day 31 post-study intervention (Visit 2). 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 (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 site 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 (Amended 15 March 2022)

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.

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

8.4.3. When to conduct an assessment visit

8.4.3.1. For a maternal MA-RTI (Amended 15 March 2022)

Conduct an assessment visit (Section 8.4.4), ideally within 72 hours after a medically attended visit due to RTI symptoms* occurs during the surveillance period. However, a visit may be conducted even beyond the 72 hours window if symptoms are ongoing.

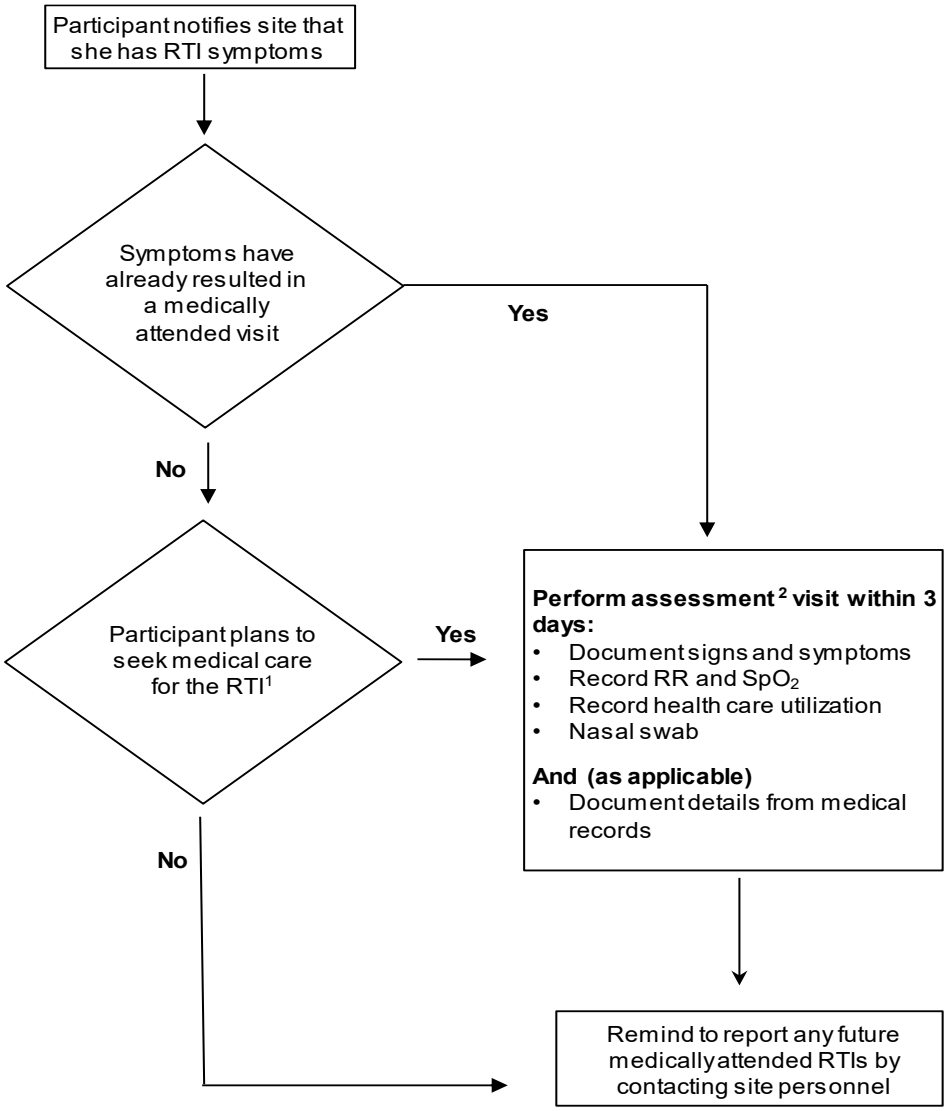
If a maternal participant informs the site that she has RTI symptoms and (a) would seek / have sought medical advice for them and (b) is already scheduled for a study visit within the timeframes described above, then the site should perform the MA-RTI assessment visit procedures (including nasal swab)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

A decision tree is provided in Figure 4.

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

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

Figure 4 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 (Amended 15 March 2022)

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 RTI, or general health in the context of the infant's RTI.

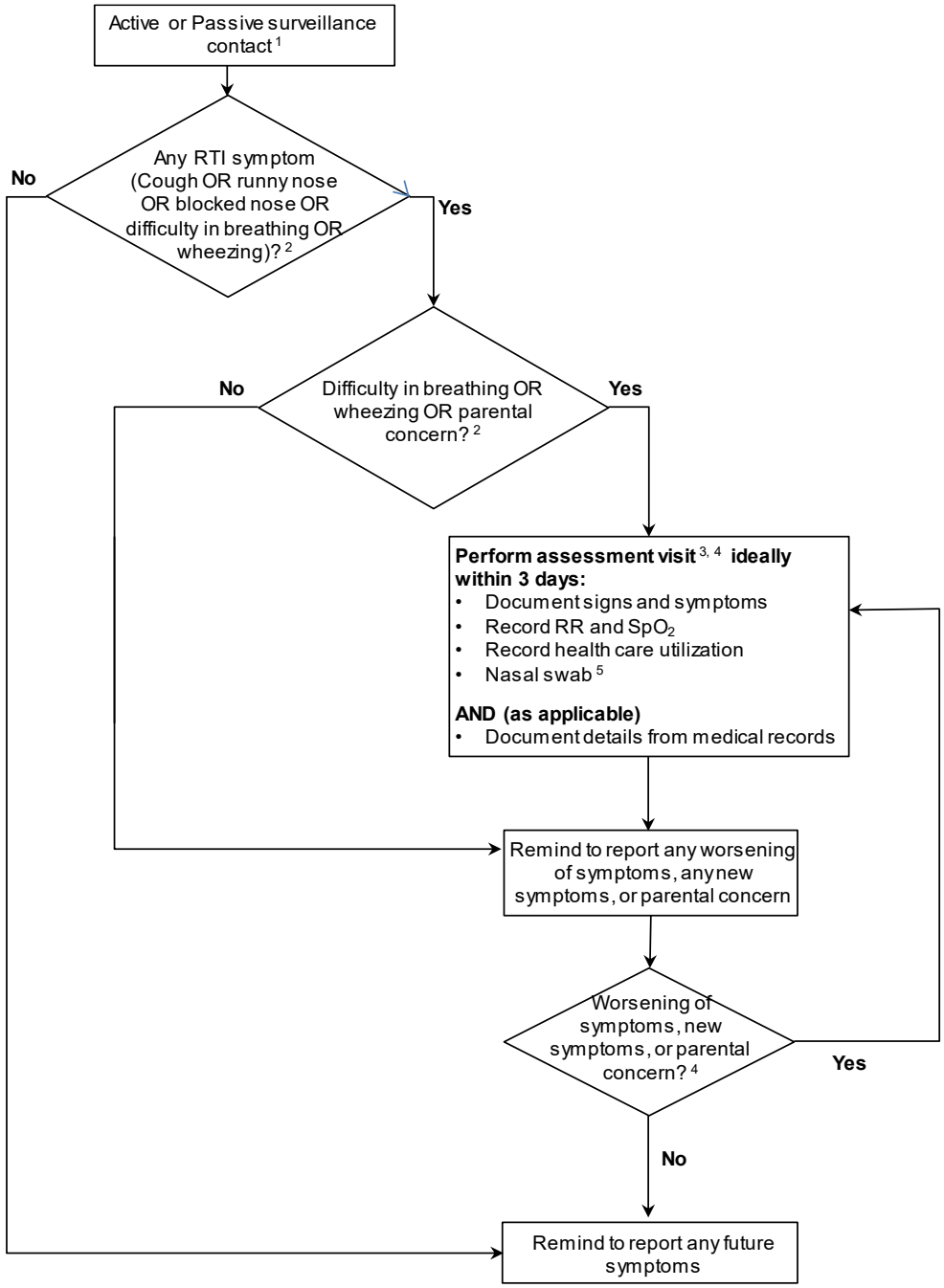
The visit should take place as soon as possible; ideally within 72 hours. However, a visit may be conducted even beyond the specified ideal window if symptoms are ongoing.

- 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 RTI.

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

A decision tree is provided in Figure 5. Refer to the SPM for additional details regarding infant RTI surveillance.

Figure 5 Decision Tree for site personnel - infant surveillance and assessment (Amended 15 March 2022)



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 12.

8.4.4. Assessment visit procedures (Amended 15 March 2022)

The purpose of each assessment visit is to objectively document signs and symptoms of a RTI 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).

Unless otherwise specified, assessment visit procedures will be the same for maternal participants with MA-RTIs* and for infant participants with RTIs.

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).

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

8.4.4.1. Clinical evaluation (Amended 15 March 2022)

At every assessment visit, the investigator/site 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*:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (Section 8.2.1.4.1), in room air, if feasible
- Results of chest auscultation
- Signs of difficulty in breathing (wheezing and tachypnoea in maternal participants)

**** Due to the stop on RTI surveillance for maternal participants, these checks will no longer be performed.***

For infant participants:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (Section 8.2.1.4.1), in room air, if feasible
- 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 (Amended 15 March 2022)

Refer to Table 10 (maternal participants)* and Table 12 (infant participants). Additional details are provided in the Central Laboratory Manual.

**** Due to the change in the study requirements, nasal swab samples of the maternal participants will no longer be collected for RTI assessment.***

8.4.4.3. Missed assessment visit (Amended 15 March 2022)

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

8.4.5. RTI hospitalization during the surveillance interval (Amended 15 March 2022)

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 10* and Table 12.

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

8.4.6. Follow-up of infant respiratory tract illnesses (RTIs)

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 Contact 2-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, MAE or SAE criteria, as outlined in Section 10.3.

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

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

8.5. Pharmacokinetics

Section is not applicable.

8.6. Genetics and/or Pharmacogenomics

Section is not applicable.

8.7. Biomarkers

Section is not applicable.

8.8. Immunogenicity

Refer to Section 8.1.

8.9. Health outcomes

Section is not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

No hypothesis driven sample size calculation was conducted since the evaluation of the study objectives are descriptive.

9.2. Sample size determination (Amended 15 March 2022)

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

Participants who withdraw from the study will not be replaced.

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

9.2.1. Safety

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

Table 20 presents the precision one can get on the percentage of participants with AEs following dosing in study vaccine group.

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

Table 20 Exact 95% confidence interval (CI) on the percentage of participants with adverse events (AEs) following dosing in RSV-MAT vaccine group

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

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

9.2.2. Immunogenicity

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

Table 21 presents the precision estimation of the fold increase from Day 1 to delivery based on standard deviation (SD) of log10 transformed titer for neutralizing antibody RSV-A and half width of the fold increase.

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

Table 21 Precision estimation on fold increase and its 95% CI with 226 participants in RSV-MAT vaccine group

Standard Deviation[1]	Fold Increase from Day 1 to delivery	No. of participants in RSV-MAT vaccine group	Half Width[2]	95% LL	95% UL	Log10 Fold
0.3	5	226	0.056	4.4	5.7	0.699
0.3	6	226	0.056	5.3	6.8	0.778
0.3	7	226	0.056	6.2	8.0	0.845
0.3	8	226	0.056	7.0	9.1	0.903
0.3	9	226	0.056	7.9	10.2	0.954
0.3	10	226	0.056	8.8	11.4	1
0.3	11	226	0.056	9.7	12.5	1.041
0.3	12	226	0.056	10.5	13.7	1.079
0.4	5	226	0.074	4.2	5.9	0.699
0.4	6	226	0.074	5.1	7.1	0.778
0.4	7	226	0.074	5.9	8.3	0.845
0.4	8	226	0.074	6.7	9.5	0.903
0.4	9	226	0.074	7.6	10.7	0.954
0.4	10	226	0.074	8.4	11.9	1
0.4	11	226	0.074	9.3	13.0	1.041
0.4	12	226	0.074	10.1	14.2	1.079

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

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

9.3. Analysis sets (Amended 15 March 2022)

Table 22 Maternal Participants (Amended 15 March 2022)

Analysis set	Description
Enrolled	All maternal participants who completed the informed consent process and signed the informed consent form ***and was determined as eligible for study participation***.
Exposed	All maternal participants who received 1 dose of a study intervention. The allocation in a group is done in function of the administered intervention.
Full Analysis - Immunogenicity	All maternal participants in the Exposed set who have at least one post-dosing immunogenicity data. The allocation in a group is done in function of the randomized intervention.
Per Protocol - Immunogenicity	All maternal participants in the Full Analysis (Immunogenicity) minus participants with protocol deviations that lead to exclusion. The analysis will be done according to the study interventions that participants received at Dose 1.
Solicited Safety	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.
Full Analysis - Immunogenicity	All infant participants in the Exposed set who have at least one post-delivery/birth immunogenicity data. The analysis will be done according to the study intervention that maternal participants received at Dose 1.
Per Protocol - Immunogenicity	All infant participants in the Full Analysis (Immunogenicity) set minus those who (a) were born less than 4 weeks post-maternal participant dosing and/ or (b) have protocol deviations that lead to exclusion.

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 (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).

9.3.1.1.2. Infant participants

- Systemic immunosuppressants or other immune-modifying drugs administered chronically (i.e. for more than 14 consecutive days), except if it is part of management of HIV infection.
  - 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 labeling information (e.g. for budesonide).

- RSV-specific immunoglobulins at any time during the study.
- 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 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 (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

The 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.

All statistical analyses are descriptive. Besides the primary analyses, sub-group analyses may be conducted based on age group, gestational age at birth (as assessed by the GAIA gestational age definition)*, pre-existing HIV infection, pre-existing obstetric complications and/or breastfeading status.

* Additional statistical analyses may also be perfomed by using the Intergrowth-21st (IG-21) standard definition [Villar, 2014].

The SAP will describe how missing data will be handled during analyses.

9.4.1.1. Safety

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

Safety analyses in **infant participants** will include summaries by study group and mother's age category (<18 years; ≥ 18 years; overall) of neonatal AESIs, MAEs, SAEs, (S)AEs leading to study withdrawal, and occurrence of RSV- associated LRTIs, severe LRTIs, RSV-associated hospitalization.

Case definition for MA-RTIs in maternal participants, RTIs and LRTIs in infant participants are described in Section 4.2.5.

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

9.4.1.2. Immunogenicity

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any study group and at any timepoint, the percentage of exposed participants with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the FAS will be performed to complement the per protocol analysis.

9.4.2. Participant disposition

Number of screened, randomized, exposed 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. Additional analyses by country and/or by site may be performed

9.4.3. Primary endpoints

9.4.3.1. Safety (Amended 15 March 2022)

	Primary Safety Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting solicited administration site and systemic events during a 7-day (i.e. Day 1 to Day 7 included) follow-up period after dosing.	The number and percentage with exact 95% CI of maternal participants reporting each solicited administration site event (any grade, each grade,) and solicited systemic event (any, each grade) during the 7-day (Day 1 to 7 days post-study intervention) follow-up period after dosing will be tabulated by maximum intensity per participant for each study group. The number and percentage of maternal participants reporting: • at least one administration site AE (solicited and unsolicited) • at least one systemic AE (solicited and unsolicited) • any AE during the 7-day (Day 1 to 7 days post-study intervention) follow-up period after dosing will be tabulated with exact 95% CI by group. The same computations will be done for Grade 3 solicited and unsolicited AEs, for any unsolicited AEs considered related to study intervention, for any Grade 3 unsolicited AEs considered related to study intervention and for any solicited and unsolicited AEs resulting in a medically attended visit (i.e., MAEs).
	Number and percentage of maternal participants reporting unsolicited AEs that occur during a 30-day (i.e. Day 1 to Day 30 included) follow-up period after dosing.	The number and percentage of maternal participants reporting unsolicited AEs within 30 days (Day 1 to 30 days post-study intervention) after dosing with exact 95% CIs will be tabulated by group and by MedDRA preferred term. Similar tabulations will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 related unsolicited AEs and for MAEs.
	Number and percentage of maternal participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from Day 1 up to 42 days post-delivery.	The number and percentage of maternal participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-delivery with exact 95% CIs will be tabulated by group and by Medical MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal, and MAEs will be prepared.
	Number and percentage of maternal participants reporting pregnancy outcomes * from Day 1 up to 42 days post-delivery. *These include live birth with no congenital anomalies, live birth with minor congenital anomalies only; live birth with at least one major congenital anomaly, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth	The number and percentage of maternal participants reporting each pregnancy outcome from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of adverse pregnancy outcomes will be prepared .

	Primary Safety Endpoints	Statistical Analysis Methods
	(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.	
	Number and percentage of maternal participants reporting pregnancy-related AESIs * and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery. * These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth) and chorioamnionitis.	The number and percentage of maternal participants reporting each pregnancy-related AESI and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of pregnancy-related AESIs and worsening of pre-existing medical conditions and/or obstetric complications will be prepared.
Infant participants	Number and percentage of infant participants reporting neonatal / infant AESIs * from birth up to 42 days post-birth. * These include small for gestational age, low birth weight including very low and extremely low birth weight (<2500 g, <1500g, <1000g), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in an extremely preterm birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth) and preterm birth.	The number and percentage of infant participants reporting each neonatal / infant AESI from birth up to 42 days post-birth will be tabulated with its exact 95% CI by group. By participant listings of neonatal / infant AESIs will be prepared.

	Primary Safety Endpoints	Statistical Analysis Methods
	Number and percentage of infant participants reporting SAE, (S)AEs leading to study withdrawal, and MAEs from birth up to 42 days post-birth.	The number and percentage of infant participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-birth with exact 95% CIs will be tabulated by group and by MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 180 days post-birth.	***The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 180 days post-birth will be tabulated with 95% CI by group.*** ***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.***
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 365 days post-birth.	***The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 365 days post-birth will be tabulated with 95% CI by group.*** ***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.***

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

9.4.3.2. Immunogenicity

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal participants	• Humoral immune responses at pre-dosing (Day 1) and at delivery: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A	For each assay, at each timepoint and by study group and age category (<18 years; ≥ 18 years; overall): • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-dosing versus pre-dosing results will be plotted using scatter plots. Results of the control group will be used as a reference. • GMR of antibody titers/concentrations at delivery over pre-dosing will be tabulated with 95% CI. • Distribution of antibody titers/concentration will be tabulated by pre-specified pre-dosing titer category. • Distribution of the fold increase of the antibody titers/concentrations (post- versus pre-dosing) will be tabulated by pre-specified pre-dosing titer category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at baseline and at delivery will be explored using scatter plots of individual values. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A will be performed at delivery using an ANCOVA model

	Primary Immunogenicity Endpoints	Statistical Analysis Methods
		on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.
Cord blood/ placental transfer	Ratio between cord blood* and maternal RSVPreF3 IgG-specific antibody concentrations at delivery. *or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	• Geometric mean of placental transfer ratio will be tabulated with 95% CI by study group. • Percentage of infants with placental transfer ratio ≥ 1 will be tabulated with exact 95 % CI by study group.
Infant participants	• Humoral immune responses at delivery*: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A *Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	For each assay, the following analysis will be performed by study group • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Distribution of RSV-A and RSVPreF3 IgG-specific antibody titers/concentration from cord blood will be tabulated. For each assay, relationship between maternal antibody titers and infant antibody titers at delivery will be evaluated graphically using scatter plots of individual results. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A will be performed at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 72 hours after birth.

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

9.4.4. Secondary endpoints

9.4.4.1. Safety (Amended 15 March 2022)

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

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

9.4.4.2. Immunogenicity

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Maternal participants	• Humoral immune responses at Day 31 post-dosing: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A • Humoral immune responses at pre-dosing (Day 1), at Day 31 post-dosing and at delivery: – Neutralizing antibody titers against RSV-B.	For each assay, at each timepoint and by study group and age category (<18 years; ≥ 18 years; overall): • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Individual post-dosing versus pre-dosing results will be plotted using scatter plots. Results of the control group will be used as a reference. • GMR of antibody titers/concentrations at each post-dosing timepoint over pre-dosing will be tabulated with 95% CI. • Distribution of antibody titers/concentration will be tabulated by pre-specified pre-dosing titer category. • Distribution of the fold increase of the antibody titers/concentrations (post- versus pre-dosing) will be tabulated by pre-specified pre-dosing titer category. Relationship between maternal RSVPreF3 IgG-specific antibody concentration and RSV-A neutralizing antibody at Day 31 post-dosing, between RSV-A neutralizing antibody and RSV-B neutralizing antibody, and between RSVPreF3 IgG-specific antibody concentration and RSV-B neutralizing antibody at baseline, at Day 31 post-dosing and at delivery will be explored using scatter plots of individual values. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A will be performed at Day 31 post-dosing, and against RSV-B at Day 31 post-dosing and at delivery using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.
Infant participants	• Humoral immune responses at delivery*: – Neutralizing antibody titers against RSV-B * Measured in cord blood sample collected at delivery or infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained).	For each assay, the following analysis will be performed by study group: • Antibody titers will be displayed using reverse cumulative curves. • GMTs will be tabulated with 95% CI and represented graphically. • Distribution of RSV-B antibody titers from cord blood will be tabulated. For each assay, relationship between maternal antibody titers and infant antibody titers at delivery will be evaluated graphically using scatter plots of individual results. Between group evaluation in terms of neutralizing antibody titers against RSV-B will be performed at delivery using an

	Secondary Immunogenicity Endpoints	**Statistical Analysis Methods**
		ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed. In addition, if cord blood samples are missing in 20% or more of infants in a single study group, and if the data permit: RSV antibody concentrations/titers in infants through time will be evaluated separately in infants with cord blood samples and in infants from whom, instead, a blood sample was obtained within 72 hours after birth.
	• Humoral immune responses at Day 43*, at Day 121* and at Day 181* after birth: – RSVPreF3 IgG-specific antibody concentrations – Neutralizing antibody titers against RSV-A and RSV-B * Measured in infant blood samples collected at Day 43 (sub-cohort 1, V2-NB), at Day 121 (sub-cohort 2, V3-NB) and at Day 181 (sub-cohort 3, V4-NB) after birth. Each infant will be randomly assigned (1:1:1) to one of 3 sub-cohorts.	For each assay, at each timepoint and by study group: • Antibody titers/concentrations will be displayed using reverse cumulative curves. • GMTs/ GMCs will be tabulated with 95% CI and represented graphically. • Distribution of RSV-A, RSV-B and RSVPreF3 IgG-specific antibody titers/concentration from cord blood will be tabulated. Between group evaluation in terms of RSVPreF3 IgG-specific antibody concentrations and neutralizing antibody titers against RSV-A and RSV-B at Day 43 (sub-cohort 1, V2-NB), at Day 121 (sub-cohort 2, V3-NB) and at Day 181 (sub-cohort 3, V4-NB) after birth using an ANCOVA model on the logarithm$_{10}$ transformation of the concentrations/titers, and including the pre-dosing logarithm$_{10}$ transformation of the concentrations/titers, the study intervention, gestational age at the time of study intervention administration (<28 $^{0/7}$; ≥ 28 $^{0/7}$ weeks), and the interval between dosing and delivery as covariates if needed.

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

9.4.5. Tertiary endpoints

CCI [redacted]

9.4.6. Other analyses

9.4.6.1. Demography and baseline characteristics analyses

These analyses will be performed on the ES and on the FAS for immunogenicity.

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

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

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

9.4.6.2. Other analyses for adolescent maternal participants

Sub-analyses to evaluate objectives and endpoints will be performed on the 15-17 YOA sub-group.

9.4.6.2.1. Safety

Due to small number of adolescent maternal participants in this trial, a Bayesian approach will be applied to predict the probability of AEs in this population. It is assumed a specific AE in an adolescent maternal participant receiving the RSV-MAT vaccine is a binary outcome (yes/no) with p as a probability that the outcome is "yes"; it is further assumed that p is a random variable having beta distribution as a prior, which will be estimated from other data sources. The prior beta distribution will be developed based on data collected in RSV-MAT vaccine recipients above 17 YOA in this trial. With the data observed in RSV-MAT vaccine recipients 15-17 YOA, a Bayesian approach will be applied to estimate the posterior distribution of p. Similar procedures will be used for estimating the posterior distribution of p_0 (the probability of having this AE for an adolescent maternal participant in placebo group). However, the prior distribution for p_0 will be assumed as a mixture of beta distributions based on both the data collected in participants above 17 YOA in the placebo group in this trial and the adolescents younger than 17 YOA in EPI-RSV-015 study [EPI-RSV-015, 2020]. Lastly, the predictive probability of the occurrence of this AE in an adolescent maternal participant 15-17 YOA will be calculated separately in the RSV-MAT vaccine group and the placebo group. A predictive probability in an adolescent maternal participant in RSV-MAT vaccine group

no worse than that in placebo group will provide reassurance that vaccination does not result in higher risk of AE. The detailed analysis plan will be described in the protocol and SAP.

9.4.6.2.2. Immunogenicity

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

9.5. Conduct of analyses (Amended 15 March 2022)

No analysis requiring statistical adjustment will be performed.

9.5.1. Sequence of analyses (Amended 15 March 2022)

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

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

9.5.2. Statistical consideration for interim analysis

Not applicable.

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 Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, 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 substantial 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/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators must provide the sponsor with full and accurate financial disclosure, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators must provide their financial interest information before initiation of the study center and again at the end of the study. Investigators are responsible for providing

a financial disclosure update if their financial interests change at any point during study participation and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative must fully explain the nature of the study to the participant/participant's 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 and participant informed assent, as appropriate, prior to participation in the study.

SAEs and/or AESIs experienced by an infant born to the exposed mothers will be reported (if become known to the site staff), even if the re-consent for infant participants is not provided.

The content of the ICF 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 center.

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 authorized 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 rescreened are required to sign a new ICF.

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

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants/participants' parent(s)/LAR(s) must be informed that:

- Her personal/their child's study-related data will be used by the sponsor in accordance with local data protection law.
- Her medical records/their child's may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

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

10.1.5. Committees structure (Amended 15 March 2022)

The protocol will be reviewed and approved by an IEC/IRB before initiation (Refer to Section 10.1.1 for further details).

Safety oversight will be provided by the SRT composed of GSK RSV team members, and by the IDMC (Refer to Section 8.2.3 for further details).

The ***GSB*** includes relevant members of the GSK study team and is responsible for ongoing safety monitoring of the entire project. The SRT will inform the ***GSB*** about any potential safety concern relevant to the study (Refer to Section 8.2.3).

10.1.6. Dissemination of clinical study data (Amended 15 March 2022)

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 applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target results summaries submission 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 randomization codes for their site only after completion of the full statistical analysis*.

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

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 (see Section 10.7.2 for the exact definition of source documents). The document 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, case report form [CRF]), the copy should fulfill the requirements for certified copies (see Section 10.7.2 for the exact definition of certified copies).

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

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see Section 10.7.2 for the exact definition of source data).

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

Quality tolerance limits (QTLs) will be pre-defined in the Study Management Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

Trial records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final 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 to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any 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.

Definitions of what constitutes source data and 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 its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites 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 enough notice 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

At the end of the study, the investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the study conclusion screen in the eCRF

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol-required safety laboratory assessments (Amended 15 March 2022)

Laboratory assessments detailed in Table 24 should either be available as part of the routine care within 15 days prior to study intervention administration or be performed within the same interval at the local laboratory as part of screening.

Table 24 Protocol-Required Safety Laboratory Assessments

Laboratory assessments	Parameters
Hematology	Leukocytes (White Blood Cells)
	Lymphocytes
	Eosinophils
	Basophils
	Hemoglobin
	Hematocrit
	Platelets
	Neutrophils
Clinical chemistry	Alanine Aminotransferase (ALT)
	Aspartate Aminotransferase (AST)
	Creatinine
	Blood Urea Nitrogen (BUN)/urea]*
Urinalysis by dipstick	Glucose
	Protein

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

Laboratory assessments (e.g., placenta pathology) may be performed on the placental tissue samples collected from maternal participants at delivery visit to support possible safety assessments, if necessary. Additional details are provided in the study SPM.

Additional assessments on the placental sample can be performed depending on local standard of practice, site capability and the investigators' medical judgment.

10.2.2. Descriptions of the assays to be performed in the study (Amended 15 March 2022)

Assay descriptions could be subject to change, due to assay re-development and/or qualification.

RSV-A and RSV-B neutralization assays

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a monolayer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL-81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (anti-RSV IgG) and a secondary antibody conjugated to horse-radish peroxidase (HRP), allowing the visualization of plaques by immunofluorescence after coloration with TrueBlueTM peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with reading software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014].

For RSV, NIBSC16/284 sample has been identified as an international reference. For RSV-A and RSV-B [McDonald, 2018; McDonald, 2020], GSK internal standards have been calibrated against the international standard and are used to convert ED60 in IU/mL in each run.

Quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR) able to discriminate RSV-A and RSV-B subtypes

Quantitative RT-PCR able to discriminate RSV-A and RSV-B subtypes: Briefly, RSV-A and RSV-B RNAs extracted from the nasal swabs are detected in a duplex PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involves nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real- time PCR reaction using a calibration curve (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

RSVPreF3 IgG ELISA

The RSVPreF3 IgG ELISAs will be based on an indirect ELISA allowing the detection and the quantification of specific IgG antibodies directed against RSVPreF3 in human serum samples.

The principle of these assays will be as follows. RSVPreF3 antigen will be adsorbed onto a 96-well polystyrene microplate. After a washing and a blocking step, dilutions of serum samples, controls and standards will be added to the coated microplate. A reference standard curve will be prepared using a pool of commercial human serum containing anti-RSV antibodies. After incubation, the microplate will be washed to remove unbound primary antibodies. Bound IgG will be detected by the addition of a secondary anti-human antibody (total IgG or IgG1-specific), conjugated to HRP. Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSVPreF3 IgG or IgG1 antibodies present in the serum sample. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

Hematocrit assay

The hematocrit is the proportion of the volume occupied by the red blood cells compared to the whole volume of the blood cells. The hematocrit value is determined by drawing blood sample into a capillary tube then centrifuged, the lengths of the columns for the red blood cells and the whole blood cells are measured using a graphic reading device. Thereafter, the proportion of the red blood cells to that of the whole blood cells is determined and expressed as a decimal or percentage fraction.

Hematocrit will be tested at Visits 1, 2 and 3 for all participants until the current Protocol Amendment 1 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 1 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.

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 (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the 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 administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- 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.

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 before the study intervention. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent/assent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- 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 intervention

10.3.2. Definition of an 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 hospitalization or prolongation of existing hospitalization Note: In general, hospitalization 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 hospitalization are also considered AEs. The event will also be considered serious if a complication prolongs hospitalization or fulfills any other serious criteria. When in doubt as to whether 'hospitalization' 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, diarrhea, 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 for additional information.
f.	Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).

g. Other situations

Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should 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; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

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

Table 25 Solicited administration site events

All age groups
Pain
Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited for maternal participants:

Table 26 Solicited systemic events

Adult
Fatigue
Fever
Nausea
Vomiting
Diarrhea
Abdominal pain
Headache

Note: maternal participants will be instructed to measure and record the temperature by an age-appropriate route (preferably oral) at least once each day, at approximately the same time each day. If additional temperature measurements are taken at other times of the day, maternal participants will be instructed to record the highest temperature in the electronic Participant Diary (eDiary).

10.3.4. Unsolicited adverse events (AEs)

An unsolicited AE is an AE that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a maternal participant who has signed the informed consent/assent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The maternal participants 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'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 or perceived as a concern by the maternal participant will be collected during an interview with the maternal participants and by review of available medical records at the next visit/contact.

10.3.5. Adverse events of special interest (AESIs)

AESIs include:

- **Worsening** of **pre-existing medical conditions and/or obstetric complications** as defined in section 8.2.1.2.
- The following **pregnancy-related AESIs** (collected as AESI if developed after study intervention administration and were not pre-existing):
  - Maternal death
  - Hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia)
  - Fetal growth restriction
  - Gestational diabetes mellitus
  - Pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), and
  - Chorioamnionitis**.**
- The following **neonatal AESIs**:
  - Small for gestational age
  - Low birth weight including very low and extremely low birth weight (<2500 g, <1500g, <1000g)
  - Congenital anomalies (major external structural defects, internal structural defects, functional defects)
  - Neonatal death (in an extremely preterm birth [22<GA<28 weeks], in a preterm live birth [28<GA<37 weeks], or in a term live birth), and preterm birth.

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

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) lead to one of the above diagnoses, should be recorded and reported as AEs but not as AESI until the

final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely.

Note: AESIs experienced by an infant born to the exposed mother will be reported (if become known to the site staff), even if the re-consent for infant participants is not provided.

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

In the absence of a diagnosis, abnormal laboratory findings assessments (e.g. clinical chemistry, hematology, urinalysis) or other abnormal results 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 must exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

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 enrollment and are expected to deliver while participating in the study.

Maternal participants who become pregnant again after administration of the study intervention 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 experience any signs or symptoms the maternal participants/infant participants' parent(s)/LAR(s) perceive as serious.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on 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 instead of individual signs/symptoms.

An Electronic Diary (eDiary), hereafter referred to as Participant Diary, will be used in this study to capture solicited administration site or systemic events for maternal participants. The maternal participant should be trained on how and when to complete the Participant Diary.

Anyone who measures administration site or systemic events and who will record the event in the Participant Diary should be trained on using 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 must be documented in the Participant Diary/maternal participant's source record.

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

Note: SAEs and/or AESIs experienced by an infant born to the exposed mother will be reported (if become known to the site staff), even if the re-consent for infant participants is not provided.

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

For time period and frequency for collecting AE, SAE and other safety information, refer to Section 8.3.1.

All solicited events that occur during 7 days following administration of the dose of study intervention (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity or whether or not they are considered related to the study intervention.

All other AEs should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

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

10.3.8.2.1. Follow-up during the study

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

All SAEs and AESIs (serious or non-serious as defined in the Section 10.3.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Non-serious MAEs 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 they are resolved, stabilized or until the participant is lost to follow-up.

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until they are resolved, stabilized or until the participant is lost to follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

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

The investigator will provide any new or updated relevant information to GSK on a previously reported SAEs/AESIs using a paper/electronic Adverse Events Form and corresponding Expedited Adverse Event Form 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 SAE/AESI as fully as possible.

10.3.8.2.3. 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 subsequent 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 Adverse Events Form and corresponding Expedited Adverse Event Form if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

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

10.3.8.3. 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 write access to the participant's eCRF is removed, 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 VCSP department within the defined reporting time frames specified in the Table 18.

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 27 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 everyday activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
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 Section 1.3 for the definition of fever and the preferred location for temperature measurement.

The maximum intensity of local injection site redness/swelling will be scored at GSK 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 judgment.

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 center 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

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB to assist in making 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 intervention?

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

If an event meets the criteria to be determined '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 study intervention, if applicable.
- An error in study intervention 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 Adverse Events Form and corresponding Expedited Adverse Event Form 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 AE the participant experiences, the maternal participant/infant participant's parent(s)/LAR(s) will be asked if she/the infant participant received medical attention (defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the 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, the investigator (or designee) must complete information in the electronic Adverse Events Form and corresponding Expedited Adverse Event Form WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 18 for the details on timeframes for reporting of SAEs/AESIs/subsequent pregnancies.

The investigator will be required to confirm the review of SAE/AESI causality within 72 hours of submission of the SAE/AESI.

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

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

If the electronic reporting system does not work, the investigator (or designee) must fax a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to the Sponsor Information) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Adverse Events Form and corresponding Expedited Adverse Event Form within 24 hours after the electronic reporting system is working again. 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 the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Country-specific requirements

Not applicable.

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations (Amended 15 March 2022)

AE:	Adverse Event
AESI:	Adverse Event of Special interest
ANCOVA:	Analysis of Covariance
BMI:	Body Mass Index
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
COVID-19:	Corona Virus Disease 2019
CRDL:	Clinical Research & Development Lead
CRF:	Case Report Form
CSR:	Clinical Study Report
DRE:	Disease-related event
eCRF:	electronic Case Report Form
EDD:	Expected Date of Delivery
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed set
ET:	Embryo-Transfer
FAS:	Full Analysis Set
FU:	Follow-up
GAIA:	Global Alignment of Immunization Safety Assessment in pregnancy

GCP:	Good Clinical Practice
GDM:	Gestational Diabetes Mellitus
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer
GSB:	***Global Safety Board***
GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus
HRP:	Horse-radish peroxidase
IAF:	Informed Assent Form
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IND:	Investigational New Drug
IRB:	Institutional Review Board
IUI:	Intrauterine insemination
LAR:	Legally Acceptable Representative
LML:	Local Medical lead
LMP:	Last Menstrual Period
LRTI:	Lower Respiratory Tract illness
LSLV:	Last Participant Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MAE:	Medically attended adverse event
MA-RTI:	Medically attended respiratory tract illness

MedDRA:	Medical Dictionary for Regulatory Activities
nAb:	Neutralizing antibody
NB:	Newborn
PCD:	Primary Completion Date
PCR:	Polymerase Chain Reaction
PPS:	Per Protocol Set
QTL:	Quality Tolerance Limit
RR:	Respiratory Rate
RSV:	Respiratory Syncytial Virus
RTI:	Respiratory Tract Illness
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SARS-COV-2:	The corona virus that is the causative agent of COVID-19.
SBIR:	Source data Base for Internet Randomization
SD:	Standard deviation
SoA:	Schedule of Activities
SPM:	Study Procedures Manual
SpO2:	Blood oxygen saturation as measured by pulse oximetry
SRT:	Safety Review Team
SUSAR:	Suspected Unexpected Serious Adverse Reaction
VCSP:	Vaccines Clinical Safety and Pharmacovigilance
WHO:	World Health Organization
YOA:	Years Of Age

10.7.2. Glossary of terms (Amended 15 March 2022)

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

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.

Body Mass Index

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

Certified copy:

A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Child in care:	A child who has been placed under the control or protection of an agency, 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.
Child:	A young human being below the legal age of majority (generally < 18 years of age).
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	EoS occurs with the last infant participant last visit (LSLV; Visit 5-NB).
Enrolled participant	'Enrolled' means a maternal participant's/infant parent's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential maternal participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 of the protocol for the definition of 'enrolled set' 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:	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, judicial 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 site staff.
Neonatal adverse events of special interest	Adverse events that occur from birth through 42 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 (Visit2-NB). However, as indicated in Table 17, any neonatal AESIs identified after Visit 2-NB should also be reported in the eCRF.
Neonate (or Newborn)	An infant 28 days old or younger.
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 number:	A unique identification number assigned to each participant who consents to participate in the study.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control) or an infant born from participants who received the study intervention. Synonym: subject
Pregnancy outcomes	Pregnancy outcomes that occur up to 42 days after delivery are listed in Table 4 and Section 8.3.4.2.
Pregnancy related adverse events of special interest:	Pregnancy related events that occur up to 42 days after delivery are to be reported as AESIs and 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 was concluded according to the pre-specified protocol or was terminated.
Randomization:	Process of random attribution of 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 follow-up period following study intervention administration.
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, laboratories and at medico-technical departments involved in the clinical trial).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
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/ study intervention schedule, etc.) at the time of enrollment.

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)*

10.9. Appendix 9: Definitions of study AESIs and pregnancy outcomes

- Table 4 and Section 10.3.5 list events of interest that must be reported as AESIs.
- Worsening of pre-existing medical conditions and/or obstetric complications should be collected as maternal AESI and reported with enough information to support worsening from baseline condition (Section 8.2.1.2).
- Diagnosis of pregnancy-related AESIs, pregnancy outcomes (Section 8.3.4.2) and neonatal AESIs should be assessed using the GAIA case definitions below. AESIs should be reported as non-serious or SAE as appropriate. The narrative for each of the cases must include enough details to permit assessment of the level of diagnostic certainty by GAIA case definition
- Articles that discuss GAIA case definitions in detail can be found in the following issues of *Vaccine*:
  - Bauwens J, Bonhoeffer J, Chen RT, editors. Harmonising Immunization 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 28
Maternal Events of Interest	
Maternal Death	Table 29
Hypertensive Disorders of Pregnancy	Table 30
Fetal Growth restriction	Table 31
Gestational Diabetes Mellitus	Table 32
Pathways to Preterm Birth	Table 33
Chorioamnionitis	Table 34
Neonatal Events of Interest	
Small for Gestational Age	Table 35
Low Birth Weight	Table 36
Congenital Anomalies	Table 37
Neonatal Death	Table 38
Preterm Birth	Table 39

Table 28 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 heartbeat, 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, mid-wife, 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 immunization safety data. Vaccine. 2016; 34(49):6057-6068.

Table 29 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 complications, 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 30 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 2 measurements over a minimum of 1 h WITHOUT severe features (see pre-eclampsia 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
Pre-eclampsia	
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 2 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 pre-eclampsia with severe features does not require proteinuria, see definition below)

In Ev = Insufficient Evidence

Hypertensive Disorders of Pregnancy Continued

Pre-eclampsia 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 2 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 31 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

I**n 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 32 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 33 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)	
Premature 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 2 hour period, with clinical criteria for documenting cervical change by exam 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
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 2 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 34 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 focuses 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 3 consecutive contractions) • Maternal WBC ≥ 15,000 per mm3 in the absence of corticosteroids. • Definite purulent fluid from the cervical os. **Clinical Definition B** Maternal fever ≥ 38 degrees Celsius on one occasion *plus 2 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 3 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 35 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 ET 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)	
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 immunization safety data. Vaccine. 2017; 35:6518-6528.

Table 36 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 37 Major Congenital anomalies

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

Major and minor characterization of congenital anomalies are assessed based on CDC classification [CDC].

Only major congenital anomalies are reported as AESIs based on the CDC classification [CDC].

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)

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)

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 38 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

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 intrauterine growth retardation if ≤2500 g AND Death of infant in first 28 days of life AND Medically-confirmed death

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 • Death of infant in first 28 days of life AND • Medically-confirmed death OR non-medically-confirmed death

Reference: Pathirana J, Munoz 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 39 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.
*	Definitions of LMP, birth weight and physical assessment in referenced article.

Adapted from 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.

10.10. Appendix 10: 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	12 March 2021
Protocol Amendment 1	15 March 2022

Detailed description of the current Protocol amendment changes:

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

- **Section 1.1, Synopsis**

The objective of the study is to evaluate the safety, reactogenicity, and immunogenicity * of the single intramuscular 120 µg dose of the study RSV maternal vaccine compared to placebo, in women with high risk pregnancies in the late second or third trimester of pregnancy and in the infants born to the vaccinated mothers.

**** Based on all available safety information following vaccination with 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, Schema**

The study is a Phase III, double-blind*, randomized, placebo-controlled, multi-center, multi-country study.

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

[...]

Approximately 378 eligible maternal participants will be enrolled *and randomized (2:1) to receive either RSV MAT vaccine or the placebo control. At least eighteen (5%) of the enrolled and randomized maternal participants will be between 15 and 17 YOA, inclusive. At the same time, infant participants (as yet unborn) will be further randomized (1:1:1) into sub-cohorts for blood sample collection for the assessment of immunogenicity at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

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

[...]

All maternal participants who receive the study intervention (exposed set [ES]) will be followed for safety and reactogenicity and evaluated for: solicited administration site and systemic adverse events (AEs) within 7 days of study intervention, unsolicited AEs within 30 days of study intervention, pregnancy outcomes and pregnancy-related adverse events of special interest (AESIs) within 42 days of delivery, serious adverse events (SAEs), medically attended respiratory tract illnesses (MA-RTIs)***** and medically attended adverse events (MAEs) throughout the study period and up to the time of the last contact.

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

[…]

Blood samples for humoral immunogenicity will be collected from sub-cohorts of infant participants at Day 43, Day 121 and Day 181 post-birth*****. A second analysis of immunogenicity based on the FAS may be performed to complement the PPS analysis (Refer to Sections 9.3 and 9.4.1.2 for details).

**** Due to the change in the study requirements, there will no longer be collection of blood samples at Visit-2NB, Visit-3NB and Visit-4NB.***

- **Section 1.3, Schedule of Activities (SoA)**

Table 1 Schedule of Activities (SoA) – Maternal participants

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Informed consent/assent	●										Section 10.1.3 **Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.**
[…]											
~~Blood sample (hematocrit: ~ 3.0 ml)~~		~~●~~		~~●~~		~~●~~					~~Sections 8.1.1 and 8.1.3~~
[…]											
Nasal swab [7]										●	Sections 8.1.1, 8.1.3, and 8.4.4 ***Nasal swab samples will no longer be collected.***

Visit / Contact	Screening	V1	C1	V2 [1]	Monthly contacts until delivery [6]	V3	V4	C2	Safety Visit - Event-driven	RSV-associated MA-RTI Visit - Event-driven [7]	Notes
Timepoint	**D (-28) – D 1**	**D1** (24 0/7 - 36 0/7 weeks of gestation)	**D8**	**D31**		**Delivery**	**D43** Post-delivery	**D181** Post-delivery			For monthly contacts: Section 8.4.2.1 ***Additional contacts and/or visits can be made between Visit-2 and the Delivery visit if deemed necessary.***
Placental tissue sample [8]						●					***Section 10.2.1 Samples will be collected at delivery from all participants, if feasible.***
[…]											
MA-RTIs (Day 1 post-study intervention to 180 days post-delivery) [7]		O [5]	O [5]	O [5]	O [5]	O [5]	O [5]	O [5]		●	Sections 8.3.1, 8.3.3, 8.4 and 10.3.8 ***MA-RTIs for the maternal participants will no longer be performed.***

V = visit; **C** = Contact; **D** = day; **MA-RTI** = medically attended respiratory tract illness; ~~**Hct** = hematocrit~~; **LAR** = Legally acceptable representative

[…]

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

[7] Due to the change in the study requirements, RTI surveillance/ assessment for the maternal participants will no longer be performed

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

Note:
~~The double-line border following Day 43 post-delivery indicates the analyses which will be performed on all data obtained up to Day 43 post-delivery (Visit 4).~~

Table 2 Schedule of activities (SoA) – Infant participants

Visit / Contact	V1-NB	***Recommended safety contact*** [5]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		Notes
									Contacts (Section 8.4.2.2.1)	Visit	
Age of infant		***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months			
Visit Day	Birth	*D8~~7~~ Post-birth*	D43 Post-birth	D91 Post-birth	D121 Post-birth	D181 Post-birth	D271 Post-birth	D366 Post-birth	Birth to Day 366 Post-birth	Event-Driven	
[…]											
Review infant RTI diary card		***O***	O	O	O	O	O	O	O	O	
[…]											
Transcribe applicable infant RTI diary card data to eCRF		***O***	●	●	●	●	●	●	●	●	
[…]											
Lifestyle characteristics [1]	●	***O***	●	●	●	●	●	●			
[…]											
Blood sample (immunology, infants) ~2.5 ml [3, 6]			● Sub-cohort 1		● Sub-cohort 2	● Sub-cohort 3					Table 12 ***Samples will no longer be collected at Visit 2-NB, Visit 3-NB and Visit 4-NB***
Concomitant vaccinations	●	***O***	●	●	●	●					Sections 6.8.2 and 6.8.3
Concomitant medications	●	***O***	●	●	●	●	●	●	●	●	
[…]											

Visit / Contact	V1 - NB	***Recommended safety contact*** [5]	V2- NB	C1- NB	V3- NB	V4- NB	C2- NB	V5- NB	RTI Surveillance		Notes
									Contacts (Section 8.4.2.2.1)	Visit	
Age of infant		***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months			
Visit Day	Birth	*D8~~7~~ Post-birth*	D43 Post - birth	D91 Post-birth	D121 Post-birth	D181 Post-birth	D271 Post-birth	D366 Post-birth	Birth to Day 366 Post-birth	Event-Driven	
[…]											
Suspected, probable and confirmed cases of COVID-19 infection (depending on the epidemiological COVID-19 situation) (Birth to 365 days post-birth)	●	***O***	●	●	●	●	●	●	●	●	Sections 8.4.7
LRTIs (including medically assessed, RSV-associated LRTIs) (Birth to 365 days post-birth)	O [4]	***O*** [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	●	Sections8.3.1, 8.3.3, 8.4and 10.3.8.
Medically assessed, RSV-associated hospitalizations (Birth to 365 days post-birth)	O [4]	***O*** [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	O [4]	●	Sections 8.3.1, 8.3.3, 8.4 and 10.3.8.
SAEs, (S)AEs leading to study withdrawal, MAEs	●	***O***	●	●	●	●	●	●	●	●	Sections7.2, 8.3.1and 10.3.8

Visit / Contact	V1 - NB	***Recommended safety contact*** [5]	V2-NB	C1-NB	V3-NB	V4-NB	C2-NB	V5-NB	RTI Surveillance		Notes
									Contacts (Section 8.4.2.2.1)	Visit	
Age of infant		***8 days***	6 weeks	3 months	4 months	6 months	9 months	12 months			
Visit Day	Birth	*D8~~7~~ Post-birth*	D43 Post-birth	D91 Post-birth	D121 Post-birth	D181 Post-birth	D271 Post-birth	D366 Post-birth	Birth to Day 366 Post-birth	Event-Driven	
[…]											
(Birth to 365 days post-birth)											

[…]

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

[6] Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.

Note

~~The double-line border following Day 43 post-birth indicates the analyses which will be performed on all data obtained up to Day 43 post-birth (Visit 2-NB).~~

Table 3 Allowed windows for study visits

Visit	Study Day [a]	Allowed visit window [b]
Maternal participants		
[…]		
Visit 3 (Delivery) [d]	-	***1 day before to 3 days after delivery[G]***
[…]		
Infant participants		
[…]		
Recommended safety contact	***Day 8***	***Day 7 - Day 10***

[…]

[G] For participants in whom a cesarean section is performed, 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.

- **Section 2.3, Benefit/Risk assessment**

The Sponsor 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 infections (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.

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-012, based on an observation of imbalance of 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 trial 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, the Sponsor 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.

~~Detailed information about the known and expected benefits and risks and expected AEs 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 will be conducted throughout this study by an external IDMC and an internal SRT.~~

~~The study includes the establishment of a surveillance system which may facilitate detection of respiratory tract infections (RTIs), in particular 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 from the ongoing study in pregnant women, the benefit-risk profile of the RSV Maternal vaccine (RSVPreF3) continues to be favorable and justifies unaltered continuation of the development program.~~

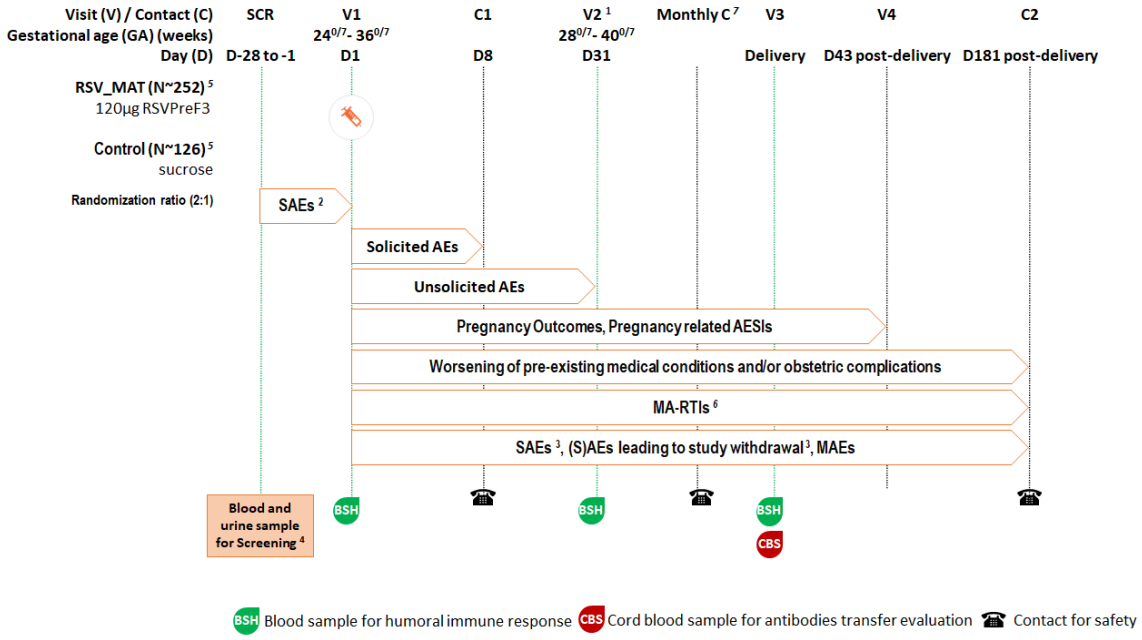
- **Section 3, Objectives and endpoints**

Table 4 Study objectives and endpoints

Objectives	Endpoints
Primary	
Safety assessment: […]	
Infant participants: • ***To evaluate safety up to 365 days post-birth (1 year of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).***	• ***Number and percentage of infant participants reporting:*** – ***SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 180 days post-birth.*** – ***SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 365 days post-birth.***
Secondary	
Safety assessment: […]	• ~~—~~
Infant participants: • ~~To evaluate safety up to 365 days post-birth (1 year of age) in infants born to maternal participants who received a single IM dose of study intervention (RSV maternal vaccine or placebo).~~	• ~~Number and percentage of infant participants reporting:~~ – ~~SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 180 days post-birth.~~ – ~~SAEs, (S)AEs leading to study withdrawal and MAEs from birth up to 365 days post-birth.~~

- **Section 4.1, Overall design**

Figure 1 Study design overview – Maternal participants



[…]

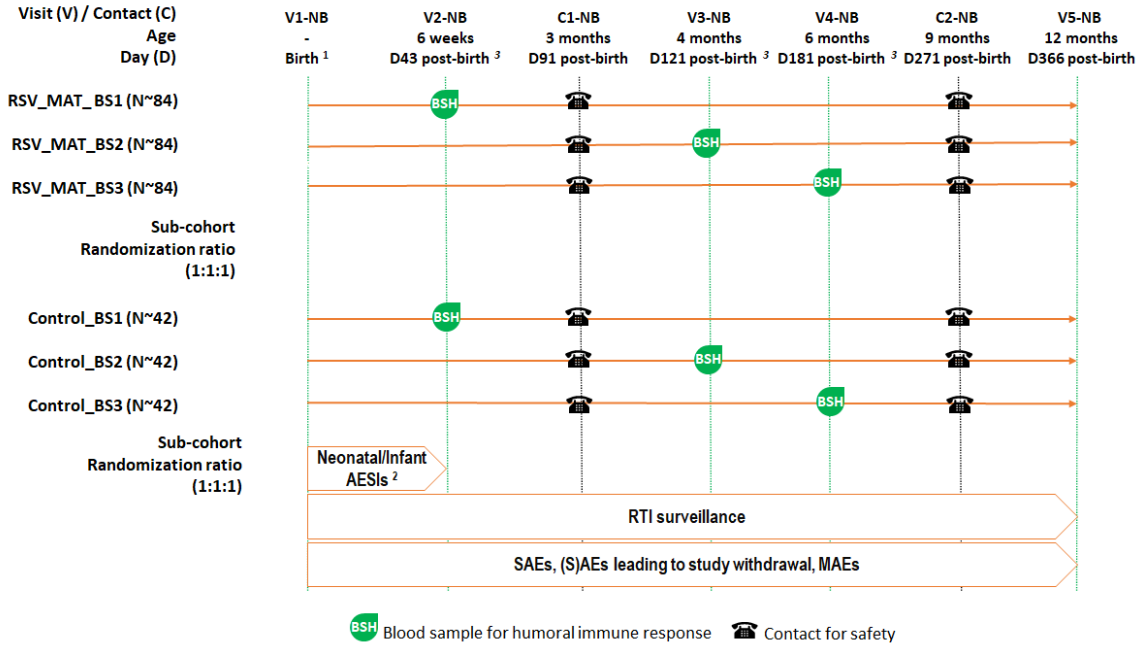
[5] Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants. Refer to section 2.3 for further details.

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

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

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

Figure 2 Study design overview – Infant participants



[…]

[3] Due to the change in the study requirements, there will no longer be collection of blood samples at Visit-2NB, Visit-3NB and Visit-4NB.

Note:

An additional recommended safety contact may be performed ~7 days post-birth if deemed necessary by the investigator or by the parent/ LAR(s).

- […]
- Experimental design: Phase III, double-blind*, randomized, placebo-controlled, multi-center, multi-country study with 1 investigational RSV MAT vaccine group in a parallel design.

  **** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants***
- […]
- Blinding: Double-blind*, as described in Table 5.

  **** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.***
- […]
- Study intervention schedule*: 1 single dose administered IM between 24 and 36 weeks of gestation (at Visit 1, Day 1) to maternal participants.

  **** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
- Randomized study intervention allocation* is 2:1 (investigational vaccine : placebo), as described in Table 5 and Section 6.3.

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

- Sampling schedule:
- Blood samples for immunogenicity/~~hematocrit~~ assessment will be taken from all maternal participants at Days 1, 31 and delivery.
- ***Placenta samples will be taken from all maternal participants at delivery Visit, whenever feasible. These samples may be tested to support possible safety assessments, if necessary. Additional details are provided in the study procedures manual (SPM).***
- […]
- Blood samples for immunogenicity***** analysis will be taken from sub-cohorts of infant participants at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

  **** Due to the change in the study requirements, there will no longer be collection of blood samples at Visit 2-NB, Visit 3-NB and Visit 4-NB.***
- Nasal swab for confirmation of RSV-A/B infection will be taken from participants***** clinically diagnosed as having a suspected case of RSV-associated RTIs at an event-driven timepoint.

  **** Due to the change in the study requirements, nasal swab samples from the maternal participants will no longer be collected.***
- Primary completion Date (PCD): ~~Visit 4 (Day 43 post-delivery for maternal participants and Visit 2-NB (Day 43 post-birth)~~***Visit 5-NB (Day 366 post-birth).***

Table 5 Study groups, intervention and blinding

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

**** Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.***
***** Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants***
~~* The double-blinding will apply from Day 1 pre-study intervention to Day 43 post-delivery/birth visit after which the first analysis will be conducted and treatment-level unblinded summaries will be provided to GSK and regulatory agency for review. No individual treatment code will be shared with investigators, site staff and participants until the end of the study.~~

- **Section 4.2.5, Case definition**

RTI cases will be classified (during data analyses) according to the definitions provided in Sections 4.2.5.1*****, 4.2.5.2 and 4.2.5.3.

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

- **Section 4.2.5.1, Maternal, medically attended respiratory tract illness (MA-RTI)**

Table 6 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

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

- **Section 4.2.5.3, RSV infection**

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

- **Section 4.3, Justification for dose**

A single formulation of the investigational RSV maternal vaccine (containing 120 µg of the RSVPreF3 antigen) ***was*** ~~is~~ planned. Available data suggest***ed*** that the 120 µg formulation ha***ds*** ~~s~~ an acceptable safety profile and tends to elicit stronger immune responses, 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 RSV MAT-001 and RSV MAT-004 studies are included in the IB to support RSV MAT-012.

Infection with RSV occurs in almost all participants by the time of reproductive age and it is extremely unlikely that a maternal participant would not have been naturally infected with RSV before. Results of study RSV MAT-001 in non-pregnant women ***and RSV MAT-004 in 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 $36^{0/7}$ 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 term 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).

*** *Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants. For details, refer to Section 2.3.***

- **Section 5.2.1.2, Prior/Concomitant therapy**

- […]
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 29 days before the study Day 1 and ending at delivery, with the exception of 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 intervention (Day 1).

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly. ***In that sense, COVID-19 vaccines may be allowed, when administered ≥ 15 days before or after study vaccination.***

- Receipt of blood or plasma products or immunoglobulin, from 90 days before study intervention administration, or planned receipt through delivery, with the exception of Rho(D) immunoglobulin, which can be given at any time. ***In that sense, antibody therapy received against COVID-19 disease should be recorded.***

- **Section 5.5, Criteria for temporarily delaying study intervention administration**

Study intervention administration may be postponed***** within the permitted time interval until transient conditions cited below are resolved:

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

- **Section 6.1, Study interventions administrated**

Table 8 Study interventions administered

[…]		
Study Interventions Name:	**RSV MAT**	**Control**
[…]		

[…]

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.

Maternal participants must be observed closely for at least 30 minutes after the administration***** of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

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

- **Section 6.3.2, Randomization to study intervention**

Approximately 378 maternal participants will be enrolled* and randomized (2:1) to receive either the RSV maternal vaccine or the placebo control at Day 1 (Visit 1). At the same time, infant participants (as yet unborn) will be further randomized (1:1:1) into sub-cohorts for blood sample collection for the assessment of immunogenicity at one of 3 timepoints (Day 43, Day 121 or Day 181 post-birth).

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

- **Section 6.3.3, Intervention allocation to the participant**

[…]

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants

- **Section 6.3.5, Blinding and unblinding**

To minimize the introduction of bias, this study will be double-blinded* from Day 1 pre-study intervention to Day 43 post-delivery/birth visit after which the first analysis will be conducted and treatment-level unblinded* summaries will be provided to GSK and regulatory agency for review. No individual treatment code will be shared with investigators, site staff and participants until the end of the study. After Day 43 delivery/birth visit, the study will be conducted as a single-blind* study.

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

Section 6.3.5.1, Emergency unblinding

[…]

Note: Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.

Section 6.3.5.2, Unblinding prior to regulatory reporting of SAEs

[…]

Note: Due to the recent safety signal, the study was fully unblinded to ensure the safety monitoring of the participants.

Section 6.4, Study intervention compliance

[…]

Note: Due to the recent safety signal, there will be no further enrollment and vaccination of maternal participants.

Section 6.6, Continued access to study intervention after the end of the study

There will be no access to RSV MAT vaccine after the end of the study. Please refer to Section 2.3 for details.

~~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 investigational vaccine during each pregnancy to achieve optimal anti-RSV antibody levels in the newborn.~~

~~Therefore, during the conclusion visit of the current study, the investigator will ask each maternal participant if she is interested in participating in a study in which the second dose of the study intervention will be administered during the subsequent pregnancy. If a participant is not interested in joining the study the reason for refusal will be documented, when available, in the participant's eCRF~~

Section 6.8.1, Maternal participants

- […]
- All antibiotics, ***antivirals,*** analgesics, and anti-pyretics taken within 7 days before dose administration.

Section 8, Study assessments and procedures

Study procedures during special circumstances

During special circumstances (e.g., the COVID-19 pandemic), the resulting limitations may affect the sites' ability to conduct the study procedures.

Enrollment* of ADDITIONAL maternal participants may be placed on hold. Decisions on re-starting enrollment* to achieve the planned sample size will be made in a manner consistent with guidance from public health and other competent authorities.

For guidance regarding the temporary delay of study intervention administration because of exposure to COVID-19, please refer to the SPM for details.

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

The following measures may be implemented for enrolled participants:

- […]
- Whenever possible, as appropriate per the judgment of the investigator and as allowed by local law, arrangements should be made for qualified personnel to collect any protocol-specified safety data/safety assessment(s) and/or biological samples at an alternate location* or at participant's home within the allowed visit window (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).

    **** Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant.***

    ~~Blood samples for central assessment of hematocrit related to immunogenicity evaluation must be collected using GSK-provided supplies.~~

Section 8.1.1, Biological samples

Table 10 Biological samples - Maternal participants

Maternal Sample type	Collected to evaluate	Minimum Quantity per participant	Unit	Time point	Additional information
Whole blood	Hematology, Biochemistry ~~Hematocrit~~	~5.5 ~~~3~~	mL ~~mL~~	Screening ~~Visit 1 (Day 1) pre-Dose~~ ~~Visit 2 (Day 31)~~ [4] ~~Visit 3 (Delivery)~~	Blood sample to be collected and analyzed locally only if not performed as per standard of care. [5]
	Immune response [1]	~10	mL	Visit 1 (Day 1) pre-Dose	-
Urine	Protein, Glucose	Dipstick	NA	Screening	Urine sample to be collected and analyzed locally only if not performed as per standard of care. [5]
Nasal Swab [2, 3, *6*]	Presence of RSV-A/B	-	-	MA-RTI Visit (Event-Driven)	Collect a nasal swab from any maternal participant who reports a MA-RTI.
				RTI hospitalization (Event-Driven)	Collect a nasal swab (if possible) from any participant hospitalized with RTI (or soon after discharge, as long as symptoms are ongoing).

[…]

[6] Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant for RTI assessment.

Table 12 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	mL	Visit 1-NB (Within 72 hours 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 2 kg baby or 2.0 ml for a 2.5 kg baby.] Refer to the Laboratory Manual for additional information. All minimum totals given below assume a body weight > 2.5 kg.
	Immune response – sub-cohort [4]	~2.5 [1]	mL	Either Visit 2-NB (Day 43 post-birth) or Visit 3-NB (Day 121 post-birth) or Visit 4-NB (Day 181 post-birth)	
Nasal swab [2, 3]	Presence of RSV-A/B	-	-	RTI Surveillance Visit - LRTIs (Event-Driven)	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 Surveillance Visit - RTI hospitalization (Event-Driven)	Collect (if possible) from any participant hospitalized with a RTI (or soon after release, as long as symptoms are ongoing).

[…]

[4] Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant for RTI assessment.

- An overall blood volume of approximately ***30***~~9~~ mL will be collected from maternal participants during the entire study period, if blood sample for assessing eligibility criteria should not be taken at screening.
- An overall blood volume of approximately ***35***~~44~~.5 mL will be collected from maternal participants during the entire study period, if blood sample for assessing eligibility criteria must be taken at screening.
- An overall blood volume of approximately 2.5 mL will be collected from infant participants during the entire study period******. If cord blood sample cannot be collected, then an overall volume of 5 mL will be collected******.

  **** Due to the change in the study requirements, there will no longer be collection of blood samples from infant participants at Visit 2-NB, Visit 3-NB and Visit 4-NB.***

Section 8.1.2, Laboratory assays

Following laboratory assays will be performed (Table 13):

- Serological assays for the determination of RSV-A/B neutralizing antibodies (nAbs) will be performed by neutralization assay with wild type virus. Further characterization of the humoral immune response will be performed using enzyme-linked immunosorbent assay (ELISA) based assays for measurement of IgG antibodies binding to the RSV PreF3 protein.

~~Hematocrit assay will be performed to evaluate changes over time in antibody titers / concentrations that may be related to volumetric changes during pregnancy.~~

Table 13 Laboratory assays

Assay type	System	Component	Method	Laboratory [1,2]
~~Hematocrit [1]~~	~~Whole Blood~~	~~Hematocrit~~	~~Per Central Laboratory SOP~~	~~Central Laboratory~~
Humoral Immunity (Antibody determination)	SERUM	RSV-A NAb	NEUT	GSK [2,3] or GSK designated lab
	SERUM	RSV-B NAb	NEUT	GSK [2,3] or GSK designated lab
	SERUM	RSV PreF3 Ab.IgG	ELISA	GSK [2,3] or GSK designated lab
Molecular Biology [3,4]	NASMUC (Nasal swab)	Respiratory Syncytial Virus A RNA	qRT-PCR	GSK [2,3] or GSK designated lab
	NASMUC (Nasal swab)	Respiratory Syncytial Virus B RNA	qRT-PCR	GSK [2,3] or GSK designated lab

ELISA = enzyme-linked immunosorbent assay; NEUT = Neutralization; qRT-PCR = Quantitative Reverse Transcription PCR; RSV-A Nab = RSV-A neutralizing antibody; RSV-B Nab = RSV-B neutralizing antibody; RSVPreF3 Ab.IgG = RSV PreF3 antibody.immunoglobulin G; SOP = Standard operating procedure

[1] ~~Hematocrit testing will be performed as part of immunogenicity assessment~~

[1,2] Refer to the list of clinical laboratories for details.

[2,3] 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.

[3,4] RSV-A/B quantitative reverse transcription PCR will be performed on all specimens collected to evaluate RTI as specified in Section 8.4.4. To evaluate tertiary objectives, an Allplex Respiratory Viruses Panel or alternative may be performed for RSV-A/B-positive samples, and (if deemed necessary) for RSV-A/B-negative samples. 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 participant should be performed as per the standard of care.

Section 8.1.3, Immunological read-outs

Table 14 Immunological read-outs

Infant participants				
Visit 2-NB (Day 43) [2]	post-birth	RSV_MAT_BS1	84	RSV-A NAb RSV-B NAb
				RSV PreF3 Ab.IgG
		Control_BS1	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 3-NB (Day 121) [2]	post-birth	RSV_MAT_BS2	84	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
		Control_BS2	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
Visit 4-NB (Day 181) [2]	post-birth	RSV_MAT_BS3	84	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG
		Control_BS3	42	RSV-A NAb
				RSV-B NAb
				RSV PreF3 Ab.IgG

[…]

[2] Due to the change in the study requirements, there will no longer be collection of blood samples from infant participants at Visit 2-NB, Visit 3-NB and Visit 4-NB.

Table 15 Hematocrit Readout (deleted and subsequent tables have been renumbered accordingly)

~~Blood sampling timepoint~~		~~Study group~~	~~Approximate No. participants~~	~~Component~~
~~Type of contact and timepoint~~	~~Sampling timepoint~~			
~~Maternal participants~~				
~~Visit 1 (Day 1)~~	~~pre-study intervention~~	~~All study groups~~	~~378~~	~~Hematocrit~~
~~Visit 2 (Day 31)[1]~~	~~post-study intervention~~	~~All study groups~~	~~378~~	~~Hematocrit~~
~~Visit 3 (Delivery)~~	~~post-study intervention~~	~~All study groups~~	~~378~~	~~Hematocrit~~

~~[1] Blood sample at Visit 2 (Day 31) wil not be collected if the delivery occurs prior to Day 31 post-study intervention.~~

Table 15 Molecular biology tests

Nasal swab sampling timepoint		No. participants	Component [3]
Type of contact (timepoint)	Sampling timepoint		
Maternal MA-RTI [1, 4]	Event-driven	Event-driven	RSV-A RNA
			RSV-B RNA

[…]

[4] Due to the change in the study requirements, nasal swab samples will no longer be collected from any maternal participant for MA-RTI assessment.

Section 8.2.1.4.2, Monthly contacts

[…]

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

Section 8.2.3, Study holding rules and safety monitoring

An internal SRT and an external IDMC (external to GSK) will review available maternal and infant safety data on a regular basis throughout the study. Any potential safety concern identified will be escalated to the GSK ***Global Safety Board (GSB)*** ~~Vaccine Safety Monitoring Board (VSMB)~~.

Section 8.2.3.1, Safety evaluation by the Safety Review Team (SRT)

The SRT includes as core members the GSK' Central Safety physician, Safety scientist, Clinical Research & Development Lead (CRDL), Epidemiologist, Global Regulatory Lead and Biostatistician of the project. The SRT is responsible for ongoing safety monitoring of the entire study and will review on a regular, ongoing basis the safety data. ~~The review will be blinded until Day 43 post-delivery/birth visit and may also be unblinded for later timepoints until study end, if required.~~ Continuous monitoring throughout the study will allow for ad-hoc data review meetings if deemed necessary by the SRT.

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

Section 8.2.3.2, Independent data monitoring committee (IDMC) evaluation

[…]

The IDMC will conduct unblinded reviews of all available safety data on an ongoing basis. The unblinded analyses will 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. No unblinded data***** will be shared with the study team.

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

In addition, there will be at least 3 planned IDMC data review meetings. The first will take place after ~~a quarter of the maternal participants (~~~63 active vaccine recipients~~)~~ have completed the Day 43 post-delivery visit (Visit 4 for maternal participants; Visit 2-NB for their enrolled infants). The second planned IDMC meeting will occur after all participants have completed follow-up to the Day 43 post-delivery/birth visit (Visit 4 for maternal participants; Visit 2-NB for their enrolled infants). The third planned IDMC meeting will occur when all data up to study end (Visit 5-NB, 12 months post-birth) are available. For each review, the IDMC will be provided with unblinded safety data as described above. Ad-hoc data reviews or meetings may be organized, if deemed necessary by the IDMC.

Section 8.2.3.3, Study holding rules

[…]

The following communication sequence must be followed:

- […]
- The GSK ***GSB***~~VSMB~~ evaluates the case after receipt of the IDMC's recommendations / and takes the decision to stop or to re-start dose administration.

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

Table 17 Timeframes for collecting and reporting of safety information (including RTI information)

[…]											
MA-RTIs [6]		M (Day 1 to 180 days post-delivery)									

[…]

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

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

Table 18 Timeframes for submitting SAE, 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 and RSV-associated hospitalizations)	24 hours* ‡	electronic Adverse Events Form and the corresponding Expedited Adverse Event Form	24 hours*¥	electronic Adverse Events Form and the corresponding Expedited Adverse Event Form
Subsequent Pregnancies	2***4 hours*** ~~weeks~~*	electronic pregnancy report	2***4 hours*** ~~weeks~~*	electronic pregnancy report

Section 8.3.3.1, Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

Table 19 Contact information for reporting SAEs, AESIs, subsequent pregnancies and study holding rules

[…] 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*** ~~***R***ix.CT-safety-vac@gsk.com~~ US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718	

Section 8.4.1.1, Medically attended respiratory tract illnesses (MA-RTIs) in maternal participants

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

Section 8.4.2.1, Maternal participants

MA-RTI surveillance***** begins at Day 1 post-study intervention and ends 180 days after delivery (Contact 2). It will be accomplished via 2 types of contact.

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

Section 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.

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

Section 8.4.3.1, For a maternal MA-RTI

Conduct an assessment visit (Section 8.4.4), ideally within 72 hours after a medically attended visit due to RTI symptoms* occurs during the surveillance period. However, a visit may be conducted even beyond the 72 hours window if symptoms are ongoing.

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

Section 8.4.3.2, For an infant RTI

Figure 5 Decision Tree for site personnel - infant surveillance and assessment (footnote)

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 12.
[6]~~Parental concern in the context of an RTI~~

Section 8.4.4, Assessment visit procedures

[…]

Unless otherwise specified, assessment visit procedures will be the same for maternal participants with MA-RTIs* and for infant participants with RTIs.

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).

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

Section 8.4.4.1, Clinical evaluation

[…]

For maternal participants*:

- Temperature
- Respiratory rate
- Blood oxygen saturation measured by pulse oximetry (Section 8.2.1.4.1), in room air, if feasible
- Results of chest auscultation
- Signs of difficulty in breathing (wheezing and tachypnoea in maternal participants)

**** Due to the stop on RTI surveillance for maternal participants, these checks will no longer be performed.***

Section 8.4.4.2, Nasal swab collection

Refer to Table 10 (maternal participants)***** and Table 12 (infant participants). Additional details are provided in the Central Laboratory Manual.

**** Due to the change in the study requirements, nasal swab samples of the maternal participants will no longer be collected for RTI assessment.***

Section 8.4.4.3, 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 traveling, 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 change in the study requirements, RTI surveillance of the maternal participants will no longer be performed.

Section 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 10***** and Table 12**.**

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

Section 9.2, Sample size determination

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

Participants who withdraw from the study will not be replaced.

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

Section 9.3, Analysis sets

Table 22 Maternal Participants

Analysis set	Description
Enrolled	All maternal participants who completed the informed consent process***,*** ~~and~~ signed the informed consent form ***and was determined as eligible for study participation***.

Section 9.4.3.1, Safety

Maternal participants	[…]	[…]
	Number and percentage of maternal participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from Day 1 up to 42 days post-delivery.	The number and percentage of maternal participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-delivery with exact 95% CIs will be tabulated by group and by Medical MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal, and MAEs will be prepared ~~(but will not be shared with investigators and site staff until the final, unblinded analysis has been completed)~~.
	Number and percentage of maternal participants reporting pregnancy outcomes * from Day 1 up to 42 days post-delivery. *These include live birth with no congenital anomalies, live birth with minor congenital anomalies only; live birth with at least one major congenital anomaly, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with only minor congenital anomalies, fetal death/still birth (antepartum or intrapartum) with at least 1 major congenital anomaly; elective/therapeutic termination with no congenital anomalies;	The number and percentage of maternal participants reporting each pregnancy outcome from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of adverse pregnancy outcomes will be prepared ~~(but will not be shared with investigators and site staff until the final, unblinded analysis has been completed~~.

	elective/therapeutic termination with only minor congenital anomalies, and elective/therapeutic termination with at least 1 major congenital anomaly.	
	Number and percentage of maternal participants reporting pregnancy-related AESIs * and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery. * These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth) and chorioamnionitis.	The number and percentage of maternal participants reporting each pregnancy-related AESI and worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 42 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of pregnancy-related AESIs and worsening of pre-existing medical conditions and/or obstetric complications will be prepared ~~(but will not be shared with investigators and site staff until the final, unblinded analysis has been completed)~~.
Infant participants	Number and percentage of infant participants reporting neonatal / infant AESIs * from birth up to 42 days post-birth. * These include small for gestational age, low birth weight including very low and extremely low birth weight (<2500 g, <1500g, <1000g), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in an extremely preterm birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth) and preterm birth.	The number and percentage of infant participants reporting each neonatal / infant AESI from birth up to 42 days post-birth will be tabulated with its exact 95% CI by group. By participant listings of neonatal / infant AESIs will be prepared ~~but will not be shared with investigators and site staff until the final, unblinded analysis has been completed~~.

	Number and percentage of infant participants reporting SAE, (S)AEs leading to study withdrawal, and MAEs from birth up to 42 days post-birth.	The number and percentage of infant participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 42 days post-birth with exact 95% CIs will be tabulated by group and by MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared ~~(but will not be shared with investigators and site staff until the final, unblinded analysis has been completed)~~.
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 180 days post-birth.	***The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 180 days post-birth will be tabulated with 95% CI by group.*** ***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.***
	Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 365 days post-birth.	***The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 365 days post-birth will be tabulated with 95% CI by group.*** ***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.***

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

Section 9.4.4.1, Safety

	Secondary Safety Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting SAEs, (S)AEs leading to study withdrawal and MAEs from Day 1 up to 180 days post-delivery.	The number and percentage of maternal participants reporting: • at least one SAE • at least one (S)AE leading to study withdrawal • at least one MAE from Day 1 up to 180 days post-delivery with exact 95% CIs will be tabulated by group and by MedDRA preferred term. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared ~~but will not be shared with investigators and site staff until the final, unblinded, analysis has been completed~~.
	Number and percentage of maternal participants reporting worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery. […]	The number and percentage of maternal participants reporting each worsening of pre-existing medical conditions and/or obstetric complications from Day 1 up to 180 days post-delivery will be tabulated with its exact 95% CI by group. By participant listings of worsening of pre-existing medical conditions and/or obstetric complications will be prepared ~~but will not be shared with investigators and site staff until the final, unblinded analysis has been completed~~. […]

	Secondary Safety Endpoints	Statistical Analysis Methods
Infant participants	~~Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 180 days post-birth.~~	~~The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 180 days post-birth will be tabulated with 95% CI by group.~~ ~~By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared but will not be shared with investigators and site staff until the final, unblinded analysis has been completed.~~
	~~Number and percentage of infant participants reporting SAEs, (S)AEs leading to study withdrawal, and MAEs from birth up to 365 days post-birth.~~	~~The number and percentage of infant participants reporting at least one SAE, (S)AE leading to study withdrawal, and MAE from birth up to 365 days post-birth will be tabulated with 95% CI by group.~~ ~~By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared.~~

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

Section 9.5, Conduct of analyses

No analysis requiring statistical adjustment will be performed. ~~However, analyses to evaluate objectives and endpoints will be performed in steps. The sequence of analyses is described in Section 9.5.1.~~

Section 9.5, Sequence of analyses

~~Analyses to evaluate objectives and endpoints are descriptive and will be performed in steps:~~

- ~~The first analysis to evaluate maternal and infant safety data up to (and if available/ needed beyond) the Day 43 post-delivery/birth visit (Visit 4 maternal participants/ Visit 2-NB infant participants), maternal immunogenicity data up to (and including) the delivery (Visit 3), and immunogenicity data based on analyses of cord blood (Visit 3) or an infant blood sample collected within 72 hours after delivery (Visit 1-NB – if a cord blood sample could not be collected) will be performed when the respective visits are completed and the data are available. At this point, the central study team including the study statistician will be unblinded (i.e. will have access to the individual participant treatment assignments), but no individual listings will be provided to the investigators, site staff and participants until the end of study. An interim CSR will be written and made available to the investigators at that time.~~

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

Section 10.1.5, Committees structure

The ***GSB***~~VSMB~~ includes relevant members of the GSK study team and is responsible for ongoing safety monitoring of the entire project. The SRT will inform the ***GSB***~~VSMB~~ about any potential safety concern relevant to the study (Refer to Section 8.2.3).

Section 10.1.6, Dissemination of clinical study data

[…]

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

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

Section 10.2.1, Protocol-required safety laboratory assessments

[…]

Laboratory assessments (e.g., placenta pathology) may be performed on the placental tissue samples collected from maternal participants at delivery visit to support possible safety assessments, if necessary. Additional details are provided in the SPM.

Additional assessments on the placental sample can be performed depending on local standard of practice, site capability and the investigators' medical judgment.

Section 10.2.2, Descriptions of the assays to be performed in the study

Hematocrit assay

The hematocrit is the proportion of the volume occupied by the red blood cells compared to the whole volume of the blood cells. The hematocrit value is determined by drawing blood sample into a capillary tube then centrifuged, the lengths of the columns for the red blood cells and the whole blood cells are measured using a graphic reading device. Thereafter, the proportion of the red blood cells to that of the whole blood cells is determined and expressed as a decimal or percentage fraction.

Hematocrit will be tested at Visits 1, 2 and 3 for all participants until the current Protocol Amendment 1 is approved (unless IEC/IRB allows for immediate implementation of this measure to reduce participant's burden, prior to full Amendment 1 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

[…]

GSB:	***Global Safety Board***

[…]

~~VSMB:~~	~~Vaccine Safety Monitoring Board~~

Section 10.7.2, Glossary of terms

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

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