Statistical Analysis Plan Amendment 3

Study ID: 219510

Official Title of Study: A Phase 3b, non-randomized, open label, multi-country, cohort study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies (RSV MAT-001, RSV MAT-004, RSV MAT-010, RSV MAT-011, RSV MAT-009, RSV MAT-012 and RSV MAT-039) during any pregnancy conceived post vaccination/ control

NCT number: NCT05705440

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TITLE PAGE

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Study Number: 219510

Abbreviated Title: RSV MAT-015

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clinicaltrials.gov	NCT05705440
EudraCT	2022-003124-41

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	20 January 2023	Protocol Amendment 1 (17 January 2023)	Not Applicable	Original version
SAP Amendment 1	13 July 2023	Protocol Amendment 2 (21 June 2023)	Remove unnecessary analysis sets. CCI [redacted] Provide analysis plan for SRT safety monitoring.	Revised for Protocol Amendment 2 and Health Authority requests.
SAP Amendment 2	16 December 2024	Protocol Amendment 2 (21 June 2023)		Addition of subgroup analyses as per Health Authority request.
SAP Amendment 3	17 Feb 2025	Protocol Amendment 2 (21 June 2023)	Adjust methods section to distinguish between first and any pregnancy calculation methods Remove secondary endpoint: Incidence of selected pregnancy outcomes, pregnancy related AESIs and infant	To have the SAP aligned with the OPS

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			AESIs by risk status and by selected risk factors for or causes of those events/outcomes during **any** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.	

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 219510 (RSV MAT-015). Details of the planned analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Study objectives, estimands and endpoints

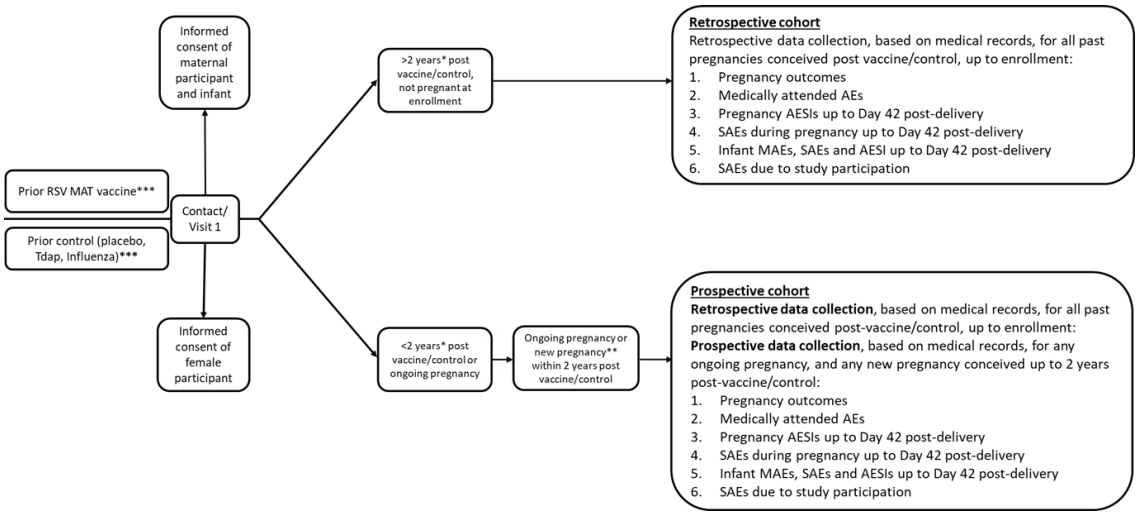
Objectives	Endpoints & Estimands
Primary	
To describe the incidence of pregnancy outcomes, pregnancy related adverse events of special interest (AESIs) and infant AESIs during the **first** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.	Incidence of pregnancy outcomes, pregnancy related AESIs and infant AESIs during the **first** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
Secondary	
To describe the incidence of pregnancy outcomes, pregnancy related adverse events of special interest (AESIs) and infant AESIs during **any** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.	Incidence of pregnancy outcomes, pregnancy related AESIs and infant AESIs during **any** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
To describe the incidence of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by risk status and by selected risk factors for or causes of those events/outcomes during pregnancies conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to day 42 post-delivery.	Incidence of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by risk status and by selected risk factors for or causes of those events/outcomes during the **first** pregnancy conceived within 2 years post-vaccination in participants enrolled in RSV MAT studies (by study arm, those previously received RSVPreF3 and control) up to Day 42 post-delivery.
Tertiary (Exploratory)	
CCI [redacted]	

1.2. Study Design

Overview of Study Design and Key Features

This study will be a combination of retrospective and prospective cohort design with two groups. RSVPreF3 vaccine group will include participants who received any RSVPreF3 vaccine in RSV MAT studies and control group will include participants who received only control (placebo, Tdap or influenza vaccine) during previous RSV MAT studies. Figure 1 and Figure 2 provide overviews of the study and prospective cohort study design, respectively.

Figure 1 Overall Study design overview



AESI: Adverse Events of Special Interest; **SAE**: Serious Adverse Event; **MAEs**: Medically attended Adverse Events

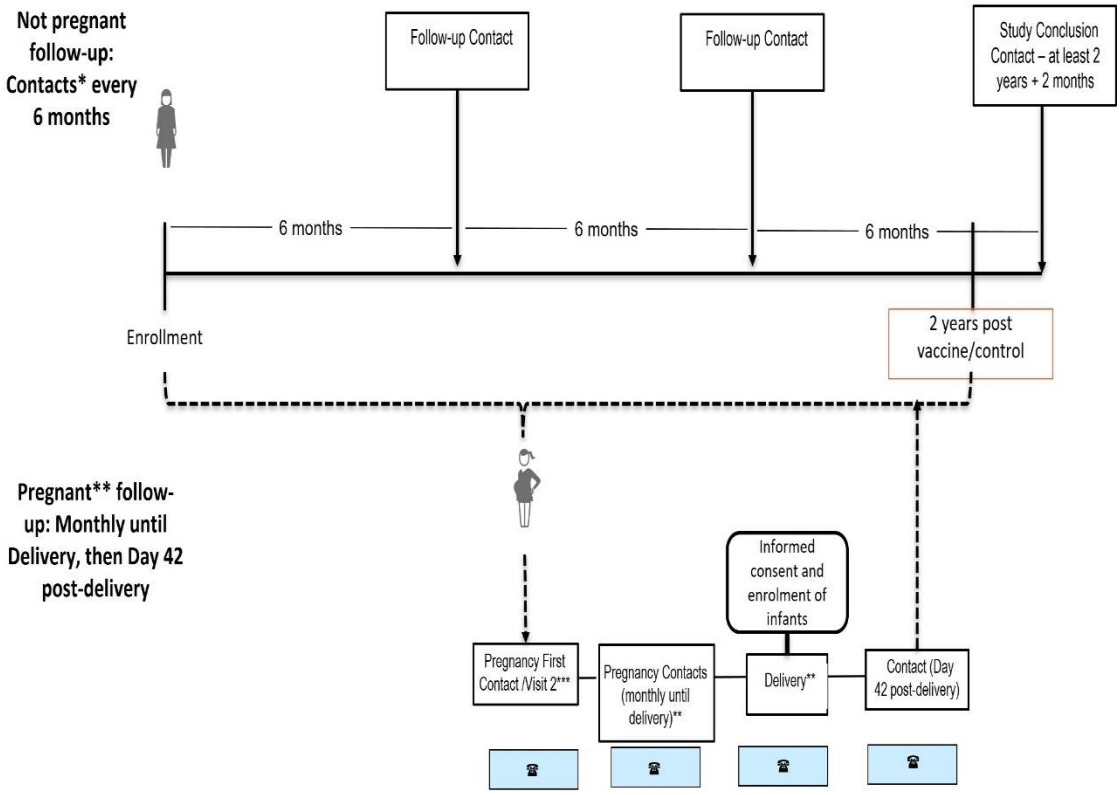
*2 years+2 months post vaccine/control to give time for the participant to be aware of a pregnancy if it is conceived very close to 2 years post-vaccination. The retrospective cohort will also include participants who have not reached 2 years+2 months post vaccine/control prior to/at enrollment but are a Woman of Nonchildbearing Potential (WONCBP) at study enrollment, or recipient of bilateral tubal ligation prior to study enrollment.

**For participants enrolled in prior studies of pregnant women (i.e., MAT-004, MAT-009, MAT-012), this study will include pregnancies conceived after the prior study pregnancy in which RSVPreF3 vaccination (or control) was administered.

*** For participants enrolled in prior RSV MAT studies i.e., RSV MAT-001, RSV MAT-004, RSV MAT-009, RSV MAT-010, RSV MAT-011, RSV MAT-012 and RSV MAT-039.

Overview of Study Design and Key Features

Figure 2 Study design overview- Prospective cohort



*Contacts every 6 months up to 2 years (+2 months) post-vaccine/control (received as part of prior RSV MAT study participation), unless a pregnancy conceived post-vaccine/control is reported.

** Once a pregnancy is reported, the participant is followed monthly during pregnancy until delivery, then again at Day 42 post-delivery. Pregnancy follow-up will include all pregnancies ongoing at enrolment or newly conceived during follow-up within 2 years post vaccine/control. If Day 42 post-delivery is <2 years+2 months, the woman returns to contacts every 6 months until 2 years (+2 months) post-vaccine/control.

***In addition to the planned study contacts, additional unplanned visits or medical procedures can be done as per the investigator's discretion.

Design Features	**Study Type:** A safety follow-up cohort study of interventional clinical trials. **Experimental design**: Phase IIIB, non-randomized, open label, multi-country, cohort study to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or controls from previous RSV MAT studies **Study Population**: All study participants from RSV MAT studies who have received either RSVPreF3 vaccine or control (placebo, Tdap only, influenza vaccine only) will be eligible to be included in this study. **Duration of the study:** The study period starts from the date of start of any pregnancy conceived after RSV MAT vaccination (RSVPreF3) or control vaccination in RSV MAT studies or from the date of current study enrollment, whichever date is earlier. The study period ends at current study enrollment for retrospective cohort participants. The study period ends at 2 years+2 months post vaccine/control for prospective cohort participants who are not pregnant at 2 years post vaccine/control. The study period ends at Day 42 post-delivery for prospective cohort participants who are pregnant at 2 years post vaccine/control or who are pregnant at enrollment.
Study intervention	Not applicable.
Study intervention Assignment	Not applicable.

Overview of Study Design and Key Features	
Concomitant Therapy	Not applicable.
Interim Analysis	Not applicable.
End-of-study definition	The participant has completed all periods of the study including the last contact (study conclusion).

2. STATISTICAL HYPOTHESES

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

2.1. Multiplicity Adjustment

No statistical multiplicity adjustment will be performed.

3. ANALYSIS SETS

Table 2 Maternal Participants

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All maternal subjects who completed the informed consent process and signed the informed consent form and were determined eligible for study participation. Note screening failures (who never passed screening even if rescreened) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Full Analysis Set (FAS)	All maternal subjects who had pregnancy defined by this study (defined in the Protocol Section 5.1).	Primary, Secondary and other analyses

Table 3 Infant Participants

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled Infant	Infants live-born to the maternal set, whose parents/LARs completed the informed consent process and signed the informed consent form.	Study Population
Full Analysis Set (FAS)	All infant subjects in the infant set who have post-delivery/birth data.	Primary, Secondary and other analyses

4. STATISTICAL ANALYSES

4.1. General Considerations

In general, all primary, secondary, and other analyses will be performed on the Full Analysis Set.

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

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

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

95% CI for relative risk will be based on Wald confidence interval [Woolf, 1955; Haldane, 1956].

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

4.1.2. Baseline Definition

Not applicable for this study.

4.2. Primary Endpoint(s) Analyses

	Primary Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs within the **first** pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs within the **first** pregnancy conceived within 2 years post-vaccine/control and up to Day 42 post-delivery will be tabulated with its exact 95% CI by study arms. By participant listings of pregnancy related outcomes and AESIs will be prepared
Infant participants	Number and percentage of infant participant reporting infant AESIs from the **first** pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The Number and percentage of infant participant reporting infant AESIs from the **first** study pregnancy conceived within 2 years post-vaccine/control and up to Day 42 post-delivery will be tabulated with its exact 95% CI by study arms. By participant listings of infant AESIs will be prepared.

4.2.1. Definition of primary endpoints

The first pregnancy during study period is defined as the first pregnancy conceived post-vaccination or control in participants enrolled in RSV MAT studies (those previously received RSVPreF3 or control) up to Day 42 post-delivery.

Pregnancy outcomes include (not limited to):

1. Live birth
2. Spontaneous abortion

3. Stillbirth
4. Elective/therapeutic termination
5. Live birth Congenital anomaly(ies)
6. Spontaneous abortion Congenital anomaly(ies)
7. Fetal death/still birth Congenital anomaly(ies)
8. Elective/therapeutic termination Congenital anomaly(ies)

Pregnancy-related AESIs	**Infant** AESIs
• Hypertensive disorders of pregnancy: – gestational hypertension, – pre-eclampsia, – pre-eclampsia with severe features including eclampsia; • Fetal growth restriction; • Pathways to preterm birth: – premature preterm rupture of membranes, – preterm labor, – insufficient cervix – provider-initiated preterm birth; • Gestational diabetes mellitus; and • Chorioamnionitis.	• Small for gestational age, • Low birth weight including very low and extremely low birth weight (<2500 g, <1500 g, <1000 g), • Congenital anomalies: – major external structural defects, – internal structural defects, – functional defects, • Neonatal death – in a non-viable live birth [<22 weeks gestation] – in an extremely pre-term birth [22.GA<28 weeks], – in a preterm live birth [28.GA<37 weeks], – in a term live birth, • Preterm birth

4.2.2. Main analytical approach

All primary analyses will be performed on the Full Analysis Set.

Main primary analyses in maternal participants will include summaries of pregnancy outcomes and pregnancy related AESIs overall and by study arms. Pathways to preterm birth will be further broken down as: extremely preterm births (GA at birth: < 28 weeks); very preterm births (GA at birth: 28 - < 32 weeks); moderate to late preterm births (32 - < 37 weeks).

Main primary analyses in infant participants will include summaries overall, by study arms and by gestational age at birth (≥ 37 weeks or < 37 weeks; overall) of infant AESIs.

Primary endpoints will be reported by study arms while stratified by CCI [redacted]

Pregnancy outcomes analytical approach:

The number and percentage of each pregnancy outcome is calculated among the maternal Full Analysis Set (for participants with medical records available), per pregnancy regardless of the number of fetuses in the concerned pregnancy.

The pregnancy related adverse events of special interest (AESIs) analytical approach:

The number and percentage of each pregnancy related adverse event of special interest is calculated based on the number of pregnancies reporting the symptom at least once. In addition, we will report the occurrence of pregnancy related adverse events of special interest. Only pregnancies based on medical record collection will be considered.

For infant participants, the infant participant reporting AESIs analytical approach:

The number and percentage of each neonatal adverse event of special interest is calculated based on the number of infants reporting the symptom at least once. In addition, we will report the occurrence of neonatal adverse events of special interest. Infants' data based on medical records only, will be considered.

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4.2.4. Additional estimands

Not applicable.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Pregnancy outcomes and AESIs from any study pregnancy

	Secondary Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs during **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The number and percentage of maternal participants reporting pregnancy outcomes and pregnancy related AESIs during **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI by study arms. By participant listings of pregnancy related outcomes and AESIs will be prepared
Infant participants	Number and percentage of infant participant reporting neonatal AESIs from **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The Number and percentage of infant participant reporting neonatal AESIs from **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI by study arms. By participant listings of neonatal AESIs will be prepared.

4.3.1.1. Definition of endpoints

The any study pregnancy is defined to include any pregnancy conceived within 2 years after vaccination/control.

Specifically for the preterm birth outcomes, analyses will also be conducted with all reported pregnancy data (conceived at any time after vaccination/control, and reported in this study).

Refer to Section 4.2.1 for definition of endpoints.

4.3.1.2. Main analytical approach

Refer to Section 4.2.2. All secondary analyses will be performed on the Full Analysis Set.

Main secondary analyses in maternal participants will include summaries of pregnancy outcomes and pregnancy related AESIs overall and by study arms. Pathways to preterm birth will be further broken down as: extremely preterm births (GA at birth: < 28 weeks); very preterm births (GA at birth: 28 - < 32 weeks); moderate to late preterm births (32 - < 37 weeks).

Main secondary analyses in infant participants will include summaries overall, by study arms and by gestational age at birth (≥ 37 weeks or < 37 weeks; overall) of infant AESIs.

Secondary endpoints will be reported by study arms while stratified by CCI [redacted]

Pregnancy outcomes analytical approach:

The number and percentage of each pregnancy outcome is calculated among all pregnancies (for pregnancies with medical records available), per event regardless of the number of fetuses in the concerned pregnancy.

The pregnancy related adverse events of special interest (AESIs) analytical approach:

The number and percentage of each pregnancy related adverse event of special interest is calculated based on the number of pregnancies reporting the symptom at least once. In addition, we will report the occurrence of pregnancy related adverse events of special interest. Only pregnancies based on medical record collection will be considered.

For infant participants, the infant participant reporting AESIs analytical approach:

The number and percentage of each neonatal adverse event of special interest is calculated based on the number of infants reporting the symptom at least once. In addition, we will report the occurrence of neonatal adverse events of special interest. Infants' data based on medical records only, will be considered.

4.3.1.4. Additional estimands

Refer to Section 4.2.4.

4.3.2. Selected pregnancy outcomes and AESIs by selected risk factors

	Secondary Endpoints	Statistical Analysis Methods
Maternal participants	Number and percentage of **selected** pregnancy outcomes and pregnancy related AESIs by risk status and by selected risk factors for or causes of those events/outcomes during **first** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The number and percentage of selected pregnancy outcomes and pregnancy related AESIs by study arms, stratified by risk status and by selected risk factors for or causes of those events/outcomes during **first** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI. By participant listings of pregnancy related outcomes and AESIs will be prepared
	Number and percentage of **selected** pregnancy outcomes and pregnancy related AESIs by risk status and by selected risk factors for or causes of those events/outcomes during **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The number and percentage of selected pregnancy outcomes and pregnancy related AESIs by study arms, stratified by risk status and by selected risk factors for or causes of those events/outcomes during **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI. By participant listings of pregnancy related
Infant participants	Number and percentage of **selected** neonatal AESIs by risk status and by selected risk factors for or causes of those events/outcomes from **first** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The Number and percentage of selected neonatal AESIs by study arms, stratified by risk status and by selected risk factors for or causes of those events/outcomes from **first** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI. By participant listings of neonatal AESIs will be prepared.
	Number and percentage of **selected** neonatal AESIs by risk status and by selected risk factors for or causes of those events/outcomes from **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery.	The Number and percentage of selected neonatal AESIs by study arms, stratified by risk status and by selected risk factors for or causes of those events/outcomes from **any** study pregnancy conceived within 2 years post-vaccination and up to Day 42 post-delivery will be tabulated with its exact 95% CI. By participant listings of neonatal AESIs will be prepared.

4.3.2.1. Definition of endpoints

Refer to Section 4.2.1 and 4.3.1.1 for definition of endpoints.

4.3.2.2. Main analytical approach

Refer to Section 4.2.2 and 4.3.1.2 for analytical approach.

The number and percentage of selected pregnancy outcomes, pregnancy related AESIs and infant AESIs by study arms, stratified by selected risk factors, will be tabulated with exact 95% CIs for both first and any study pregnancy during study period. Their relative risk estimates with 95% CIs and observed p-values will be reported for all comparisons accordingly. We will finalize the selected pregnancy outcomes, pregnancy related AESIs and infant AESIs prior to running the final analysis and will document the final list decided prior to final analysis.

Regarding preterm birth outcome, the comparisons will be conducted by study arms and by the combination of study arms and preterm birth history (Yes/No) in prior MAT study. The potential risk factors to be explored may include maternal smoking/household smoke exposure, maternal substance abuse, infections during pregnancy, COVID infection during pregnancy (yes/no), history of abortion, prior preterm delivery (any), multiple gestation pregnancy, and short inter-pregnancy interval (less than 18 months between pregnancies), pregnancy complications such as preeclampsia and fetal distress, Parity, maternal age, maternal race, maternal ethnicity, pre pregnancy BMI or obesity, country of residence or CCI [redacted] prior concomitant medications/vaccination in the parent studies, concomitant medications/vaccination. We will finalize the list of risk factors prior to running the final analysis and will document the final list decided prior to final analysis.

4.3.2.3. Sensitivity analyses

Refer to Section 4.2.3.

4.3.2.4. Additional estimands

Refer to Section 4.2.4.

4.4. Exploratory Endpoints Analyses

CCI

[redacted]

4.5. Other Safety Analyses

Besides those pregnancy outcomes and AESIs defined in the primary endpoints in Section 4.2.1, the other safety data which will be recorded and reported include medically attended AEs, SAEs, SAEs due to study participation, and SAEs related to a GSK product.

The safety analyses will be based on the Maternal Full Analysis Set and Infant Full Analysis Set, with medical records data collection, unless otherwise specified.

Concomitant medications will be coded using the GSKDRUG dictionary. The number and percentage of maternal participants taking concomitant medications up to Day 42 post-delivery will be summarized. A listing will also be provided.

The number and percentage of infants taking concomitant medications/vaccinations from birth up to Day 42 post-delivery will be summarized by group. A listing will also be provided.

Listings and a subset of analysis outputs will be provided to SRT for safety monitoring. The planned outputs are shown in Section 6.3. Other outputs will be provided if deemed necessary.

4.5.1. Adverse Events

Safety analyses in maternal participants will include summaries by study arms of MAEs, SAEs, SAEs due to study participation, and SAEs related to a GSK product.

Safety analyses in infant participants will include summaries by study arms and gestational age at birth (≥ 37 weeks; <37 weeks; overall) of MAEs, SAEs and SAEs due to study participation.

For MAEs until Day 42 post-delivery (Mothers: conception to Day 42 post-delivery; Infants: birth to Day 42), the number and percentage of maternal or infant participants with each MAE with exact 95% CIs will be tabulated by study arms and displayed by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. By-participant listings will be prepared.

For SAEs and SAEs due to study participation, the number and percentage of participants with each SAE with exact 95% CIs will be tabulated by study arms and by MedDRA preferred term. By-participant listings will be prepared.

The number and percentage of maternal (or infant) participants and maternal pregnancies (based on pregnancies instead of subject) reporting

- at least one MAE
- at least one SAE
- at least one SAEs due to study participation

from study pregnancy conceived up to Day 42 post-delivery (or from delivery up to Day 42 post-delivery for infant participants) with exact 95% CIs will be tabulated by study arms.

A summary of number and percentage of participants with any recorded adverse events by maximum severity will be produced.

A separate summary will be provided for study intervention (administrated from previous RSV MAT studies) related MAEs and SAEs, respectively. A study intervention-related MAE (or SAE) is defined as a MAE (or SAE) for which the investigator classifies the possible relationship to study intervention from previous RSV MAT studies as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing.

Summaries of life-threatening and fatal SAEs by PT will also be created.

By participant listings of MAEs, SAEs and SAEs due to study participation will be prepared.

4.5.1.1. COVID-19 Assessment and COVID-19 AEs

Maternal and infant COVID-19 cases identified during the study (as per standard of care) will be captured from patient self-report. Additionally, COVID-19 cases documented in medical records will be reported as medically-attended AE or SAE according to standard criteria, as outlined in the protocol Section 10.2.

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

Numbers and percentage of participants with a suspected, probable or confirmed COVID-19 infection will be summarized by study arms.

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

Number and percentage of participants who had COVID-19 test positive will be summarized by severity and study arms. The severity definition is adapted from the CDC of US [CDC, 2022].

- Asymptomatic: test positive for COVID but have no symptoms
- Mild: have COVID symptoms, but not moderate or severe (as defined below)
- Moderate: experienced shortness of breath or had difficulty breathing
- Severe: were hospitalized

4.6. Other Analyses

4.6.1. Risk factor analyses for selected outcome

If deemed necessary, logistic regression will be used for assessing association between selected risk factor(s) and selected pregnancy outcomes or AESIs (probability of event occurrence), statistically adjusting for potential confounding effects of other covariates.

CCI

4.6.2. Subgroup analyses

Subgroup analyses of preterm birth, neonatal death and other selected primary or secondary endpoints will be made to assess consistency of observed risk rate across different subgroups.

For the endpoints of preterm birth, it may be further broken down as: extremely preterm births (GA at birth: < 28 weeks); very preterm births (GA at birth: 28 - < 32 weeks); moderate to late preterm births (32 - < 37 weeks), if deemed necessary and data allow.

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

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4.6.2.1. Based on demographics, baseline and lifestyle characteristics

The following subgroups are planned to be examined:

- Age group at previous vaccination: 18-<35 years; >=35 years
- Age group at the time of deliver: 18-<35 years; >=35 years
- Pre-pregnancy BMI group: <30, >=30
- infant Sex: female vs male
- Prior preterm delivery
- Multiple gestation pregnancy
- RSV MAT-009 participants with preterm birth

- Retrospective or prospective cohort
- Gravidity
- CCI [redacted]
- [redacted]

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined. Other selected demographics and lifestyle characteristics may also be included.

4.6.2.2. Based on prior parent studies

Subgroup analysis based on previous RSV MAT studies and other clinical studies participation will be performed.

Subgroup analysis for MAT-009 participants will specifically analyse separately among those with prior RSV MAT-009 participation, and among that subgroup by mothers who previously experienced: an infant with preterm birth in the prior study, infant with neonatal death in the prior study, and selected severe pregnancy outcome and AESIs.

4.6.2.3. Based on study cohorts

We plan to examine the primary and secondary endpoints by prior treatment arms while stratified by retrospective and prospective cohorts. If there is evident discrepancy for a primary/secondary endpoint between cohorts within a study arm, that endpoint will be further assessed regarding subject characteristics, medical history, concomitant medication and other risk factors. And a second analysis of primary and secondary objectives will be performed by stratifications of both prior treatment arms and cohorts.

4.7. Interim Analyses

Not applicable.

4.8. Changes to Protocol Defined Analyses

CCI [redacted], this is an addition to the originally planned statistical analysis specified in the Protocol Amendment 2 (Dated: 21-JUN-2023).

5. SAMPLE SIZE DETERMINATION

All analyses will be descriptive and thus no hypothesis driven sample size calculation was conducted.

All study participants (approximately 8240) from prior RSV MAT studies will be considered for enrolment in this study based on the eligibility criteria. Assuming the study will start on December 7th, 2022, the study potential subjects include: (1) those who had deliveries defined in the Protocol Section 5.1.1 (to be enrolled to Retrospective cohort); (2) those with ongoing pregnancy, or who at enrolment have not conceived but subsequently conceive within two years since the vaccination/control in previous RSV MAT studies (to be enrolled to Prospective cohort). The actual sample size will mainly depend on: (1) the enrolment rate of those subjects who participated in the previous RSV MAT studies; (2) the incidence rate of pregnancy conceived post RSVPreF3 (or control) vaccination during study period.

To estimate the incidence rate of first pregnancy conceived post RSVPreF3 (or control) vaccination, we considered the likelihood of pregnancy among participants in prior studies of non-pregnant women and pregnant women separately (approximately 8240 total). Among non-pregnant women (approximately 2540), we estimate approximately 10% will have a pregnancy during the time period of this study [Curtin, 2013]. Assuming 60% enroll in this study, we estimate approximately 150 non-pregnant women in prior studies who enroll in this study will have a pregnancy. Among pregnant women (approximately 5700), we estimated approximately 50% would have another pregnancy. From data on inter-pregnancy intervals in US women, we estimated approximately 30% of those subsequent pregnancies will occur during the time period of this study [Thoma, 2016]. Assuming 60% enroll in this study, we estimate approximately 500 non-pregnant women in prior studies who enroll in this study will have a pregnancy. In total, we estimate approximately 650 enrolled study participants will have at least one pregnancy of interest for this study and contribute to the total number of pregnancies from which incidence rates for events will be calculated.

The lowest rate of the safety signal observed in a MAT-009 study group was approximately 5%. A sample size of 300 pregnancy participants will provide 100% probability to detect at least one event (e.g., preterm birth event), providing the true rate is 5%. Assuming only 100 of 300 pregnancy participants are from the previous RSVPreF3 group, it can provide 99.4% probability to detect at least one event on the condition of the true event rate at 5%. For a sample size of 300 pregnancy participants, it will still provide a probability of 78%, 95% or 99% to observe at least one participant with event of interest, even if the true event rate is as low as 0.5%, 1% or 1.5%, respectively. A sample size of 650 pregnancy participants will provide a probability of 96% or 100% to observe at least one participant with event of interest, even if the true event rate is as low as 0.5% or 1%, respectively. The Table 4 presents more scenarios of sample size consideration regarding event rates.

Table 4 Sample size, event rate and probability

Sample size	Event Rate	Probability to observe at least one event
300	0.5%	78%
	1%	95%
	1.5%	99%
	3%	100%
	5%	100%
	7%	100%
500	0.5%	92%
	1%	99%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%
650	0.5%	96%
	1%	100%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%
1000	0.5%	99%
	1%	100%
	1.5%	100%
	3%	100%
	5%	100%
	7%	100%

In consideration of the precision of 95% Clopper-Pearson confidence interval (CI) for the event rate, if observed 5% participants experienced a pregnancy outcome AESI among 300 participants, the two-sided 95% CI would be within (2.8%, 8.1%). And among 650 participants, the two-sided 95% CI would be within (3.5%, 7%). The Table 5 presents the precision one can get in more scenarios. Even approximately 300 participants with pregnancy information are included in the study would still provide reasonable precision to detect and estimate most of the events of interest in the study.

Table 5 95% CI on the percentage of participants with event(s) of interest

Sample size	Number of Event(s)	% of Event	95% CI	
			Lower Limit	Upper Limit
300	1	0.33	0.0	1.8
	3	1	0.2	2.9
	5	1.67	0.5	3.8
	9	3	1.4	5.6
	15	5	2.8	8.1
	21	7	4.4	10.5
	30	10	6.8	14.0
500	1	0.2	0.0	1.1
	5	1	0.3	2.3
	10	2	1.0	3.6
	15	3	1.7	4.9
	25	5	3.3	7.3
	35	7	4.9	9.6
	50	10	7.5	13.0
650	1	0.15	0.0	0.9
	7	1	0.4	2.1
	10	1.5	0.7	2.8
	20	3	1.8	4.6
	33	5	3.5	7.0
	46	7	5.2	9.2
	65	10	7.8	12.6
1000	5	0.5	0.2	1.2
	10	1	0.5	1.8
	15	1.5	0.8	2.5
	30	3	2.0	4.3
	50	5	3.7	6.5
	70	7	5.5	8.8
	100	10	8.2	12.0

Note: Precision estimation using PASS2019 19.0.1 (Clopper-Pearson Confidence Intervals for One Proportion).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Participant Disposition

Participant disposition will be summarized by study arms using descriptive statistics:

- Number of maternal participants screened, enrolled, conceived, completed the study as well as those who prematurely withdrew including withdrawal reasons in each arm and overall will be tabulated.
- Number of infant participants enrolled and withdrawn including withdrawal reasons will be tabulated by arm and overall.

6.1.2. Demographic and Baseline Characteristics

These analyses will be performed on the Enrolled set and on the Full Analysis Set.

For all maternal participants, demographic characteristics (e.g., age at previous study vaccine administration <18, 18-24, 25-34 and >=35 years; overall), age at 1st and 2nd pregnancy, gestational age at birth (≥ 37 weeks or < 37 weeks), other baseline and lifestyle characteristics will be summarized by arm using descriptive statistics. The interval in days between previous RSV MAT study delivery and current study pregnancy will be calculated and summarized by arm using descriptive statistics.

For infants, demographic characteristics (e.g., gestational age at time of delivery (≥ 37 weeks; <37 weeks), sex, weight, length, head circumference, race and ethnicity), 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 arm using descriptive statistics.

Past medical conditions and current medical conditions as of screening will be summarized respectively.

Demographics and baseline characteristics as well as the lifestyle characteristics may be reported by CCI [redacted]

6.1.3. Protocol Deviations

Important protocol deviations will be summarized by arm.

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

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

Protocol deviations which result in exclusion from the analysis set will also be summarized by arm.

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

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

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

6.1.4. Prior and Concomitant Medications

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

- The number and percentage of maternal participants taking concomitant medications /vaccinations from pregnancy until Day 42 post-delivery will be summarized by arm. A listing will also be provided.
- The number and percentage of infants taking concomitant medications/ vaccinations from birth up to 42 days after birth will be summarized by arm. A listing will also be provided.

6.1.5. Study Intervention Compliance

Not applicable.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

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

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

The study period starts from the date of start of any pregnancy conceived after RSV MAT vaccination (RSVPreF3) or control vaccination in RSV MAT studies or from the date of current study enrollment, whichever date is earlier. The study period ends at current study enrollment for retrospective cohort participants. The study period ends at 2 years+2 months post vaccine/control for prospective cohort participants who are not pregnant at 2 years post vaccine/control. The study period ends at Day 42 post-delivery for prospective cohort participants who are pregnant at 2 years post vaccine/control or at study enrollment.

6.2.2. Study Day and Reference Dates

The safety reference date is the conceived date of the study pregnancy and will be used to calculate study day for safety measures.

The study day is calculated as below:

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

6.2.3. Handling of Partial Dates

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

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

The following exceptions apply.

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>
• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
</td></tr>
<tr><td>Adverse Events</td><td>
• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. the conceived date of the study pregnancy), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
– Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.2.4. Data derivation

6.2.4.1. Age in days

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

Age = date of event minus date of birth

6.2.4.2. Age in months

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

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

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

6.2.4.3. Age in years

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

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

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

As day of birth is not collected for maternal participants, the day for DOB will be imputed as noted above, then age in years will be calculated.

6.2.4.4. Weight

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

Weight in kilograms = Weight in pounds / 2.2

6.2.4.5. Height

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

Height in centimeters = Height in inches x 2.54

6.2.4.6. Body mass index (BMI)

BMI will be calculated as follows:

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

6.2.4.7. Temperature

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

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

6.2.4.8. Onset day

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

6.2.4.9. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 03MAR2022 and ends on 12MAR2022 has a duration of 10 days.

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

6.2.4.10. Counting rules for combining solicited and unsolicited adverse events

All SAEs will be considered systemic events.

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

6.2.4.11. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

6.2.5. Display of decimals

6.2.5.1. Percentages

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

6.2.5.2. Differences in percentages

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

6.2.5.3. Relative risks

Two decimals will be displayed for all relative risk and their confidence intervals.

6.2.5.4. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, BMI) will be presented with one decimal.

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

The minimum and maximum of transformed height variables will be displayed with no decimals.

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

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

6.3. Appendix 3 TFL for SRT safety monitoring

The Table Figure Listing (TFL) is planned for SRT safety monitoring. Other TFL may be provided if deemed necessary.

6.3.1. Listings

The planned listings include:

Demography and lifestyle characteristics – Maternal participants

Demography and lifestyle characteristics – Infant participants

General medical/vaccination history – Maternal participants

Vaccination administration from parent study

Listings of all AEs – Maternal participants

Listings of all AEs – Infant participants

Listings of medically attended AEs – Maternal participants

Listings of medically attended AEs – Infant participants

Listings of SAEs – Maternal participants

Listings of SAEs due to study participation – Maternal participants

Listings of SAEs – Infant participants

Listings of SAEs due to study participation – Infant participants

Listing of fatal AEs - Maternal participants

Listings of pregnancy outcomes

Listing of pregnancy related AEs of special interests during study pregnancy and up to 42 days post-delivery

Listing of neonatal AEs of special interest from birth up to 42 days post birth

6.3.2. Summary Table and Listing

Table #	Table Title
Table 1	Summary of demography and baseline characteristics - Maternal participants
Table 2	Summary of demography and baseline characteristics - Infant participants
Table 3	Number and percentage of infants with birth weight below the 3rd and 10th percentile, as per the IG-21 standards - Infant participants
Listing 4	Listing of infants with birth weight below the 3rd and 10th percentile, as per the IG-21 standards - Infant participants
Table 5	Number and percentage of infants with birth weight below the 3rd and 10th percentile, as per the IG-21 standards - Pre-term subgroup < 37 weeks - Infant participants
Listing 6	Listing of infants with birth weight below the 3rd and 10th percentile, as per the IG-21 standards - Pre-term subgroup < 37 weeks - Infant participants

Table #	Table Title
Table 7	Number and percentage of infants with birth head circumference below the 3rd and 10th percentile, as per the IG-21 standards - Infant participants
Listing 8	Listing of infants with birth head circumference below the 3rd and 10th percentile, as per the IG-21 standards - Infant participants
Table 9	Number and percentage of infants with birth head circumference below the 3rd and 10th percentile - Pre-term subgroup < 37 weeks, as per the IG-21 standards - Infant participants
Listing 10	Listing of infants with birth head circumference below the 3rd and 10th percentile, as per the IG-21 standards - Pre-term subgroup < 37 weeks - Infant participants
Table 11	Summary of study completion with reasons for withdrawal - Maternal participants
Table 12	Summary of study completion with reasons for withdrawal - Infant participants
Table 13	Summary of medically attended adverse events - Maternal subjects
Table 14	Summary of SAE - Maternal subjects
Table 15	Summary of AESI - Maternal subjects
Table 16	Summary of medically attended adverse events - Infant subjects
Table 17	Summary of non-medically attended adverse events - Infant subjects
Table 18	Summary of SAE - Infant subjects
Table 19	Summary of AESI - Infant subjects
Table 20	Summary of participants with at least one grade 3 adverse event - Maternal participants
Table 21	Summary of participants with at least one grade 3 adverse event - Maternal pregnancies
Table 22	Summary of participants with at least one grade 3 related adverse event - Maternal participants
Table 23	Summary of participants with at least one grade 3 related adverse event - Maternal pregnancies

Table #	Table Title
Table 24	Summary of participants with at least one serious adverse event during study pregnancy and up to 42 days post-delivery - Maternal participants
Table 25	Summary of participants with at least one serious adverse event during study pregnancy and up to 42 days post-delivery - Maternal pregnancies
Table 26	Summary of participants with at least one serious adverse event from birth up to 42 days post birth - Infant participants
Table 27	Summary of participants with at least one medically attended adverse event during study pregnancy and up to 42 days post-delivery - Maternal participants
Table 28	Summary of participants with at least one medically attended adverse event during study pregnancy and up to 42 days post-delivery - Maternal pregnancies
Table 29	Summary of participants with at least one medically attended adverse event from birth up to 42 days post birth – Infant participants
Table 30	Pregnancy outcomes during study pregnancy and up to 42 days post-delivery - Maternal participants
Table 31	Selected pregnancy outcomes during study pregnancy and up to 42 days post-delivery - Maternal participants from MAT-009
Table 32	Pregnancy outcomes during study pregnancy and up to 42 days post-delivery by age group - Maternal participants
Table 33	Number and percentage of pregnancy related AEs of special interests during study pregnancy and up to 42 days post-delivery - Maternal participants
Table 34	Number and percentage of participants reporting the occurrence of neonatal AEs of special interest from birth up to 42 days post birth – infant participants
Table 35	Number and percentage of participants reporting the occurrence of neonatal AEs of special interest from birth up to 42 days post birth by gestational age at birth – infant participants
Table 36	Summary of medical history - Maternal participants

7. REFERENCES

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