**Protocol**

**217354**

# A Phase III, randomized, open-label, active vaccine-controlled crossover study to evaluate the reactogenicity, safety and immune response of unadjuvanted RSV maternal vaccine in healthy non-pregnant girls from 9 to 17 years of age, and in non-pregnant adult women from 18 to 49 years of age.

**EudraCT number:** 2021-004003-41

**Date of Document:** 17 MARCH 2022

**Clinical Study Protocol**
Sponsor:
**GlaxoSmithKline Biologicals SA (GSK)**

| | |
|---|---|
| **Primary study intervention(s) and number(s)** | GlaxoSmithKline (GSK) Biological Respiratory Syncytial Virus (RSV) RSVPreF3 candidate vaccine (GSK3888550A) |
| **Other study intervention(s)** | GSK Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine (*Boostrix* [US formulation SB776423])<br>GSK Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (dTpa) vaccine (*Boostrix* [ex-US formulation SB263855]) |
| **eTrack study number and abbreviated title** | 217354 (RSV MAT-039) |
| **EudraCT number** | 2021-004003-41 |
| **Date of protocol** | Final: 11 August 2021 |
| **Date of protocol amendment** | Amendment 1 Final: 17 March 2022 |
| **Title** | A Phase III, randomized, open-label, active vaccine-controlled crossover study to evaluate the reactogenicity, safety and immune response of unadjuvanted RSV maternal vaccine in healthy non-pregnant girls from 9 to 17 years of age, and in non-pregnant adult women from 18 to 49 years of age. |
| **Brief title** | A study to evaluate the safety and immune response to an unadjuvanted RSV maternal vaccine in healthy non-pregnant females from 9 to 49 years of age. |

***Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2***

# Protocol Amendment 1 Sponsor Signatory Approval

| | |
|---|---|
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| **Sponsor signatory** | Joon Hyung Kim, Clinical Epidemiology Project Lead, RSV maternal, Clinical R&D |
| **Signature** | _____ |
| **Date** | _____ |

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

# Protocol Amendment 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 (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- 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 study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-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 study.
- 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** | 217354 (RSV MAT-039) |
| **EudraCT number** | 2021-004003-41 |
| **Date of protocol** | Final: 11 August 2021 |
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| **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 Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: refer to 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 Section 6.3.5.1.

# PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES TABLE

**Amendment 1** (17 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 or the scientific value of the study.**

**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 study in pregnant women, 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, GSK has nevertheless decided to stop enrolment and vaccination for all actively enrolling RSV MAT studies.
- There will be no new participants included in this study. However, safety monitoring of all 8 study participants (of the planned 252 study participants) enrolled and vaccinated in RSV MAT-039 study in a study site in the US will continue during the rest of the study period.
- The vaccination planned at visit 2 is removed. Therefore, Contact 2 at Day 38 and Visit 3 at Day 61 are not applicable anymore. Visit 4a (Day 181) and Visit 4b (Day 211) are replaced by a telephone contact at Day 181.
- A blood sample for immunogenicity assessment in the study participants who received first dose of RSV Maternal vaccine will continue to be collected at Visit 2 only. No other blood samples will be collected.
- All planned objectives will be analysed and reported in a descriptive manner for the 8 enrolled participants.

## List of main changes in the protocol and their rationale:

| Section # and title | Description of change | Brief rationale |
|---|---|---|
| 1.2 Schema | Changes in the schema were done to align with the updated study design | Update to reflect the changes based on GSK's decision to stop vaccination and recruitment in all RSV maternal studies. |
| 1.3 Schedule of activities<br>2.3 Benefit risk assessment | Aligned with the updated study design | |
| 3 Study objectives and endpoints | All safety objectives are now considered as primary and all immunogenicity objectives are considered as secondary | |
| 4 Study design<br>5 Study population<br>6 Study intervention and concomitant therapy | The contents of these sections may not be applicable as there are no more study activities planned, | |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis (Amended 17 March 2022)

**Rationale:**

GSK is developing an investigational respiratory syncytial virus (RSV) maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization. This study is a Phase 3 study to evaluate safety, reactogenicity, and immunogenicity of RSV maternal vaccine in non-pregnant girls 9 to17 years of age (YOA) (pediatric study group*) ***and in*** non-pregnant adult women 18 to 49 YOA (adult study group).

* For purpose of this study we will classify all females between 9-17 YOA as "girls" with the understanding that this age range includes children (9-11 year of age) and adolescents: (12 to 18 [further dependent on the region]). [ICH E11, 2017]

Objectives and endpoints/estimands of the RSV MAT-039 study are presented in Table 3**.**

## 1.2. Schema (Amended 17 March 2022)

This is a phase 3 study to evaluate safety, reactogenicity, and humoral immunogenicity of RSV maternal vaccine in healthy non-pregnant girls 9-17 YOA (pediatric study group) and in non-pregnant adult women 18-49 YOA (adult study group).

A total of 252 participants will be enrolled in the study (126 in each age group). Each group will be further sub-divided into two groups (63 each), of which one will receive RSV maternal vaccine followed by dTpa *(Boostrix)* vaccine 30 days later and the other subgroup will receive dTpa vaccine followed by RSV maternal vaccine 30 days later. The randomization will ensure the following:

- Approximately 63, 9-17 YOA participants in the RSV_dTpa-P group
- Approximately 63, 9-17 YOA participants in the dTpa_RSV-P group
- Approximately 63, 18-49 YOA participants in the RSV_dTpa-A group
- Approximately 63, 18-49 YOA participants in the dTpa_RSV-A group

Blood samples for humoral immunogenicity will be collected from all participants prior to RSV maternal vaccine administration, Day 31 post RSV maternal vaccine administration, and Day 181 post RSV maternal vaccine administration. (See Section 4.1 for details).

***Based on all safety information available from RSV MAT-009 study (following administration of RSV MAT vaccine), there will be no further enrollment and vaccination of participants in this study.***

***There will be no more blood samples collected as part of this study, except the study participants who has received RSV maternal vaccine at Visit 1. A blood sample will be collected and a urine pregnancy test will continue to be performed for them at Visit 2.***

***Participants who are enrolled and are due to receive dTpa during their Visit 2 will no longer receive the dTpa as part of this study. However, as per the local standard of care and or immunization recommendation and after consultation with their attending physician; the participant can always receive any commercially available dTpa vaccine. GSK will bear the cost of the vaccine.***

All participants who receive the ***first dose of*** study interventions (RSV maternal vaccine or dTpa) will be followed for safety and reactogenicity and evaluated for both solicited administration site (local) and systemic events within 7 days of vaccination, unsolicited AEs within 30 days of vaccination, SAEs and pregnancy outcomes throughout the study period (180 days after ***first dose of study interventions***).

All safety data will be reviewed by a Safety Review Team (SRT) and an independent data monitoring committee (IDMC). (See Section 8.2.3 for more details)

## 1.3. Schedule of Activities (SoA) (Amended 17 March 2022)

### Table 1 Schedule of Activities

| Type of contact | Visit 1 | | Contact 1 | Visit 2 | | Contact 2 | |
|---|---|---|---|---|---|---|---|
| Time points | Day 1 | | Day 8 | Day 31 | | Day 181 | |
| Sampling time points | Pre-1st Vaccination | Post-1st Vaccination | Post Vaccination | | | Post-Vaccination | |
| Informed consent | ● | | | | | | See Section 10.1.2 for details] |
| Assign participant number | ● | | | | | | |
| Check inclusion/exclusion criteria | ● | | | | | | ***Recheck clinical status before randomisation and/or 1st dose of study intervention***. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria] |
| Collect demographic data[1] | ● | | | | | | See Section 8.2.1.1 for more information] |
| Medical and vaccination history | ● | | | | | | See Section 8.2.1.2 for more information] |
| Physical examination and vital signs[2,4] | ● | | | ● | | | See Section 8.2.1.3 for more information] |
| Urine pregnancy test[3] | ● | | | ● | | | See Section 8.2.1.4 for more information] |
| Pre-vaccination body temperature | ● | | | | | | The preferred location for measuring temperature will be oral cavity/axillary |
| Randomization | ● | | | | | | [See Section 6.3 for more information] |
| Check contraindications to subsequent vaccine(s) administration | | | | | | | See Sections 7.1.1 and 8.2.1.5 for more information] |

| **Type of contact** | **Visit 1** | | **Contact 1** | **Visit 2** | | **Contact 2** | |
|---|---|---|---|---|---|---|---|
| **Time points** | **Day 1** | | **Day 8** | **Day 31** | | **Day 181** | |
| **Sampling time points** | **Pre-1st Vaccination** | **Post-1st Vaccination** | **Post Vaccination** | | | **Post-Vaccination** | |
| Blood sampling for humoral immune response (~5 mL) | ● | | | ● | | | See Section 8.1.1 for more information]. ***This is applicable for study participants who received RSV maternal vaccine at Visit 1.*** |
| Study group and treatment number allocation (SBIR) | O | | | | | | See Section 6.3.2 and 6.3.3 for more information] |
| Vaccine administration | ● | | | | | | See Section 6.1 for more information] |
| Recording of administered treatment number | | ● | | | | | |
| 30 minutes post-vaccination observation period | | O | | | | | |
| Distribution of participant card | | O | | | | | |
| Training on use of e-diary | | O | | | | | |
| Distribution of e-diary device[7] | | O | | | | | |
| Review of e-diary | | | | | | | See Section 10.3.8 for more information] |
| Return of e-diary device[11] | | | | | O | | |
| Collection of solicited adverse events (Days 1 to 7 post-vaccination)[8] | | O | O | | | | See Section 10.3.8 for more information] |
| Recording of unsolicited adverse events for 30 days (days 1 to 30 post-vaccination) | | ● | ● | | ● | | See Section 10.3.8 for more information] |
| Recording of AEs/SAEs leading to withdrawal | | ● | ● | | ● | ● | See Section 10.3.8 for more information] |
| Recording of SAEs[7] | | ● | ● | | ● | ● | See Section 10.3.8 for more information] |
| Recording of MAEs | | ● | ● | | ● | | See Section 10.3.8 for more information] |
| Recording of pregnancies (if any) | | | ● | | ● | ● | See Section 10.3.8 for more information] |
| Recording of concomitant medications/vaccinations associated with an AE | | ● | ● | | ● | ● | See Section 6.8 for more information] |

| **Type of contact** | **Visit 1** | | **Contact 1** | **Visit 2** | | **Contact 2** | |
|---|---|---|---|---|---|---|---|
| **Time points** | **Day 1** | | **Day 8** | **Day 31** | | **Day 181** | |
| **Sampling time points** | **Pre-1st Vaccination** | **Post-1st Vaccination** | **Post Vaccination** | | | **Post-Vaccination** | |
| Phone contact | | | ● | | | ● | |
| Screen failed participants | ● | | | | | | |
| Suspected, probable and confirmed cases of COVID-19 infection | ● | | ● | ● | | ● | |
| Screening Conclusion | ● | | | | | | |
| Study conclusion | | | | | | | See Section 4.4 for more information |

TC= Telephone contact

● 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] Date of birth (month and year or year only, as per local regulations), race, ethnicity.

[2] Physical examination including (height and weight) BMI as well as resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest.
At Day 1 (Visit 1) physical exams to be done and vital signs be measured.
At Day 31 (Visit 2) height and weight to be taken, physical exams to be done and vital signs be measured. However, BMI will not be calculated

[3] Urine pregnancy test is sufficient to determine the eligibility to enter the study. Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

[4] Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature in this study is the oral cavity.

[6]

[7]The e-diary device will be distributed /or an app will be installed to the participants device at the day of vaccination.

[8]SAEs related to study participation or concurrent GSK intervention product will be monitored from the time of screening to the time of the immunization. Both will be conducted on the same visit.

[11] Return of the e-Device is not applicable if the participant has a “Bring Your Own” e-device.

**Table 2 Intervals between study visits**

| Interval | Optimal timing | Allowed interval (Study day) |
|---|---|---|
| Visit 1*→ Contact 1 | 8 days | 7 - 9 days |
| Visit 1→ Visit 2 | 31 days | 31 - 45 days |
| Visit 1 →***Contact 2*** | 180 days | 165 - 195 days |

*The interval between study visits begins at the time of vaccination during Visit 1 timepoint.

# 2. INTRODUCTION (AMENDED 17 MARCH 2022)

## 2.1. Study rationale

GlaxoSmithKline Biologicals SA (GSK) is developing an investigational respiratory syncytial virus (RSV) maternal vaccine (RSVPreF3) against RSV disease in infants through maternal immunization with the aim of preventing RSV-associated lower respiratory tract illnesses in their infants by transfer of maternal antibodies. The vaccine candidate is an engineered version of the RSV fusion (F) surface glycoprotein, stabilized in the pre-fusion conformation. This study will be a Phase 3 randomized, open label, active vaccine-controlled crossover study to the evaluate safety, reactogenicity, and immunogenicity of RSV maternal vaccine in healthy non-pregnant adolescent girls from 9 to 17 years of age (YOA), and in non-pregnant adult women from 18 to 49 YOA. The lower age cut-off is set as 9 years of age corresponding to the earliest onset of puberty in girls per ICH E11 guideline.

The RSV maternal vaccine was being developed by GSK to be administered to pregnant women. By including pregnant adolescents in the target population for vaccination, their infants were expected to be protected from RSV for first 6 months of life thus increasing the number of infants who can benefit from this vaccine. RSV prevention is even more crucial in this population as babies of adolescent mothers face higher risks of low birth weight, preterm delivery, and severe neonatal conditions [WHO, 2016]. Hence these babies also have a higher risk of developing severe RSV disease [CHMP, 2018] which justifies the need to vaccinate the pregnant adolescent population with maternal RSV vaccine.

Because it is not feasible to conduct a study including all age groups of pregnant adolescents due to the low occurrence of young adolescent pregnancies this study is conducted in non-pregnant girls including a direct comparison to non-pregnant adult women in terms of immunological non-inferiority. RSV MAT-039 is part of an approved Pediatric Investigation Plan in Europe.

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

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

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

The 120-µg dose has demonstrated robust immunogenicity and there were no safety concerns. It was, therefore, selected for evaluation in the Phase 3 studies: the ongoing trial RSV MAT-009 (NCT 04605159) which is a Phase III double-blind study to assess safety and efficacy of an RSV maternal unadjuvanted vaccine, in pregnant women and infants born to vaccinated mothers. Also ongoing is the RSV MAT-012 trial, that is designed to assess the safety, reactogenicity and immunogenicity in the high-risk obstetric population.

The objective of this study is to evaluate the immunogenicity as well as safety and reactogenicity of RSV maternal vaccine in healthy non-pregnant girls 9-17 YOA (pediatric study group*) and in non-pregnant adult women 18-49 YOA (adult study).

* For purpose of this study we will classify all females between 9-17 YOA as "girls" with the understanding that this age range includes children (9-11 year of age) and adolescents: (12 to 18 [further dependent on the region]). [ICH E11, 2017]

In this study, Boostrix will be used as an active vaccine. Two formulations of dTpa vaccine, each containing either 300 µg or 500 µg of Aluminum are licensed in the US and outside of the US (ex-US), respectively. Boostrix-US formulation (dTpa_300) will be administered to participants in centers located in the US, while the Boostrix-ex-US formulation (dTpa_500) will be administered to participants in centers ex-US [Christy, 1995]. Even though two different formulations for Boostrix are available, both have a similar immunogenicity and safety profiles. [Theeten, 2005]

Objectives and endpoints/estimands of the RSV MAT-039 study are presented in Section 3.

- ***Following review of data collected so far from the RSV MAT-009 study in pregnant women, 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, GSK has nevertheless decided to stop enrolment and vaccination for all actively enrolling RSV MAT studies.***
- ***There will be no new participants included in this study. However, safety monitoring of all 8 study participants (of the planned 252 study participants)***

***enrolled and vaccinated in RSV MAT-039 study in a study site in the US will continue during the rest of the study period.***

- ***The vaccination planned at visit 2 is removed. Therefore, Contact 2 at Day 38 and Visit 3 at Day 61 are not applicable anymore. Visit 4a (Day 181) and Visit 4b (Day 211) are replaced by a telephone contact at Day 181.***
- ***A blood sample for immunogenicity assessment in the study participants who received first dose of RSV Maternal vaccine will continue to be collected at Visit 2 only. No other blood samples will be collected.***
- ***All planned objectives will be analysed and reported in a descriptive manner for the 8 enrolled participants.***

## 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 vaccine and epidemiology studies of RSV infection.

## 2.3. Benefit/Risk assessment (Amended 17 March 2022)

GSK has included provisions in this trial to ensure participant's safety. Safety monitoring has been and will be conducted throughout this study by an unblinded Independent Data Monitoring Committee (IDMC) and by ***the Sponsor.*** 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 pregnant study participants in our active studies 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 in pregnant women. 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 RSV MAT-009 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, as a precautionary measure GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling both pregnant women on February 25, 2022 and non-pregnant women on March 1, 2022. The study remains ongoing for safety follow-up. Participants already vaccinated will continue to be monitored until the end of the study.***

# 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS (AMENDED 17 MARCH 2022)

**Table 3 Study objectives, endpoints and estimands**

| Objectives | Endpoint(s) and estimand(s) |
|---|---|
| **Primary** | |
| • ***To evaluate the safety following administration of RSV maternal vaccine in the pediatric (9-17 YOA) and adult (18-49 YOA) study groups during the entire study period. (180 days post RSV maternal vaccination)*** | ***The number and percentage of participants in each study group reporting*** <br>• ***SAEs during the entire study period*** <br>• ***AEs/SAEs/leading to study withdrawal during the entire study period*** |
| • To evaluate the reactogenicity and safety following administration of RSV maternal vaccine and dTpa control vaccine in the pediatric and adult study groups up to 30 days (including day of study intervention administration). | • The number and percentage of participants in each study group reporting <br>• Each solicited administration site event collected during the 7 days follow-up post Dose 1 (Day 1 to Day 7 post intervention including day of vaccination) <br>• Each solicited systemic event during the 7 days follow-up period post Dose 1 <br>• Each unsolicited AE collected during the 30 days follow-up period post Dose 1 <br>• SAEs/MAEs during the 30 days follow-up period post Dose 1 <br>• AEs/SAEs/MAEs leading to study withdrawal for the 30 days follow-up period post Dose 1 |
| **Secondary** | |
| • ***To evaluate the immunogenicity following the administration of RSV maternal vaccine in terms of RSV A neutralizing Ab titers in pediatric (9-17 YOA) and in adult (18-49 YOA) groups.*** | • ***RSV A neutralizing antibody titers at pre-dosing and Day 31 post RSV maternal vaccine administration*** |
| • To evaluate the immunogenicity (RSVPreF3 IgG, RSV A Neutralizing Ab and RSV B Neutralizing Ab) of RSV maternal vaccine in the pediatric (9-17 YOA) and 18-49 YOA (adult) groups. | • RSV B Neutralizing Ab titers and RSVPreF3 IgG ELISA concentration at pre-dosing and Day 31, post RSV maternal vaccine administration. |

Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

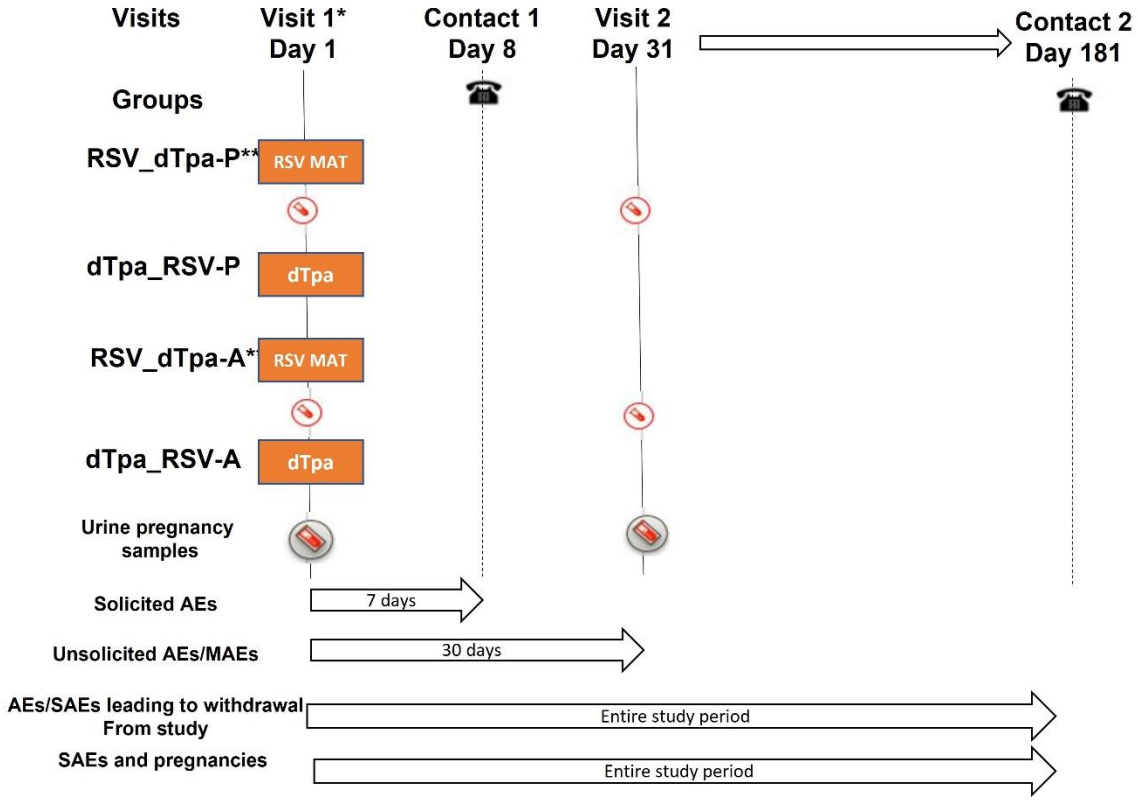
# 4. STUDY DESIGN (AMENDED 17 MARCH 2022)

## 4.1. Overall design

This study will be a Phase 3 study to evaluate immunogenicity, safety and reactogenicity of RSV maternal vaccine in healthy non-pregnant girls 9 to17 YOA (pediatric study group) compared to non-pregnant adult women 18 to 49 YOA (adult study group).

A total of 252 participants ***were planned to*** be enrolled evenly in 2 age groups, (9-17 YOA and 18-49 YOA). Within each age group, approximately 126 participates will be randomized in 1:1 fashion either receiving RSV maternal vaccine followed by dTpa vaccine 30 days later or receiving *Boostrix* vaccine followed by RSV maternal vaccine 30 days later. See section 6.3.2 for more detail on the randomization strategy.

**Figure 1 Study design overview**




* Screening and vaccination will happen on Visit 1 (Day 1).
** (RSV_dTpa-P & RSV_dTpa-A) Blood sampling to be done at Visit 1 and Visit 2 for participants receiving RSV maternal vaccine at Visit 1.***A urine pregnancy test will be done at Visit 2 if the participant has received RSV maternal vaccine in their first visit.***

- **Study Type**: Cross over design.
- **Study Duration**: The study interventions were administered at Visit 1 and the participant will be followed for 6 months (180 days post RSV maternal vaccine administration) subsequent the RSV maternal vaccine until the study conclusion.
- **Blinding**: This study will be an open label study.
- **Control Used**: dTpa will be used as an active control for safety and reactogenicity evaluation and to maximize the benefit to participants*.

  **** The participants in RSV_dTpa-P and RSV_dTpa-A group will be provided with an option to decide to receive dTpa vaccination as part of standard of care/local recommendation on immunization outside this study.***

- **Sample Collection Time Points**
  - RSV_dTpa-P: Day 1, Day 31
  - RSV_dTpa-A: Day 1, Day 31
- Vaccination schedules are described in Table 2.
- Randomized intervention allocation is described in in Table 4 and Section 6.3.

- Study (intervention) groups are described in Table 4.
- **Data collection**: e-Diaries will be used to collect solicited event data. Unsolicited Adverse event data will be collected through questioning at study visits/contacts and reported into the eCRF, as appropriate. See Section 8.3.2 for more detail.
- Safety monitoring will be conducted by SRT and IDMC.

**Table 4 Study groups, intervention, and blinding**

| Study groups** | Number of participants# | Age (Min-Max | Study intervention(s)* | Blinding |
|---|---|---|---|---|
| | | | | Visit1→Visit 4a or Visit 4b |
| RSV_dTpa-P | 63 | 9-17 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | Open Label |
| dTpa_RSV-P | 63 | 9-17 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |
| RSV_dTpa-A | 63 | 18-49 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |
| dTpa_RSV-A | 63 | 18-49 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |

*RSVPreF3=RSV maternal Vaccine
#Only 8 study participants have been enrolled in the study.
***There will no further enrolment and vaccination in all the study groups.***

## 4.2. Scientific rationale for study design

This study is part of a clinical development plan of the RSV maternal vaccine for the protection of infants from RSV lower respiratory tract infections through maternal immunization. This study will evaluate the immunogenicity, safety and reactogenicity of the RSV maternal vaccine in non-pregnant girls from 9 to 17 YOA in order to show that the humoral immunogenicity is non inferior to the immunogenicity, safety and reactogenicity observed in non-pregnant adult women aged 18 to 49 YOA.

***Following the decision to stop all RSV maternal studies, this study will only explore immunogenicity and safety of RSV MAT vaccine in study participants (who received fist dose at Visit 1) 9 to 17 years of age and 18 to 49 years of age and non-inferiority between the groups will not be assessed.***

## 4.3. Justification for dose

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

It is assumed that nearly all humans are infected with RSV in their early life and have pre-existing neutralizing antibody. Results of study RSV MAT-001 in non-pregnant women indicate that a single dose of the study vaccine is sufficient to boost the neutralizing antibodies induced by previous natural infections.

## 4.4. End of Study definition

A participant is considered to have completed the study if she is available for the last scheduled contact as described in the protocol.

End of Study (EoS): Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.

The Primary Completion Date (PCD) is the day that the final participant is examined for all primary outcomes ***(Day 181).***

Refer to Section 10.8.2 for the definition of EoS.

# 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 jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

## 5.1. Inclusion criteria

All participants must satisfy ALL the following criteria at study entry:

### 5.1.1. Inclusion criteria (Healthy Non-pregnant Adult Women from 18-49 YOA)

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the e-diary, return for follow-up visits)
- Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study-specific procedure.
- A healthy female participant, as established by medical history and clinical examination, between and including 18 to 49 YOA at the time of the first study intervention administration.
- Body mass index (based on participant's report) 17.0 to 39.9 kg/m$^2$, inclusive for adult participants.
- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administrations.

- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

### 5.1.2. Inclusion criteria (Healthy non-pregnant Girls from 9-17 YOA)

- Participants and participants' parent(s)/Legally Acceptable Representative(s) (LAR), who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the e-diary return for follow-up visits)
- Written or witnessed/thumb printed informed consent obtained from the participant*/parent(s)/LAR(s) of the participant prior to performance of any study-specific procedure.
  - * Written informed consent obtained from parents/LARs and written informed assent obtained from the participant if she is less than 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 participant should be obtained at the time of the legal age.
- A healthy female participant between and including 9 and 17 YOA at the time of the first study intervention administration.
  - Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, or bilateral ovariectomy.
- Body mass index by age between 5 percentile and 95 percentile (inclusive) for pediatric participants.
- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - has a negative pregnancy test on the day of study intervention administration, and is abstinent during the entire treatment period and for 1 month before and after completion of the study intervention administration series (and if so, this is to be documented in the source documents at each vaccination visit)
  - or has practiced adequate contraception for 1 month prior to study intervention administration and has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration series.

## 5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. (Please see Section 5.5 for more information on delay of vaccination for temporary exclusion Criteria). The potential participant MAY NOT be included in the study if ANY exclusion criterion applies:

### 5.2.1. Medical conditions

- Any clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s)
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required)
- Current autoimmune disorder (based on medical history and physical examination;), for which the participant has received immune-modifying therapy within 6 months, before study vaccination
- Hypersensitivity to latex
- Acute or chronic clinically significant abnormality or poorly controlled pre-existent co-morbidities or any other clinical conditions, as determined by physical examination or medical history that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study
- Significant or uncontrolled psychiatric illness
- Documented HIV-positive participant
- Any clinically significant* hematological parameter and/or biochemical laboratory abnormality from the test requested by the investigator based on medical judgment prior to enrolment
  - *The investigator should use his/her clinical judgment to decide whether the test is needed, and which abnormalities are clinically significant. If he/she decides to run this test, the investigator will need to review the test results before proceeding with the administration of the study vaccine. See section 5.5 for more detail.
- Lymphoproliferative disorder or malignancy within 5 years before study vaccination (excluding effectively treated non-melanoma skin cancer).

### 5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study intervention(s) during the period beginning 30 days before the first doses (Day -29 to Day 1), or their planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before the first dose and ending 30 days after the last dose of study intervention(s)* administration with the exception of any licensed influenza vaccine which may be administered ≥ 15 days before or after study vaccinations (dTpa and RSV maternal vaccines).
  - * In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organized by public health authorities outside the routine

immunization program, the time period described above can be reduced if necessary for that vaccine (if it is used according to the local governmental recommendations and that the Sponsor is notified accordingly). Therefore, COVID-19 vaccines will be allowed, when administered ≥ 15 days before or after study vaccinations (dTpa and RSV maternal vaccines).

- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study intervention(s) or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s) to 2 months after first vaccination. For corticosteroids, this will mean prednisone equivalent ≥ 5 mg/day for adult participants/ ≥0.5 mg/kg/day. Inhaled and topical steroids are allowed.
- Previous experimental vaccination against RSV.
- Boostrix (dTpa) administration for which the vaccination is not aligned with the local recommendations for dTap vaccination or not aligned with the locally approved Boostrix (dTpa) prescribing information.

### 5.2.3. 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/invasive medical device).

Note: 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’.

### 5.2.4. Other exclusions

- Pregnant or lactating female
- Female planning to become pregnant or planning to discontinue contraceptive precautions
- Alcoholism or substance use disorder within the past 24 months based on the presence of two or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglected major roles to use, withdrawal tolerance, use of larger amounts or longer, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving (based on the DSM-5 criteria, [Hasin, 2013]);
- Any study personnel or their immediate dependants, family, or household members
- Child in care. Please refer to the Glossary of terms for the definition of child in care.

## 5.3. Lifestyle considerations

No lifestyle considerations are necessary for this study.

### 5.3.1. Demographic data

Demographic data for 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; Kollmann, 2013; Pérez, 2009] 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

Not applicable

## 5.4. Screening failures

Screen failures are participants who consent to take part in this study but are determined ineligible and not subsequently assigned to a study intervention.

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

Note: Demography and required forms at Visit 1 should be completed for screening failures.

## 5.5. Criteria for temporarily delaying enrolment/study intervention administration

Enrolment/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved. Participants must be rescreened:

- Participants with abnormal clinically significant* hematological/biochemical values at screening, and *if* expected to be temporary at the discretion of the investigator.
  - *The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Acute disease and/or fever at the time of enrollment. Refer to the SoA 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 enrolled and/or vaccinated at the discretion of the investigator.
- Use of systemic antibiotic or antiviral treatment within 48 hours prior to study vaccination.

# 6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention. Refer to the Study Procedures Manual (SPM) for additional details.

## 6.1. Study interventions administered (Amended 17 March 2022)

### Table 5 Study interventions administered

| | RSV maternal Vaccine* | | *Boostrix (dTpa_500)* | *Boostrix (dTpa_300)#* |
|---|---|---|---|---|
| **Study intervention name:** | RSVPreF3 | NaCl Solution | dTpa | dTpa |
| **Study intervention Formulation** | RSVPreF3 (120 µg) | Sodium Chloride (NaCl) (0.9%); Water for injections | DT[1] (≥ 2 IU);<br>TT[1] (≥ 20 IU);<br>PT (8 µg)[1];<br>FHA (8 µg)[1];<br>PRN (2.5 µg)[1];<br>[1]adsorbed on $Al(OH)_3$ (0.3 mg $Al^{3+}$) and $AlPO_4$ (0.2 mg $Al^{3+}$);<br>Water for injections q.s. 0.5 mL | DT[1] (≥ 2 IU);<br>TT[1] (≥ 20 IU);<br>PT (8 µg)[1];<br>FHA (8 µg)[1];<br>PRN (2.5 µg)[1];<br>[1]adsorbed on $Al(OH)_3$ (0.3 mg $Al^{3+}$);<br>Water for injections q.s. 0.5 mL |
| **Presentation** | Powder for solution for injection (vial)<br>Solution for solution for injection (syringe) | | Suspension for injection (syringe) | Suspension for injection (syringe) |
| **Type** | Study | | Control | Control |
| **Product Category** | Combination Product | | Combination Product | Combination Product |
| **Route of administration:** | IM | | IM | IM |
| **Location** | Arm | | Arm | Arm |
| **Laterality **** | non-dominant | | non-dominant | non-dominant |
| **No of doses** | 1 | | 1 | 1 |
| **Volume to be administered:** | whole content*** | | whole content**** | whole content**** |
| **Side/site route** | IM/non-dominant arm | | IM/non-dominant arm | IM/non-dominant arm |
| **Packaging, labelling and TM** | Refer to the SPM for more details | | Refer to the SPM for more details | Refer to the SPM for more details |
| **Manufacturer:** | GSK | | GSK | GSK |

* RSV maternal Vaccine=RSVPreF3

** 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 content 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 more details.

**** The entire content of the of the syringe will be administered. Refer to the SPM for more detail.

***#This dose form of Boostrix is not applicable in the study anymore as no non-US sites were initiated before the decision to stop the study.***

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

## 6.2. Preparation, handling, storage, and accountability

The study intervention(s) 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 intervention(s). Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the Study Procedures Manual (SPM) for more details on storage and handling of the study intervention(s)

## 6.3. Measures to minimise bias: randomisation and blinding (Amended 17 March 2022)

### 6.3.1. Participant identification

Each participating country and site will have a range of participant identification number and enrolled subjects will be assigned to those numbers sequentially.

### 6.3.2. Randomisation to study intervention

A total of 252 participants will be enrolled evenly in 2 age groups, (9-17 YOA and 18-49 YOA). Within each age group, approximately 126 participants will be 1:1 randomized either receiving RSV maternal vaccine followed by dTpa vaccine 30 days later or receiving dTpa vaccine followed by RSV maternal vaccine 30 days later. Study is stopped after enrolling 8 subjects (7 adult and one adolescent) hence no more randomization and intervention will be applicable.

### 6.3.3. Intervention allocation to the participant

The randomization algorithm will use a stratification procedure accounting for participants age at the time of study intervention administration (9-17 YOA, 18-49 YOA) and a minimization procedure accounting for (a) Center and (b) Study. Minimization factors will have equal weight in the minimization algorithm.

Once a participant identification number is allocated, the randomisation system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR)

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.

### 6.3.4. Allocation of participants to assay subsets

Not applicable

### 6.3.5. Blinding and unblinding

This is an open-label study; however, an electronic system will be used for allocation of treatment numbers. Potential bias will be reduced by the using the allocation system on the internet and adjudications

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 groups and the identity of the participant.

#### 6.3.5.1. Emergency unblinding

Not applicable since this is an unblinded study

## 6.4. Study intervention compliance

When the study intervention is administered at the site, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

The intervention number administered, and the administration date and time will be recorded in the source documents.

## 6.5. Dose modification

Section is not applicable.

## 6.6. Continued access to study intervention after the end of the study

Not applicable

## 6.7. Treatment of overdose

Not applicable

## 6.8. Concomitant therapy

At each study visit/contact, the investigator or his/her delegate should question the participant and/or the 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:

- All concomitant medication associated with an adverse event, including vaccines/products, except vitamins and dietary supplements, administered after the study intervention until the end of the study.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to the sections 5.2 and 9.2.1 for further details.
- Any concomitant medications/products/vaccines listed in Section 5.2.2 during the period specified in that section.
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.3.1 and 10.3.8. These must also be recorded in the Expedited Adverse Event report.
- Prophylactic medication related to the effects (actual or anticipated) of study vaccine/product administration (e.g., medication administered either in the absence of ANY symptom and in anticipation of a reaction to the study vaccine, or to prevent re-occurrence of one or more post-vaccination AEs such as headache).

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

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- Adverse event requiring expedited reporting to GSK
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

### 7.1.1. Contraindications to subsequent study intervention(s) administration

Contraindications of study interventions do not apply since this is a single (experimental) dose study.

## 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 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:

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

*If a participant is withdrawn from the study because she/the participant's parent(s)/LAR(s) has withdrawn consent and 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 participant will be considered 'lost to follow-up' if she fails to return for scheduled visits and cannot 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

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 summarised 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), 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).

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**

- During special circumstances (e.g., the COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. Please refer to the SPM for details.

For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Enrollment of additional 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.
- The following measures may be implemented for enrolled participants:
  - If it is not possible to conduct a protocol-specified, scheduled or event-driven visit as described in Section 1.3 the visit may be replaced with a contact conducted by SMS, email, telephone, videotelephony or telemedicine. In such cases:
    - Protocol-specified clinical data that
      - cannot be collected by study staff during the contact (e.g., physical examination results) BUT

  - are available within the allowed interval (Table 2) 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* within the visit interval (Table 2).
  - Samples should not be collected if they cannot be processed in a timely manner and / or appropriately stored until the intended use.
  - Blood samples for central assessment must be collected using GSK-provided supplies.
- "Medically attended visits" will include instances where, due to the special circumstances, the participant cannot seek medical advice for symptoms/an illness by visiting a medical facility or arranging for a home visit, and seeks this advice instead via telephone, SMS, email, videotelephony or telemedicine, or other means.

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.

*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 participant 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 17 March 2022)

Please refer to the central laboratory manual for details on biospecimen management (handling, storage and shipment).

**Table 6 Biological samples**

| Sample type Collected to Evaluate* | Time point (RSV_dTpa-P, RSV_dTpa-A) | Minimum Quantity per participant | Unit | Additional Information |
|---|---|---|---|---|
| Whole blood for immune response | Visit 1 (Day 1) | ~5 | mL | Immune response: 5 mL (~ 2 mL serum). |
| Whole blood for immune response | Visit 2 (Day 31) | ~5 | mL | Immune response: 5 mL (~ 2 mL serum). |
| | | **~10** | **mL** | |
| Urine for Pregnancy** | Visit 1 (Day 1) and Visit 2 (Day 31) | | | |

*The blood sample to be taken for immune response must be taken before administering the study intervention.
***Urine sample was collected for all subjects at Visit 1. At Visit 2, urine sample will only be collected for study participants enrolled in RSV dTpa-P and RSV dTpa-A groups.***

### 8.1.2. Laboratory assays (Amended 17 March 2022)

All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK.

**Table 7 Laboratory assays**

| Sampling time points | System | Component | Method* | Groups | Laboratory |
|---|---|---|---|---|---|
| Visit 1** (Day 1 prior to immunization) | Serum | Respiratory Syncytial Virus A Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus B Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus PreF3 Ab.IgG concentration | ELI | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| Visit 2*** (Day 31 prior to immunization) | Serum | Respiratory Syncytial Virus A Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus B Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus PreF3 Ab.IgG concentration | ELI | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |

*NEU=Neutralization Assay; ELI=ELISA or enzyme-linked immunosorbent assay
** for participants receiving RSV maternal vaccine at Visit 1
*** ***Visit 2(Day 31 prior to immunization) is no more applicable after the study stop***

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 17 March 2022)

***The following readouts are applicable to only 8 participants enrolled in the study.***

**Table 8 Immunological read-outs**

| Blood sampling timepoint | | Approximate No. participants | Component |
|---|---|---|---|
| **Type of contact and timepoint** | **Sampling timepoint** | | |
| Visit 1* (Day 1) | pre- 1st vaccination | 126 | Respiratory Syncytial Virus A Ab neutralizing |
| | | 126 | Respiratory Syncytial Virus B Ab neutralizing |
| | | 126 | Respiratory Syncytial Virus PreF3 Ab.IgG concentration |
| Visit 2 (Day 31) | post 1st vaccination | 252 | Respiratory Syncytial Virus A Ab neutralizing |
| | | 252 | Respiratory Syncytial Virus B Ab neutralizing |
| | | 252 | Respiratory Syncytial Virus PreF3 Ab.IgG concentration |

* for participants receiving RSV maternal vaccine at Visit 1

### 8.1.4. Immunological correlates of protection

#### 8.1.4.1. *RSV Maternal Vaccine*

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

#### 8.1.4.2. *Boostrix*

For this study, no assays will be performed for immunogenicity assessment of *Boostrix* antigens.

## 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.

### 8.2.1. Pre-intervention administration procedures

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

#### 8.2.1.1. Collection of demographic data

Demographic data such as date of birth, sex, childbearing potential, race and ethnicity will be recorded in the participant's eCRF.

#### 8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant/parent(s)/LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the study intervention in the eCRF. All prior therapy including hematological products (e.g. plasma transfusion, blood transfusion etc.), medications, and vaccines received by the participant in the last 30 days prior to study start should be collected and recorded. In case of seasonal flu and/or COVID-19 vaccine administration, this information is applicable ≥ 15 days before or after study vaccinations. dTpa vaccine history must be collected and recorded for the last 10 years.

#### 8.2.1.3. History directed physical examination

Perform a full physical examination of the participant at the Visit 1 (Day 1) and Visit 2 (Day 31), including assessment of oral (preferred)/axillary body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.

#### 8.2.1.4. Pregnancy test (Amended 17 March 2022)

Female participants (9 to 49 YOA) of childbearing potential as well as pre-menarche girls must perform a urine pregnancy test before the administration of any dose of study intervention (dTpa or RSV maternal vaccine). Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

A serum pregnancy test may be performed (instead of a urine pregnancy test) if required by country, local or ethics committee regulations.

***Urine for pregnancy test during the Visit 2 will still be performed for subjects who have received RSV maternal vaccine in their first visit.***

Refer to Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

#### 8.2.1.5. Warnings and precautions to administration of study intervention

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

### 8.2.2. Clinical safety laboratory tests

Not applicable for this study.

### 8.2.3. Study holding rules and safety monitoring

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

#### 8.2.3.1. Safety evaluation by the Safety Review Team

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, reviewing the unblinded safety data on a regular, ongoing basis. The SRT will inform the IDMC about any potential safety concern at any point during the study and may request ad-hoc safety evaluations by the IDMC.

#### 8.2.3.2. Independent Data Monitoring Committee Evaluation

An unblinded IDMC will be established by GSK. The IDMC will monitor the safety data and the scientific validity of the study. The IDMC and SRT will review safety data (as clean as possible) on an ongoing basis. Additional details concerning the IDMC's structure and processes will be provided in the IDMC charter.

#### 8.2.3.3. Study holding rules

The safety holding rules are defined in Table 9. Holding rules 1a-b will be assessed by the investigator on a continuous basis.

**Table 9 Study holding rules**

| Holding Rule | Event | Number of participants |
|---|---|---|
| 1a | Any death within 30 days from study dose administration of the interventions (RSV maternal vaccine and dTpa) that cannot be reasonably attributed to a cause other than vaccination as per Investigator assessment | ≥ 1 |
| 1b | Any life-threatening SAE within 30 days from study dose administration of the interventions (RSV maternal vaccine and dTpa) that cannot be reasonably attributed to a cause other than vaccination as per Investigator assessment | ≥ 1 |

The following communication sequence must be followed:

If at any time, there is a safety concern identified by the SRT or if a holding rule is met, a hold on study dose administration can be implemented pending further investigation.

Table 9 presents the safety holding rules 1 (a-b) to be assessed by the investigator on an ongoing basis. Meeting a holding rule will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event relative to study dose administration. While vaccinations are on hold, the investigator should not consent subjects into the study.

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform GSK immediately and enter the data in the electronic case report form (eCRF). (e.g. holding rules 1a-b). Refer to Table 12 for contact information. It is Sponsor's responsibility to put the enrolment or the study intervention administration on hold at all centers. The IDMC will be informed once a holding rule is met.

GSK will inform all investigators if holding rules 1a-b are met.

Additional safety data, if required, will also be reviewed by the IDMC to allow for an overall assessment of the benefit/risk profile of vaccination. The IDMC may recommend that the study be placed on hold for reasons not covered by the holding rules if deemed necessary.

## 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

An overview of the protocol required reporting periods for AEs, SAEs, and pregnancies is given in Table 10.

**Table 10 Timeframes for collecting and reporting of safety information (Amended 17 March 2022)**

| Event | V1 | | C1 | | V2 | Contact 2 |
|---|---|---|---|---|---|---|
| | D1 | D7 | D8 | D30 | D31 | 180 days post RSV vaccination*** |
| Solicited administration site event and systemic AEs | | | | | | |
| | | | | | | |
| | | | | | | |
| Unsolicited AEs | | | | | | |
| | | | | | | |
| | | | | | | |
| AEs leading to withdrawal from the study | | | | | | |
| | | | | | | |
| | | | | | | |
| SAEs* | | | | | | |
| | | | | | | |
| | | | | | | |
| MAEs | | | | | | |
| | | | | | | |
| | | | | | | |
| Pregnancies | | | | | | |
| | | | | | | |

. V=Visit; D=Day; C=Contact

* SAEs related to study participation or concurrent GSK medication/vaccine will be monitored from the time of screening to the time of the immunization. Both will be conducted on the same visit.

*** ***For all study groups at Day 181***

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 10. Investigators are not obligated to actively seek AEs or 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 12.

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

Detection and recording of AE/SAE/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/pregnancy.

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

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 11. 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 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 preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/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 Section 10.3.10 for further details regarding the reporting of SAEs/pregnancies.

**Table 11 Timeframes for submitting SAE, 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 | 24 hours*‡ | electronic Expedited Adverse Events Report | 24 hours* | electronic Expedited Adverse Events Report |
| Pregnancies | 24 hours* | electronic pregnancy report | 24 hours* | electronic pregnancy report |

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee).
‡‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

#### 8.3.3.1. Contact information for reporting SAEs, pregnancies and study holding rules

**Table 12 Contact information for reporting SAEs, pregnancies and study holding rules**

| | |
|---|---|
| **Study contact for questions regarding SAEs, pregnancies**<br>Refer to the local study contact information document | **Study contact for reporting of study holding rules**<br>As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the Local Medical Lead (LML). |
| **Back up study contact for reporting SAEs, pregnancies**<br>Available 24/24 hours and 7/7 days:<br><br>**GSK Clinical Safety & Pharmacovigilance**<br>Outside US & Canada sites:<br>Fax: +32 2 656 51 16 or +32 2 656 80 09<br>Email address: ogm28723@gsk.com<br>US sites only:<br>Fax: 1 610 787 7053<br>Canadian sites only:<br>Fax: 1 866 903 4718 | **Back up study contact for escalation of holding rules**<br>Refer to the local study contact information document. |

### 8.3.4. Treatment of adverse events

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

### 8.3.5. COVID-19 Infection

COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE or SAE criteria, as outlined in Section 10.2.

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

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

### 8.3.6. Participant card

The investigator (or designee) must provide the participant/participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant/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 participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back up.

### 8.3.7. Medical device deficiencies

The study intervention is a combination product constituted of a device and biologic product (e.g. pre-filled syringes). Refer to the Section 10.6.1 for the definition of combination product and medical device deficiency.

#### 8.3.7.1. Detection, follow-up and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6.1 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or related of the device deficiency to the incident. Follow-up applies to all participants, including those who discontinue study intervention or the study.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

#### 8.3.7.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to section 10.6 for details of reporting.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

## 8.4. Pharmacokinetics

Not applicable

## 8.5. Genetics

Not applicable

## 8.6. Biomarkers

Not applicable

## 8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1 and Section 9.3.2.1.

## 8.8. Health outcomes

Not applicable

# 9. STATISTICAL CONSIDERATIONS (AMENDED 17 MARCH 2022)

***This section will not be applicable as the study has been stopped. However only descriptive statistics will be provided for immunogenicity, safety and reactogenicity at an individual level.***

## 9.1. Statistical hypotheses

***No hypothesis test will be performed. All analyses will be descriptive.***

## 9.2. Analysis sets

**Table 13 Analysis sets**

| Analysis set | Description |
|---|---|
| **Enrolled** | All participants who completed the informed consent process and signed the informed consent form. |
| **Exposed** | All participants who received the study intervention (RSV maternal vaccine or dTpa). Analysis per group using the Exposed Set is based on the administered intervention. |
| **Full Analysis - Immunogenicity** | All participants who received at least 1 dose of the study intervention (RSV maternal vaccine) and have post-vaccination immunogenicity data. |
| **Per Protocol - Immunogenicity** | All participants in the Full Analysis set (Immunogenicity) who received RSV maternal vaccine to which they were randomized minus participants with protocol deviations that lead to exclusion. |
| **Unsolicited Safety** | All participants in the Exposed Set that report unsolicited AEs/report not having unsolicited AEs |
| **Solicited Safety** | All participants in the Exposed Set who have solicited safety data |

### 9.2.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned below or ones listed in the Section 7.1.1, she may be eliminated from per protocol analysis.

If the participant has a protocol deviation deemed as major, she may be eliminated from the per protocol analysis sets.

Major protocol deviations leading to exclusion will be defined in the Statistical Analysis Plan (SAP) and will be finalized prior to the first analysis.

Key major deviations include, but are not limited to, the following:

- Participants enrolled who did not meet entry criteria including age at enrollment
- Participants incorrectly vaccinated
- Participants who did not receive study vaccinations as planned in protocol
- Participants who did not have blood draws as planned in protocol
- Participants with a blood draw outside of allowed time window

## 9.3. Statistical analyses

### 9.3.1. Primary endpoint(s)/estimand(s) analysis

#### 9.3.1.1. Safety

All safety analyses will be performed on the Solicited Safety, Unsolicited Safety and Exposed sets. Safety endpoints including solicited AEs, unsolicited AEs, SAEs, AEs leading to study termination will be descriptively summarized. Numbers of participants reporting above AEs will be reported.

| | **Primary Safety Endpoints** | **Statistical Analysis Methods** |
|---|---|---|
| **Pediatric and Adult participants** | The number of participants in each study group reporting Each solicited administration site event collected during the 7 days follow-up period post Dose 1 (Day 1 to Day 7 post intervention including day of vaccination)<br>• Each solicited systemic event collected during the 7 days follow-up period post Dose 1<br>• Each unsolicited AE collected during the 30 days follow-up period post Dose 1<br>• SAEs/MAES collected during the 30 days follow-up period post Dose 1<br>• AEs/SAEs leading to study withdrawal for the 30 days follow-up period post Dose 1<br><br>***The number of participants in each study group reporting***<br>• ***SAEs during the entire study period.***<br>***AEs/SAEs leading to study withdrawal during the entire study period.*** | The number of adult and pediatric 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 Day 7 post intervention including day of vaccination) follow-up period after dosing will be tabulated by maximum intensity per participant for each study group.<br>The number of participants reporting:<br>• at least one administration site AE (solicited)<br>• at least one systemic AE (solicited)<br>during the 7-day follow-up period after dosing will be tabulated .<br>The number and percentage of participants reporting:<br>• at least one AE (unsolicited)<br>• at least one SAE/MAE<br>• at least one AE/SAE leading to study withdrawal<br>during the 30-days post Dose 1 follow-up period after dosing will be tabulated .<br>The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).<br>***The number of both the pediatric and adult participants reporting:***<br>• ***at least one SAE***<br>• ***at least one (S)AE leading to study withdrawal during the entire study period will be tabulated by group/doses and by MedDRA preferred term.***<br>***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared, but will not be released until the final, unblinded, analysis has been completed.*** |

### 9.3.2. Secondary endpoint(s)/estimand(s) analyses

#### 9.3.2.1. Immunogenicity

| | Secondary Immunogenicity Endpoints | Statistical Analysis Methods |
|---|---|---|
| **Pediatric and Adult participants** | ***RSV A neutralizing antibody titers at pre-dosing and Day 31 post RSV maternal vaccine administration*** | ***For RSV A neutralizing antibody titers at pre- dosing and Day 31 post RSV maternal vaccine administration :***<br>• ***Antibody titers/concentrations will be displayed using reverse cumulative curves.***<br>• ***Individual antibody titers at pre-dosing and Day 31 will be listed.***<br>• ***Individual post-dosing versus pre-dosing results will be plotted using scatter plots.***<br>• ***Individual fold increase of antibody titers at Day 31 post RSV maternal vaccine administration over pre-dosing will be tabulated .*** |
| | ▪ RSV B Neutralizing Ab titers and RSVPreF3 IgG ELISA concentration at pre-dose, Day 31 post RSV maternal vaccine administration. | For each assay, at each timepoint:<br>Antibody concentrations/titers will be displayed using reverse cumulative curves.<br>• Individual antibody titers/concentrations at pre-dosing and Day 31 will be listed<br>• Individual post-dosing versus pre-dosing results will be plotted using scatter plots.<br>• Individual fold increase of antibody titers/concentrations at each post-dosing timepoint over pre-dosing will be tabulated.<br>Relationship between RSVPreF3 IgG-specific antibody concentration, RSV A neutralizing antibody, and RSV B neutralizing antibody at baseline and each post RSV maternal vaccine administration timepoint will be explored using scatter plots of individual values. |

## 9.4. Conduct of analyses

No interim analyses are planned.

### 9.4.1. Sequence of analyses

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

The details of the statistical analysis will be presented in the protocol and the statistical analysis plan.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Informed Assent Form (IAF), Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/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 will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study 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.

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

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

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

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

Re-consent must be obtained in accordance with local laws and regulations for participants who become legally emancipated during the study, i.e. reach the legal age of consent. The participant can provide consent by signing/witnessing/thumb printing an ICF, similar to that provided to the parent(s)/LAR(s) at study start, which summarises the study and includes a consent statement and documents that the participant agrees to continue participating in the study.

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:

- His/her personal/their child's study-related data will be used by the sponsor in accordance with local data protection law.
- His/her medical records/their child's may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- GSK will 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

Safety oversight will be provided by an SRT composed of GSK RSV team members and also by an IDMC.

### 10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols 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 study 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.

GSK intends to make anonymized patient-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding.

### 10.1.7. Data quality assurance

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

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

All participant data 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 study records that include all pertinent observations on each of the site's study participants 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.

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 Clinical Study Report (CSR).

Study 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 the Glossary of terms.

### 10.1.9. Study and site start and closure

**First act of recruitment**

The study start date is the date on which the first subject is enrolled/ randomized and is considered the first act of enrollment.

**Study/Site termination**

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
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 Last Subject Last Visit (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. Descriptions of the assays to be performed in the study

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

**RSV-A and RSV-B neutralization assays**

The RSV-A and RSV-B neutralization assays are functional assays that measure 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 with serial dilutions of the test serum. Then, the serum-virus mixture is transferred onto a Vero cells culture and incubated for two days to allow infection of Vero cells. Thereafter, RSV-infected cells are detected by the visualization of the number of plaques.

**RSVPreF3 IgG ELISA**

The ELISA assay is based on an indirect ELISA allowing the detection and the quantification of specific IgG antibodies directed against RSVPreF3 in human serum samples and related to reference standard. 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).

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

## 10.3.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence (an unfavourable/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)
- Significant failure of an expected pharmacologic or biological action.
- 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.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

| 10.3.1.2. Events NOT Meeting the AE Definition |
|---|
| • Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).<br>• 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.<br>• 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.<br>• Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.<br>• 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. |

### 10.3.2. Definition of an SAE

| An SAE is any untoward medical occurrence that: | |
|---|---|
| a. | Results in death |
| b. | Is life-threatening<br>Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe. |
| c. | Requires hospitalisation or prolongation of existing hospitalisation<br>Note: In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. |
| d. | Results in disability/incapacity<br>Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption. |
| e. | Is a congenital anomaly/birth defect in the offspring of a study participant |

| | |
|---|---|
| f. | Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) |
| g. | Other situations<br><br>Medical or scientific judgement 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 hospitalisation but may jeopardise 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 hospitalisation. |

### 10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

**Table 14 Solicited administration site events**

| All age groups |
|---|
| Pain |
| Redness |
| Swelling |

b. Solicited systemic events

The following systemic events will be solicited:

**Table 15 Solicited systemic events**

| Fever |
|---|
| Headache |
| GI Symptoms (Nausea, Vomiting, Diarrhea, Abdominal pain) * |
| Fatigue |

* Nausea, vomiting, diarrhea and abdominal pain are collected individually.

Note: participants/participants' parent(s)/LAR(s) will be instructed to measure and record the axillary or oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants/participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the e-diary.

### 10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

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

Unsolicited AEs that are not medically attended or perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

### 10.3.5. Adverse events of special interest (AESIs)

Not applicable

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

If the investigator considers it necessary to conduct laboratory tests to rule out any SAE/Medically attended SAE during the participation in the study, those results should be shared with the central team.

In the absence of a diagnosis, abnormal laboratory findings assessments 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 Sections 10.3.1 and 10.3.2).

The investigator must exercise his or her medical and scientific judgement 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. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

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

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

The participants/participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should they experience any signs or symptoms they 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) will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the eDiary.

Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.

Note: eDiary may be completed by a minor participant under the supervision of the participant's parent(s)/LAR(s) provided the minor is capable of assessing and reporting the information to be recorded on eDiary. The ultimate accountability for completion of the eDiary remains with the participant's parent(s)/LAR(s). The investigator should discuss this accountability with the participant's parent(s)/LAR(s). Please see SPM for more detail

Collect and verify completed eDiary during discussions with the participant/participant's parent(s)/LAR(s) on Visit 2 (Day 31) and Visit 3 (Day 61).

Any unreturned eDiary device will be sought from the participant/participant's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

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

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

All solicited events that occur for 7 days following administration of each dose (RSV maternal vaccine or dTpa*)* of study intervention (Day 1 to Day 7) and (Day 31 to Day 38) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within this time frame 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, pregnancies or any other events of interest

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until the end of the study or until the participant is lost to follow-up**.**

##### *10.3.8.2.1. Follow-up during the study*

If a participant dies during their participation in the study or during a recognised 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 SAE using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE as fully as possible.

##### *10.3.8.2.3. Follow-up of pregnancies*

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period 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 and pregnancy information after removal of write access to the participant's eCRF

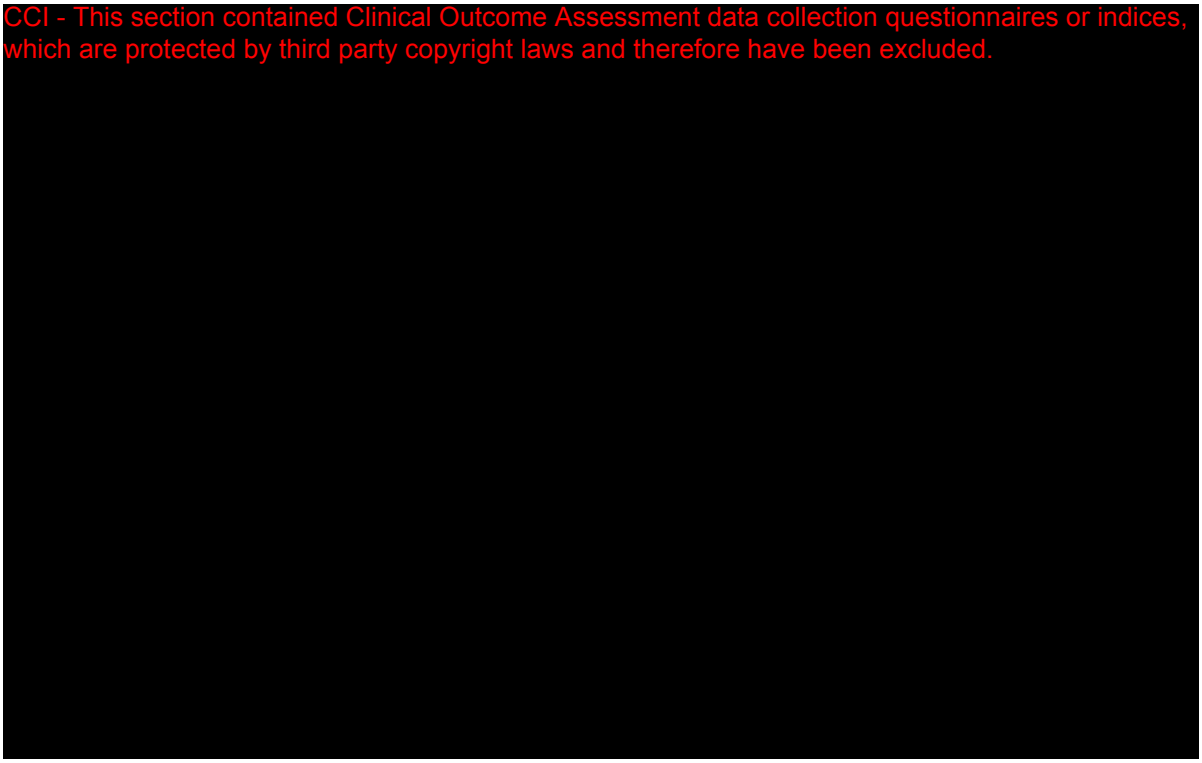
When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK VCSP department within the defined reporting timeframes specified in the Table 11).

### 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 16 Intensity scales for solicited events in adults and children of 6 years of age or more**




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

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

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

An AE that is assessed as Grade 3 CCI 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 judgement. 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 and/or SmPC and/or Prescribing Information for marketed products 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 Expedited Adverse Events Report to GSK.

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

#### 10.3.9.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant/participant's parent(s)/LAR(s) will be asked if she received medical attention (defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). Only serious medical attended visits will be recorded in the eCRF/ Expedited Adverse Events Report, and/if solicited in the eDiary.

#### 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, pregnancies and other events

#### 10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report 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 11 for the details on timeframes for reporting of SAEs/pregnancies.

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

Refer to 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 or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report 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 pregnancy information

### 10.4.1. Definitions

#### 10.4.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

#### *10.4.1.1.1. Women not considered as women of childbearing potential*

- Premenarchal

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

### 10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 17).

**Table 17 Highly effective contraceptive methods**

| |
|---|
| Highly Effective Contraceptive Methods That Are User Dependent<br>*Failure rate of <1% per year when used consistently and correctly.* |
| Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Injectable<br>• Oral |
| Highly Effective Methods That Are User Independent |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Bilateral tubal occlusion |
| Vasectomised partner<br>*(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)* |
| Male partner sterilisation prior to the female participant's entry into the study, and this male is the sole partner for that participant,<br>*(The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).* |
| Sexual abstinence<br>(*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)* |

## 10.4.3. Collection of pregnancy information

### 10.4.3.1. Female participants who become pregnant

Refer to Sections 8.3.1, 8.3.2, 10.3.8.1, 10.3.8.2 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will be followed to determine the outcome of the pregnancy.

## 10.5. Appendix 5: Genetics

Not applicable.

## 10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

### 10.6.1. Definition of medical device AE and adverse device effect (ADE)

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An 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 medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (i.e. user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

### 10.6.2. Definition of medical device SAE, SADE and USADE

| **A medical device SAE is any serious adverse event that:** |
|---|
| a. Led to death |
| b. Led to serious deterioration in the health of the participant, that either resulted in:<br>– A life-threatening illness or injury. 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, if it were more severe.<br>– A permanent impairment of a body structure or a body function.<br>– Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.<br>– Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. |
| c. Led to fetal distress, fetal death or a congenital abnormality or birth defect |
| **Serious Adverse Device Effect (SADE) definition** |
| • A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.<br>• Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate. |
| **Unanticipated SADE (USADE) definition** |
| • An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB. |

### 10.6.3. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Refer to paper ‘Medical device or combination product with device deficiency/incident report form’ for details on transmission of this information to the sponsor.
- GSK will review all device deficiencies, determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting in Section 8.3.3.1

## 10.7. Appendix 7: Country-specific requirements

**Germany**

A booster for Tdap-IPV (e.g. Boostrix-Polio) is recommended in the age group 9-17 YOA. However, IPV mono vaccines are licensed and can be administered separately. For MAT-039 study, Boostrix and IPV will be given separately in the group 9-17 YOA [IPV is allowed any time except the period starting 30 days before the first dose and ending 30 days after the last dose of study intervention(s) administration].

## 10.8. Appendix 8: Abbreviations and glossary of terms

### 10.8.1. List of abbreviations

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE: | Adverse Event |
| CLS: | Clinical Laboratory Sciences |
| COVID-19 | Corona Virus Disease 2019 |
| CSR | Clinical Study Report |
| DRE | Disease-related event |
| eCRF: | electronic Case Report Form |
| EoS: | End of Study |
| GCP: | Good Clinical Practice |
| GSK: | GlaxoSmithKline |
| IB: | Investigator Brochure |
| ICF: | Informed Consent Form |
| ICH: | International Council on Harmonisation |
| LML | Local Medical Lead |
| LSLV: | Last Subject Last Visit |
| MedDRA: | Medical Dictionary for Regulatory Activities |
| QTL | Quality Tolerance Limit |
| RRA: | Recruitment/Randomization Agreement |
| SAE: | Serious Adverse Event |
| SBIR: | Source data Base for Internet Randomization |
| SmPC: | Summary of Product Characteristics |
| SPM: | Study Procedures Manual |
| WOCBP | Woman of Childbearing Potential |

### 10.8.2. Glossary of terms

| | |
|---|---|
| Adverse event: | Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<br><br>An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of 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 study 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 study, 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<br><br>In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned. |
| Caregiver: | A ‘caregiver’ is someone who<br>– lives in the close surroundings of a participant and has a continuous caring role or<br>– has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g. a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).<br>In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures. |
| Certified copy: | A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. |

| | |
|---|---|
| Child in care: | A child who has been placed under the control or protection of an agency, organisation, 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. |
| Combination product: | Combination product comprises any combination of<br>– drug<br>– device<br>– biological product<br>Each drug, device and biological product included in a combination product is a constituent part. |
| Eligible: | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |
| Enrolment: | The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF. |
| 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 studies. |
| Evaluable: | Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis. |
| Immunological correlate of protection: | A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint. |
| 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 study, including a product with a marketing authorisation 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.<br><br>Synonym: Investigational Medicinal Product |
| Investigator: | A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.<br><br>The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions |
| Legally acceptable representative: | An individual, judicial or other body authorised under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study.<br><br>The terms legal representative or legally authorised representative are used in some settings. |
| Medical device deficiency: | A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer. |
| 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).<br><br>Synonym: subject |
| Participant number: | A unique identification number assigned to each participant who consents to participate in the study. |
| Pharmacogenomics | The International Council on Harmonisation (ICH) E15 Guidance for Industry defines pharmacogenomics as the, “Study of variation of DNA and RNA characteristics as related to drug or treatment response.”<br><br>Pharmacogenetics, a subset of pharmacogenomics, is “the study of variations in DNA sequence as related to drug response.” Pharmacogenomic biomarkers include |

| | |
|---|---|
| | germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues.<br><br>Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action).<br><br>Proteomic and metabolomic biomarker research is not pharmacogenomics. |
| 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 study was concluded according to the pre-specified protocol or was terminated. |
| Protocol amendment: | The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study. |
| Protocol administrative change: | A protocol administrative change addresses changes to only logistical or administrative aspects of the study. |
| Randomisation: | Process of random attribution of intervention to participants to reduce selection bias. |
| Remote visit: | This term refers to the visit conducted in the place other than the study site. |
| Self-contained study: | Study with objectives not linked to the data of another study. |
| 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 study necessary for the reconstruction and evaluation of the study. 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 study). |
| Study intervention: | Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study. |
| Study monitor: | An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites. |
| Telemedicine: | Telemedicine refers to the use of information technologies and electronic communications to provide clinical services to patients virtually. The digital transmission of medical imaging, virtual medical diagnosis and evaluations, and video consultations with specialists are all examples of telemedicine. |
| 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. |
| Virtual visit: | This term refers to study visits conducted using multimedia or technological platforms. |

## 10.9. Appendix 9: 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 | 11 August 2021 |
| Protocol Amendment 1 | 17 March 2021 |

**Detailed description of the current Protocol amendment:**

**Section 1.2 Schema**

***Based on all safety information available from RSV MAT-009 study (following administration of RSV MAT vaccine), there will be no further enrollment and vaccination of participants in this study.***

***There will be no more blood samples collected as part of this study, except the study participants who has received RSV maternal vaccine at Visit 1. A blood sample will be collected and a urine pregnancy test will continue to be performed for them at Visit 2.***

***Participants who are enrolled and are due to receive dTpa during their Visit 2 will no longer receive the dTpa as part of this study. However, as per the local standard of care and or immunization recommendation and after consultation with their attending physician; the participant can always receive any commercially available dTpa vaccine. GSK will bear the cost of the vaccine.***

All participants who receive the ***first dose of*** study interventions (RSV maternal vaccine or dTpa) will be followed for safety and reactogenicity and evaluated for both solicited administration site (local) and systemic events within 7 days of vaccination, unsolicited AEs within 30 days of vaccination, SAEs and pregnancy outcomes throughout the study period (180 days after ***first dose of study interventions***).

All safety data will be reviewed by a Safety Review Team (SRT) and an independent data monitoring committee (IDMC). (See Section 8.2.3 for more details)

**Section 1.3 Schedule of activities**

Contact 3 and Visit 3 removed. Visit 4 updated to telephone contacts.

**Table 2 Intervals between study visits**

| Interval | Optimal timing | Allowed interval (Study day) |
|---|---|---|
| Visit 1*→ Contact 1 | 8 days | 7 - 9 days |
| Visit 1→ Visit 2 | 31 days | 31 - 45 days |
| ~~Visit 2 → Contact 2~~ | ~~8 days~~ | ~~7 - 9 days~~ |
| ~~Visit 2 → Visit 3/Contact 3~~ | ~~31 days~~ | ~~31 - 45 days~~ |
| Visit 1 → ~~Visit 4a**~~ ***Contact 2*** | 180 days | 165 - 195 days |
| ~~Visit 2 → Visit 4b***~~ | ~~180 days~~ | ~~165 - 195 days~~ |

*The interval between study visits begins at the time of vaccination during Visit 1 timepoint.
~~** RSV_dTpa-P, RSV_dTpa-A groups only~~
~~*** dTpa_RSV-P, dTpa_RSV-A groups only~~

## Section 2.1 Study Rationale

- ***Following review of data collected so far from the RSV MAT-009 study in pregnant women, 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, GSK has nevertheless decided to stop enrolment and vaccination for all actively enrolling RSV MAT studies.***
- ***There will be no new participants included in this study. However, safety monitoring of all 8 study participants (of the planned 252 study participants) enrolled and vaccinated in RSV MAT-039 study in a study site in the US will continue during the rest of the study period.***
- ***The vaccination planned at visit 2 is removed. Therefore, Contact 2 at Day 38 and Visit 3 at Day 61 are not applicable anymore. Visit 4a (Day 181) and Visit 4b (Day 211) are replaced by a telephone contact at Day 181.***
- ***A blood sample for immunogenicity assessment in the study participants who received first dose of RSV Maternal vaccine will continue to be collected at Visit 2 only. No other blood samples will be collected.***
- ***All planned objectives will be analysed and reported in a descriptive manner for the 8 enrolled participants.***

## Section 2.3 Benefit/Risk assessment

***Following a recommendation from the IDMC, the Sponsor made the decision to pause the enrollment, randomization and vaccination of pregnant study participants in our active studies 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 in pregnant women. 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 RSV MAT-009 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.***

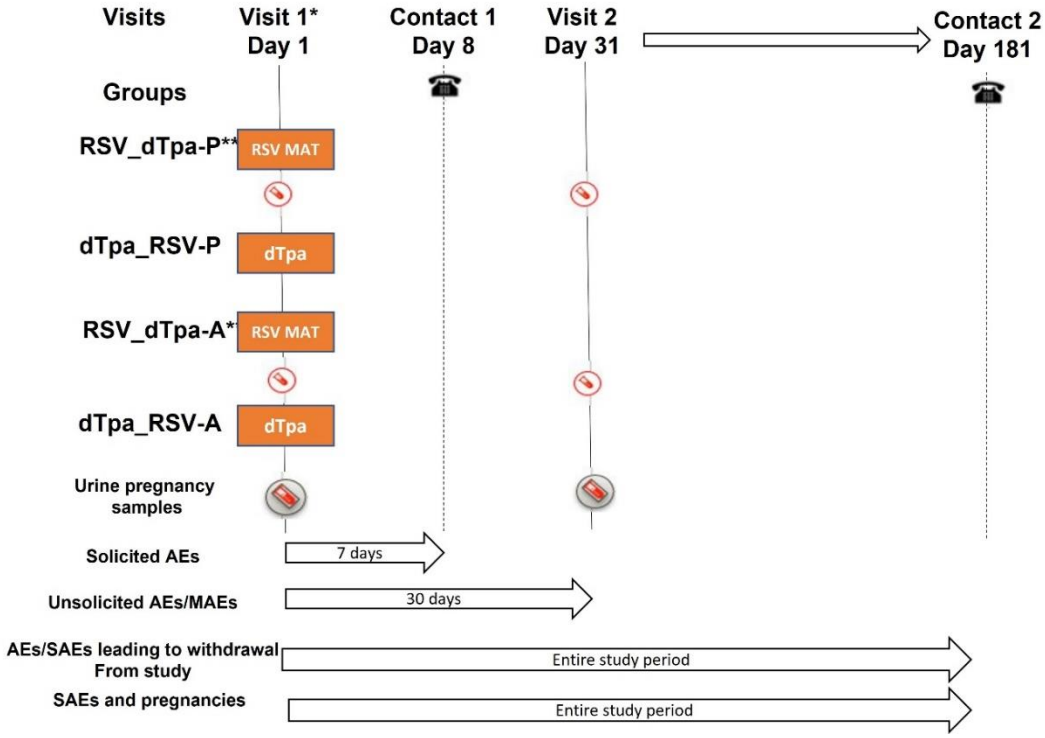
***The safety signals are being investigated and, although at this time a cause has not been determined, as a precautionary measure GSK stopped active enrollment and further vaccination of participants in the RSV MAT studies enrolling both pregnant women on February 25, 2022 and non-pregnant women on March 1, 2022. The study remains ongoing for safety follow-up. Participants already vaccinated will continue to be monitored until the end of the study.***

## Table 3 Study objectives, endpoints and estimands

| Objectives | Endpoint(s) and estimand(s) |
|---|---|
| **Primary** | |
| • ***To evaluate the safety following administration of RSV maternal vaccine in the pediatric (9-17 YOA) and adult (18-49 YOA) study groups during the entire study period. (180 days post RSV maternal vaccination)*** | ***The number and percentage of participants in each study group reporting***<br>• ***SAEs during the entire study period***<br>• ***AEs/SAEs/leading to study withdrawal during the entire study period*** |
| • To evaluate the reactogenicity and safety following administration of RSV maternal vaccine and dTpa control vaccine in the pediatric and adult study groups up to 30 days (including day of study intervention administration). | The number and percentage of participants in each study group reporting<br>• Each solicited administration site event collected during the 7 days follow-up post Dose 1 (Day 1 to Day 7 post intervention including day of vaccination)<br>• Each solicited systemic event during the 7 days follow-up period post Dose 1<br>• Each unsolicited AE collected during the 30 days follow-up period post Dose 1<br>• SAEs/MAEs during the 30 days follow-up period post Dose 1<br>• AEs/SAEs/MAEs leading to study withdrawal for the 30 days follow-up period post Dose 1 |
| **Secondary** | |
| • ***To evaluate the immunogenicity following the administration of RSV maternal vaccine in terms of RSV A neutralizing Ab titers in pediatric (9-17 YOA) and in adult (18-49 YOA) groups.*** | **RSV A neutralizing antibody titers at pre-dosing and Day 31 post RSV maternal vaccine administration** |
| • To evaluate the immunogenicity (RSVPreF3 IgG, RSV A Neutralizing Ab and RSV B Neutralizing Ab) of RSV maternal vaccine in the pediatric (9-17 YOA) and 18-49 YOA (adult) groups. | • RSV B Neutralizing Ab titers and RSVPreF3 IgG ELISA concentration at pre-dosing and Day 31, post RSV maternal vaccine administration. |

## Section 4.1 Overall design

**Figure 2 Study design overview**




* Screening and vaccination will happen on Visit 1 (Day 1).
** (RSV_dTpa-P & RSV_dTpa-A) Blood sampling to be done at Visit 1 and Visit 2 for participants receiving RSV maternal vaccine at Visit 1.***A urine pregnancy test will be done at Visit 2 if the participant has received RSV maternal vaccine in their first visit.***

- **Study Type**: Cross over design.
- **Study Duration**: The study interventions were administered at Visit 1 and the participant will be followed for 6 months (180 days post RSV maternal vaccine administration) subsequent the RSV maternal vaccine until the study conclusion.
- **Blinding**: This study will be an open label study.
- **Control Used**: dTpa will be used as an active control for safety and reactogenicity evaluation and to maximize the benefit to participants*.

  **** The participants in RSV_dTpa-P and RSV_dTpa-A group will be provided with an option to decide to receive dTpa vaccination as part of standard of care/local recommendation on immunization outside this study.***

- **Sample Collection Time Points**
  - RSV_dTpa-P: Day 1, Day 31, Day 181
  - RSV_dTpa-A: Day 1, Day 31, Day 181
- Vaccination schedules are described in Table 2.
- Randomized intervention allocation is described in in Table 4 and Section 6.3.
- Study (intervention) groups are described in Table 4.

- **Data collection**: e-Diaries will be used to collect solicited event data. Unsolicited Adverse event data will be collected through questioning at study visits/contacts and reported into the eCRF, as appropriate. See Section 8.3.2 for more detail.
- Safety monitoring will be conducted by SRT and IDMC.

**Table 4 Study groups, intervention, and blinding**

| Study groups** | Number of participants# | Age (Min-Max | Study intervention(s)* | Blinding |
|---|---|---|---|---|
| | | | | Visit1→Visit 4a or Visit 4b |
| RSV_dTpa-P | 63 | 9-17 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | Open Label |
| dTpa_RSV-P | 63 | 9-17 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |
| RSV_dTpa-A | 63 | 18-49 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |
| dTpa_RSV-A | 63 | 18-49 YOA | *RSVPreF3* *Boostrix* (dTpa_300 or dTpa_500) | |

*RSVPreF3=RSV maternal Vaccine
#Only 8 study participants have been enrolled in the study.
***There will no further enrolment and vaccination in all the study groups.***

**Table 5 Study interventions administered**

| | RSV maternal Vaccine* | | *Boostrix (dTpa_500)* | *Boostrix (dTpa_300)#* |
|---|---|---|---|---|
| **Study intervention name:** | RSVPreF3 | NaCl Solution | dTpa | dTpa |
| **Study intervention Formulation** | RSVPreF3 (120 µg) | Sodium Chloride (NaCl) (0.9%); Water for injections | DT[1] (≥ 2 IU); TT[1] (≥ 20 IU); PT (8 µg)[1]; FHA (8 µg)[1]; PRN (2.5 µg)[1]; [1]adsorbed on $Al(OH)_3$ (0.3 mg $Al^{3+}$) and $AlPO_4$ (0.2 mg $Al^{3+}$); Water for injections q.s. 0.5 mL | DT[1] (≥ 2 IU); TT[1] (≥ 20 IU); PT (8 µg)[1]; FHA (8 µg)[1]; PRN (2.5 µg)[1]; [1]adsorbed on $Al(OH)_3$ (0.3 mg $Al^{3+}$); Water for injections q.s. 0.5 mL |
| **Presentation** | Powder for solution for injection (vial) | | Suspension for injection (syringe) | Suspension for injection (syringe) |
| | Solution for solution for injection (syringe) | | | |
| **Type** | Study | | Control | Control |
| **Product Category** | Combination Product | | Combination Product | Combination Product |
| **Route of administration:** | IM | | IM | IM |
| **Location** | Arm | | Arm | Arm |
| **Laterality ** ** | non-dominant | | non-dominant | non-dominant |
| **No of doses** | 1 | | 1 | 1 |
| **Volume to be administered:** | whole content*** | | whole content**** | whole content**** |
| **Side/site route** | IM/non-dominant arm | | IM/non-dominant arm | IM/non-dominant arm |
| **Packaging, labelling and TM** | Refer to the SPM for more details | | Refer to the SPM for more details | Refer to the SPM for more details |
| **Manufacturer:** | GSK | | GSK | GSK |

* RSV maternal Vaccine=RSVPreF3

** 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 content 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 more details.

**** The entire content of the of the syringe will be administered. Refer to the SPM for more detail.

***#This dose form of Boostrix is not applicable in the study anymore as no non-US sites were initiated before the decision to stop the study.***

## Section 8.1.1 Biological samples

## Table 6 Biological samples

| Sample type Collected to Evaluate* | Time point (RSV_dTpa-P, RSV_dTpa-A) | Minimum Quantity per participant | Unit | Additional Information |
|---|---|---|---|---|
| Whole blood for immune response | Visit 1 (Day 1) | ~5 | mL | Immune response: 5 mL (~ 2 mL serum). |
| Whole blood for immune response | Visit 2 (Day 31) | ~5 | mL | Immune response: 5 mL (~ 2 mL serum). |
| | | **~10** | **mL** | |
| Urine for Pregnancy** | Visit 1 (Day 1) and Visit 2 (Day 31) | | | |

*The blood sample to be taken for immune response must be taken before administering the study intervention.

*****Urine sample was collected for all subjects at Visit 1. At Visit 2, urine sample will only be collected for study participants enrolled in RSV dTpa-P and RSV dTpa-A groups.***

## Section 8.1.2 Laboratory Assays

## Table 7 Laboratory assays

| Sampling time points | System | Component | Method* | Groups | Laboratory |
|---|---|---|---|---|---|
| Visit 1** (Day 1 prior to immunization) | Serum | Respiratory Syncytial Virus A Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus B Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus PreF3 Ab.IgG concentration | ELI | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| Visit 2*** (Day 31 prior to immunization) | Serum | Respiratory Syncytial Virus A Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus B Ab neutralizing | NEU | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |
| | Serum | Respiratory Syncytial Virus PreF3 Ab.IgG concentration | ELI | RSV_dTpa-P RSV_dTpa-A | GSK or GSK designated lab |

*NEU=Neutralization Assay; ELI=ELISA or enzyme-linked immunosorbent assay

** for participants receiving RSV maternal vaccine at Visit 1

****** Visit 2(Day 31 prior to immunization) is no more applicable after the study stop***

## Section 8.1.3 Immunological readouts

***The following readouts are applicable to only 8 participants enrolled in the study.***

## Table 8 Immunological read-outs

| Blood sampling timepoint | | Approximate No. participants | Component |
|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | |
| Visit 1* (Day 1) | pre- 1st vaccination | 126 | Respiratory Syncytial Virus A Ab neutralizing |
| | | 126 | Respiratory Syncytial Virus B Ab neutralizing |
| | | 126 | Respiratory Syncytial Virus PreF3 Ab.IgG concentration |
| Visit 2 (Day 31) | post 1st vaccination | 252 | Respiratory Syncytial Virus A Ab neutralizing |
| | | 252 | Respiratory Syncytial Virus B Ab neutralizing |
| | | 252 | Respiratory Syncytial Virus PreF3 Ab.IgG concentration |

* for participants receiving RSV maternal vaccine at Visit 1

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

| Event | V1 | | C1 | | V2 | Contact 2 |
|---|---|---|---|---|---|---|
| | D1 | D7 | D8 | D30 | D31 | 180 days post RSV vaccination*** |
| Solicited administration site event and systemic AEs | | | | | | |
| | | | | | | |
| | | | | | | |
| Unsolicited AEs | | | | | | |
| | | | | | | |
| | | | | | | |
| AEs leading to withdrawal from the study | | | | | | |
| | | | | | | |
| | | | | | | |
| SAEs* | | | | | | |
| | | | | | | |
| | | | | | | |
| MAEs | | | | | | |
| | | | | | | |
| | | | | | | |
| Pregnancies | | | | | | |
| | | | | | | |

. V=Visit; D=Day; C=Contact

* SAEs related to study participation or concurrent GSK medication/vaccine will be monitored from the time of screening to the time of the immunization. Both will be conducted on the same visit.

****** For all study groups at Day 181***

## Section 9 Statistical considerations

***This section will not be applicable as the study has been stopped. However only descriptive statistics will be provided for immunogenicity, safety and reactogenicity at an individual level.***

## Section 9.1 Statistical hypotheses

***No hypothesis test will be performed. All analyses will be descriptive.***

## Section 9.3.1.1 Safety

| | Primary Safety Endpoints | Statistical Analysis Methods |
|---|---|---|
| **Pediatric and Adult participants** | The number of participants in each study group reporting Each solicited administration site event collected during the 7 days follow-up period post Dose 1 (Day 1 to Day 7 post intervention including day of vaccination)<br>• Each solicited systemic event collected during the 7 days follow-up period post Dose 1<br>• Each unsolicited AE collected during the 30 days follow-up period post Dose 1<br>• SAEs/MAES collected during the 30 days follow-up period post Dose 1<br>• AEs/SAEs leading to study withdrawal for the 30 days follow-up period post Dose 1<br><br>***The number of participants in each study group reporting***<br>• ***SAEs during the entire study period.***<br>***AEs/SAEs leading to study withdrawal during the entire study period.*** | The number of adult and pediatric 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 Day 7 post intervention including day of vaccination) follow-up period after dosing will be tabulated by maximum intensity per participant for each study group.<br>The number of participants reporting:<br>• at least one administration site AE (solicited)<br>• at least one systemic AE (solicited)<br>during the 7-day follow-up period after dosing will be tabulated .<br>The number and percentage of participants reporting:<br>• at least one AE (unsolicited)<br>• at least one SAE/MAE<br>• at least one AE/SAE leading to study withdrawal<br>during the 30-days post Dose 1 follow-up period after dosing will be tabulated .<br>The same computations will be done for Grade 3 solicited and unsolicited AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for any AEs resulting in a medically attended visit (i.e., MAEs).<br>***The number of both the pediatric and adult participants reporting:***<br>• ***at least one SAE***<br>• ***at least one (S)AE leading to study withdrawal during the entire study period will be tabulated by group/doses and by MedDRA preferred term.***<br>***By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared, but will not be released until the final, unblinded, analysis has been completed.*** |

## Section 9.3.2.1 Immunogenicity

| | Secondary Immunogenicity Endpoints | Statistical Analysis Methods |
|---|---|---|
| **Pediatric and Adult participants** | ***RSV A neutralizing antibody titers at pre-dosing and Day 31 post RSV maternal vaccine administration*** | ***For RSV A neutralizing antibody titers at pre- dosing and Day 31 post RSV maternal vaccine administration :***<br>• ***Antibody titers/concentrations will be displayed using reverse cumulative curves.***<br>• ***Individual antibody titers at pre-dosing and Day 31 will be listed.***<br>• ***Individual post-dosing versus pre-dosing results will be plotted using scatter plots.***<br>• ***Individual fold increase of antibody titers at Day 31 post RSV maternal vaccine administration over pre-dosing will be tabulated .*** |
| | ▪ RSV B Neutralizing Ab titers and RSVPreF3 IgG ELISA | For each assay, at each timepoint: |

| | **Secondary Immunogenicity Endpoints** | **Statistical Analysis Methods** |
|---|---|---|
| | concentration at pre-dose, Day 31 post RSV maternal vaccine administration. | Antibody concentrations/titers will be displayed using reverse cumulative curves.<br>• Individual antibody titers/concentrations at pre-dosing and Day 31 will be listed<br>• Individual post-dosing versus pre-dosing results will be plotted using scatter plots.<br>• Individual fold increase of antibody titers/concentrations at each post-dosing timepoint over pre-dosing will be tabulated.<br>Relationship between RSVPreF3 IgG-specific antibody concentration, RSV A neutralizing antibody, and RSV B neutralizing antibody at baseline and each post RSV maternal vaccine administration timepoint will be explored using scatter plots of individual values. |

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