Statistical Analysis Plan

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

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TITLE PAGE

Protocol 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.
Study Number:	217354 (RSV MAT-039)
Compound Number:	GSK3888550A
Abbreviated 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.

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s)

EudraCT number 2021-004003-41

Registry	**ID**
Clintrials.gov	

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	08 Dec. 2021	V1.0 11 August 2021	Not Applicable	Original version
SAP Amendment 1	19 May 2022	V2.0 Protocol Amendment 1 17 March 2022	Hypothesis tests are removed from the analysis plan. All analyses will be descriptive.	The study has been stopped and only 8 participants were enrolled in the study.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217354 (RSV MAT-039). Details of the planned analyses are provided. Since the study has been stopped and only 8 participants were enrolled, descriptive statistics will be provided for safety, reactogenicity, and immunogenicity at an individual level.

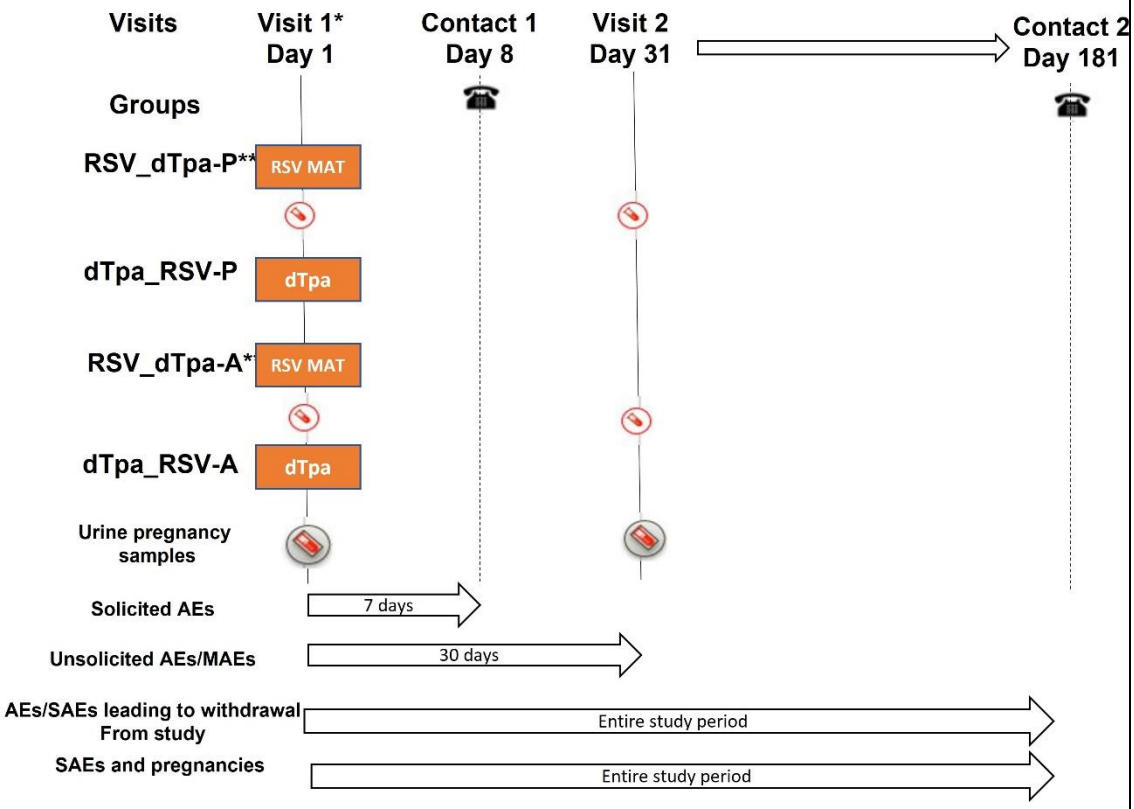
1.1. Objectives, Estimands and Endpoints

Table 1 Study objectives, estimands and endpoints

Objectives	Endpoints and Estimands
Primary	
• 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 of participants in each study group reporting • Each solicited administration site event collected during the 7 days follow-up post study intervention period (Day 1 to Day 7 post intervention including day of vaccination) • Each solicited systemic event during the 7 days follow-up period post study intervention • Each unsolicited AE collected during the 30 days follow-up period post study intervention • SAEs/MAEs during the 30 days follow-up period post study intervention • AEs/SAEs/MAEs leading to study withdrawal for the 30 days follow-up period post study intervention
• 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 of participants in each study group reporting • SAEs during the entire study period. • AEs/SAEs/leading to study withdrawal during the entire study period
Secondary	
To evaluate the immunogenicity (RSV A Neutralizing Ab, RSV B Neutralizing Ab, and RSVPreF3 IgG) of RSV maternal vaccine in the pediatric (9-17 YOA) and 18-49 YOA (adult) groups. 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 Ab, RSV B neutralizing Ab titers, and RSVPreF3 IgG antibody concentrations at pre-dosing and Day 31 post RSV maternal vaccine administration.

1.2. Study Design

Overview of Study Design and Key Features



* 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.***

Design Features	This study will be a Phase 3 study to evaluate safety, reactogenicity, and humoral immunogenicity of RSV maternal vaccine in healthy non-pregnant girls 9 to17 YOA (pediatric study group) and in non-pregnant adult women 18 to 49 YOA (adult study group). • **Study Type**: Cross over design. • **Study Duration**: The study interventions will be administered at Visit 1 and the participant will be followed for 6 months (180 days post RSV maternal vaccine administration) subsequent to the RSV maternal vaccine and 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*.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td>* 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.</td></tr>
<tr><td>Study intervention</td><td>Study groups, intervention and blinding
<table>
<tr><th>Study groups**</th><th>Number of participants#</th><th>Age (Min-Max)</th><th>Study intervention(s)*</th><th>Blinding Visit1→Co 2</th></tr>
<tr><td>RSV_dTpa-P</td><td>63</td><td>9-17 YOA</td><td>RSVPreF3
Boostrix (dTpa_300 or dTpa_500)</td><td rowspan="4">Open Label</td></tr>
<tr><td>dTpa_RSV-P</td><td>63</td><td>9-17 YOA</td><td>RSVPreF3
Boostrix (dTpa_300 or dTpa_500)</td></tr>
<tr><td>RSV_dTpa-A</td><td>63</td><td>18-49 YOA</td><td>RSVPreF3
Boostrix (dTpa_300 or dTpa_500)</td></tr>
<tr><td>dTpa_RSV-A</td><td>63</td><td>18-49 YOA</td><td>RSVPreF3
Boostrix (dTpa_300 or dTpa_500)</td></tr>
</table>
*RSVPreF3=RSV maternal Vaccine. P=Pediatric (9-17 YOA); A=Adult (18-49 YOA).
#Only 8 study participants have been enrolled in the study.
**There will no further enrolment and vaccination in all the study groups.</td></tr>
<tr><td>Study intervention Assignment</td><td>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.

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.</td></tr>
<tr><td>Conduct of Analyses</td><td>No interim analysis is planned. The final analysis will be performed when all data up to study end are available.</td></tr>
</table>

2. STATISTICAL HYPOTHESES

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

2.1. Multiplicity Adjustment

N/A.

3. ANALYSIS SETS

3.1. Definition

Table 2 Analysis Sets definitions

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who completed the informed consent process and signed the informed consent form. All participants who completed the informed consent process and signed the informed consent form.	Study Population
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.	Safety
Full Analysis Set (FAS)-Immunogenicity	All participants who received the study intervention (RSV maternal vaccine) and have post-vaccination immunogenicity data.	Immunogenicity
Per-Protocol (PP)-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. 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.	Immunogenicity
Solicited Safety	All participants in the Exposed Set who have solicited safety data	Safety
Unsolicited Safety	All participants in the Exposed Set that report unsolicited AEs/report not having unsolicited AEs	Safety

3.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify participants to be eliminated from analysis. Detail is provided below for each set.

3.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all), 800 (Fraudulent data) and code 900 (invalid informed consent or fraudulent data) will be used for identifying subjects eliminated from ES.

3.2.2. Elimination from Full Analysis Set (FAS) - Immunogenicity

A participant will be excluded from the FAS analysis under the following conditions.

Table 3 Elimination code and condition

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1050	Randomisation failure	All	Immunogenicity
2100.Vx	Serological results not available	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity

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

3.2.3. Elimination from Per-protocol analysis Set (PPS) - Immunogenicity

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

Table 4 Elimination code and condition

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All
900	Invalid informed consent	All	All
1030	Study vaccine not administered at all	All	Safety, immunogenicity
1040.Vx+*	Administration of concomitant vaccine(s) forbidden in the protocol	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity
1050	Randomisation failure	All	Immunogenicity
1070**	Participants got vaccinated with the correct vaccine but containing an incorrect volume	All	Immunogenicity
1070**	Vaccination not according to protocol (site of injection, route of administration, wrong replacement of study treatment administered)	All	Immunogenicity
1070**	Study treatment not prepared as per protocol (e.g. reconstitution)	All	Immunogenicity
1070**	Other deviations related to wrong study treatment/administration/dose	All	Immunogenicity
1070**	Study treatment administered while contraindication	All	Immunogenicity
1080	Vaccine temperature deviation	All	Immunogenicity
1090	Expired vaccine administered	All	Immunogenicity
2010	Protocol violation (inclusion/exclusion criteria) DOB – VAC – 9-49 years	All	Immunogenicity
2040.Vx+*	Administration of any medication forbidden by the protocol	Visit 2/Day 31 Contact 2/Day 181	Immunogenicity

2040.Vx+*	Device, excluded by the protocol, was administered	Visit 2/Day 31 Contact 2/Day 181	Immunogenicity
2050.Vx+*	Intercurrent medical conditions which are exclusionary as per protocol	Visit 2/Day 31 Contact 2/Day 181	Immunogenicity
2060.Vx+*	Concomitant infection related to the vaccine which may influence immune response	Visit 2/Day 31	Immunogenicity
2070.Vx+*	Concomitant infection not related to the vaccine but may influence immune response	Visit 2/Day 31	Immunogenicity
2090.Vx	Subjects did not comply with blood sample schedule: • For PPS at Day 1, check the interval from Visit 1 to day 1 BS = 0 day; • For PPS at Day 31, check the interval from Visit 1 to day 31 BS = 31 – 45 days;	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity
2100.Vx	Serological results not available	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity
2120.Vx	Obvious incoherence or abnormality or error in data	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity
2130.Vx	Testing performed on samples not aligned with ICF	Visit 1/Day 1 Visit 2/Day 31	Immunogenicity

*Attribution of these elimination codes to subject need CRDL review of individual listing
** Attribution of code 1070 to a subject requires CRDL confirmation
Vx+ indicates subjects whose immunogenicity data will be eliminated from a specific visit onwards; Vx indicates subjects whose immunogenicity data will be eliminated from a specific visit.
DOB-Date of Birth, VAC-Vaccination, BS- Blood Sample

3.2.4. Elimination from solicited safety set

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

4. STATISTICAL ANALYSES

4.1. General Considerations

All safety analyses will be performed on the Solicited Safety, and Exposed sets. Safety endpoints including solicited AEs, unsolicited AEs, SAEs, AEs leading to study termination will be descriptively summarized.

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

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

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

Pre-dosing is defined as Day 1 for RSV_dTpa-P and RSV-dTpa-A groups.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint(s) Analyses

4.2.1. Safety

4.2.1.1. Analysis of safety and reactogenicity planned in the protocol

All safety analyses will be performed on the Solicited Safety and Exposed sets. Safety endpoints including solicited AEs, unsolicited AEs, SAEs, AEs, MAE's leading to study termination will be listed.

	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 study intervention (Day 1 to Day 7 post intervention including day of vaccination) • Each solicited systemic event collected during the 7 days follow-up period post study intervention • Each unsolicited AE collected during the 30 days follow-up period post study intervention • SAEs/MAEs collected during the 30 days follow-up period post study intervention • AEs/SAEs leading to study withdrawal for the 30 days follow-up period post study intervention The number of participants in each study group reporting • SAEs during the entire study period. 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. The number of participants reporting: • at least one administration site AE (solicited) • at least one systemic AE (solicited) during the 7-day follow-up period after dosing will be tabulated. The number of participants reporting: • at least one AE (unsolicited) • at least one SAE/MAE • at least one AE/SAE leading to study withdrawal during the 30-days post study intervention follow-up period after dosing will be tabulated. 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). The number of both the pediatric and adult participants reporting: • at least one SAE • 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. By participant listings of SAEs, (S)AEs leading to study withdrawal and MAEs will be prepared, but will not be released until the final analysis has been completed.

AE= Adverse event; **SAE**= Serious Adverse event; **CI**= Confidence interval; **MAE** = medically attended adverse event

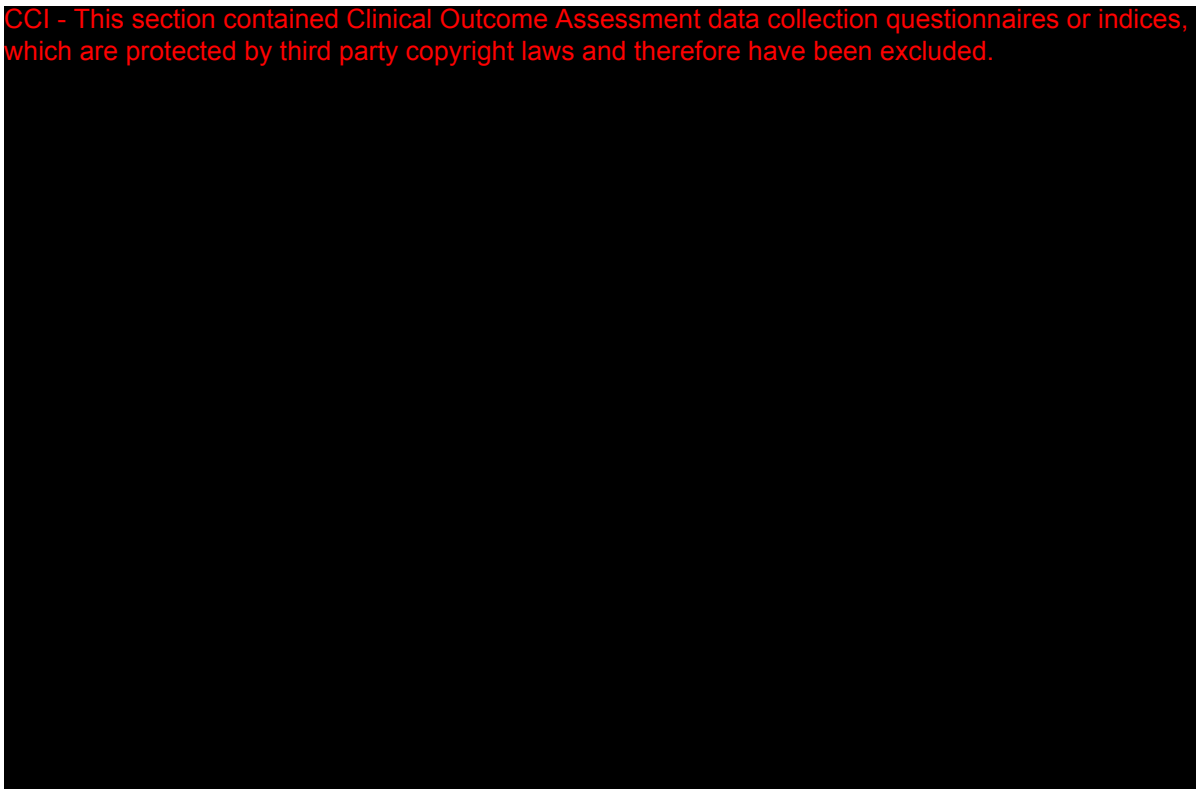
4.2.1.2. Additional considerations

4.2.1.2.1. Analysis of solicited events

The analysis of solicited events will be performed on Solicited Safety Set. The following administration site events will be solicited: Pain, Redness, and Swelling. The following systemic events will be solicited: Fever, Headache, GI Symptoms (Nausea, Vomiting, Diarrhea, Abdominal pain), and Fatigue. The intensity of the solicited events will be assessed as described:

Table 5 Intensity scales for solicited events in adults and children of 6 years of age or more

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.



Duration in days of solicited administration site and systemic events within 7 days after study intervention will be listed. The derivation rule of duration in days for solicited events is detailed in section 6.2.4.9.

4.2.1.2.2. Analysis of unsolicited adverse events

The analysis of unsolicited events will be performed on Exposed Set.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Immunogenicity

4.3.1.1. Analysis of immunogenicity planned in the protocol

The analysis will be based on the Full Analysis set.

	Secondary Immunogenicity Endpoints	Statistical Analysis Methods
Pediatric and Adult participants	▪ RSV A Neutralizing Ab titers, RSV B Neutralizing Ab titers, and RSVPreF3 IgG antibody concentrations at pre-dose and Day 31 post RSV maternal vaccine administration.	For RSV A, RSV B neutralizing antibody titers and RSVPreF3 IgG antibody concentration at pre- dosing and Day 31 post RSV maternal vaccine administration: • Individual antibody titers at pre-dosing and Day 31 will be listed. • Individual post-dosing versus pre-dosing results will be plotted using scatter plots. • Individual fold increase of antibody titers at Day 31 post RSV maternal vaccine administration over pre-dosing will be tabulated.

RSV A = Respiratory syncytial virus subtype A; **RSV B** = Respiratory syncytial virus subtype B; **RSVPreF3 IgG** = Respiratory syncytial virus PreF3 immunoglobulin G.

4.4. Tertiary Endpoint(s) Analyses

N/A.

4.5. Other Safety Analyses

Other safety analyses will be based on the Exposed set, unless otherwise specified.

4.5.1. Combined solicited and unsolicited events

The combined analysis of solicited and unsolicited events will be performed on Exposed Set. A listing of participants with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	Injection site pain	10022086
Redness	Redness at injection site	10022098
Swelling	Swelling at injection site	10053425
Fatigue	Fatigue	10016256
Fever	Fever	10016558
Nausea	Nausea	10028813
Vomiting	Vomiting	10047700
Diarrhea	Diarrhea	10012727
Abdominal pain	Abdominal pain	10000081
Headache	Headache	10019211

Please note – to check for AE term in CDISC during dry run

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

4.5.2. COVID-19 Assessment and COVID-19 AEs

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

The listing of participants with a suspected, probable or confirmed COVID-19 infection will be provided based on Exposed Set.

The listing of participants who had a COVID-19 test performed and the listing of participants with positive, negative and indeterminate results will be provided on Exposed Set.

4.5.3. Additional Safety Assessments (if applicable)

The listing of vital signs will be provided at all timepoint(s). The information is collected on Exposed Set and Per-protocol Set. The parameters include but may not be limited to systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, heart rate, respiratory rate, height, weight and body mass index (BMI).

4.6. Other Analyses

4.6.1. Subgroup analyses

N/A.

4.7. Conduct of Analyses

No interim analyses are planned.

4.7.1. 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.

4.8. Changes to Protocol Defined Analyses

Reverse cumulative curves of antibody titers/concentrations will be removed from the analysis plan. The analysis is not applicable.

Exploring the relationship between RSVPreF3 IgG-specific antibody concentration, RSV A nAb, and RSV B nAb at baseline and Day 31 post RSV maternal vaccine administration will be removed from the analysis plan. Individual RSV A nAb, RSV B nAb and RSVPreF3 IgG titers/concentrations at baseline and Day 31 post RSV maternal vaccine administration will be provided.

5. SAMPLE SIZE DETERMINATION

Approximately 252 participants were planned to be randomized to achieve approximately 226 evaluable participants allowing for 10% dropout rate.

Participants who withdraw from the study will not be replaced.

Since there are only 8 participants enrolled in this study, all analyses will be in a descriptive manner. The sample size/power calculations are not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

Participant disposition will be summarized by group using descriptive statistics:

- Number of participants screened, randomised, exposed and withdrawn including withdrawal reasons in each group and overall will be tabulated.

6.1.2. Demographic and Baseline Characteristics

6.1.2.1. Analysis of demographics/baseline characteristics

These analyses will be performed on the Exposed set.

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be listed.

6.1.2.2. Additional considerations

- Demographic characteristics will also be summarized on Enrolled Set for web public disclosure.
- Subject disposition will be summarized by group using descriptive statistics:
- Number of participants screened, randomised, exposed and withdrawn including withdrawal reasons in each group and overall will be tabulated.
- The listing of past medical history and current medical conditions will be providedon Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) term. Un-coded medical conditions or medical history will be listed under ‘Other’ category.
- Vaccination history will be coded using GSK Drug dictionaries. The listing of vaccination history will be provided on Exposed Set.

6.1.3. Protocol Deviations

Important protocol deviations will be listed based on Exposed Set.

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

- Data will be reviewed prior to freezing the database to ensure all important deviations captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.
- An individual listing of protocol deviation will be provided.

Protocol deviations which result in exclusion from the analysis set will also be listed. Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

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

An individual listing of important protocol deviations leading to elimination will be provided.

6.1.4. Concomitant Medications and Vaccinations

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

- The listing of participants taking concomitant medications /vaccinations within 7 days following vaccination, 30 days following study intervention administration, and 180 days following study intervention administration will be provided.

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

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

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date is the date of randomization OR the study intervention start date and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

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

6.2.2. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

6.2.3. Handling of missing data

6.2.3.1. Dates

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

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

The following exceptions apply:

- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before study dose' is selected, the imputed date will be one day before the first (or only) study dose given during that month.

- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before study dose' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

6.2.3.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

6.2.3.3. Daily recording of solicited events

6.2.3.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited events, a solicited event will be considered present only when a daily recording of grade 1 or more is present.

6.2.3.4. Unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

Missing severity, relationship with study intervention, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

6.2.4. Data derivation

6.2.4.1. Age at first dose in years

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

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

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

6.2.4.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

6.2.4.3. Height

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

Height in centimeters = Height in inches x 2.54

6.2.4.4. Body mass index (BMI)

BMI will be calculated as follows:

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

6.2.4.5. Temperature

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

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

6.2.4.6. Numerical serology results

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

IS.ISORRES	**Derived value**
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

The cut-off tests for immunogenicity evaluation will be as per following:

System	**Component**	**Method**	**Unit**	**Cut-off *(LLOQ)***
Serum	RSV-A Neutralising Antibody	NEUTRALISATION	ED60	18
Serum	RSVPreF3 IgG antibody concentrations	ELISA	EU/mL	*25*
Serum	RSV-B Neutralising Antibody	NEUTRALISATION	ED60	*30*

Note: the assay cut-off (LLOQ), ULOQ and units may be further adjusted at time of analysis when notified by the lab.

6.2.4.7. Onset day

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

6.2.4.8. Duration of events

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

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

6.2.4.9. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs will be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

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

6.2.4.10. Counting rules for occurrences of solicited events

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

6.2.5. Display of decimals

6.2.5.1. Percentages

Percentages will be displayed with one decimal except for 100% in which case no decimal will be displayed.

6.2.5.2. Differences in percentages

Differences in percentages will be displayed with two decimals.

6.2.5.3. Demographic/baseline characteristics statistics

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

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

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

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

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

7. REFERENCES

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

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