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GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, observer-blind, randomized, multi-country study to assess the reactogenicity and safety of the Porcine circovirus (PCV) free liquid formulation of GSK's oral live attenuated human rotavirus (HRV) vaccine as compared to the lyophilized formulation of the GSK's HRV vaccine, when administered as a 2-dose vaccination in infants starting at age 6-12 weeks.
eTrack study number and Abbreviated Title	208236 (ROTA-096)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan - amendment 1	Final: 15 October 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3 June 2019)

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
ES	Exposed Set
eTMF	Electronic Trial Master File
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
ToC	Table of Content
UL	Upper Limit of the confidence interval

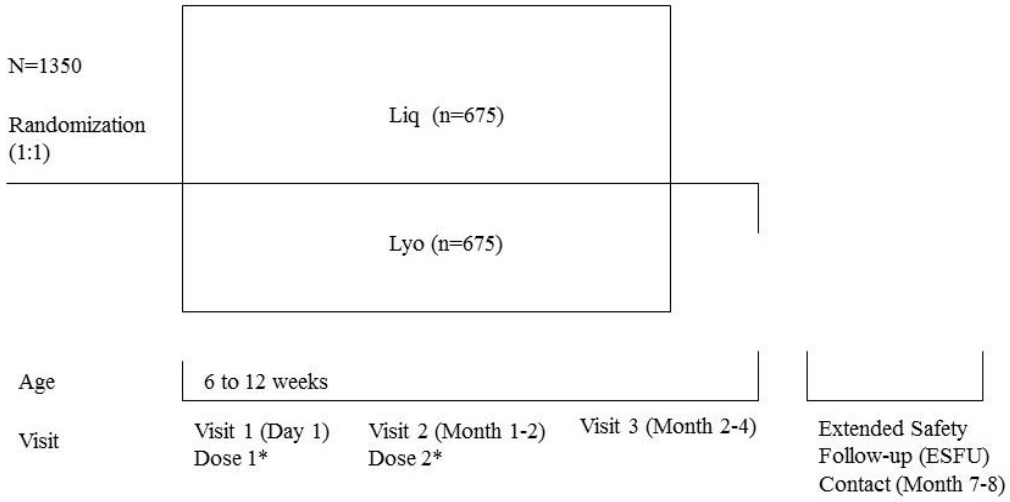
1. DOCUMENT HISTORY

Date	Description	Protocol Version
11 June 2019	First version	Final version 2: 09 November 2018
15 October 2020	Amendment 1*	Final version 2: 09 November 2018

* following CBER request to comply with the CDISC Vaccines Therapeutic Area guide, the SDTM have been updated. One of the updates requires that solicited events which continue beyond the observation period be stored in the Adverse Events (AE) domain. This amendment aims at clarifying that these solicited events will not be included in the summaries of unsolicited adverse events. Some summaries will be generated according to whether Number and percentage of subjects vaccinated, completed and withdrawn from the study with reason for study withdrawal – subjects receiving their first dose on or before October 31st 2019

2. STUDY DESIGN

Figure 1 Study design overview



The Extended safety follow-up (ESFU) contact (by telephone call or any other convenient procedure) will take place 6 months after the last dose of the study vaccines.
N=Target number of subjects, n=Target number of subjects in each study group.
*Two doses of the study vaccines will be administered to subjects at 1-month or 2-months interval.

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician will review the safety data on a regular basis to evaluate if there is any safety concern with the PCV-free liquid HRV vaccine.

Table 1 Study groups, treatments and epoch foreseen in the study

Study groups	Number of subjects	Age at Dose 1 (Min-Max)	Treatment name	Vaccine/Product names
Liq	675	6-12 weeks	HRV Liquid (oral administration)	HRV PCV-free
Lyo	675	6-12 weeks	HRV Lyophilized (oral administration)	HRV Lyo
				HRV Diluent

- Control: active control, GSK's lyophilized HRV vaccine.
- Vaccination schedule:
  - Two doses of HRV vaccines to be administered according to 0, 1-2-month schedule.
  - Concomitant administration of routine childhood vaccines will be allowed according to the local immunization practices in each participating country.
- Treatment allocation: Randomized with balanced allocation (1:1) using GSK's central internet randomization system (SBIR). Refer to Section 7.2.2.2 of the protocol for a detailed description of the randomization method.
- Blinding: observer-blind.

The following group names will be used in the TFLs:

Group order in tables	Group label in tables	Group definition for footnote
1	Liq	HRV vaccine liquid formulation
2	Lyo	HRV vaccine lyophilised formulation

3. OBJECTIVES/ENDPOINTS

Table 2 Study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the reactogenicity of the liquid HRV vaccine and lyophilized HRV vaccine in terms of solicited adverse events (AEs) during the 8-day (Day 1-Day 8) follow-up period after each vaccination.	• Occurrence of each solicited general AE within 8 days (Day 1–Day 8) after each vaccination.
To assess the safety of the liquid HRV vaccine and lyophilized HRV vaccine in terms of unsolicited AEs during the 31-day (Day 1-Day 31) follow-up period after each vaccination and serious adverse events (SAEs) during the entire study period.	• Occurrence of unsolicited AEs within 31 days (Day 1–Day 31) after any vaccination, according to the medical dictionary for regulatory activities (MedDRA) classification. • Occurrence of SAEs throughout the study period (i.e. from Dose 1 of the HRV vaccine to study conclusion at the end of the follow-up period).

4. ANALYSIS SETS

4.1. Definition

The following analysis sets will be used for this study:

Analysis set	Description
Enrolled	All subjects who were randomised or vaccinated
Exposed	All subjects who received at least 1 dose of the study treatment. For the sake of analysis, the study group is defined by the treatment administered at Dose 1.

4.2. Criteria for eliminating data from Analysis Sets

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

4.2.1. Elimination from Enrolled Set

Only subjects with codes 800 and 900 (invalid informed consent or fraudulent data) will be eliminated from the Enrolled Set.

4.2.2. Elimination from Exposed Set

All subjects with code 1030 (Study vaccine not administered at all) or codes 800 or 900 (invalid informed consent or fraudulent data) will be eliminated from the Exposed Set.

5. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in Section 10.1 and will not be repeated here. The study specific data derivation rules and statistical methods will be described in section 9.

5.1. Important protocol deviations

The following deviations will be considered important protocol deviations. Only codes 800, 900, and 1030 will lead to elimination from analysis sets (see section 4.2).

Code	Decode: Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Study vaccine dose not administered but subject number allocated: subjects enrolled but not vaccinated
1050	Randomisation failure: forced or manual randomization*. First dose of vaccine administration not aligned with the randomized treatment.
1040	Administration of concomitant vaccine(s) forbidden in the protocol: Administration of a non study HRV vaccine or non routine vaccine starting from 30 days before the first vaccination up to study end.
1060	Randomisation code broken at the investigator site: Subjects unblinded in the central randomization system or unblinding reported as protocol deviation
1070	Study vaccine dose not administered according to protocol: • Subjects vaccinated with the correct vaccine but who regurgitated for one of the 2 doses and did not receive a vaccine replacement; • subjects for whom the second administered dose is not aligned with the first dose (e.g. lyo as second dose after a first dose with liquid) • Subject who did not receive the second dose • Route of vaccination which is not oral
1080	Vaccine temperature deviation: Subjects who have received a vaccine which had a temperature deviation qualified as inappropriate for use by Quality Assurance.
1090	Expired vaccine administered: Subjects who received an expired vaccine
2010	Protocol violation linked to the inclusion/exclusion criteria: Ineligible subjects who was vaccinated (i.e. Age at dose 1 is not between 42-90 days, gestational age is < 29 weeks or other eligibility criteria – see section 6.1 of the protocol)
2040	Administration of any medication forbidden by the protocol: administration of • Any investigational or non-registered drug between Visit 1 to Visit 3. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days) during the study period between Visit 1 to Visit 3. For corticosteroids, this will mean prednisone (0.5 mg/kg/day, or equivalent). • Immunoglobulins and/or any blood products administered during the study period between Visit 1 to Visit 3. • Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
2080	Non-compliance with vaccination schedule (including wrong and unknown dates): Subjects who did not comply with the interval for dose 2 (Dose 2 should be between 28-83 days after Dose 1).
2500	Short follow-up: subjects with a safety follow-up period after the last dose of HRV vaccine that is less than 180 days.
2600	Subject did not provide any post-vaccination solicited safety data: Vaccinated subjects without complete documentation of solicited symptoms i.e. for a vaccine dose administered, at least one solicited symptom is not documented as being present or absent.

* Forced randomization: In case of supplies shortage for the next assigned vaccine according to the randomization schedule at the clinical site, the randomization system will use the forced randomization procedure in order to continue to enrol and vaccinate subjects. The system moves seamlessly to the next treatment/randomization number for which vaccine supplies are available. The site will not be aware of the forced randomization event.

Manual randomization: In case the randomization system is unavailable, the investigator has the option to perform randomization by selecting supplies available at the site according to a pre-defined rule. In case the randomization system is available, a vaccine different from the randomized treatment may have been administered at dose 1.

5.2. Demography

5.2.1. Analysis of demographics/baseline characteristics planned in the protocol

The median, mean, range and standard deviation of age (in weeks) at each study vaccine dose and of the gestational age at birth will be computed by study group. The median, mean and standard deviation of length (in centimetres) and weight (in kilograms) at Visit 1 will be computed by study group. The distribution of racial and sex composition of the study population will be presented.

The distribution of subjects enrolled in each country/site will be tabulated across and per study group.

Important protocol deviations (as defined in section 5.1) will be tabulated by study group.

5.2.2. Additional considerations

None

5.3. Exposure

5.3.1. Analysis of exposure planned in the protocol

Number of enrolled, vaccinated (at least 1 vaccination, full vaccination course) subjects and reason for withdrawal, included in each study group and in total will be described.

5.3.2. Additional considerations

None

5.4. Analysis of safety and reactogenicity

5.4.1. Analysis of safety and reactogenicity planned in the protocol

The primary safety analysis will be performed on the Exposed set.

The percentage of doses and of subjects reporting at least 1 AE (solicited or unsolicited) during the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination will be computed, along with exact 95% CI. The same calculations will be done for AEs (solicited or unsolicited) rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of doses and of subjects reporting each individual solicited general AE will be computed, over the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited AE rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. For fever, additional analyses will be performed by 0.5°C increments. These calculations will also be performed by country, sex and frequent race.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate preferred term. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 1-Day 31) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination, for unsolicited AEs rated as grade 3 with causal relationship to vaccination and those that resulted in a medically attended visit. These calculations will also be performed by country.

For each study group, the percentage of subjects who started taking at least 1 concomitant medication, antipyretic medication and prophylactic antipyretic medication during the 8-day (Day 1-Day 8) and 31-day (Day 1-Day 31) follow-up periods post-vaccination will be tabulated by dose, by subject for each dose and across the 2 doses.

Subjects who experienced at least 1 SAE during the entire study period (from Dose 1 till ESFU contact at Month 7-8) will be summarised by study group and all SAEs will be tabulated.

5.4.2. Additional considerations

The definition of frequent race is any race (cDISC categories) with at least 40 subjects overall. The ‘Other races’ subgroup will include all races that do not meet this criterion.

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain the final analyses of all endpoints.

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES

The following sections describe additional derivation rules which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Data derivation

In all summaries of vaccine exposure the following will apply.

Co-administered vaccines will be those given on the same day as the study vaccine (HRV). Concomitant vaccinations will be all vaccines given on any other days.

9.2. Counting rules for occurrence of unsolicited adverse events

Following CBER request to comply with the CDISC Vaccines Therapeutic Area guide, the SDTM have been updated on October 2020. One of the updates requires that solicited events which continue beyond the observation period be stored in the Adverse Events (AE) domain. These solicited events will not be included in the summaries of unsolicited adverse events.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an AE is between Dose 1 and Dose 2, the relative dose will be Dose 1.

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 eCRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day 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 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be 1 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 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that

year. If 'before vaccination' is selected, the imputed date will be 1 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.

10.1.2.2. Daily recording of solicited AEs

When a specific solicited AE is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the solicited AE in question), all daily measurements will be imputed as Grade 0.

When a specific solicited AE is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the solicited AE in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

When the occurrence of a specific solicited AE is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the solicited AE in question) but the group of solicited AEs is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

The following table shows how subjects contribute to each category for a specific solicited AE over the Day X to Day Y post-vaccination period:

Solicited AE category	Subjects included in the calculation of the numerator
Any	All subjects with at least 1 occurrence of the solicited AE at grade 1, grade 2, or grade 3 between Day X and Day Y or with the solicited AE marked as present and at least 1 missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least 1 occurrence of the solicited AE at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All subjects with at least 1 occurrence of the solicited AE at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All subjects with at least 1 occurrence of the solicited AE at grade 3 between Day X and Day Y

10.1.2.3. Unsolicited adverse events

Unsolicited AE summaries will include SAEs unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in weeks

Age at vaccination will be displayed in weeks. It will be calculated as the number of complete weeks the date of birth (DOB) and the date of vaccination. For example:

DOB = 10JUN2019, Date of vaccination = 28JUL2019 -> Age = 6 weeks

DOB = 10JUN2019, Date of vaccination = 29JUL2019 -> Age = 7 weeks

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Length

Length will be presented in centimeters. Lengths reported in feet and inches will be converted as follows:

Length in centimeters = (Feet x 12 + Inches) x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. 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

10.1.3.6. Onset day

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

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events 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 1 occurrence.

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as only 1 occurrence regardless of the number of days on which it occurs.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with 1 decimal

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (age, length, weight, body mass index (BMI)) will be presented with 1 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 maxima and minima of transformed length variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with 1 decimal.

The maximum and minima of transformed body temperatures will be displayed with 1 decimal.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.2. TFL ToC

A TFL ToC detailing the tables, figures, and listings that will be produced will be provided separately.

11. REFERENCES

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

CONFIDENTIAL

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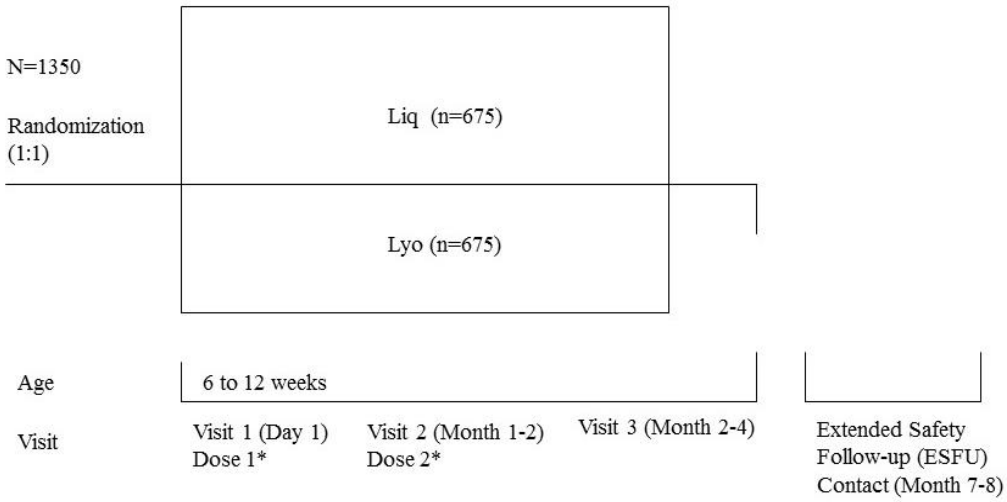

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5.4.1. Analysis of safety and reactogenicity planned in the protocol

The primary safety analysis will be performed on the Exposed set.

The percentage of doses and of subjects reporting at least 1 AE (solicited or unsolicited) during the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination will be computed, along with exact 95% CI. The same calculations will be done for AEs (solicited or unsolicited) rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit.

The percentage of doses and of subjects reporting each individual solicited general AE will be computed, over the 8-day (Day 1-Day 8) solicited follow-up period post-vaccination, along with exact 95% CI. The same calculations will be done for each individual general solicited AE rated as grade 3 in intensity, those assessed as causally related to vaccination, those rated as grade 3 in intensity with causal relationship to vaccination and those that resulted in a medically attended visit. For fever, additional analyses will be performed by 0.5°C increments. These calculations will also be performed by country, sex and frequent race.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate preferred term. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 1-Day 31) follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination, for unsolicited AEs rated as grade 3 with causal relationship to vaccination and those that resulted in a medically attended visit. These calculations will also be performed by country.

For each study group, the percentage of subjects who started taking at least 1 concomitant medication, antipyretic medication and prophylactic antipyretic medication during the 8-day (Day 1-Day 8) and 31-day (Day 1-Day 31) follow-up periods post-vaccination will be tabulated by dose, by subject for each dose and across the 2 doses.

Subjects who experienced at least 1 SAE during the entire study period (from Dose 1 till ESFU contact at Month 7-8) will be summarised by study group and all SAEs will be tabulated.

5.4.2. Additional considerations

The definition of frequent race is any race (cDISC categories) with at least 40 subjects overall. The ‘Other races’ subgroup will include all races that do not meet this criterion.

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain the final analyses of all endpoints.

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES

The following sections describe additional derivation rules which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Data derivation

In all summaries of vaccine exposure the following will apply.

Co-administered vaccines will be those given on the same day as the study vaccine (HRV). Concomitant vaccinations will be all vaccines given on any other days.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an AE is between Dose 1 and Dose 2, the relative dose will be Dose 1.

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 eCRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day 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 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be 1 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 1 of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or

only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be 1 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.

10.1.2.2. Daily recording of solicited AEs

When a specific solicited AE is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the solicited AE in question), all daily measurements will be imputed as Grade 0.

When a specific solicited AE is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the solicited AE in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

When the occurrence of a specific solicited AE is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the solicited AE in question) but the group of solicited AEs is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited AE summary tables.

The following table shows how subjects contribute to each category for a specific solicited AE over the Day X to Day Y post-vaccination period:

Solicited AE category	**Subjects included in the calculation of the numerator**
Any	All subjects with at least 1 occurrence of the solicited AE at grade 1, grade 2, or grade 3 between Day X and Day Y or with the solicited AE marked as present and at least 1 missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least 1 occurrence of the solicited AE at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All subjects with at least 1 occurrence of the solicited AE at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All subjects with at least 1 occurrence of the solicited AE at grade 3 between Day X and Day Y

10.1.2.3. Unsolicited adverse events

Unsolicited AE summaries will include SAEs unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Age at vaccination in weeks

Age at vaccination will be displayed in weeks. It will be calculated as the number of complete weeks the date of birth (DOB) and the date of vaccination. For example:

DOB = 10JUN2019, Date of vaccination = 28JUL2019 -> Age = 6 weeks

DOB = 10JUN2019, Date of vaccination = 29JUL2019 -> Age = 7 weeks

10.1.3.2. Weight

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

Weight in kilograms = Weight in pounds / 2.2

10.1.3.3. Length

Length will be presented in centimeters. Lengths reported in feet and inches will be converted as follows:

Length in centimeters = (Feet x 12 + Inches) x 2.54

10.1.3.4. Body mass index (BMI)

BMI will be calculated as follows:

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

10.1.3.5. 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

10.1.3.6. Onset day

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

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events 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 1 occurrence.

10.1.3.8. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarised, each event recorded as having occurred during a specific period will be counted as only 1 occurrence regardless of the number of days on which it occurs.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with 1 decimal

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (age, length, weight, body mass index (BMI)) will be presented with 1 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 maxima and minima of transformed length variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with 1 decimal.

The maximum and minima of transformed body temperatures will be displayed with 1 decimal.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.2. TFL ToC

A TFL ToC detailing the tables, figures, and listings that will be produced will be provided separately.

11. REFERENCES

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