Statistical Analysis Plan

Study ID: 218702

Study Official Title: A single-arm, open-label, multi-center, phase IV trial to evaluate the reactogenicity, safety, and immunogenicity of quadrivalent seasonal influenza vaccine (Fluarix Tetra) in participants aged 65 years and older in India

NCT ID: NCT05648357

Date of the Document: 17Nov2023

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A single-arm, open-label, multi-center, phase IV trial to evaluate the reactogenicity, safety, and immunogenicity of quadrivalent seasonal influenza vaccine (*Fluarix Tetra*) in participants aged 65 years and older in India.

Study Number: 218702

Compound Number: GSK2321138A

Abbreviated Title: FLU D-QIV-018 IN PMS

Acronym: NA

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK).

Regulatory Agency Identifier Number(s): Not Applicable

Registry	**ID**

Statistical Analysis Plan (SAP) Template v3.0 14 September 2022

Statistical Analysis Plan Signature Page

Statistical Analysis Plan v2.0, 14-Nov-2023 for 218702 – Protocol – v2.0 – 5-May-2023.

Name and Function	Signature	Date
Author: PPD Sr Statistician, Biostatistics, Real-World Solutions, IQVIA	DocuSigned by PPD PPD I approve this document November 17, 2023 | 1:53:09 AM PST [illegible]83B35E9F626DA0D4D3	November 17, 2023
Author: PPD Manager, Biostatistics, Real-World Solutions, IQVIA	DocuSigned by PPD PPD I approve this document November 17, 2023 | 8:29:07 PM JST 90F[illegible]F7745FAB9E9F38A1B5C2715	November 17, 2023
Approved By: PPD PPD, Vaccines Clinical Statistics, GSK	DocuSigned by PPD PPD I approve this document November 17, 2023 | 7:34:17 AM PST EE870CBEC3504609897A4231C7F32442	November 17, 2023

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LIST OF ABBREVIATIONS

Abbreviation	Definition of Terms
AE	Adverse Event
CI	Confidence Interval
eCRF	Electronic Case Report Form
ENR	Enrolled Set
ES	Exposed Set
FLU	Influenza
GMI	Mean Geometric Increase
GMT	Geometric Mean Titers
GSK	GlaxoSmithKline
HI	Haemagglutination-inhibiting
IM	Intramuscular
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
PD	Protocol Deviation
PPS	Per Protocol Set
PASS	Power and Sample Size
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System Software
SCR	Seroconversion Rate
SD	Standard Deviation

Abbreviation	Definition of Terms
SOC	System Organ Class
SPR	Seroprotection Rate
SSS	Solicited Safety Set
WHO DD	World Health Organization Drug Dictionary

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP v1.0	11-Jan-2023	218702 - Protocol – v1.0 – 22-Jun-2022	Not Applicable	Original version
SAP v2.0	14-Nov-2023	218702 – Protocol – v2.0 – 5-May-2023	Updated Sections: List of Abbreviations 1.1 Objectives and Endpoints 1.2 Study Design 3 Analysis Set 3.1. Criteria for Eliminating Data from Analysis Sets 4.1.4 End of Study Definition 4.3.1.1 Definition of endpoints 4.3.1.2 Main analytical approach 6.1.2. Protocol Deviations 6.1.3 Demographic and Baseline Characteristics 6.1.4 Baseline Vital Signs 6.1.5 Medical History/Current Medical Conditions New section: 4.4.1.3 Serious Adverse Event	Updated per protocol amendment

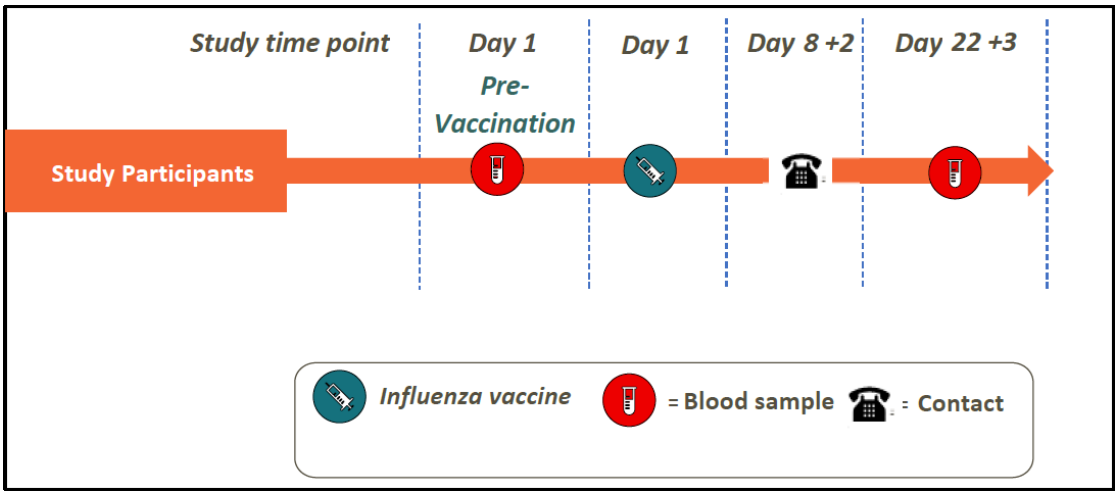
1. INTRODUCTION

The purpose of this Statistical analysis plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 218702. Details of the planned analyses are provided.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate reactogenicity and safety of *Fluarix Tetra* single dose 0.5 mL intramuscular (IM) in participants aged 65 years and above in India.	• Number and percentage of subjects with solicited Adverse Events (AEs) (administration-site as well as systemic) for 7 days from the date of vaccination (Day 1). • Number and percentage of subjects with unsolicited AEs starting from the date of vaccination for 21 days. • Number and percentage of subjects with Serious Adverse Events (SAEs) from the date of vaccination for 21 days.
Secondary	
• To evaluate immunogenicity of *Fluarix Tetra* single dose 0.5 mL IM in Participants aged 65 years and above in India.	• Geometric mean titers (GMT) of serum haemagglutination-inhibiting (HI) antibodies against the four-influenza vaccine strains at baseline (Day 1) and on Day 22. • Mean geometric increase (GMI) at Day 22 post-vaccination. • Seroconversion rate (SCR) at Day 22 post-vaccination. • Seroprotection rate (SPR) at baseline (Day 1) and on Day 22 post-vaccination.

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Type of design: a prospective, multi-center, single-arm, open-label, phase IV trial. • Study population**:** 250 participants aged 65 years and above in India will be enrolled. • Safety data collection: a diary card will be provided to trial participants. Data will be collected from completed diary card ~~daily~~ by the participant and a telephone call follow-up by investigator team will be performed to assess participant's health status. • Sample data collection: blood samples will be collected pre-vaccination at Day 1 and post-vaccination at Day 22. Samples will be tested at GSK or GSK designated laboratory.
Study intervention	• Vaccination schedule: A single 0.5 mL IM dose of *Fluarix Tetra* (NH2023-2024) will be administered. • Duration of the trial: 22 days per participant.
Study intervention Assignment	Single-arm, open-label.
Interim Analysis	There will be no interim analysis.

2. STATISTICAL HYPOTHESES

All analyses will be descriptive. No hypothesis will be tested.

2.1. Multiplicity Adjustment

Since there is no hypothesis testing, no adjustment of type I error will be needed.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled Set (ENR)	• The Enrolled Set will include all participants who entered the study (i.e., received study intervention or underwent a post screening study procedure).	• Study Population
Exposed Set (ES)	• The Exposed Set will include all participants from the Enrolled Set who received the trial vaccine.	• Primary endpoint • Secondary endpoint • Safety
Per Protocol Set (PPS)	• The Per Protocol Set will include all eligible participants from the Enrolled Set who received trial intervention as per protocol, had immunogenicity results pre- and post-dose, complied with the allowed dosing/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.	• Secondary endpoint
Solicited Safety Set (SSS)*	• The Solicited Safety Set will include all participants from the exposed set who returned the dairy card.	• Safety

* A diary card is considered returned when data on solicited AE is captured in the database.

3.1. Criteria for Eliminating Data from Analysis Sets

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

A participant will be excluded from the ES under the following conditions:

Elimination code	Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Participants not receiving a single dose of the trial vaccine

A participant will be excluded from the PPS under the following conditions:

Elimination code	Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Participants not receiving a single dose of the trial vaccine
1040	Administration of forbidden vaccination
1070	Study vaccine dose not administered according to protocol
1080	Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria)
2020	No immunogenicity data at Day 1
2040	Administration of any medication forbidden by the protocol
2070	Intercurrent medical conditions *
2090	Non-compliance with blood sampling schedule (including wrong and unknown dates)
2100	No immunogenicity data at Day 22

* Intercurrent medical conditions: FLU; Guillain-Barré Syndrome history; Disease requiring immune modifying agents; Acute infectious disease or Acute respiratory illness; Acute or chronic clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality.

A participant will be excluded from the SSS under the following conditions:

Elimination code	Condition under which the code is used
800	Fraudulent data
900	Invalid informed consent
1030	Participants not receiving a single dose of the trial vaccine
1520	Solicited AE information not collected for the participant

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

Unless otherwise specified, continuous data will be summarised using descriptive statistics: number of non-missing values (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (Min) and maximum (Max). When appropriate, 95% confidence interval (CI) of the geometric mean will be provided.

Unless otherwise specified, categorical data will be summarized using descriptive statistics: number and percentages of participants. When appropriate, associated 95% Clopper-Pearson (exact) CIs (Clopper CJ, 1934) will be provided. Percentages will be computed using the number of participants with non-missing data as the denominator.

Number of missing will be reported.

4.1.2. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and defined as the Day 1 of the most recent dose of study vaccination.

4.1.3. Baseline Definition

Unless otherwise specified, baseline will be defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline. AEs and medications commencing on the reference start date will be considered post-baseline unless otherwise indicated based on available start date/time combination or collected Electronic Case Report Form (eCRF) information that identifies the individual event/medication as starting prior to first study vaccination administration.

4.1.4. End of Study Definition

A participant is considered to have completed the trial if he/she has completed all scheduled visits of the trial. Else he/she is considered as withdrawal.

Possible reasons for withdrawal:

Protocol deviation (PD), especially for inclusion/exclusion criteria
SAE
Solicited AE
Unsolicited non-serious AE

Consent withdrawal, not due to an AE
Investigator discretion to discontinue the participants with appropriate reason
Migrated/moved from the trial center
Lost to follow-up
Sponsor trial termination
Other (please specify)

A Participant will be considered lost to follow-up if he or she fails to attend 2nd scheduled visit (Day 22) and is unable to be contacted by the trial center.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of Endpoints

Number and percentage of subjects with solicited AEs (administration-site as well as systemic) for 7 days from the reference start date (Day 1).

Number and percentage of subjects with unsolicited AEs starting from reference start date for 21 days i.e. up to Day 21.

Number and percentage of subjects with SAEs from the reference start date for 21 days i.e. up to Day 21.

4.2.2. Main Analytical Approach

The primary endpoint analyses related to solicited AEs will be performed on the SSS. The primary endpoint analyses related to unsolicited AEs will be performed on the ES.

The number and percentage of participants reporting solicited administration-site AE (any, Grade 3, medically attended), systemic AE (any, Grade 3 or Grade 4, medically attended) and either administration-site or systemic AE (any, Grade 3, medically attended) during the follow-up period (Day 1 – Day 7) will be tabulated with exact Clopper-Pearson 95% CI.

The number and percentage of participants reporting at least 1 unsolicited AE (any, Grade 3, related, Grade 3 related, medically attended) classified by the Medical Dictionary for Regulatory Activities (MedDRA) during the 21-day follow-up period (Day 1 - Day 21) will be tabulated with exact 95% CI, overall and by MedDRA System Organ Class (SOC) and Preferred Term (PT).

The number and percentage of participants reporting at least 1 SAE (any, fatal, related, fatal related) during the trial period (Day 1 - Day 21) will be tabulated with exact 95% CI, overall and by MedDRA SOC and PT.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary Endpoints

4.3.1.1. Definition of Endpoints

1. GMT of serum HI antibodies against each of the four-influenza vaccine (or vaccine-like) strains at the reference start date (Day 1) and on Day 22:

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers will be log10-transformed. GMTs and their 95% CI are computed by exponentiating (base 10) the mean and 95% CI of the log10 titers. The GMT at a given time point will be calculated using the following formula:

$$GMT = 10^{\left(\frac{\sum_{i=1}^{n} \log 10(t_i)}{n}\right)}$$

Where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers at the time point.

2. GMI at Day 22: GMI will be defined as the fold increase in post-vaccination serum HI GMTs (Day 22) compared to the reference start date (Day 1).

GMT and GMT ratio with 2-sided 95% CI for intervention group which is derived from one sample t-test on log10 transformed titer will be tabulated. GMI will be calculated using the following formula:

$$GMI = 10^{(sum\ of\ log10\ (titer\ at\ Day\ 22/titer\ at\ Day\ 1))}$$

GMT with 2-sided 95% CI will be computed using the following Statistical Analysis System Software (SAS) code:

```
proc ttest data=ds_in dist=lognormal;
        var titer;
        ods output "Confidence Limits" = ds_out;
run;
```

GMI with 2-sided 95% CI will be computed using the following SAS code:

```
proc ttest data=ds_in dist=lognormal test=ratio;
        paired titerday22*titerday1;
        ods output "Confidence Limits" = ds_out;
run;
```

3. SCR at Day 22: SCR will be defined as the percentage of subjects who have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer.

The SCR will be calculated using the following formula:

$$SCR = \frac{Number\ of\ subjects \text{ who have either a pre-vaccination titer} < 1{:}10 \text{ and a post-vaccination titer} \geq 1{:}40 \text{ or a pre-vaccination titer} \geq 1{:}10 \text{ and at least a 4-fold increase in post-vaccination titer}}{The\ total\ number\ of\ subjects\ with\ pre\ and\ post-vaccination\ titer}$$

4. SPR at Day 1 and Day 22. SPR will be defined as the percentage of subjects with a serum HI titer ≥ 1:40.

The SPR will be calculated using the following formula:

$$SPR = \frac{Number\ of\ subjects\ with\ a\ serum\ HI\ titer\ \geq 1{:}40\ at\ Day\ 1\ (or\ Day\ 22)}{The\ total\ number\ of\ subjects\ with\ Day\ 1\ (or\ Day\ 22) - vacination\ titer}$$

4.3.1.2. Main Analytical Approach

The secondary endpoint analysis will be performed on the PPS and ES.

GMTs of HI antibodies on Days 1 and 22 will be tabulated, with 95% CI.

GMI at Day 22 will be tabulated, with 95% CI.

SCRs at Day 22 will be tabulated, with 95% CI.

SPRs on Day 1 and Day 22 will be tabulated, with 95% CI.

4.4. Exploratory Endpoint(s) Analyses

Not Applicable.

4.4.1. Other Safety Analyses

4.4.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AE verbatim terms will be recorded and coded using the latest version of MedDRA. The concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO DD). Details refer to 6.1.7.

4.4.1.2. Solicited Adverse Events

Adverse events that comprise the primary interest of the trial are designated as solicited AEs. The pre-specified solicited AEs is listed below:

Solicited administration-site events:

- Pain
- Redness
- Swelling

Solicited systemic events:

- Fever
- Headache
- Myalgia (Muscle pain)
- Arthralgia (Joint pain)
- Fatigue
- Shivering
- Sweating
- Gastrointestinal symptoms (including nausea, vomiting, diarrhea and/or abdominal pain)

4.4.1.3. Serious Adverse Event

An SAE is any untoward medical occurrence that:
a. Results in death
b. Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c. Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an outpatient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
d. Results in disability/incapacity Note: The term '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.
e. Is a congenital anomaly/birth defect in the offspring of a trial participant
f. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g. Other situations Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also 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 or convulsions that do not result in hospitalization.

4.4.1.4. Assessment of Intensity

Intensity for solicited AEs will be assessed as follows:

Table 1 Intensity scales for solicited events

Adverse Event	Intensity Grade	Parameter
Pain at administration-site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities
	2	Moderate: Painful when limb is moved and interferes with everyday activities
	3	Severe: Significant pain at rest. Prevents normal everyday activities
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Muscle aches that are easily tolerated
	2	Moderate: Muscle aches that interfere with normal activity
	3	Severe: Muscle aches that prevent normal activity
Arthralgia	0	None
	1	Mild: Joint pain that is easily tolerated
	2	Moderate: Joint pain that interferes with normal activity
	3	Severe: Joint pain that prevents normal activity
Shivering (chills)	0	None
	1	Mild: Shivering (chills) that is easily tolerated
	2	Moderate: Shivering (chills) that interferes with normal activity
	3	Severe: Shivering (chills) that prevents normal activity
Sweating	0	None
	1	Mild: Sweating that is easily tolerated
	2	Moderate: Sweating that interferes with normal activity

Adverse Event	Intensity Grade	Parameter
	3	Severe: Sweating that prevents normal activity
Gastrointestinal symptoms: nausea, vomiting, diarrhoea and/or abdominal pain	0	None
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Redness at administration-site	Record greatest surface diameter in mm	
Swelling at administration-site	Record greatest surface diameter in mm	
Temperature*	Record temperature in °C/°F	

* Fever is defined as temperature ≥ 38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be the oral route.

The maximum intensity of administration-site injection site redness/swelling will be scored as follows:

0: ≤ 20 mm

1: > 20 to 50 mm

2: > 50 to 100 mm

3: > 100 mm

The maximum intensity of fever will be scored as follows:

0: < 38.0°C (< 100.4°F)

1: ≥ 38.0 – 38.4°C (≥100.4 – 101.2°F)

2: ≥ 38.5 – 38.9°C (≥ 101.3 – 102.1°F)

3: ≥ 39.0 – 40.0°C (≥ 102.2 – 104.0°F)

4: > 40.0°C (>104.0°F)

The maximum intensity of solicited systemic events will be collected as follows:

1: Mild

2: Moderate

3: Severe

Intensity for unsolicited AEs will be assessed as follows:

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 one of the following categories:

1 Mild = An AE which is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.

2 Moderate = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 Severe = An AE which prevents normal, everyday activities. In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

Severity is classed as Grade 1(mild)/ Grade 2 (moderate)/ Grade 3 (severe) (increasing severity). If a patient has an unsolicited AE more than once within that SOC/PT, the unsolicited AE with higher grade will be used in the corresponding severity summaries. Highest severity from Day 1 to Day 7 (for solicited AEs), Highest severity beyond Day 7 (for solicited AEs) and Highest severity (for unsolicited AEs) will be presented in listing. AEs with Grade 3 will be summarized.

4.4.1.5. Assessment of Causality

Causality is not assessed for solicited AEs. For unsolicited AEs, the investigator must assess the relationship between study vaccine and the occurrence of each unsolicited AE/SAE using clinical judgement.

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 vaccine/product?

YES: There is a reasonable possibility that the study vaccine/product contributed to the AE.

NO: There is no reasonable possibility that the AE is causally related to the administration of the study vaccine/product. There is other, more likely cause and administration of the study vaccine/product is not suspected to have contributed to the AE.

4.4.1.6. Assessment of Outcomes

Outcome of any unsolicited AE occurring within 21 days (Day 1 to Day 21) post-vaccination will be assessed as:

- Recovered/resolved

- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal

4.4.1.7. Other Safety Analyses Endpoints

For the analysis of vaccine safety, the following parameters and the 95% CI will be calculated:

- The percentage of participants with at least 1 administration-site AE (solicited and/or unsolicited), with at least 1 general AE (solicited and/or unsolicited) and with any AE (solicited and/or unsolicited) during the solicited follow-up period after vaccination will be tabulated with exact 95% CI on the ES.
- The percentage of participants reporting each individual solicited administration-site (any, Grade 3) and general (any, Grade 3 or 4, related, medically attended) AE during the solicited follow-up period after vaccination will be tabulated with exact 95% CI on the SSS.
- The duration statistics (in terms of number of days, See section 6.2.2) of each solicited administration-site and general AE during the Day 7 post-vaccination follow-up period will be tabulated on the SSS.
- The percentage of participants reporting ongoing solicited (administration-site and general) AEs at the end of the solicited follow-up period will be tabulated with exact 95% CI on the SSS.
- Temperature will be reported per 0.5°C cumulative increments beginning (≥ 38, ≥ 38.5, ≥ 39, ≥ 39.5, ≥ 40) during the solicited follow-up period for the SSS.
- The percentage of participants with at least 1 report of an unsolicited AE (any, Grade 3, related, Grade 3 related, medically attended) classified by the MedDRA during the follow-up period will be tabulated with exact 95% CI on the SSS.
- The percentage of participants who started to receive at least 1 concomitant medication during the follow-up period will be tabulated with exact 95% CI for the ES.

- The percentage of participants with at least 1 report of SAE (any, related, fatal, fatal related) classified by MedDRA during the trial period will be tabulated with exact 95% CI for the ES.
- The percentage of participants with at least 1 report of a MAE (medically attended event) classified by MedDRA during the trial period will be tabulated with exact 95% CI for the ES.
- SAEs and withdrawals due to AE(s) will be described in detail in Listings for the ES.

4.5. Other Analyses

4.5.1. Subgroup Analyses

Immunogenicity secondary endpoints, as described in Section 4.3.1.2, will be summarized by influenza (FLU) vaccination history, if there are at least 30 participants in each subgroup. FLU vaccination history will be defined as FLU vaccination administered in the past 3 years before enrollment (Yes; No).

4.6. Interim Analyses

There are no interim analyses in the study.

4.7. Changes to Protocol Defined Analyses

The following changes to the originally planned statistical analysis specified in the protocol v1.0 (Dated:22-Jun-2022) were performed:

Protocol section and verbatim	Change to protocol
Section 6.3: The Enrolled Set will include all eligible participants with informed consent signed.	The Enrolled Set definition was updated to match GSK standard definition of the Enrolled Set (See Section 3): The Enrolled Set will include all participants who entered the study (i.e., received study intervention or underwent a post screening study procedure).The Enrolled Set will include all eligible participants with informed consent.

Protocol section and verbatim	Change to protocol
Section 6.4.5: Characteristics of participants who returned and who did not return the diary card will be described.	'Characteristics' term mentioned in the protocol section has been clarified to 'Number of participants'. This analysis is covered by the description of the number of participants with elimination code 1520 (Solicited AE information not collected for the participant) and the number of participants in the SSS (See Section 6.1.1).

5. SAMPLE SIZE DETERMINATION

Approximately 250 participants will be enrolled in this trial to achieve 200 evaluable participants considering that some participants may drop out of the study or some may not be included in data analysis due to missing or invalid data.

Table 2 95% Clopper-Pearson (exact) Confidence Intervals and probabilities to observe at least one participant with AE for N=250 participants, with varying percentages of participants with AEs.

		95% CI[1]			N = 250
	Category	**Lower Limit (%)**	**Upper Limit (%)**	**Width (%)**	**Probability to observe ≥1 participant with AE (%)[2]**
0.1%	Uncommon	0.00	1.67	1.67	22.1
1%	Common	0.17	3.17	3.00	91.9
10%	Very common	6.58	14.41	7.83	>99.99
50%		43.63	56.37	12.73	>99.99

CI= confidence interval; AE= adverse event.
1. Calculations done using SAS version 9.4 and validated using Power and Sample Size (PASS) software (PASS, 2019).
2. Calculated using the binomial distribution.

Table 2 shows 95% Clopper-Pearson CIs for the proposed N=250 and varying incidence of solicited/ unsolicited AEs. The AE incidences shown correspond to the categories uncommon (≥1/1 000 to <1/100), common (≥1/100 to <1/10) and very common (≥1/10).

With N=250, the width observed for the 95% CIs is always < 13%, and for uncommon and common AEs it is ≤ 3%.

Table 2 also shows, in the last column, the probability of observing at least one participant with AE. This probability is at least 91.9% for common and very common AEs.

Table 3 95% Clopper-Pearson exact Confidence Intervals and probabilities to observe at least one participant with SAE for N=250 participants, with cumulative incidence up to 1% over a 6-month period.

		Clopper-Pearson 95% CI[1]			
Months after vaccination	**Cumulative incidence of SAE (%)[2]**	**Lower Limit (%)**	**Upper Limit (%)**	**Width (%)**	**Probability to observe ≥1 participant with SAE (%)[3]**
1	0.17	0.00	1.79	1.79	34.1
2	0.33	0.00	2.09	2.09	56.6
3	0.50	0.02	2.38	2.35	71.4
4	0.67	0.06	2.65	2.59	81.2
5	0.83	0.11	2.91	2.80	87.7
6	1.00	0.17	3.17	3.00	91.1

1. Calculations done using SAS version 9.4 and validated using PASS (PASS, 2019) software.
2. Assuming linear increase in incidence from date of vaccination to 1% at 6 months.
3. Calculated using binomial distribution.

Table 3 shows 95% Clopper-Pearson CIs for 250 participants by cumulative incidence of SAE. The width of the 95% CIs is ≤ 3% throughout. The probability of observing at least 1 participant with SAE is >56% for cumulative incidence from Month 2 onwards (Clopper CJ, 1934).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

A summary of the number of vaccinated, completed and withdrawn participants will be tabulated, as well as the reason for withdrawal from the ENR.

A summary of the number of enrolled and excluded participants from the analysis sets will be tabulated, as well as the reason for elimination for the ENR.

A summary of the number of participants by centre will be tabulated for the ENR.

A summary of the number of participants completed per visit or collected lab sample will be tabulated for the ES.

6.1.2. Protocol Deviations

Listings of PDs leading to elimination and PDs not leading to elimination will be reported for the ENR. This listing will also make reference to their corresponding categories as per the protocol deviation management plan (PDMP). A summary of PD's leading to elimination from the ES, from the SSS and from the PPS will be provided for the ENR and ES respectively.

6.1.3. Demographic and Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the ES and PPS. No statistical testing will be carried out for demographic or other baseline characteristics. The following demographic and other baseline characteristics will be reported for this study:

Age (years) –The age is derived by:
Age = "Informed consent date" (IC.DSSTDTC) - "Birth Year" (DM.BRTHDTCY) concatenated with 30-06 (both "Informed consent date" and "Birth Year" are collected by Electronic Data Capture (EDC) system)
Sex (Male; Female)
Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Unknown; Not Reported)
Race (American Indian or Alaska Native; Asian - Central / South Asian Heritage; Black or African American, Native Hawaiian or Other Pacific Islander; White - Arabic / North African Heritage; White - Caucasian / European Heritage; Unknown; Not Reported)
FLU vaccination history over the last 3 years (Yes; No)

6.1.4. Baseline Vital Signs

Vital signs will be assessed pre-vaccination at Day 1. Vital signs data will be presented for the ES and PPS. No statistical testing will be carried out for vital signs. The following vital signs will be reported for this study:

Heart Rate (beats/minutes)
Respiratory Rate (breaths/minutes)
Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)

Vital signs data will be presented together with demographic and baseline characteristics.

6.1.5. Medical History/Current Medical Conditions

Pre-existing conditions present in a participant before the administration of the study vaccine will be captured on the "Medical History/Current Medical Conditions" page of the eCRF and coded using the latest version of MedDRA central coding dictionary.

Medical events occurring before the start of receipt of trial vaccine but after obtaining informed consent will be recorded on the Medical History/ Current Medical Conditions section of the eCRF, not the AE section.

Medical History/Current Medical Conditions information will be presented for the ES.

The number and percentage of participants presenting each condition will be tabulated by MedDRA SOC and PT, for past and current conditions respectively. A patient presenting several conditions by PT will only contribute once to the PT.

6.1.6. Vaccine Administration

The following *Fluarix Tetra* influenza vaccine administration data will be presented in listings for the ENR.

Temperature (Celsius) (°C=(°F-32)/1.8)
Temperature Anatomical Location (In the mouth, In the armpit, In the ear)
Temperature done or taken (Yes; No)
Vaccine administered (Yes; No)
Vaccination date
Anatomical Location (Deltoid; Thigh, Buttock)
Directionality (Upper; Lower)
Side (Left; Right)

6.1.7. Concomitant Medications, Concomitant Vaccination and Vaccination History

Concomitant medications will be coded using thelatest version of WHO DD. Trade name is preferred for vaccine. The concomitant medications, concomitant vaccination and vaccination history will be summarized for counting and percentage by medication class and by vaccine name, respectively. Details refer to section 4.4.1.7. A listing will contain but not be limited to medication/vaccination, start day, start/end date, route, dose, unit, frequency and indication for the ENR.

Concomitant medications: any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment (within 2 days before the time of enrollment) or receives during the trial.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Number of Occurrences of Each AE

For solicited administration-site and systemic AEs, the number of occurrences will be:

Equal to zero if the leading question 'Did the AE occur?' is 'No' or 'Not done/Unknown'.
Equal to one if the leading question 'Did the AE occur?' is 'Yes'.

For unsolicited AE, AEs with different PTs and/or start dates will be counted as distinct occurrences in a same patient.

6.2.2. Duration of Each AE

The duration of each solicited AE during the solicited event period (Day 1 to Day 7), in days, will be summarized using descriptive statistics (n, mean, SD, minimum, median and maximum).

For solicited AEs, if the AE leading question 'Did AE occur?' is 'Yes', then the duration will be calculated as the sum of the individual days when the AE occurred: defined as 'Day X occur?' being 'Yes' or 'Not done/Unknown'.

Example: AE leading question 'Did AE occur?' is 'Yes'.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	AE Duration
Yes	Not Done/ Unknown	Not Done/ Unknown	Yes	No	No	No	4 days

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	AE Duration
Yes	No	No	Yes	Yes	Yes	Yes	5 days
Not Done/ Unknown	Not Done/ Unknown	Not Done/ Unknown	Not Done/ Unknown	Not Done/ Unknown	Not Done/ Unknown	Not Done/ Unknown	7 days

6.2.3. Handling of Missing Data

It is optimal to prevent missing data, to the extent possible, through strategies set forth in the design and conduct of a trial. For the current trial, we will aim to minimize missing information; for a given participants and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

The data will be analyzed as they are recorded in the trial eCRF. The number of missing values for data elements will be reported in tables and listings. Missing relationship with study vaccine, and outcome of unsolicited AEs will not be replaced and will appear as 'Missing' when displayed in a listing.

6.2.3.1. Handling of Missing Severity of AE

Estimate the missing severity of all kinds of AEs (solicited and unsolicited) by the maximal severity/grade observed in the overall population.

6.2.3.2. Handling of Missing/Partial Dates

When missing/partial dates of concomitant medications are used to classify time windows, the following standard rules will be applied:

If only the day is missing:
- For the start date, the first day of the month (01) will be used.
- For the stop date, the last day of the month will be used.

If both day and month are missing:
- For the start date, the first day of the month (01) and July will be used if the year is prior to the year of study entry. If the year is the same as study entry, then the first day (01) of January will be used.
- For the stop date, the last day of the month (31) and July will be used if the year is prior to the year of study entry. If the year is the same as study entry, then the last day (31) of December will be used, unless this is after the patient completion/withdrawal date; in this case, the date of completion/withdrawal will be used.

If year is missing:
- For the start date, the year of study entry will be used.
- For the end date, the date of completion/withdrawal will be used.
- If the start date is completely missing, the date of study entry will be used.

If end date is completely missing, then the therapy will be assumed to be 'Ongoing'; in this case, the date of completion/withdrawal will be used. The following rules apply for missing/partial start dates of unsolicited AE:

- Unsolicited AE start dates with missing day:
  - If the event starts in the same month as the date of vaccination (Day 1), the contents of AE.AESTTPT (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 date of vaccination (Day 1). If 'before study dose' is selected, the imputed date will be one day before the date of vaccination (Day 1).
- Unsolicited AE start dates with missing day and month:
  - If the event starts in the same year as the date of vaccination (Day 1), the contents of AE.AESTTPT (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 date of vaccination (Day 1). If 'before study dose' is selected, the imputed date will be one day before the date of vaccination (Day 1).
- Unsolicited AE start dates with missing day, month, and year:
  - The contents of AE.AESTTPT (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 date of vaccination (Day 1). If 'before study dose' is selected, the imputed date will be one day before the date of vaccination (Day 1).

All other cases of incomplete unsolicited AE start date will follow the standard rules above.

6.2.4. Decimal Places

Decimal places for categorical data: for percentages one decimal place will be displayed. Zero decimal place will be displayed if percentage equals to 100.

Decimal places for continuous data will be as follows:

The mean, median baseline characteristics will be presented with one decimal. SD will be presented with one more decimal than mean.

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

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

The 1 decimal will be used when displaying GMT and its confidence limits. GMI and their confidence limits will be displayed with 2 decimals regardless of the actual values.

7. REFERENCES

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

Nauta, J. (2010). Statistics in Clinical Vaccine Trials. Heidelberg: Springer.

PASS. (2019). 2022. Power Analysis and Sample Size Software. Kaysville, Utah, USA. ncss.com/software/pass: NCSS, LLC.

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Certified Delivered	Security Checked	11/17/2023 3:27:01 AM
Signing Complete	Security Checked	11/17/2023 3:29:12 AM
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