SAP Core Body

Title: A Phase III Randomized, Modified Double-blind, Active-controlled, Multi-center Study to Describe the Immunogenicity and Safety of the Quadrivalent Recombinant Influenza Vaccine (RIV4) versus a Quadrivalent-inactivated Influenza Vaccine (IIV4) (Fluarix® quadrivalent) in Participants 18 Years of Age and Older in South Korea

Study Code: VAP00016

NCT identifier: NCT05144945

Study Phase: III

SAP Core Body Version: 2.0

SAP Core Body Date: 28 Feb 2023

Protocol Version Number: 5.0

The SAP Code Body should be used in conjunction of the study protocol and the SAP TLF.

Version History

Previous Version(s)*	Date	Comments (optional)
1.0	7 Nov 2022	From SAP Version 1.0 to Version 2.0, in Appendix 2, updated the method to do the posterior distribution estimation and provided SAS example code.

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1 Overall Design

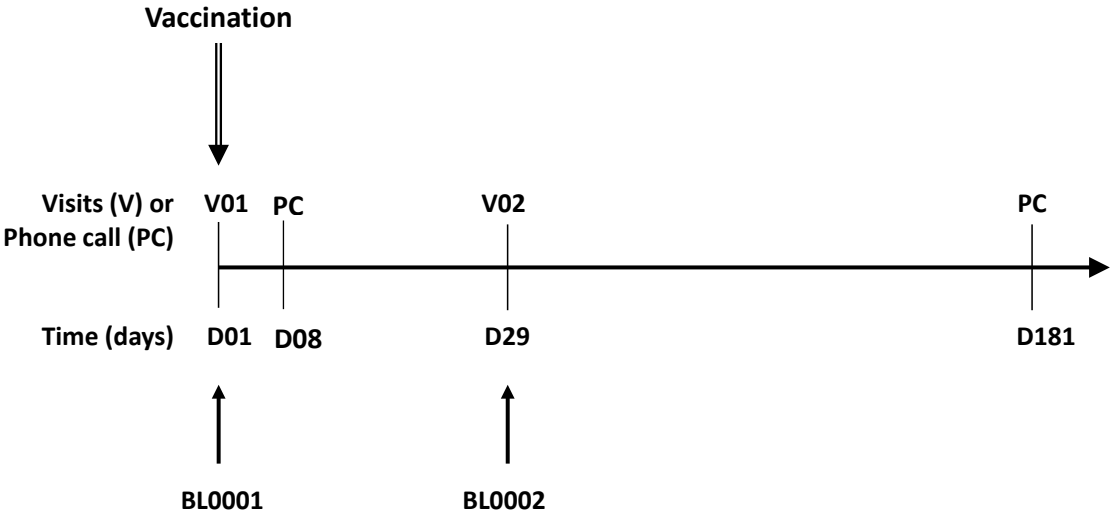
This study is a Phase III, parallel, randomized, modified double-blind, active-controlled, multi-center clinical study planned to be conducted in 300 participants 18 years of age and older in South Korea to describe the immunogenicity and safety of the RIV4 versus a locally licensed IIV4 (Fluarix® quadrivalent) that will serve as a control arm.

In each age group (18-49 years of age and ≥ 50 years of age), eligible participants will be randomized in a 1:1 ratio through the Interactive Response Technology (IRT) to receive a single intramuscular (IM) injection of either RIV4 or IIV4 at D01.

Participants will attend 2 visits and will provide a pre-vaccination blood sample (BL0001) at D01 and a post-vaccination blood sample (BL0002) at D29.The duration of each participant's participation will be approximately 6 months (180 days).

The design of the study is summarized in Table 4.1 of the protocol.

Figure 1.1: Graphical study design



Abbreviations: BL, Blood sampling; V, Visit; PC, Phone call

Detailed study design is provided in Sections 4.1 and 1.1 of the protocol.

2 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 2.1.

Table 2.1: Objectives and endpoints

Primary* Objectives	Primary Endpoints
Immunogenicity	
• To describe the immune response induced by RIV4 and IIV4 in 18-49 and ≥ 50 years of age participants by HAI measurement method.	• HAI antibody (Ab) titers obtained on Day (D) 01 and D29 • Individual HAI titers ratio D29/D01 • Seroconversion: titer < 10 (1/dilution [1/dil]) at D01 and post-injection titer ≥ 40 (1/dil) at D29, or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in titer (1/dil) at D29 • Titer ≥ 40 (1/dil) at D01 and D29 • Detectable titer ≥ 10 (1/dil) on D01 and D29
Safety †	
• To describe the safety profile of all participants in RIV4 and IIV4 groups	• Presence of any unsolicited systemic AE reported in the 30 minutes after vaccination • Presence of solicited injection site, and systemic reactions occurring up to 7 days after vaccination, (ie, pre-listed in the participant's diary card [DC] and case report form [CRF]) • Presence of unsolicited (spontaneously reported) AEs up to 28 days after vaccination • Presence of serious adverse events (SAEs), including adverse events of special interest (AESIs), throughout the trial period Other endpoints recorded or derived as described in Section 4.2

*This study has no secondary or exploratory objectives.

† Details on safety endpoints (terminology, definitions, and intensity scales) are presented in Table 10.1 and Table 10.2 of the protocol.

3 Statistical Considerations

3.1 Statistical Hypotheses

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

3.2 Sample Size Determination

A total of approximately 300 participants will be enrolled as follows:

- 75 participants from 18 to 49 years of age in RIV4 group
- 75 participants ≥ 50 years of age in RIV4 group
- 75 participants 18 to 49 years of age in IIV4 group
- 75 participants ≥ 50 years of age in IIV4 group

Assuming a drop-out rate of 5%, a total of 71 evaluable participants per group of age and vaccine is anticipated.

No formal power calculation has been performed, but based on the planned sample size the estimation precision is provided as follows:

For proportions, the expected precision of estimation (using PASS14) is: 71 participants per treatment group provide a maximum width of 95% confidence interval (CI) of 24.2% for single proportions and a maximum width of 95% CI of 32.0% for differences between proportions (when the group proportions are 50%).

For quantitative data, the distance from the mean to the limits of 95% CI is equal to 0.154 for single mean and 0.216 for difference in means (when the estimated standard deviation is 0.65).

In case of any unexpected situations where this planned number is not reached (due to an unexpected high number of withdrawals or unevaluable data) then additional participants might be recruited before database lock to achieve that planned sample size. Such assessment and decision will be performed in a blind manner during the course of the trial before database lock or any statistical analysis.

3.3 Populations for Analysis

The following populations for analysis are defined:

Safety Analysis Set (SafAS)

Safety Analysis Set (SafAS): Participants who have received a dose of the study vaccines. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately). SafAS will be used for safety analyses.

Full analysis set (FAS)

Full analysis set (FAS): Subset of randomized participants who received a dose of the study vaccine and had a post-vaccination blood sample. Participants will be analyzed according to the intervention to which they were randomized. The FAS will be used for immunogenicity analysis.

Per-protocol analysis set (PPAS)

Per-protocol analysis set (PPAS): Subset of the FAS. Participants presenting with at least one of the following conditions will be excluded from the PPAS:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive vaccine
- Participant received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Participant did not receive vaccine in the proper time window
- Participant did not provide the post-dose serology sample at Visit 2 in the proper time window, or a post-dose serology sample was not drawn
- Participant received a protocol-prohibited therapy/medication/vaccine

PPAS will be used for immunogenicity analysis.

Participants with data in CRF

Participants with data in CRF: Participants with data in CRF are participants for whom data were recorded at a visit.

Randomized participants

Randomized participants: a randomized participant is a participant for whom a randomized group has been allocated by IRT.

Participants with data in CRF and randomized participants will be used to summarize participants' disposition, demographic and baseline characteristics.

3.4 Statistical Analysis

3.4.1 General Considerations

The statistical analysis will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

No hypotheses testing was planned in this study.
All statistical analysis results will be provided by age group and by vaccine group.

No replacement will be done for safety and immunogenicity missing data and outliers. Analysis will be done using the collected data. Nevertheless, for unsolicited systemic AEs, missing relationship will be considered as related to study vaccine at the time of analysis.

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	Number of participants Percentage of participants
	Continuous data	Mean, standard deviation (SD), minimum and maximum.
Baseline characteristics	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation (SD), quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of participants. Unsolicited: Number and percentage (95% CIs) of participants and number of events.
Immunogenicity results	**Categorical data (seroconversion, cutoff)**	Number and percentage (95% CIs) of participants.
	Continuous data (titer / data)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), i.e., using the inverse of the beta integral with SAS®).

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

3.4.2 Primary Endpoints

The primary endpoints for immunogenicity and safety are shown in Table 2.1.

3.4.2.1 Immunogenicity

The analysis of Hemagglutinin inhibition (HAI) Ab response measured at D01 and D29 will be performed by age subgroup, intervention group and pooled age group, including but will not be limited to:

- Geometric mean of HAI Ab titer (GMT) and 95% CI at D01 and D29
- Geometric mean fold-rise (GMFR) of HAI Ab titer and its 95%CI. Fold-rise is computed as individual titer ratio of post-vaccination value divided by baseline value.
- Number and percentage of participants with seroconversion (seroconversion rate): titer < 10 (1/dilution [1/dil]) at D01 and post-injection titer ≥ 40 (1/dil) at D29, or titer ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in titer (1/dil) at D29
- Number and percentage of participants with titer ≥ 40 (1/dil) at D01 and D29
- Number and percentage of participants with detectable titer ≥ 10 (1/dil) at D01 and D29

The 95% CIs for the GMTs and GMFR will be calculated using a normal approximation of $\log_{10}$-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method (1).

The ratios of GMTs (RIV4/IIV4) in each age group and pooled age group will be obtained between groups with the 95% CIs calculated using a normal approximation of $\log_{10}$-transformed titers. The differences in the seroconversion rates between groups in each age group and pooled age group will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction (2).

Reverse cumulative distribution curves in each age group and pooled age group against each strain will be performed for baseline (D01) and post-vaccination immunogenicity (D29).

The primary immunogenicity analyses will be performed on the Per-Protocol Analysis Set (PPAS) and on the Full Analysis Set (FAS). Details of both analyses sets are described in Section 3.3.

3.4.2.2 Safety

The following safety data will be summarized using Clopper-Pearson method to estimate the 95% CI by age subgroup, intervention group and pooled age subgroups. The current Medical Dictionary for Regulatory Activities (MedDRA) version will be used for the coding of all AEs/reactions.

Solicited Reactions

Number and percentage of participants with:

- Presence of solicited injection site reactions and solicited systemic reactions occurring up to 7 days after injection
- Each solicited reaction according to time of onset, maximum intensity, and number of days of occurrence and action taken

Unsolicited Events and Reactions

Number and percentage of participants with:

- Any unsolicited immediate systemic event in the 30 minutes after injection according to System Organ Classes (SOC) and Preferred Terms (PT)
- Any unsolicited event and reaction 28 days after injection according to SOC and PT
- Any unsolicited event/reaction according to time of onset, maximum intensity, and duration

SAEs

Number and percentage of participants with:

- Any SAE within 28 days after injection and throughout the entire study according to SOC and PT, seriousness, and outcome

AESIs

Number and percentage of participants with:

- Any AESI within 28 days after injection and throughout the entire study according to SOC and PT, seriousness, and outcome

3.4.2.3 Complementary analysis

In addition, as a complementary analysis to support bridging discussion, Bayesian method will be used to evaluate the probability of non-inferiority in terms of GMTs for post-vaccination HAI Ab titer. The posterior probability of the true ratio of GMTs (RIV4/IIV4) to be higher than the commonly accepted non-inferiority margin (0.667) will be calculated using the Bayesian approach to support bridging with previous non-inferiority trials.

Further details about the statistical methodology are provided in the Appendix 2.

3.4.3 Handling of Missing Data and Outliers

3.4.3.1 Safety

Generally, no replacement will be done for safety missing data and outliers.

3.4.3.1.1 Immediate

For unsolicited systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

3.4.3.1.2 Causal Relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.3.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.3.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses. If either the start date or end date is missing or partially missing, the duration will be considered missing. Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed

3.4.3.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.3.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. Lower Limit Of Quantification [LLOQ] and Upper Limit Of Quantification [ULOQ] management will be performed as described in Section 4.2.3.1.

3.5 Interim Analyses

No interim analysis is planned for this study.

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study.

3.6 Data Monitoring Committee (DMC)

Not applicable.

4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focusses on complementary/additional information not detailed in the protocol.

4.1 Complementary Information for Endpoints Assessment Methods

Not applicable.

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Safety

4.2.1.1 Solicited Reactions

4.2.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as “No” and with all daily records missing (Unknown) then all daily intensities will be derived as None.

2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3. Note the intensity could be considered “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.2.1.1.2 Maximum Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.2.1.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Time of onset period is displayed as D1-D4, D5-D8.

4.2.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

The number of days of occurrence during the solicited period is displayed as 1-3 days, 4-7 days and 8 days.

4.2.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period.

The overall number of days of occurrence is:

(End date - vaccination date) + (number of days of occurrence within the solicited period) -

length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

The overall number of days of occurrence is displayed as 1-3 days, 4-7 days, 8 days or more and Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
    - Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

4.2.1.2 Unsolicited AEs

4.2.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and the intensity is not None.

Events for which the intensity is None are not included in safety analysis but are included in separate listings.

4.2.1.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but < 25 mm in adults).

Intensity for the other unsolicited AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.2.1.2.3 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of vaccination:

> Time of Onset = start date of the unsolicited AE - date of vaccination before the unsolicited AE + 1.

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 28 days" after vaccination, which corresponds to AEs with a time of onset between 1 and 29 days or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination, so will be included in these tables.

Time of onset period is displayed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

Note: To further clarify the analysis,

- Any SAEs or AESIs collected throughout the study with time of onset > D29 after vaccination will not be presented in tables of unsolicited AEs within 28 days but only in tables of SAEs or AESIs.
- Any unsolicited AEs (planned to report up to 28 days) with time of onset between D01 and D29 or missing after vaccination will be presented in the tables of unsolicited AEs within 28 days.
- Any unsolicited AEs (planned to report up to 28 days) with time of onset > D29 after vaccination will not be presented in any tables but listed separately.
- Any unsolicited AEs with null (0) or negative time of onset will be excluded from the above tables and listed separately.

4.2.1.2.4 Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

Duration will be displayed by period as 1-3 days, 4-7 days, 8 days or more and Missing.

4.2.1.2.5 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

SAEs will be analyzed using the following periods:

- Within 28 days after vaccination
- During the study (i.e., all SAEs occurred during the study)

4.2.1.2.6 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

AESIs will be analyzed using the same time periods as SAEs described in Section 4.2.1.2.5:

- Within 28 days after vaccination
- During the study (i.e., all AESIs occurred during the study)

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.5 Causal Relationship

This information will be summarized as collected in the field "Relationship to study vaccine". Missing causal relationship will be handled as described in Section 3.4.3.1.2. Relationship to study procedure is only presented in the listing.

4.2.2.6 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- For participants disposition: if participants did not complete the study due to AE as recorded in Completion at End of Study form
- For safety overview: if participants did not complete the study due to AE as recorded in Completion at End of Study form or had any solicited or unsolicited AEs causing study discontinuation / termination as recorded in solicited reaction or unsolicited AE forms within the time period indicated
- For summary of unsolicited AEs by SOC / PT: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Termination" checked that is at least Grade 1 or missing and is within the time period indicated

4.2.3 Immunogenicity

4.2.3.1 Computed Values for Analysis

In order to appropriately manage extreme values (< LLOQ and ≥ ULOQ) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

4.2.3.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values as described in Section 4.2.3.1 and is computed as follows:

- Calculate the fold-rise of values as the ratio of post-baseline computed value divided by baseline computed value

For HAI assay, if the computed value is ≥ 4-fold rise, then the derived ≥ 4-fold rise indicator will be "Yes" for that test, otherwise ≥ 4-fold rise will be "No".

Note: If baseline or post-baseline is missing, then the fold-rise is missing.

4.2.3.3 Seroconversion

Seroconversion is defined for HAI assay as either computed titer value < 10 (1/dilution [1/dil]) at D01 and post-injection computed titer value ≥ 40 (1/dil) at D29, or computed titer value ≥ 10 (1/dil) at D01 and a ≥ 4-fold increase in computed titer value (1/dil) at D29.

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

The calendar age will be used for demographics summary and age subgroups definition and will be analyzed as collected in CRF.

The age group of a participant in the study will be based on the calendar age as follows:

- "18 to 49 years" means from the day of their 18th birthday to the day before their 50th birthday
- "≥ 50 years" means from the day of the participant's 50th birthday

4.2.4.2 Duration of a Participant in the Trial

The duration of a participant's participation in the study is computed as follows:

- Maximum (Visit dates, Termination date, Follow-up date) – D01 date + 1.

4.2.4.3 Duration of the Study

The duration of the study is computed in days as follows:

Maximum of all participants (Visit dates, Termination date, Follow-up date) - minimum of all participants (D01 date) +1

4.2.4.4 Duration of a Participant in the Active Phase

The duration of a participant's participation in the active phase is computed as follows:

- Maximum (D29 date, Termination date) – D01 date + 1.

4.2.4.5 Duration of the Active Phase

The duration of the active phase is computed in days as follows:

Maximum of all participants (D29 dates, Termination dates) - minimum of all participants (D01 date) +1

5 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

Ab	Antibody
AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
BL	Blood sampling
CRF	Case report form
D	Day
DC	diary card
DMC	Data Monitoring Committee
FAS	Full analysis set
GM	Geometric mean
GMT	Geometric mean of titer
GMTR	Geometric mean of titer ratio
GMFR	Geometric mean fold-rise
HAI	Hemagglutinin inhibition
IM	intramuscular
IIV4	Quadrivalent-inactivated influenza vaccine
IRT	Interactive Response Technology
LLOQ	Lower level of quantitation
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
RIV4	Recombinant influenza vaccine, Quadrivalent
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SOC	(Primary) System organ class

PT	Preferred term
TLF	Tables, listings and figures
ULOQ	Upper level of quantitation

6.2 Appendix 2 Bayesian approach

Calculation of the posterior probability of the GMT ratio being > 0.667

Based on Bayesian approach (3), we are going to calculate the posterior probability of the true GMT ratio for each strain between RIV4 and IIV4 to be higher than the commonly accepted non-inferiority margin (0.667), which is equivalent to true mean difference on the $\log_{10}$ scale > -0.176.

We assume that HAI $\log_{10}$titer x_i for each strain for any group IIV4 or RIV4 follows normal distributions with known variance σ^2. Considering the following sampling model for data from the two groups:

$$X_{i,1}=\mu+\delta+\epsilon_{i,1}$$
$$X_{i,2}=\mu-\delta+\epsilon_{i,2}$$
$$\{\epsilon_{i,j}\}\sim i.i.d.normal\ (0,\sigma^2)$$

Using this parameterization where $\theta_1 = \mu+\delta$ and $\theta_2 = \mu-\delta$, representing group mean on the $\log_{10}$ scale for each group. We see that δ represents half the population difference in means, as $(\theta_1 - \theta_2)/2 = \delta$, and μ represents the pooled average, as $(\theta_1 + \theta_2)/2 = \mu$. Assuming standard deviation of HAI $\log_{10}$ titer is known and equal to the sample standard deviation for each strain. Sine σ is known, no prior is needed for it. Convenient conjugate prior distributions for the unknown parameters μ, δ are

$$p(\mu,\delta) = p(\mu)\times p(\delta)$$
$$\mu \sim normal(\mu_0,\gamma_0^2)$$
$$\delta \sim normal(\delta_0,\tau_0^2)$$

Then the full conditional distribution of μ and δ are as follows:

$$\{\mu|x_{i,1},x_{i,2},\delta,\sigma^2\}\sim normal(\mu_n,\gamma_n^2),\text{ where}$$
$$\mu_n=\gamma_n^2\times[\mu_0/\gamma_0^2+\sum_{i=1}^{n1}(x_{i,1}-\delta)/\sigma^2+\sum_{i=1}^{n2}(x_{i,2}+\delta)/\sigma^2]$$
$$\gamma_n^2=[1/\gamma_0^2+(n1+n2)/\sigma^2]^{-1}$$

$$\{\delta|x_{i,1},x_{i,2},\mu,\sigma^2\}\sim normal(\delta_n,\tau_n^2),\text{ where}$$
$$\delta_n=\tau_n^2\times[\delta_0/\tau_0^2+\sum_{i=1}^{n1}(x_{i,1}-\mu)/\sigma^2-\sum_{i=1}^{n2}(x_{i,2}-\mu)/\sigma^2]$$
$$\tau_n^2=[1/\tau_0^2+(n1+n2)/\sigma^2]^{-1}$$

For the prior distribution of μ and δ, with reference to US studies (PSC12 and PSC16) we give prior settings as Appendix Table 1 shown. The priors on γ_0^2 and τ_0^2 tend to make these prior

distributions reasonably diffuse (essentially non-informative on the $\log_{10}$ scale). Given a hypothetical observed data with $\delta = 0, \mu = 2.5, \sigma = 0.65$, the prior distribution and marginal posterior distribution of δ is shown in Appendix Figure 1. It is shown that these priors are so vague that the likelihood (the data contribution) has a strong influence on the posterior distribution estimation.

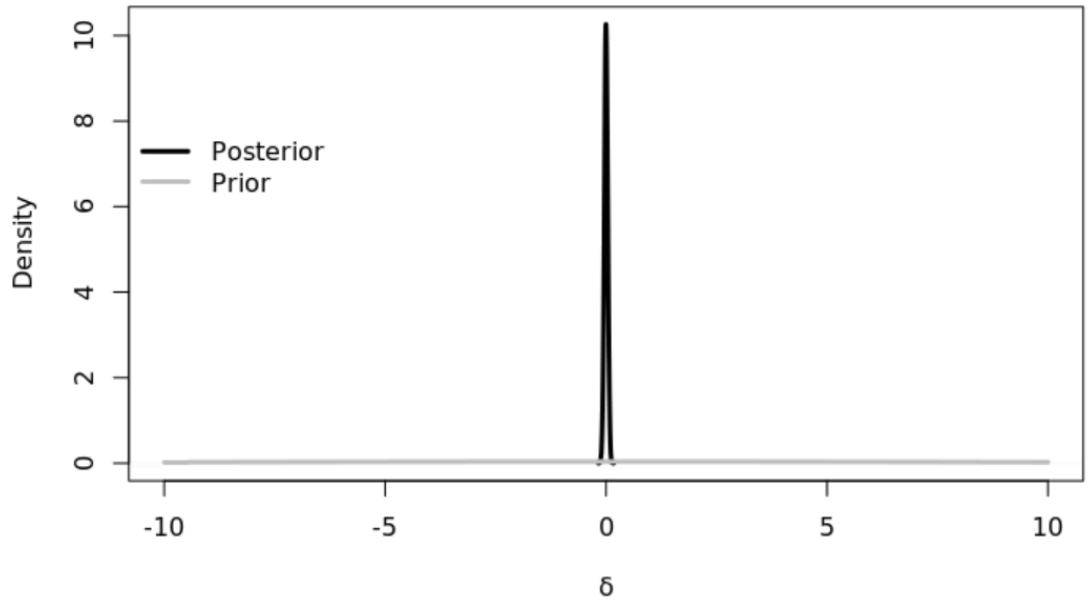
Appendix Table 1: prior settings for unknown parameters

Parameter	value
μ_0	2.0
γ_0^2	1^2
δ_0	- 0.176/2
τ_0^2	10^2

Therefore, based on the above prior distribution, we can then calculate the posterior probability *Pr* $(2\delta > -0.176|\text{data})$. The Markov chain Monte Carlo (MCMC) procedure is utilized to obtain samples from the posterior distribution. SAS example code is provided below.

The statistical criterion for demonstrating success (posterior probability threshold) is not proposed due to the not powered sample size and the nature of the descriptive study. But the corresponding threshold might be proposed in the bridge report for descriptive evaluation purpose.

Appendix Figure 1: Prior and posterior distributions for δ given a hypothetical observed data with $\delta = 0, \mu = 2.5, \sigma = 0.65$



SAS example code for the posterior probability calculation:

```
/*============prepare data*============*/
data aa;
  set add.adis;
  if paramn=1 and avisitn=2;  ***paramn: parameter index in ADaM adis. Sample code only focus
on one parameter;
                        ***avisitn=2 is used to filter the post-vaccination titers.
  avallog=log10(aval);
  keep usubjid param paramn trt01pn trt01p aval avallog;
 run;

 /*=========== retrieve initial values =========*/
/*get the poopled mean and SD from data */
proc summary data=aa;
   var avallog;
   output out=_stats(drop=_type_ _freq_)  mean=mu_pool n=n  std=SD;
run;

/*got the group mean difference between RIV4 and IIV4*/
ods listing close;
ods output statistics = _stats_diff ;
proc ttest data=aa alpha=0.05 ci=equal;
   class trt01pn  ;
   var avallog;
run;
ods listing;

/*set inital value to mu_pool, del;  set SD as a fixed value obtained from data*/
proc sql  noprint;
   select mean/2 into: del from _stats_diff (where=(method="Pooled"));
   select mu_pool into: mu_pool  from _stats  ;
   select sd into: sd from _stats ;
quit;

%put &del.  &mu_pool.  &sd.;

/*============Start MCMC procedures:=========*/
/*generate posterior samples for mu and del*/
proc mcmc data=aa outpost=postout seed=123 nmc=10000 thin=2 monitor=(_parms_ ) statistics;
   ods select PostSumInt;                    *** Postsumint= summary statistics;
   parm mu_pool &mu_pool. del &del. ;
/* specify parameters to estimate and assign initial values to them*/
   prior mu_pool ~ normal(mean=2, var=1);  /*specify prior distributions for the parameter mu that
represents the pooled average */
   prior del ~ normal(mean=-0.088, var=100 );
```

```
   /*enable different avallog to have different mean and variance, depending on their group
indicator*/
  if trt01pn = 1 then do;
     mu = mu_pool + del;
  end;
  else do;
     mu = mu_pool - del;
  end;
  s2=&sd. * &sd.;  /*Assuming standard deviation of HAI log10 titer is known and equal to the
sample standard deviation*/
  model avallog ~ normal(mu, var=s2);
run;



/*get the posterior probability of the GMT ratio being > 0.667, which is equivalent to mean
difference on the log10 scale > -0.176.*/
proc format;
value  delfmt low- -0.088=" mean difference on the log10 scale <= -0.176"
          -0.088 <- high= ' mean difference on the log10 scale > -0.176' ;
run;

ods output  OneWayFreqs=stat1;
proc freq data = postout;
tables del /nocum;
format del delfmt.;
run;
```

7 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

2. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90.

3. Hoff PD. A First Course in Bayesian Statistical Methods. Springer-Verlag, New York, Springer Texts in Statistics, 2009.