NCT05513391

SAP Core Body

Title: Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine Compared with Egg-Based Standard-Dose Quadrivalent Influenza Vaccine in Children 3 to 8 Years of Age.

Study Code: VAP00026

Study Phase: Phase III

SAP Core Body Version: 4.0

SAP Core Body Date: 31-August-2023

Protocol Version Number: 3.0

Version History

Previous Version(s)	Date	Comments
1.0	21 April 2022	
2.0	12 July 2023	Addition of an interim analysis
3.0	10 August 2023	Clarifications regarding steps in individual and overall PPoS calculation for SC rates, and the inclusion of different seeds to be used in simulations of RIV4 and IIV4 data
4.0	31 August 2023	Clarification regarding the futility criteria

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1 Overall Design

The design of the study is summarized in Table 1.1.

Table 1.1: Overall design

Type of design	Parallel, multi-center
Phase	Phase III
Control method	Active-controlled Control Product = Fluarix® Quadrivalent (or other commercial names), Egg-based Influenza vaccine (split virion, inactivated) (IIV4) (GlaxoSmithKline Biologicals)
Study population	Healthy children aged 3 to 8 years
Level and method of blinding	Modified double-blind (participant, Sponsor, and Investigator blinded)
Study intervention assignment method	Randomization and stratification by age group and previous vaccination status for influenza
Number of participants	Approximately 1412 participants 3 to 8 years of age (approximately 50% participants in the age group 3-5 years and 50% participants in the age group 6-8 years, and approximately 50% participants previously vaccinated and 50% participants previously unvaccinated in each age group)
Intervention groups	Randomization in a 1:1 ratio to receive either RIV4 or IIV4. Participants will receive either 1 or 2 doses 28 days apart of either RIV4 or IIV4 depending on whether they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively
Total duration of study participation	Approximately 6 months for participants previously vaccinated against influenza and approximately 7 months for participants previously unvaccinated against influenza
Countries/Region	USA and Europe
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Safety Management Team (SMT)

Table 1.2: Schedule of activities for previously vaccinated participants 3-8 years of age (simplified compared to the protocol)

Phase III Study, 2 Visits, 1 Vaccination, 2 Blood Samples, 6 Months' Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	Phone Call 1*	Visit 2	Phone Call 2 6-month follow-up†
Study timelines (Days)		D01	D09	D29	D181
Time interval (Days)		NA	V01 + 8D	V01 + 28D	V01 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:					
Informed consent	X	X			
Inclusion/exclusion criteria	X	X			
Collection of demographic data§§	X	X			
Collection of medical history*** (Significant medical history)	X	X			
Collection of concomitant medications	X Reportable concomitant medications	28 days after vaccination			
History of Influenza vaccination	X	X			
Randomization Contact Interactive Response Technology (IRT) system for randomization, participant number, dose number and SN subset	X	X			
Blood sampling (BL) (5 mL)	X	BL0001**		BL0002	
Vaccination (vac)	X	X			
Immediate surveillance (30 min)	X	X			
Collection of solicited injection site and systemic reactions	X	7 days after vaccination			
Collection of unsolicited adverse events (AEs)	X	28 days after vaccination			
Collection of medically attended AEs (MAAEs)	X	28 days after vaccination			
Collection of information on SAEs, including AESIs	X	To be reported at any time during the study			

Visit/Contact	*Collection of information in the CRF*	Visit 1	Phone Call 1*	Visit 2	Phone Call 2 6-month follow-up†
Study timelines (Days)		D01	D09	D29	D181
Time interval (Days)		NA	V01 + 8D	V01 + 28D	V01 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:					
End of Active Phase participation record	X			X	
Six months follow-up participant record	X				X

CRF: case report form

* The Investigator or an authorized designee will remind the participant's parent(s) or legally acceptable representative(s) to bring back the DC/eDC at the next visit and will answer any questions.

† The Investigator or an authorized designee will interview the participant's parent(s) or legally acceptable representative(s) to collect the information recorded in the MA, and will attempt to clarify anything unclear

** Blood sample to be drawn before vaccination§§ To comply with US Food and Drug Administration expectations, Sponsors are to enroll participants who reflect the demographic for clinically relevant populations with regards to age, gender, race, and ethnicity (FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and Food and Drug Administration staff [Internet]. 2016. Available from: https://www.fda.gov/media/75453/download)

*** Including history of laboratory-confirmed influenza illness over the 3 previous influenza seasons

Table 1.3: Schedule of activities for previously unvaccinated participants 3-8 years of age (simplified compared to the protocol)

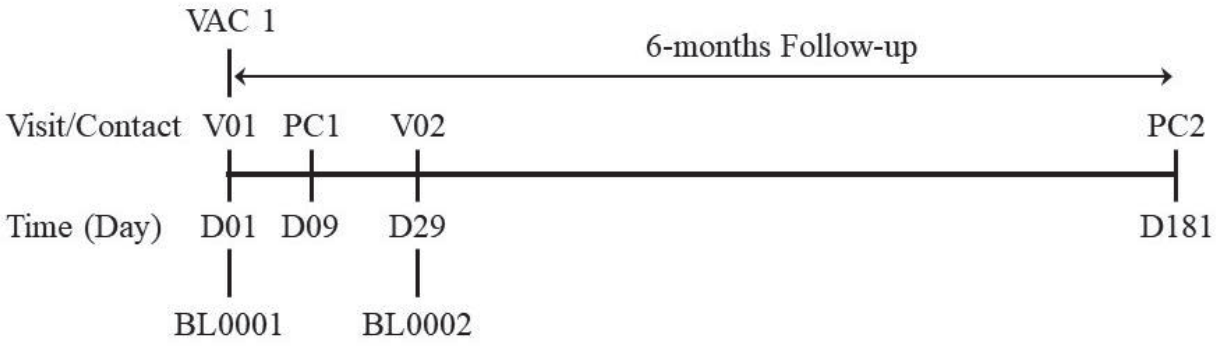
Phase III Study, 3 Visits, 3 Phone Calls, 2 Vaccinations, 2 Blood Samples, 7 Months' Duration Per Participant

Visit	***Collection of information in the CRF***	**Visit 1**	**PC 1***	**Visit 2**	**PC 2***	**Visit 3**	**PC3 6-month safety follow-up†**
Study timelines (Days)		D01	D09	D29	D37	D57	D209
Time interval (Days)			V01 + 8D	V01+28D	V02 + 8D	V02 + 28D	V02 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:							
Informed consent	X	X					
Inclusion/exclusion criteria	X	X					
Collection of demographic data††	X	X					
Collection of medical history‡‡ (Significant medical history)	X	X					
Collection of concomitant medications	X Reportable concomitant medication	28 days after each vaccination					
History of Influenza vaccination	X	X					
Randomization Contact IRT system for randomization, participant number, dose number and SN subset	X	X					
Blood sampling (BL) (5 mL)	X	BL0001§				BL0002	
Definitive contraindications	X			X			
Vaccination (VAC)	X	VAC1		VAC2			

Visit	***Collection of information in the CRF***	**Visit 1**	**PC 1***	**Visit 2**	**PC 2***	**Visit 3**	**PC3 6-month safety follow-up†**
Study timelines (Days)		D01	D09	D29	D37	D57	D209
Time interval (Days)			V01 + 8D	V01+28D	V02 + 8D	V02 + 28D	V02 + 180D
Time windows (Days)		NA	[+2 D]	[-2, +7 D]	[+2 D]	[-2, +7 D]	[+14 D]
Visit procedures:							
Immediate surveillance (30 min)	X	X		X			
Collection of solicited injection site and systemic reactions	X	7 days after vaccination		7 days after vaccination			
Collection of unsolicited AEs	X	28 days after each vaccination					
Collection of MAAEs	X	28 days after each vaccination					
Collection of information on SAEs, including AESIs	X	To be reported at any time during the study					
End of Active Phase participation record	X					X	
Six months follow-up participant record	X						X

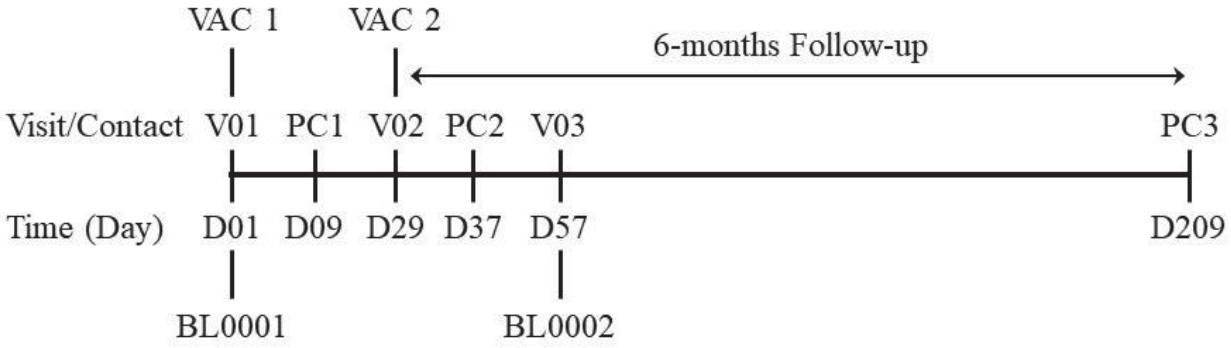
CRF: case report form
* The Investigator or an authorized designee will remind the participant's parent(s) or legally acceptable representative(s) to bring back the DC/eDC at the next visit and will answer any questions.
† The Investigator or an authorized designee will interview the participant's parent(s) or legally acceptable representative(s) to collect the information recorded in the MA, and will attempt to clarify anything unclear
§ Blood sample to be drawn before vaccination
†† To comply with US Food and Drug Administration expectations, Sponsors are to enroll participants who reflect the demographic for clinically relevant populations with regards to age, gender, race, and ethnicity (FDA. Collection of race and ethnicity data in clinical trials: Guidance for industry and Food and Drug Administration staff [Internet]. 2016. Available from: https://www.fda.gov/media/75453/download)
‡‡ Including history of laboratory-confirmed influenza illness over the 3 previous influenza seasons

Figure 1.1 – Graphical study design for participants previously vaccinated



BL: blood sample
VAC: vaccination
PC: phone call

Figure 1.2 – Graphical study design for participants previously unvaccinated



BL: blood sample
VAC: vaccination
PC: phone call

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

2 Objectives and Endpoints

Table 2.1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of RIV4 vs licensed IIV4 for the 4 strains based on the egg-derived antigen in all participants aged 3 to 8 years	• Individual HAI titer 28 days after the last vaccination (D29 or D57[1]) • Seroconversion (SC) (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29 or D57, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D29 or D57)
Secondary	
Immunogenicity • To summarize the HAI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg-derived antigen in participants aged 3 to 8 years	• Individual HAI titer on D01 and 28 days after the last vaccination (D29 or D57) • Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 28 days after the last vaccination (D29 or D57) • Individual HAI titer ratio: 28 days after the last vaccination (D29 or D57) / D01 • Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29 or D57, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold rise in titer [1/dil] at D29 or D57) • Participants with titers ≥ 40 (1/dil) on D01 and 28 days after the last vaccination (D29 or D57)
Safety • To assess the safety profile of each vaccine in all participants and by age group	• Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination • Occurrence of solicited (pre-listed in the participant's diary card [DC]/electronic DC [eDC] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 8 days after each vaccination

[1] Depending on vaccination schedule/influenza previous vaccination: 1 dose received during the study = D29 and 2 doses received during the study = D57

Objectives	Endpoints
	• Occurrence of unsolicited AEs up to 28 days after each vaccination • Occurrence of medically attended adverse event (MAAEs) up to 28 days after each vaccination • Occurrence of serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study • Occurrence of AESIs throughout the study
Exploratory	
• To describe the neutralizing antibody immune response based on the egg-derived antigen in a randomized subset of participants[2]	• Individual seroneutralization (SN) antibody (Ab) titer on D01 and 28 days after the last vaccination (D29 or D57) • Individual SN Ab titer ratio (fold increase in post-vaccination titer relative to D01) at 28 days after the last vaccination (D29 or D57) • Participants with SN Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after the last vaccination (D29 or D57) • Fold-increase in SN Ab titer (post/pre) ≥ 2 and ≥ 4 at 28 days after the last vaccination (D29 or D57) • Detectable SN Ab (SN Ab titer ≥ 10 [1/dil]) at D01 and 28 days after the last vaccination (D29 or D57)

[2] At least 400 participants from each vaccine group (RIV4 and IIV4) will be randomized to be included in the subset. Among the participants randomized in the subset, approximately 50% of them will be in the 3 to 5 years subgroup and 50% of them in the 6 to 8 years subgroup. In addition, approximately 50% of participants will be previously vaccinated against influenza and 50% of participants will be previously unvaccinated against influenza.

3 Statistical Considerations

Following the planned recruitment period of 2022-2023 season, only approximately 25% out of the 1412 targeted participants aged 3 to 8 years had been enrolled and vaccinated in the study. It was decided to add to the statistical analysis initially planned, an interim analysis at the end of 2022-2023 season to evaluate safety and calculate the predictive power of success (PPoS) for each of the 8 non-inferiority (NI) statistical tests included in the primary objective, the overall study PPoS, the PPoS of the 4 GMTs and PPoS of the 4 SC rates; creating consequently the possibility of stopping this study if warranted.

3.1 Statistical Hypotheses

Primary Objective:

Statistical Methodology for analyzing the primary 8 endpoints of geometric mean titers (GMTs) and SC rates.

NI of RIV4 as compared to IIV4 in participants 3 to 8 years of age will be conducted for GMTs and SC rates.

For each strain, the NI methodology will be applied to compare the post-vaccination GMTs and the SC rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis.

The primary analysis will be conducted into 2 steps starting with testing for NI of GMTs between RIV4 and IIV4. If NI of GMTs based on the 4 strains is demonstrated, then NI for SC will be also tested.

Step1: Geometric Mean Titers

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H0 need to be rejected to demonstrate NI in GMTs.

H_0: $GMT_{RIV4} / GMT_{IIV4} \leq 0.667$

H_A: $GMT_{RIV4} / GMT_{IIV4} > 0.667$

or equivalently,

H_0: $\log_{10}(GMT_{RIV4}) - \log_{10}(GMT_{IIV4}) \leq \log_{10}(0.667)$

H_A: $\log_{10}(GMT_{RIV4}) - \log_{10}(GMT_{IIV4}) > \log_{10}(0.667)$

Step 2: Seroconversion

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H0 need to be rejected to demonstrate NI in SCs.

H_0: $P_{RIV4} - P_{IIV4} \leq -10\%$

H_A: $P_{RIV4} - P_{IIV4} > -10\%$

Secondary Objectives:

There are no statistical hypotheses to be tested in the secondary objectives.

3.2 Sample Size Determination

A total of approximately 1200 evaluable participants 3 to 8 years of age will be assessed (approximately 50% participants enrolled in the age group 3-5 years and 50% participants enrolled in the age group 6-8 years) in this study. Approximately 50% of participants enrolled within age group will be primed, and the other 50% will be unprimed.

Assuming similar GMTs in both groups and a standard deviation of log titers of 0.6 with a NI margin of 1.5 (or 1/1.5 = 0.667); NI for GMTs would be demonstrated with a power of approximately 99.6%.

Assuming in each vaccine group the same expected SC rates (0.5, 0.5, 0.7, 0.7) for each of the 4 strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria), based on conservative estimates from historical data, and a NI margin of 10%, the NI for SC can be demonstrated with a statistical power of approximately 82.0% (93.7%, 93.7%, 96.7% and 96.7% for each strain, respectively).

Hence, the overall study power is estimated to be approximately 82.0% (82.0% = 99.6%[GMTs] x 82.0%[SC]).

As shown above, to keep the study power above 80%, the sample size was increased accordingly, to have an overall Type II error <20% for the 8 NI tests.

Assuming 15% attrition rate in this age group; a total of approximately 1412 participants 3 to 8 years of age will be enrolled in this study.

3.3 Populations for Analyses

For the purposes of analysis, the following analysis sets will be defined:

Participant Analysis Set	Description
Randomized	All participants randomized by study IRT to one of the study groups.
Safety Analysis Set (SafAS)	Participants who have received at least one dose of the study vaccine. All participants will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine and had a post-vaccination blood sample. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from FAS who were randomized in the exploratory subset (FAS-SN). Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following criteria 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 complete the vaccination schedule 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 or at visit 3 in the proper time window ([D26, D39] or VAC2+[D26, D39] respectively) or a post-dose serology sample was not drawn at visit 2 or visit 3 Participant received protocol-prohibited medications impacting or that may have an impact on the immune response, as specified in the database following data review of concomitant medications. Any other deviation identified during the study conduct and identified as relevant by the clinical team during data review, ie, indicated as excluding participants from this analysis set in the manual deviations dataset. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from PPAS who were randomized in the exploratory subset (PPAS-SN). In the event of a local or national immunization program with any other vaccine as needed, participants who receive 1 or more doses of the vaccine listed above at any time during the study will not be withdrawn from the study.

3.4 Statistical Analyses

3.4.1 General Considerations

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above (SAS Institute, Cary, North Carolina, USA).

For descriptive purposes, the following statistics will be presented:

Table 3.1: Descriptive statistics produced

Disposition and follow-up description	**Categorical data**	At least number of participants (Percentage of participants are also possible).
	Continuous data	Mean, standard deviation, minimum and maximum.
Baseline characteristics	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs] for main endpoints) of participants. Unsolicited: Number and percentage (95% CIs for main endpoints) of participants and number of events.
Immunogenicity results	**Categorical data (seroconversion, cutoff)**	Number and percentage (95% CIs for main endpoints) of participants.
	Continuous data (titer / concentration)	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) ie, using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that $\log_{10}$ transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on $\log_{10}$ (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.

For each participant, randomized study group will be assigned from the randomization number assigned to the participant, and injected vaccine/study group will be derived from the label of the vaccine(s) injected on D01, as collected in the CRF.

3.4.2 Primary Endpoints

The immunogenicity parameters will be calculated in each study group with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs.

Statistical Methodology for analyzing the primary 8 endpoints (GMTs and SC rates).

Non-inferiority of RIV4 as compared to IIV4 in participants 3 to 8 years of age will be conducted for GMTs and SC rates.

For each strain, the NI methodology will be applied to compare the post-vaccination GMTs and the SC rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis.

The primary analysis will be conducted into 2 steps starting with testing for NI of GMTs between RIV4 and IIV4. If NI of GMTs based on the 4 strains is demonstrated, then NI for SC will be also tested.

Step1: Geometric Mean Titers

Assuming that log10 transformation of the data follows a normal distribution, the log10 (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of geometric means (GMs).

The statistical methodology is based on a 2-sided 95% CI of the ratio of the GMTs (RIV4 divided by IIV4) at 28 days after the last vaccination. Non inferiority for GMTs is demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio is > 0.667 for each of the 4 virus strains.

As appropriate according to the number of participants in the respective subgroups, ANCOVA will be conducted for each strain with a model including the terms log10 of HAI titer at D01, priming status, age subgroup, season and the treatment represented by the vaccine administered as independent factors, and log10 HAI titer of each virus strain separately of the last vaccination as a response variable. ANCOVA will be conducted using Proc Mixed in SAS (all terms in the model are fixed). In Proc Mixed, the "Estimate" statement will allow to derive the difference (RIV4 minus IIV4) of the Least Squares-means and the 95% CI in their original log10 values. By exponentiating the difference (RIV4 minus IIV4) and its 95% CI; the 95% CI of ratio (RIV4/IIV4) will be obtained and be used to derive GMTs NI final results.

In the interim analysis, the statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs (RIV4 divided by IIV4) at 28 after the last vaccination. NI for GMTs will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio is > 0.667 for each of the 4 virus strains. The 95% CI will be calculated using normal approximation of log-transformed titers. The Per-Protocol Analysis Set (PPAS) will be used as the primary analysis set.

Step 2: Seroconversion rates

The statistical methodology is based on a 2-sided 95% CI of the difference in SC rates (RIV4 minus IIV4) at 28 days after last vaccination. NI for SC rates is demonstrated if the lower limit of the 2-sided 95% CI is > -10% for the 4 strains. The 95% CI of the rate difference is computed using the Wilson Score method without continuity correction.

As a sensitivity analysis, a generalized linear model (binomial-identity model) based on a link function named "identity link" will be used. The regression coefficient for the treatment (vaccines administered) in the binomial-identity model represent the proportions difference (difference between RIV4 and IIV4). The model will include priming status, age subgroup, season, and the treatment term (represented by the vaccines administered) as independent factors. The difference (RIV4 – IIV4) and its 95% CI obtained will be used to derive the SC NI results.

In the sensitivity analysis, the statistical methodology will be based on a 2-sided 95% CI of the difference in SC rates (RIV4 – IIV4) at 28 days after last vaccination. The NI for SC rates will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for the 4 strains.

In the interim analysis, no sensitivity analysis will be conducted for SC due to the limited number of participants included in the interim analysis.

Non-inferiority will be assessed on PPAS as the main analysis set and will be confirmed on the FAS.

3.4.3 Secondary Endpoints

Immunogenicity

The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio. The 95% CI of proportions difference (ie, difference between vaccine groups in SC) will be calculated using Wilson Score method without continuity correction. All analyses will be conducted by study group.

In particular, the following descriptive statistics will be displayed:

- GMTs of individual HAI titer on D01 and 28 days after the last vaccination (D29 or D57)
- Percentage of participants with detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 28 days after the last vaccination (D29 or D57)
- GMs of Individual HAI titer ratio: 28 days after the last vaccination (D29 or D57) / D01
- SC rates (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29 or D57, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D29 or D57)
- Percentage of participants with titers ≥ 40 (1/dil) on D01 and 28 days after the last vaccination (D29 or D57)

- The RCDCs of pre-vaccination titer prior to the first vaccination (D01), and post-vaccination titer at D29 after last vaccination will be generated for each study group. The RCDCs will include the plots of the 2 study groups the same figure.

The analysis will be conducted for each immunogenicity variable on the PPAS, and on FAS if the attrition rate from FAS to PPAS is greater than 10%.

In addition, subgroup analysis will be performed; in particular, immunogenicity will be described according to season, sex, race, previous influenza vaccination status (received a seasonal influenza vaccine in the last past influenza season or not), baseline seropositivity status (seropositive and seronegative are defined as baseline antibody titer ≥ 1:10 or < 1:10), and age subgroups (3 to 5 and 6 to 8 years) as appropriate according to number of participants in the respective subgroups. Subgroup analyses will be performed on PPAS.

Safety

For the main safety parameters, 95% CIs of point estimates will be calculated using exact binomial method (Clopper-Pearson method) for single proportions and using the normal approximation for quantitative data.

All analyses will be descriptive; no hypotheses will be tested.

The number of participants with documented safety will be used as denominator of the frequencies.

For solicited reactions, the denominator will be the total number of participants who have non-missing data for the endpoint considered.

For unsolicited AEs, the denominator will be the total number of participants who were vaccinated.

In terms of contents, solicited reactions will be presented by time to onset, maximum severity, number of days of occurrence and action taken; unsolicited AEs will be presented by causal relationship, time of onset, maximum severity and duration; SAEs will be presented by causal relationship, seriousness and outcome.

Subgroup analyses will also be performed; in particular, the main safety endpoints will be described according to age subgroups (3 to 5 and 6 to 8 years), previous vaccination status, sex and race, as appropriate according to number of participants in the respective subgroups.

3.4.4 Exploratory Endpoint

The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed titers for GMTs. All analyses will be conducted by study group. For some parameters (eg. GMTs, 4-fold increase) difference or ratio between groups may be calculated with 95%CI. The 95% CI of ratios of GMTs or 4-fold increase rate will be calculated using the same method as for the primary objective.

Neutralizing Ab titers will be measured for each influenza strain with the SN method.

In particular, the following endpoints will be described with 95% CIs:

- GMTs of individual SN Ab titer on D01 and 28 days after the last vaccination (D29 or D57)
- GMs of individual SN Ab titer ratio (fold increase in post-vaccination titer relative to D01) at 28 days after the last vaccination (D29 or D57)
- Percentage of participants with SN Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after the last vaccination (D29 or D57)
- Percentage of participants with fold-increase in SN Ab titer (post/pre) ≥ 2 and ≥ 4 at 28 days after the last vaccination (D29 or D57)
- Percentage of participants with detectable SN Ab (SN Ab titer ≥ 10 [1/dil]) at D01 and 28 days after the last vaccination (D29 or D57)
- The RCDCs of pre-vaccination titer prior to the first vaccination (D01) and post-vaccination titer at D29, after last vaccination will be generated for each study group. The RCDCs will include the plots of the 2 groups on the same figure.

The analysis will be conducted for each immunogenicity variable on the PPAS subset (PPAS-SN) and on the FAS subset (FAS-SN) if the attrition rate from FAS-SN to PPAS-SN is greater than 10%.

In addition, as appropriate according to the number of participants in the respective subgroups, the descriptive summary of SN immunogenicity main parameters will also be produced by:

- Serological SN status at baseline (< 10 and ≥ 10 1/dil)
- Previous influenza vaccination status
- Age subgroup
- Sex
- Race
- Season

3.4.5 Handling of Missing Data and Outliers

3.4.5.1 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

3.4.5.1.1 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.

3.4.5.1.2 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 the 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(s) at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.5.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

3.4.5.1.4 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 missing. 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.

3.4.5.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.5.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.3.1.

3.5 Interim Analysis

During the recruitment period of 2022-2023 season, only approximately 25% out of the 1412 targeted participants aged 3 to 8 years had been enrolled and vaccinated in the study.

Thus, it was decided to conduct an interim analysis to review safety and assess the likelihood of the study success by the end of enrollment (1412 participants) based on the immunogenicity data accumulated after randomizing and vaccinating approximatively 366 children (approximately 25% of participants).

For this interim analysis:

- A Firewall Internal Committee (FIC) including Senior members from Clinical, Safety and Biostatistics, not involved in the study conduct, will be set up to review the content of the results including the interim analysis of immunogenicity and summaries of safety and recommend if the stopping of this study is warranted

- An unblinded statistical team will be in charge of breaking the blind of the enrolled participants after database lock, conducting the interim statistical analysis and communicating unblinded results to the FIC. Should the study continue for a second season after the results of the interim analysis, the unblinded statistical team will not be involved in the upcoming conduct of the study.
- The recommendation for stopping the study will be based on the following criteria:
    - The overall PPoS of the 4 GMTs and 4 SC NI statistical tests, based on a guidance of PPoS of less or equal [redacted], considering also the trend across the different PPoS calculated:
        - The individual PPoS to meet NI for each vaccine strain and each parameter (Geometric Mean Titre [GMT] and Seroconversion [SC] rate)
        - The overall PPoS of the 4 GMTs NI statistical tests
        - The overall PPoS of the 4 SC NI statistical tests
    - RIV4 immunogenicity results with regards to comparator in each age, priming status and baseline serological status subgroup will also be considered to inform the decision.
    - Safety results will also be reviewed.

A charter will be written to define the roles and responsibilities of every party in the conduct of the interim analysis, the FIC functioning, and the issuance of recommendation for stopping the study.

3.5.1 Safety

Considering the safety endpoints described in Section 2 and the corresponding calculation methods defined in Sections 4.2.1 and 4.2.2, safety summaries on data up to D29 after the last vaccination will be presented.

Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs will be summarized by age group and by vaccine group.

Furthermore, the following listings of safety collected during the 2022-2023 flu season will be generated and presented to FIC:

- All SAEs.
- All Grade 3 solicited ARs.
- All AEs leading to study discontinuation

3.5.2 Immunogenicity

Sanofi decided to assess the likelihood of success in this study at the end of study. Hence, it was decided to calculate the predictive power of each endpoint (GMT and SC) based on data collected at the end of the first season, which is the flu season 2022-2023.

The predictive power is defined as the probability that the final study result will be successful, given the data observed thus far – at the time of the interim analysis (4).

In addition, the following summary statistics will be generated and presented:

- GMT for each strain at D01 and D29 or D57
- The geometric mean titer ratios (GMTR): geometric mean of the post-vaccination/pre-vaccination ratio for each strain
- Seroconversion rate at D29 or D57 based on the baseline titer at D01
- Proportion of participants with titers ≥ 1:40 (1/dilution [dil]) for each strain at D01 and D29 or D57.

The immunogenicity analysis will be conducted on the PPAS, and on FAS if the attrition rate from FAS to PPAS is greater than 10%.

3.5.2.1 Calculating the individual PPoS (GMTs and SC rates).

In-house, 2 SAS Macros are to be used in calculating PPoS based on simulations. The first SAS macro will calculate PPoS of GMT for each vaccine strain separately, and the second SAS macro will calculate PPoS of seroconversion rate for each vaccine strain separately.

All NI inferiority testing will be conducted as per Section 3.1.

The main steps to calculate the individual PPoS for GMT and SC rate are described in Table 3.3 and

Table 3.4 respectively.

Table 3.2 presents the current numbers of participants at main study timepoints considered in the analysis.

Table 3.2: Study Design – Current Planned Number of Randomized Participants at Main Study Timepoints

		RIV4	**IIV4**
Study Planning (protocol & SAP)	Number of participants to be enrolled by the end of the study	$N_F = 706$	$N_C = 706$
Interim	Approximate number of participants enrolled up to interim analysis	$N_{i1F} = 183$	$N_{i1C} = 183$
Remainder of the Study	Approximate number of participants to be enrolled by the end of the study	$N_{rF} = N_F - N_{i1F}$ (706-183=523)	$N_{rC} = N_C - N_{i1C}$ (706-183=523)

Table 3.3: Description and Definition of the Main Steps in Calculating PPoS for NI Based on GMTs for each Vaccine Strain, Separately

Main Steps	Steps' Definition of each of the 4 Antigens GMT separately
1	The total number of participants to be enrolled in the whole study is approximately 1412, randomized with a 1:1 ratio between RIV4 and IIV4 vaccine groups. The interim data includes 366 randomized participants, randomized with a 1:1 ratio between the vaccine groups. The PPAS will be used as the main analysis set for PPoS calculation. All the randomized participants in the remainder of the study are going to be generated with a 1:1 ratio between the vaccine groups.
2	At the interim analysis: - For each vaccine group and each strain calculate the mean and standard deviation of LOG10(titer) - use the predictive distribution to derive B times datasets (e.g. 100.000) of the participants not yet enrolled in the study (to reach the approximately 1200 planned PPAS subjects overall in both vaccines) – with a seed value in SAS of 1545313 (for RIV4) and 4878646 (for IIV4)
3	Combine the interim dataset and the B datasets of the after interim to constitute the final and complete B datasets using the same sequence number. The final complete B datasets will be used to derive the 2-sided 95% CI of the difference (between RIV4 and IIV4) between the LOG10(mean) of each antigen for each one of the B complete datasets.
4	Use the 2-sided 95% CI of the difference (between the mean LOG10(titer) of RIV4 and the mean of LOG10(titer) of IIV4) for each B dataset to calculate the PPoS by deriving the proportion of datasets with the NI success. NI success in each complete dataset of each vaccine strain will be determined by comparing the lower bound of the 95% CI to the NI margin (-0.176)

Table 3.4: Description and Definition of the Main Steps in Calculating PPoS for NI Based on SC rates for each Vaccine Strain, Separately

Main Steps	Steps' Definition of each of the 4 vaccine Strains separately
1	The total number of participants to be enrolled in the whole study is approximately 1412, randomized with a 1:1 ratio between RIV4 and IIV4 vaccine groups. The interim data includes 366 randomized participants, randomized with a 1:1 ratio between the vaccine groups. The PPAS will be used as the main analysis set for PPoS calculation. All randomized participants in the remainder of the study are going to be generated with a 1:1 ratio between the vaccine groups.
2	At the interim analysis: - For each vaccine group and each strain, calculate the proportion P_{RIV4} and the proportion P_{IIV4} corresponding the SC rates - use the predictive distribution of these parameters to derive B times datasets (e.g. 100.000) of the participants not yet enrolled in the study (to reach the approximately 1200 planned PPAS subjects overall in both vaccines) – with a seed value in SAS of 1545313 (for RIV4) and 4878646 (for IIV4)
3	Combine the interim datasets and the B datasets of the after interim to constitute the final and complete B datasets using the same sequence number. The final complete B datasets will be used to deriving the 2-sided 95% CI of the difference between SC of each antigen for each one of the B complete datasets.
4	Use the 2-sided 95% CI of the difference (between SC of RIV4 and SC of IIV4) for each B dataset to calculate the PPoS by deriving the proportion of datasets with the NI success. NI success in each complete dataset will be determined by comparing the lower bound of the 95% CI to the NI margin

The age of subjects was stratified into 2 strata, planning to reach approximately 50% of subjects of age 2 to 5 years, and approximately 50% of subjects of age 6 to 8 years.

Each age subgroup was stratified into 2 strata, planning to reach approximately 50% of subjects primed, and approximately 50% of subjects who are unprimed.

Hence, 4 subsets (2 age subgroup times 2 vaccination status) of subjects were formed. Each subset should include approximately 25% of subjects to be vaccinated in this study.

If the distribution of the study subsets in the interim PPAS dataset is substantially different from what was planned in the protocol, which is approximately 25% of subjects in each subset, a complementary calculation of PPOS may be performed, thus running the above steps 1 and 2 in each of the 4 subsets to reach 300 PPAS subjects overall in each subset (age subgroup and vaccination status), and adding an extra step 2bis, concatenating the 4 strata within each of the B datasets, before performing step 3 and step 4.

3.5.2.2 Overall PPoS of the 4 GMTs, ~~and~~ overall PPoS of the 4 SCs, and Study overall PPoS (4 GMTs and 4 SC rates)

Correlations between vaccines' strain titers are generally low. Hence, the overall PPoS for NI of the 4 GMTs will be calculated by multiplying the 4 individual PPoS for NI calculated based on the GMTs. Likewise, the overall PPoS for NI of the 4 SCs will be calculated by multiplying the 4 individual PPoS for NI calculated based on SCs.

The study overall PPoS will be calculated by multiplying the 8 individual PPoS (GMTs and SC rate) calculated above.

3.5.2.3 FIC Futility Recommendation

FIC will review the results of the interim analysis and will make recommendations towards stopping for futility or safety reasons, based on the totality of information provided, including:

- The overall PPoS of the 4 GMTs and 4 SC NI statistical tests, based on a guidance of PPoS of less or equal [redacted], considering also the trend across the different PPoS calculated:
  - The individual PPoS to meet NI for each vaccine strain and each parameter (Geometric Mean Titre [GMT] and Seroconversion [SC] rate)
  - The overall PPoS of the 4 GMTs NI statistical tests
  - The overall PPoS of the 4 SC NI statistical tests
- RIV4 immunogenicity results with regards to comparator in each age, priming status and baseline serological status subgroup will also be considered to inform the decision.
- Safety results will also be reviewed.

3.5.2.4 Data Included in the Interim Analysis

Immunogenicity and safety data will be summarized by vaccine group at the timepoint D29 after the last vaccination.
However, the listings of SAEs, grade 3 ARs and AEs leading to discontinuation will include all data (including the data collected beyond D29 after the last vaccination) included in the database.

3.6 Data Monitoring Committee (DMC)

No independent Data Monitoring Committee (DMC) is planned.

Participant safety data will be continuously monitored by the Sponsor's internal safety management team (SMT), led by the Global Safety Officer, to detect any safety signals during the study period.

In addition, this study included an early safety data review (ESDR), when at least 10% of participants had been vaccinated and provided safety data for 7 days after vaccination.

A separate SAP was dedicated to theses analyses.

4 Complementary Information on Assessment Method

4.1 Complementary Information for Endpoint Assessment Method

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 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. 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, D01-D04, D05-D09.

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. 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.

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 presence is:

- (End date - vaccination date) + (number of days of presence 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.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement will 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 is not a Grade 0 intensity event.

Grade 0 events 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 Last Vaccination

Last vaccination before an unsolicited AE will be derived from the pre-visit numbers provided in the clinical database and will be calculated as follows:

- If an unsolicited AE has a non-missing pre-visit number, the pre-visit number will be used to determine the last vaccination before the unsolicited AE
- If the pre-visit number is missing and the start date is complete (ie, including day), then the start date will be used to determine the last vaccination before the unsolicited AE
- If an unsolicited AE has a missing pre-visit number and a partial start date (at least day missing), the unsolicited AE will be considered as post injection 1.

4.2.1.2.4 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 + 1 (if D01 is the first vaccination day).

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 each vaccination, which corresponds to AEs with a time of onset between D1 and D29 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 D01-D04, D05-D08, D09-D15, D16 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.2.1.2.5 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.

4.2.1.2.6 Medically-Attended Adverse Event

An event will be considered as an MAAE if ”Yes” is checked for “Is the event an MAAE?” in the CRF. MAAE will be analyzed within 28 days after each vaccination, from D29 to 180 days after each vaccination, and within 180 days after each vaccination.

4.2.1.2.7 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 within 28 days after each vaccination, from D29 to 180 days after each vaccination, and within 180 days after each vaccination.

4.2.1.2.8 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 within 28 days after each vaccination, from D29 to 180 days after each vaccination, and within 180 days after each vaccination.

4.2.2 Other Safety Endpoints

4.2.2.1 Pregnancy

Not applicable.

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 3.4.4.1.2. 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 to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Active Phase" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "Completion at End of Active Phase" form, question" What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.
- System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" 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

For the derivation of immunogenicity endpoints, all values strictly under the lower limit of quantification (LLOQ) will be treated as LLOQ/2, and all values above or equal to the upper limit of quantification (ULOQ) will be treated as ULOQ.

[redacted]

4.2.3.2 Fold-rise

For the HAI immune response, the derived endpoint fold-rise is driven by both baseline (D01) and post-baseline (D29 or D57) computed values as described in Section 4.2.3.1 and is computed as individual ratio:

- 28 days after the last vaccination divided by D01.

Note: if pre-vaccination (D01) or post-vaccination (D29 or D57) values is missing, the fold-rise is missing.

4.2.3.3 Seroconversion

For HAI assay, seroconversion is defined as a binary indicator. If a pre-vaccination (D01) titer < 10 (1/dil): post-vaccination titer ≥ 40 (1/dil) on 28 days after the last vaccination (D29 or D57), or ≥ 4-fold-rise for participants with a pre-vaccination titer ≥ 10 (1/dil), the derived seroconversion indicator will be "Yes", otherwise will be "No".

Note: if pre-vaccination (D01) or post-vaccination (D29 or D57) value is missing, the seroconversion is missing.

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

The age of a participant in the study will be the calendar age in years at the time of inclusion, as collected in the eCRF.

4.2.4.2 Duration of a Participant in the Trial

4.2.4.3 The duration of a participant in the trial, including the D181 safety follow-up, is computed as follows:

- Maximum (visit dates, termination date, safety follow-up date) – V01 date + 1.

The duration of a subject in the active phase of the trial is computed as follows:

- Maximum (V02 or V03 dates, termination date) – V01 date + 1.

4.2.4.4 Duration of the Study

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

- Maximum (Visit dates, Termination date, safety follow-up date) – minimum (V01 date) + 1

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

- Maximum (latest date of V02 or V03, latest date of termination during the active phase) − minimum (V01 date) + 1,

The duration of the D181 safety follow-up phase of the study is computed in days as follows:

- Maximum (date of D181 safety follow-up) − minimum (V02 or V03 dates, termination dates during the active phase) + 1.

5 Changes in the Conduct of the Trial or Planned Analysis

Following the planned recruitment period of 2022-2023 season, only approximately 25% out of the 1412 targeted participants aged 3 to 8 years had been enrolled and vaccinated in the study.

An interim analysis will be performed at the end of the 2022-2023 vaccination season. Safety summaries and the calculation of separate PPoS for each of the 8 NI statistical tests included in the primary objective will be assessed. An unblinded independent statistician will be in charge of breaking the blind of the enrolled participants in the 2022-2023 season after database lock, conducting the interim analysis and communicating the results to a firewall Internal Committee (FIC) who will make the decision of recommending or not recommending the stopping of this study.

A final analysis will be conducted once the 6-months safety data has been collected and the final database lock has occurred.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
ESDR	Early Safety Data Review
DMC	Data Monitoring Committee
FAS	Full analysis set
FIC	Firewall Internal Committee
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	Geometric mean
GMT	Geometric mean of titer
GMC	Geometric mean of concentration
HAI	Hemagglutination Inhibition
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NC	Not computed
NI	Non inferiority
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SC	Seroconversion
SOC	System organ class
SN	Seroneutralization
PPoS	Predictive Power of Success

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

7 References

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