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Application Type	BLA (Efficacy Supplement)
STN	125285/613
CBER Received Date	May 31, 2024
PDUFA Goal Date	March 31, 2025
Division / Office	DCTR /OVRR
Committee Chair	Paul Keller
Clinical Reviewer	Cynthia Nolletti
Project Manager	Donna A. Elhindi
Priority Review	No
Reviewer Name	Woobeen Lim, VEB/DB/OBPV
Concurrence	Sang Ahnn, Concurring Reviewer, VEB/DB/OBPV
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, VEB/DB/OBPV
Applicant	Sanofi Pasteur Inc.
Established Name	Influenza Vaccine
Trade Name	Flublok® Quadrivalent; Flublok®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Sterile solution for injection supplied in 0.5 mL single dose prefilled syringes
Dosage Form(s) and Route(s) of Administration	A single 0.5 mL dose, intramuscular (IM) injection
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by influenza A virus subtypes and influenza type B virus contained in the vaccine in persons 9 years of age and older

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GLOSSARY

AE	Adverse Event
BLA	Biologics License Application
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
FIC	Firewall Internal Committee
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titers Ratio
GMC	Geometric Mean Concentration
HAI	Hemagglutination Inhibition
IIV4	Quadrivalent Influenza Vaccine
LLOQ	Lower Limit of Quantification
NI	Non-Inferiority
PPAS	Per-Protocol Analysis Set
PPoS	Predictive Power of Success
pIMD	potential Immune-Mediated Disease
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
RIV4	Quadrivalent Recombinant Influenza Vaccine
SAE	Serious Adverse Event.
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Seroconversion
SPR	Seroprotection rate
SN	Seroneutralization
ULOQ	Upper Limit of Quantification

1. Executive Summary

Protein Sciences Corporation, now a Sanofi Company, submitted a Biologics License Application (BLA) Efficacy Supplement (STN 125285/613) on May 31, 2024, to seek an indication expansion of Flublok® Quadrivalent and Flublok® that includes individuals 9 to 17 years of age.

This submission was based on clinical data collected from two Phase III studies, VAP00026 and VAP00027. These two studies were deferred pediatric studies conducted under the frame of a Pediatric Research Equity Act (PREA) Post-marketing Requirement (PMR) of Flublok licensure.

Study VAP00026 was a Phase III, randomized, modified double-blind, active-controlled (standard-dose quadrivalent influenza vaccine, IIV4), multi-center study planned in approximately 1412 children aged 3 to 8 years of age in USA and Europe to assess immunogenicity and safety of quadrivalent recombinant influenza vaccine (RIV4, Flublok® Quadrivalent) compared with IIV4 in children 3 to 8 years of age. The primary immunogenicity objective was to demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of RIV4 vs IIV4 for the 4 strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) assessed by geometric mean titers (GMTs) and seroconversion (SC) rates in all participants aged 3 to 8 years.

Study VAP00026 was initiated on November 10, 2022. However, the recruitment period was closed early on February 28, 2023, due to parents' reluctance to have their children undergo blood draws. Subsequently, the applicant performed an interim futility analysis to determine whether study termination could be justified, and as a result, the study was discontinued due to futility after having enrolled 26% of planned participants during the 2022-2023 season.

The primary immunogenicity objective to demonstrate the non-inferior HAI immune response of RIV4 vs IIV4 for the 4 strains in subjects aged 3 to 8 years based on GMTs and SC rates 28 days after the last vaccination on per-protocol analysis set (PPAS) of subjects accumulated during the 2022-2023 season was not met.

- The non-inferiority (NI) criterion for HAI immune response of RIV4 versus licensed IIV4 based on GMTs and SC rates was met for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain:
    - The lower limits of the 2-sided 95% CIs of the GMT ratios (GMTRs) between RIV and IIV4 (GMT RIV4 / GMT IIV4) post vaccination were higher than 0.667 for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain, with a GMTR of 0.515 (95% CI: 0.397; 0.668)
    - The lower limits of the 2-sided 95% CIs of the differences in SC rates (RIV4 - IIV4) were higher than -10% for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain with a difference in SC rates of -6.91% (95% CI: -14.02%; 0.10%)

The results of the interim analysis using the immunogenicity data accumulated after enrolling 366 younger children (approximately 26% of planned participants) during the 2022-2023 season indicated that the predictive power of success (PPoS) to assess the probability of the study success based on the primary objective after having enrolled all planned participants was low at 0.4%. This PPoS was less than the pre-defined futility criteria in the Firewall Internal Committee (FIC) charter, which recommended continuation of enrollment to trial VAP00026 if PPoS was greater than 20%. The individual PPoS of the GMT and SC statistical tests to meet NI for A/H1N1, A/H3N2 and B/Yamagata was 100%, except for SC statistical test for B/Yamagata, which was 99.8%. However, the individual PPoS of the NI testing for B/Victoria was 0.9% for the GMT and 44.8% for the SC tests.

Study VAP00027 was a Phase III, non-randomized, open-label, uncontrolled, multi-center study to assess the immunogenicity and safety of the RIV4 conducted in 1308 participants aged 9 to 49 years (648 children and adolescents 9 to 17 years of age and 660 adults 18 to 49 years of age) in Europe and the US. The primary immunogenicity objective was to demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years.

The primary objective was met as the NI criteria for HAI immune response induced by RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by GMTs and SC rates at D29 were met. NI was demonstrated for all 8 endpoints included in the NI assessment (4 ratios of GMTs and 4 differences in SC rates) as the lower limits of the 95% CIs were higher than 0.667 for the ratios of GMTs and higher than -10% for the differences of SC rates for all 4 strains on PPAS of subjects. The GMT ratios between the two age groups (GMT of 9 to 17 years/GMT of 18 to 49 years) were:

- A/H1N1 strain: 1.98 (95% CI: 1.73; 2.27)
- A/H3N2 strain: 3.27 (95% CI: 2.76; 3.87)
- B/Victoria lineage strain: 1.57 (95% CI: 1.35; 1.82)
- B/Yamagata lineage strain: 1.22 (95% CI: 1.09; 1.37)

The differences in SC rates between groups (SC of 9 to 17 years – SC of 18 to 49 years) were:

- A/H1N1 strain: 1.92% (-2.78%; 6.62%)
- A/H3N2 strain: -0.59% (-4.41%; 3.23%)
- B/Victoria lineage strain: 3.29% (-1.57%; 8.14%)
- B/Yamagata lineage strain: 14.3% (9.17%; 19.3%)

Overall, no notable safety concerns were identified in reports of solicited reactions or unsolicited adverse events in both studies VAP00026 and VAP00027.

I defer to the clinical reviewer on the immunogenicity conclusions regarding extension of indication to individuals 9 to 17 years of age.

2. Clinical and Regulatory Background

Quadrivalent recombinant influenza vaccine (RIV4) was approved in the U.S. in October 2016 for active immunization to prevent influenza caused by the influenza A subtypes and type B lineages contained in the vaccine indicated for individuals 18 years and older under the trade name Flublok Quadrivalent.

In this submission, Sanofi seeks extension of indications to children and adolescents in 9 to 17 years of age in an effort to fulfill a PREA PMR by conducting Studies VAP00026 and VAP00027 as follows:

- PREA PMR #1 is a safety and immunogenicity study of Flublok Quadrivalent in children in 3 through 8 years (VAP00026)
- PREA PMR #2 is a safety and immunogenicity study of Flublok Quadrivalent in children and adolescents in 9 through 17 years of age and adults aged 18 through 49 years (VAP00027).

Of note, Study VAP00026 was initiated on November 10, 2022 with a targeted enrollment of 1412 participants at 31 sites but the recruitment period was closed early on February 28, 2023 with a total of 366 enrolled participants, which is approximately 26% of the planned number of participants. Recruitment was severely impacted by parents' reluctance to have their children undergo blood draws. Therefore, the applicant had to revise its initial endorsed plan and related timelines. Sanofi added an interim futility analysis to determine if the stopping of this study can be justified.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to Bioresearch Monitoring inspections review memo.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to reviews of other review disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review focuses on the immunogenicity and safety results from two clinical studies, VAP00026 and VAP00027. The submitted data and Clinical Study Reports were reviewed.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review was based on the submitted CSRs, electronic datasets, and case report forms (CRFs) for studies VAP00026 and VAP00027 dated May 31, 2024 in BLA Amendment 125285/613, BLA Amendment 125285/553 dated September 29, 2023 on the summary of key results from the interim analysis, and related documents such as the protocol and protocol amendments, and the statistical analysis plan (SAP).

SAS transport datasets were used for verification of the applicant's results. The SAS datasets were provided by the applicant at the time of the BLA supplement submission and were primarily located in Module 5 of the eCTD submission package.

In addition to the BLA supplement, this statistical review memo refers to the following INDs:

- IND15784.111 dated April 17, 2023 requesting CBER comments and advice regarding inclusion of interim analysis for futility to review safety and assess the likelihood of the study success based on the immunogenicity data accumulated after randomizing and vaccinating 366 younger children.
- IND15784.117 dated December 21, 2023, Response to Information Request dated 20Nov2023 that the applicant decided to stop Study VAP00026 for futility due to PPoS < 1%.

5.3 Table of Studies/Clinical Trials

Two clinical trials were submitted to support the application (Table 1).

Table 1: Overview of clinical studies supporting the efficacy supplement STN BL: 125285/613

Study Identifiers	Objectives of the Study	Study Design and Type of Control	Test Products and Dosage Regimen	Number of Subjects (Actual Sample Size)	Healthy Subjects or Diagnosis of Patients	Study Status and Type of Report
VAP00027 (NCT05513053)	Primary Objective: To demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of quadrivalent recombinant influenza vaccine (RIV4) for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years. Secondary Objectives: To summarize the HAI immune response induced by RIV4 in all participants. To describe the safety profile of RIV4 vaccine in all participants and by age group.	Phase III, non-randomized, open-label, uncontrolled	One injection of RIV4 containing 45 µg of HA per strain (2022-2023 influenza season)	N = 648 children and adolescents aged 9 to 17 years N = 660 adults aged 18 to 49 years	Healthy participants aged 9 to 49 years	Complete Full CSR
VAP00026 (NCT05513391)	Primary Objective: To demonstrate the non-inferior HAI immune response of RIV4 vs licensed quadrivalent influenza vaccine (IIV4) for the 4 strains based on the egg-derived antigen in all participants. Secondary Objectives: To summarize the HAI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg-derived antigen in participants. To assess the safety profile of each vaccine in all participants and by age group.	Phase III, randomized, modified double-blind, active-controlled 2-arm	One or 2 injections of RIV4 or IIV4 containing HA per strain (2022-2023 influenza season) 28 days apart	N = 183 in RIV4 N = 183 in IIV4	Healthy children aged 3 to 8 years	Study terminated early in Dec 2023 Full CSR

Source: Modified from Module 5.2 Tabular Listing of all Clinical Studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 VAP00026

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

6.1.1 Objectives

Primary Immunogenicity Objective
To demonstrate the non-inferior HAI immune response of quadrivalent recombinant influenza vaccine (RIV4) vs licensed quadrivalent influenza vaccine (IIV4) for the 4 strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) based on the egg-derived antigen in all participants aged 3 to 8 years

Secondary Objectives

1. 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
2. Safety: To assess the safety profile of each vaccine in all participants and by age group

6.1.2 Design Overview

VAP00026 study was a Phase III, randomized, modified double-blind, active-controlled (quadrivalent influenza vaccine, IIV4), multi-center study to demonstrate the non-inferior 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 and to describe the immunogenicity and safety profile of RIV4 compared to IIV4 in participants aged 3 to 8 years.

Participants were enrolled on the day of their first vaccination to receive either RIV4 or IIV4 and were followed for 6 months after the last vaccination. Following the US Advisory Committee on Immunization Practices recommendations for influenza vaccine, the dosing regimen was either a single dose or two doses of either vaccine 28 days apart depending on the previous vaccination against influenza as follows:

- Previously unvaccinated participants were defined as participants who had not received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These participants received 2 doses of the study vaccine 28 days apart after enrolling in the study. Participants who had received only one dose of any influenza vaccine in the past or participants whose vaccination history was unknown were also considered as previously unvaccinated participants when enrolling and received 2 doses of the study vaccine 28 days apart.
- Previously vaccinated participants were defined as participants who had received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These participants received only 1 dose of the study vaccine after enrolling in the study.

6.1.3 Population

The planned sample size and the actual number of participants in each analysis set for Study VAP00026 are presented in Table 2.

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) were expected to be randomized where approximately 50% of participants were planned to be previously vaccinated or unvaccinated against influenza within each arm.

However, following the planned recruitment period of 2022-2023 season, only approximately 26% (N = 366) out of the 1412 targeted participants aged 3 to 8 years had been enrolled and vaccinated in the study, and according to an interim analysis to evaluate safety and calculate predictive power of success (PPoS), the applicant decided to terminate enrollment into VAP00026 due to futility since the PPoS for meeting the primary objective of the study was < 1%. This was lower than the Firewall Internal Committee (FIC) recommendation for stopping the study when PPoS is ≤20%.

Therefore, the following number of participants for randomized, full analysis set (FAS), per-protocol analysis set (PPAS), and safety analysis set (SafAS) were finalized after the study was stopped for futility.

Table 2: VAP00026 study sample size

	RIV4				**IIV4**				**Total**
	Previously vaccinated against influenza (1 dose)		**Previously unvaccinated against influenza (2 doses 28 days apart)**		**Previously vaccinated against influenza (1 dose)**		**Previously unvaccinated against influenza (2 doses 28 days apart)**		
Planned	N= 706				N= 706				N= 1412
	N= 353		N= 353		N= 353		N= 353		
	Approx 50% aged 3 to 5 years	Approx 50% aged 6 to 8 years	Approx 50% aged 3 to 5 years	Approx 50% aged 6 to 8 years	Approx 50% aged 3 to 5 years	Approx 50% aged 6 to 8 years	Approx 50% aged 3 to 5 years	Approx 50% aged 6 to 8 years	
Randomized	N= 183				N= 183				N= 366
	N= 105		N= 78		N= 105		N= 78		
Full Analysis Set (FAS)	N=171				N=169				N= 340
	N=100		N= 71		N=100		N= 69		
Per-protocol Analysis Set (PPAS)	N=160				N=158				N= 318
	N= 97		N= 63		N= 96		N= 62		
Safety Analysis Set (SafAS)	N= 181				N= 181				N=362
	N= 104		N= 77		N= 103		N= 78		

Source: Modified from Table S1 of VAP00026 Clinical Study Report.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized to receive one of the two vaccines (Table 3).

Table 3: Study interventions, dose, mode of administration, and batch numbers

Intervention Name	RIV4/2022-2023/NH	IIV4/2022-2023/NH
Use	Experimental	Active comparator
Investigational medicinal product (IMP) and non-investigational medicinal product (NIMP)	IMP	IMP
Type	Vaccine	Vaccine
Dose Form	Solution for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe
Dosage Level	0.5 mL per dose	0.5 mL per dose
Number of Doses / Dosing Interval	1 or 2 doses 28 days apart	1 or 2 doses 28 days apart
Unit Dose Strengths	45 µg of HA of each of the following strains per dose: • A/Wisconsin/588/2019 (H1N1)pdm09-like virus • A/Darwin/6/2021 (H3N2)- like virus) • B/Austria/1359417/2021 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	15 µg of HA of each of the following strains per dose: • Victoria/2570/2019 (H1N1)pdm09-like virus • A/Darwin/9/2021 (H3N2)-like virus • B/Austria/1359417/2021 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B/Yamagata lineage)-like virus
Route of Administration	IM injection	IM injection

Source: Modified from Table S2 of VAP00026 Clinical Study Report.

6.1.6 Sites and Centers

This was multi-center study, conducted in 31 sites in in the US and Europe.

6.1.7 Surveillance/Monitoring

Please refer to clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

1. Individual HAI titer 28 days after last vaccination (Day [D]29 or D57)
2. Seroconversion, defined as:

   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

The post-vaccination GMTs and SC rates between the groups were compared to test non-inferiority of RIV4 vs IIV4 with a 1-sided Type I error rate of 0.025 for each strain. Since the primary objective included 8 endpoints (GMTs and SC rates for each of the 4 strains), all 8 NI hypotheses had to be rejected at 0.025 significance level, and thus no formal adjustment for multiplicity was necessary.

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

Secondary Immunogenicity Endpoints

1. Individual HAI titer on D01 and 28 days after the last vaccination (D29 or D57)
2. Detectable HAI titer, i.e., with a titer ≥ 10 (1/dil) at D01 and 28 days after the last vaccination (D29 or D57)
3. Individual HAI titer ratio: 28 days after the last vaccination (D29 or D57) / D01
4. Seroconversion
5. Participants with titers ≥ 40 (1/dil) on D01 and 28 days after the last vaccination (D29 or D57)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses

For primary immunogenicity analyses, NI of RIV4 as compared to IIV4 in participants 3 to 8 years of age was conducted for the post-vaccination GMTs and SC rates with a 1-sided Type I error rate of 0.025 for each strain.

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

Step1: Geometric Mean Titers

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H_0 needs to be rejected to demonstrate NI in GMTs.

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

where GMT_{RIV4} and GMT_{IIV4} denote the GMTs for RIV4 and IIV4 groups, respectively.

For calculation of GMTs, the log10 (data) was used for the statistical analysis. It was assumed that log10 transformation of the data follows a normal distribution.

ANCOVA was conducted for each strain with a model including the terms for 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.

Reviewer's comment: The independent variable "season" was not included in the actual ANCOVA model fitting for calculation of GMTs in the final CSR. This appears to be due to the study termination for futility when all participants were enrolled over only one influenza season (2022-2023). The omission of "season" in the model is acceptable.

Step 2: Seroconversion

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H_0 needs to be rejected to demonstrate NI in SCs.

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

where P_{RIV4} and P_{IIV4} denote the seroconversion rates for RIV4 and IIV4 groups, respectively.

Non-inferiority was assessed on PPAS as the main analysis set and was planned to be confirmed on the FAS if the attrition rate from FAS to PPAS was greater than 10%.

Since the primary objective included 8 endpoints (GMTs and SC rates for each of the 4 strains), all 8 NI hypotheses had to be rejected at 0.025 significance level, and thus no formal adjustment for multiplicity was necessary.

For secondary immunogenicity analyses, there were no statistical hypotheses to be tested.

Interim Futility analysis

Following the planned recruitment period of 2022-2023 season, only approximately 26% (N = 366) out of the 1412 targeted participants aged 3 to 8 years had been enrolled in the study and an interim analysis at the end of the season was conducted to review safety and to assess the likelihood of the study success by the end of enrollment (e.g., when enrolment of 1412 participants is reached) based on the immunogenicity data accumulated after randomizing and vaccinating approximatively 366 children.

The predictive power of success (PPoS) of the overall study was calculated based on each of the 8 NI statistical tests included in the primary objective. The predictive power is defined as the probability that the final study result will be successful, given the data observed until the time of the interim analysis. The futility criteria were set as follows:

- The overall PPoS of the 4 GMTs and 4 SC NI statistical tests, based on a guidance PPoS ≤ 20%, also considering the consistency across different endpoints:
    - The overall PPoS of the 4 GMTs NI statistical tests
    - The overall PPoS of the 4 SC NI statistical tests
    - The individual PPoS to meet NI for each vaccine strain and each parameter (GMTs and SC rates)

- RIV4 immunogenicity results with regards to comparator in each age, priming status and baseline serological status subgroups to inform the decision, and
- Safety results of Flublok (RIV4)

For calculation of the individual PPoS for GMTs and SC rates in-house, 2 SAS macros were used based on simulations. The first SAS macro would calculate PPoS of GMT for each vaccine strain separately, and the second SAS macro would calculate PPoS of seroconversion rate for each vaccine strain separately.

All NI inferiority testing was conducted following analyses of primary immunogenicity objectives, and the main steps to calculate the individual PPoS for GMT and SC rate are described in Table 4.

The subjects' age was stratified into 2 strata, 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, approximately 50% of primed subjects, and approximately 50% of unprimed subjects.

Since correlations between vaccines' strain titers are generally low, the overall PPoS for NI of the 4 GMTs was calculated by multiplying the 4 individual PPoS for NI calculated based on the GMTs. Likewise, the overall PPoS for NI of the 4 SCs was calculated by multiplying the 4 individual PPoS for NI calculated based on SCs.

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

Table 4: Description and Definition of the Main Steps in Calculating PPoS for NI Based on GMTS and 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 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: 1. For each vaccine group and each strain, calculate a. the mean and standard deviation of LOG10(titer) *(for GMTs)* b. the proportion PRIV4 and the proportion PIIV4 corresponding the SC rates *(for SC rates)* 2. 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) for GMTs or SC for SC rates of each antigen for each one of the B complete datasets.
4	Use the 2-sided 95% CI of the difference 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 for GMTs and -10% for SC rates)

Source: Modified from Tables 3.3 and 3.4 of VAP00026 Statistical Analysis Plan Version 4.0.

Sample size

A total of approximately 1200 evaluable participants 3 to 8 years of age were planned to be enrolled in this study where approximately 50% participants would be in the age group 3-5 years and 50% participants in the age group 6-8 years. Also, approximately 50% of participants enrolled within age group would be primed, and the other 50% unprimed.

Assuming similar GMTs in both groups and a standard deviation of 0.6 for log-transformed titers 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 for each of the 4 strains (i.e. 0.5, 0.5, 0.7, and 0.7 for A/H1N1, A/H3N2, B/Yamagata and B/Victoria, respectively), 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 was estimated to be approximately 82.0% (= 99.6% [GMTs] × 82.0% [SC]).

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

Reviewer's comment: The decision to discontinue the study was based on the predictive probability of success at the interim analysis for futility. At the termination of the study, the number of enrolled participants reached 26% of the originally planned total sample size.

Subgroup analysis

Subgroup analysis on immunogenicity endpoints was performed 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 were performed on PPAS.

Populations for analyses

The following analysis sets were defined for analysis:

- 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 had 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 were 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. Participants were 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 were 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, i.e., indicated as excluding participants from this analysis set in the manual deviations dataset

Handling of missing data and outliers

Missing immunogenicity data were not imputed and no search for outliers were performed. All values of immunogenicity endpoints strictly under the lower limit of quantification (LLOQ) were treated as LLOQ/2, and all values above or equal to the upper limit of quantification (ULOQ) were treated as ULOQ.

For the analysis of the results of HAI performed in duplicate, the individual geometric mean of both values was computed for each blood sample and each strain, after managing extreme values as described above. The computed value was then considered the titer for that particular blood sample.

The derived endpoint fold-rise in the HAI immune response was driven by both baseline (D01) and post-baseline (D29 or D57) computed values as described above and was computed as individual ratio of 28 days after the last vaccination divided by D01. The fold-rise was missing if pre-vaccination (D01) or post-vaccination (D29 or D57) values was missing. Similarly, the seroconversion was missing if pre-vaccination (D01) or post-vaccination (D29 or D57) value was missing.

No replacement was done for safety missing data and outliers.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The number and percentage of participants included in each analysis population are provided in Table 5 for FAS and PPAS, and in Table 6 for SafAS.

Among the 366 randomized participants, 340 (92.9%) were included in the FAS, with 171 (93.4%) participants in the RIV4 group and 169 (92.3%) participants in the IIV4 group.

Among the 366 randomized participants, 318 (86.9%) were included in the PPAS, with 160 (87.4%) participants in the RIV4 group and 158 (86.3%) participants in the IIV4 group.

Since the attrition rate from FAS to PPAS was lower than 10%, the statistical analyses in the FAS were not performed.

Among the 366 randomized participants, 362 (98.9%) were included in the SafAS, with 181 (98.9%) participants in the RIV4 group and 181 (98.9%) participants in the IIV4 group.

Table 5: Immunogenicity analysis sets by randomized group - Randomized study participants

Group			RIV4 (N=183) n/M (%)	IIV4 (N=183) n/M (%)	All (N=366) n/M (%)
All	FAS		171/183 (93.4)	169/183 (92.3)	340/366 (92.9)
		Not injected	2/183 (1.1)	2/183 (1.1)	4/366 (1.1)
		Did not provide a post-dose serology sample	12/183 (6.6)	14/183 (7.7)	26/366 (7.1)
	PPAS		160/183 (87.4)	158/183 (86.3)	318/366 (86.9)
Previously vaccinated	FAS		100/105 (95.2)	100/105 (95.2)	200/210 (95.2)
		Not injected	1/105 (1.0)	2/105 (1.9)	3/210 (1.4)
		Did not provide a post-dose serology sample	5/105 (4.8)	5/105 (4.8)	10/210 (4.8)
	PPAS		97/105 (92.4)	96/105 (91.4)	193/210 (91.9)
Previously unvaccinated	FAS		71/78 (91.0)	69/78 (88.5)	140/156 (89.7)
		Not injected	1/78 (1.3)	0/78 (0)	1/156 (0.6)
		Did not provide a post-dose serology sample	7/78 (9.0)	9/78 (11.5)	16/156 (10.3)
	PPAS		63/78 (80.8)	62/78 (79.5)	125/156 (80.1)

Source: Modified from Table 6 of VAP00026 Clinical Study Report.

Table 6: Safety analysis sets by randomized group - Randomized study participants

Group	Age group	RIV4 (N=183) n (%)	IIV4 (N=183) n (%)	All (N=366) n (%)
All	All	181/183 (98.9)	181/183 (98.9)	362/366 (98.9)
	3 to 5 years	81/82 (98.8)	91/93 (97.8)	172/175 (98.3)
	6 to 8 years	100/101 (99.0)	90/90 (100)	190/191 (99.5)
Previously vaccinated	All	104/105 (99.0)	103/105 (98.1)	207/210 (98.6)
	3 to 5 years	42/43 (97.7)	47/49 (95.9)	89/92 (96.7)
	6 to 8 years	62/62 (100)	56/56 (100)	118/118 (100)
Previously unvaccinated	All	77/78 (98.7)	78/78 (100)	155/156 (99.4)
	3 to 5 years	39/39 (100)	44/44 (100)	83/83 (100)
	6 to 8 years	38/39 (97.4)	34/34 (100)	72/73 (98.6)

Source: Modified from Table 7 of VAP00026 Clinical Study Report.

6.1.10.1.1 Demographics

The demographic characteristics of randomized participants are summarized by randomized group in Table 7.

Overall, 366 participants were randomized in the study, and there were slightly more (N=188; 51.4%) female participants than male (N=178; 48.6%), resulting in the male/female sex ratio of 0.95. The distribution of sex was also balanced in each vaccination group (0.93 in RIV4 and 0.97 in IIV4).

Of the 366 participants randomized in the study, 175 (47.8%) were aged 3 to 5 years and 191 (52.2%) were aged 6 to 8 years. The mean age (± standard deviation) of participants was 5.60 (± 1.68) years.

For most participants, the racial origin was “White” (280 [76.5%] participants) and ethnicity was “Not-Hispanic or Latino” (317 [86.6%] participants).

Of the 366 participants randomized in the study, 210 and 156 participants were previously vaccinated and unvaccinated against influenza, respectively. In each priming status group, participants aged 3 to 8 years were equally distributed between the RIV4 and IIV4 groups (Table 2).

Reviewer’s comment: The demographic characteristics were similar between age subgroups (3-5 years and 6-8 years) and between priming status groups.

Table 7: Baseline demographic by randomized group - Randomized study participants

		RIV4 (N=183)	IIV4 (N=183)	All (N=366)
Sex: n/M (%)				
Male		88/183 (48.1)	90/183 (49.2)	178/366 (48.6)
Female		95/183 (51.9)	93/183 (50.8)	188/366 (51.4)
Missing		0	0	0
Sex ratio: Male/Female		0.93	0.97	0.95
Age (Year)				
	M	183	183	366
	Mean (SD)	5.73 (1.72)	5.48 (1.64)	5.60 (1.68)
	Min; Max	3.00; 8.00	3.00; 8.00	3.00; 8.00
	Median	6.00	5.00	6.00
	Q1; Q3	4.00; 7.00	4.00; 7.00	4.00; 7.00
	3 to 5 years	82/183 (44.8)	93/183 (50.8)	175/366 (47.8)
	6 to 8 years	101/183 (55.2)	90/183 (49.2)	191/366 (52.2)
Racial origin: n/M (%)				
	White	144/183 (78.7)	136/183 (74.3)	280/366 (76.5)
	Asian	0/183	0/183	0/366
	Black	31/183 (16.9)	33/183 (18.0)	64/366 (17.5)
	American Indian or Alaska Native	3/183 (1.6)	0/183	3/366 (0.8)
	Native Hawaiian or Other Pacific Islander	0/183	1/183 (0.5)	1/366 (0.3)
	Mixed origin	4/183 (2.2)	13/183 (7.1)	17/366 (4.6)
	Unknown	1/183 (0.5)	0/183	1/366 (0.3)
	Not reported	0/183	0/183	0/366
	Missing	0	0	0
Ethnicity: n/M (%)				
	Hispanic or Latino	19/183 (10.4)	29/183 (15.8)	48/366 (13.1)
	Not Hispanic or Latino	163/183 (89.1)	154/183 (84.2)	317/366 (86.6)
	Unknown	1/183 (0.5)	0/183	1/366 (0.3)

Source: Modified from Table 8 of VAP00026 Clinical Study Report.

6.1.11 Efficacy Analyses

Reviewer's comment: Since PPoS for meeting the primary objective of the study was less than 1% at the interim analysis, the study was stopped for futility when approximately only 26% of the planned number of participants were enrolled and vaccinated. Therefore, the efficacy analyses below are based on the immunogenicity data accumulated after randomizing and vaccinating 366 children.

6.1.11.1 Analyses of Primary Endpoints

The primary immunogenicity objective was to demonstrate the non-inferior HAI immune response of RIV4 vs IIV4 for the 4 strains based on the egg-derived antigen in all participants aged 3 to 8 years. The NI data based on the GMTs and SC rates 28 days after

the last vaccination (D29 or D57) for the PPAS are presented in Table 8 and Table 9, respectively.

The NI of HAI immune response of RIV4 versus licensed IIV4 was demonstrated separately in 3 of the 4 strains based on the GMTs in the PPAS, regardless of the previous vaccination status. As shown in Table 8, 28 days after the last vaccination, the lower limits of the 2-sided 95% confidence intervals (CIs) of the geometric mean titers ratios (GMTRs) between RIV and IIV4 (GMT RIV4 / GMT IIV4) were higher than 0.667 for A/H1N1 strain, A/H3N2 strain, and B/Yamagata lineage strain, but not for B/Victoria lineage strain, with a GMTR of 0.515 (95% CI: 0.397; 0.668).

Similarly, for the NI of HAI immune response of RIV4 versus licensed IIV4 was also demonstrated separately in 3 of the 4 strains based on the SC rates in the PPAS. As shown in Table 9, 28 days after the last vaccination, the lower limits of the 2-sided 95% CIs of the differences in SC rates (RIV4 - IIV4) were higher than -10% for A/H1N1 strain, A/H3N2 strain, and B/Yamagata lineage strain, but not for B/Victoria lineage strain with a difference in SC rates of -6.91% (95% CI: -14.02%; 0.10%).

Overall, the primary objective of this study was not met since the non-inferior HAI immune response of RIV4 versus licensed IIV4 was not demonstrated for B/Victoria lineage strain on the participants recruited during the 2022-2023 season before the study termination due to futility.

Reviewer's comment: I verified the primary analysis based on the data submitted in the Standard Data Tabulation Model (SDTM) format, and my results were consistent with those reported by the Applicant.

Table 8: Immunogenicity primary objective: Non-inferiority of immune response in terms of GMTs at D29 after last vaccine injection of RIV4 vs IIV4- Per-Protocol Analysis Set

	RIV4			IIV4			RIV4 / IIV4		
Antigen/ strain	**M**	**GMT**	**(N=160) (95% CI)**	**M**	**GMT**	**(N=158) (95% CI)**	**GMT Ratio**	**95% CI**	**Non-Inferiority**
A/H1N1	159	998	(779; 1279)	158	640	(493; 831)	1.28	(0.948; 1.73)	Y
A/H3N2	159	2398	(1914; 3004)	158	889	(722; 1095)	2.53	(1.93; 3.30)	Y
B/Victoria	159	337	(263; 432)	158	605	(480; 762)	0.515	(0.397; 0.668)	Y
B/Yamagata	159	789	(634; 983)	158	708	(590; 850)	1.02	(0.799; 1.30)	N

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013 M: number of participants with available data for the considered endpoint.
The study was stopped for futility - when approximately 26% of the planned number of subjects were vaccinated, because of the very low PPoS. The statistical test for non-inferiority (NI) was conducted on all the subjects enrolled before stopping the study for futility. The results of this analysis (NI) are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).
Source: Adapted from Table 9 of VAP00026 Clinical Study Report.

Table 9: Immunogenicity primary objective: Non-inferiority of immune response in terms of seroconversion rates after vaccination RIV4 vs IIV4- Per-Protocol Analysis Set

	RIV4 (N=160)			IIV4 (N=158)			RIV4 minus IIV4		
Antigen/ strain	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority
A/H1N1	134/158	84.8	(78.2; 90.0)	122/157	77.7	(70.4; 84.0)	7.10	(-1.55; 15.7)	Y
A/H3N2	130/158	82.3	(75.4; 87.9)	105/157	66.9	(58.9; 74.2)	15.4	(5.80; 24.7)	Y
B/Victoria	135/158	85.4	(79.0; 90.5)	145/157	92.4	(87.0; 96.0)	-6.91	(-14.02; 0.10)	N
B/Yamagata	140/158	88.6	(82.6; 93.1)	130/157	82.8	(76.0; 88.4)	5.81	(-1.99; 13.6)	Y

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013 M: number of participants with available data for the considered endpoint.
The study was stopped for futility - when approximately 26% of the planned number of subjects were vaccinated, because of the very low PPoS. The statistical test for non-inferiority (NI) was conducted on all the subjects enrolled before stopping the study for futility. The results of this analysis (NI) are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).
Source: Adapted from Table 10 of VAP00026 Clinical Study Report.

Futility analysis results

The results of interim analysis to assess the likelihood of the study success by the end of enrollment (1412 participants) based on the immunogenicity data accumulated after randomizing and vaccinating 366 younger children (approximately 26% of participants) are presented in Table 10.

The individual PPoS of the GMT and SC statistical tests to meet NI for A/H1N1, A/H3N2 and B/Yamagata was 100%, except for SC statistical test for B/Yamagata, which was 99.8%.

On the other hand, the individual PPoS of the NI testing for B/Victoria was 0.9% for the GMT and 44.8% for the SC tests.

The overall PPoS of the 4 GMTs NI statistical tests was 0.9% and of the 4 SC NI statistical tests was 44.7%.

Therefore, the overall PPoS of the 4 GMTs and 4 SC NI statistical tests when comparing RIV4 to IIV4 was 0.4%. This was less than the pre-defined futility criteria in the FIC charter that recommended continuation of enrollment to trial VAP00026 when PPoS was greater than 20%. The fairly low overall PPoS was due to poorer GMT response of RIV4 as compared to IIV4 for the B/Victoria strain.

The VAP00026 interim analysis indicated that the probability to demonstrate the NI defined in the primary objective, at the end of the study, was expected to be very low, and that RIV4 is not non-inferior to IIV4 in its immunogenicity assessment in the 3 to 8 years of age population.

Table 10: Predictive Power of Overall Study Success, Predictive Power of GMTs, Predictive Power of Seroconversion Rates and Predictive Power of each antigen - Per-Protocol Analysis Set

	Strains	GMT ratio/Difference (%)	(95% CI)	PPoS (%)
	RIV4/IIV4			
GMT	A/H1N1	1.56	(1.09; 2.23)	100
	A/H3N2	2.70	(1.99; 3.66)	100
	B/Victoria	0.558	(0.398; 0.782)	0.9
	B/Yamagata	1.11	(0.838; 1.48)	99.8
Overall GMT	All Strains	-	-	0.9
Seroconversion	A/H1N1	7.10	(-1.55; 15.7)	100
	A/H3N2	15.4	(5.80; 24.7)	100
	B/Victoria	-6.91	(-14.02; 0.10)	44.8
	B/Yamagata	5.81	(-1.99; 13.6)	100
Overall SC	All Strains	-	-	44.7
Overall Study		-	-	0.4

Antigen/strain assessment for RIV4 and IIV4: A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013.
For simulating data for RIV4, the seed 1545313 was used. For simulating data for IIV4 the seed 4878646 was used.
The seed used for IIV4 was determined by adding 3 to each digit included in the seed used for simulating the data of RIV4.
Source: Adapted from Table 2.39 under Module 1.11.3 of Clinical Information Amendment STN: 125285.553.0

Reviewer's comment: The overall PPoS was < 1% and failed to meet the criterion to continue the study (PPoS ≥ 20%). This was primarily due to the low immune response of RIV4 as compared to IIV4 for the B/Victoria strain. According to my analysis using bootstrapping method that simulated the applicant's PPoS analysis by taking random samples of N = 1,412 from the original dataset (N = 366) with replacement, the probability of success to meet the primary objective was also very low (< 1%). In particular, the 95% CI of the GMT ratio for the B/Victoria strain was (0.453; 0.59), which was lower than the NI margin of 0.667. The applicant's decision to halt the study appears reasonable.

6.1.11.2 Analyses of Secondary Endpoints

Individual HAI Antibody Titers

The secondary objective of this study was to summarize the HAI immune response induced by RIV4 and IIV4 for the 4 strains in participants aged 3 to 8 years.

A summary of HAI antibody GMTs, detectable HAI titers, and SC rates to each strain at pre-dose (D01) and 28 days after the last vaccination (D29 or D57 depending on the priming status) as well as the GMTRs between pre- and post-dose is presented for the PPAS in Table 11.

At D01, the GMTs against all influenza strains ranged from 20.9 (95% CI: 16.9; 25.8) for B/Victoria lineage strain to 141 (95% CI: 103; 193) for A/H3N2 strain in the RIV4 group and from 18.4 (95% CI: 14.9; 22.7) for B/Victoria lineage strain to 112 (95% CI: 81.1; 156) for A/H3N2 strain in the IIV4 group.

At D29 or D57, GMTs against each strain were highest for the A/H3N2 strain (2398, 95% CI: 1914 – 3004; 889, 95% CI: 722 – 1095) and lowest for the B/Victoria lineage strain (337, 95% CI: 263 – 432; 605, 95% CI: 480 – 762) in the RIV4 group and in the IIV4 group, respectively.

The GMTRs between pre- and post-dose against each strain in the RIV4 group and in the IIV4 group, respectively, were:

- A/H1N1: 14.2 (95% CI: 10.7; 18.6) and 13.8 (95% CI: 10.2; 18.8)
- A/H3N2: 17.1 (95% CI: 12.9; 22.6) and 7.86 (95% CI: 5.89; 10.5)
- B/Victoria lineage: 16.0 (95% CI: 12.8; 20.1) and 32.7 (95% CI: 24.8; 43.1)
- B/Yamagata lineage: 12.2 (95% CI: 9.96; 14.9) and 13.1 (95% CI: 10.2; 16.8)

HAI Antibody Titers >= 40 and Detectable HAI Titers

At D01, the percentage of participants with HAI titers ≥ 40 (1/dil) (i.e., seroprotection) was similar between both vaccination groups, ranging from 35.8% (95% CI: 28.4; 43.8) in RIV4 and 33.8% (95% CI: 26.4; 41.7) in IIV4 for B/Victoria lineage strain (lowest) to 76.1% (95% CI: 68.7; 82.5) in RIV4 and 70.1% (95% CI: 62.2; 77.1) in IIV4 for A/H3N2 strain.

At 28 days after the last vaccination, the percentage of participants with HAI titers ≥ 10 (1/dil) (i.e., seropositivity) was similarly high in both vaccination groups for all 4 strains between RIV4 and IIV4 groups, ranging from 98.1% to 100%.

At 28 days after the last vaccination, the seroprotection rates were high in both vaccination groups for all 4 strains. Except for the B/Victoria lineage strain, the percentage was similar across antigen strains between RIV4 and IIV4 groups, ranging from 96.2% to 99.4%. For the B/Victoria lineage strain, the percentage was lower in the RIV4 group (92.5% [95% CI: 87.2; 96.0]) than in the IIV4 group (96.8% [95% CI: 92.8; 99.0]). Overall, high seropositivity and seroprotection rates were observed post vaccination for both vaccine groups.

Seroconversion Rates

At D29 or D57, the SC rates were higher in the RIV4 than IIV4 group except for the B/Victoria lineage strain, ranging from 82.3% (A/H3N2) to 88.6% (B/Yamagata). For the B/Victoria lineage, the SC rates were 85.4% (95% CI: 79.0; 90.5) in RIV4 group and 92.4% (95% CI: 87.0; 96.0) in IIV4 group.

Table 11: Summary of HAI antibody response for each antigen - Per-Protocol Analysis Set

RIV4 (N = 160)					
	Antigen	**A/H1N1**	**A/H3N2**	**B/Victoria**	**B/Yamagata**
	M	159	159	159	159
Pre-dose (D01)	Geometric Mean (95% CI) Participants with titers < 10 (1/dil): (95% CI) Participants with titers >= 10 (1/dil): (95% CI) Participants with titers >= 40 (1/dil): (95% CI)	70.5 (52.2; 95.2) 34 (21.4) (15.3; 28.6) 125 (78.6) (71.4; 84.7) 104 (65.4) (57.5; 72.8)	141 (103; 193) 20 (12.6) (7.9; 18.8) 139 (87.4) (81.2; 92.1) 121 (76.1) (68.7; 82.5)	20.9 (16.9; 25.8) 48 (30.2) (23.2; 38.0) 111 (69.8) (62.0; 76.8) 57 (35.8) (28.4; 43.8)	65.2 (50.9; 83.5) 23 (14.5) (9.4; 20.9) 136 (85.5) (79.1; 90.6) 111 (69.8) (62.0; 76.8)
	M	159	159	159	159
Post-dose (D29 or D57)	Geometric Mean (95% CI) Participants with titers < 10 (1/dil): (95% CI) Participants with titers >= 10 (1/dil): (95% CI) Participants with titers >= 40 (1/dil): (95% CI)	998 (779; 1279) 2 (1.3) (0.2; 4.5) 157 (98.7) (95.5; 99.8) 155 (97.5) (93.7; 99.3)	2398 (1914; 3004) 0 (0; 2.3) 159 (100) (97.7; 100) 156 (98.1) (94.6; 99.6)	337 (263; 432) 1 (0.6) (0; 3.5) 158 (99.4) (96.5; 100) 147 (92.5) (87.2; 96.0)	789 (634; 983) 0 (0; 2.3) 159 (100) (97.7; 100) 158 (99.4) (96.5; 100)
	M	158	158	158	158
Post-dose response based on pre-dose (D29 or D57/D01)	Seroconversion; n (%) (95% CI)	134 (84.8) (78.2; 90.0)	130 (82.2) (75.4; 87.9)	135 (85.4) (79.0; 90.5)	140 (88.6) (82.6; 93.1)
	Ratio of titers (GMTR) (95% CI)	14.2 (10.7; 18.6)	17.1 (12.9; 22.6)	16.0 (12.8; 20.1)	12.2 (9.96; 14.9)

Source: Modified from Table 11 of VAP00026 Clinical Study Report.

Table 11: Summary of HAI antibody response for each antigen - Per-Protocol Analysis Set (continued)

IIV4 (N = 158)					
	Antigen	**A/H1N1**	**A/H3N2**	**B/Victoria**	**B/Yamagata**
	M	157	157	157	157
Pre-dose (D01)	Geometric Mean (95% CI) Participants with titers < 10 (1/dil): (95% CI) Participants with titers >= 10 (1/dil): (95% CI) Participants with titers >= 40 (1/dil): (95% CI)	46.5 (33.9; 63.7) 46 (29.3) (22.3; 37.1) 111 (70.7) (62.9; 77.7) 86 (54.8) (46.6; 62.7)	112 (81.1; 156) 29 (18.5) (12.7; 25.4) 128 (81.5) (74.6; 87.3) 110 (70.1) (62.2; 77.1)	18.4 (14.9; 22.7) 58 (36.9) (29.4; 45.0) 99 (63.1) (55.0; 70.6) 53 (33.8) (26.4; 41.7)	54.7 (42.8; 70.1) 20 (12.7) (8.0; 19.0) 137 (87.3) (81.0; 92.0) 104 (66.2) (58.3; 73.6)
	M	158	158	158	158
Post-dose (D29 or D57)	Geometric Mean (95% CI) Participants with titers < 10 (1/dil): (95% CI) Participants with titers >= 10 (1/dil): (95% CI) Participants with titers >= 40 (1/dil): (95% CI)	640 (493; 831) 3 (1.9) (0.4; 5.4) 155 (98.1) (94.6; 99.6) 152 (96.2) (91.9; 98.6)	889 (722; 1095) 1 (0.6) (0; 3.5) 157 (99.4) (96.5; 100) 155 (98.1) (94.6; 99.6)	605 (480; 762) 0 (0; 2.3) 158 (100) (97.7; 100) 153 (96.8) (92.8; 99.0)	708 (590; 850) 0 (0 ; 2.3) 158 (100) (97.7; 100) 157 (99.4) (96.5; 100)
	M	157	157	157	157
Post-dose response based on pre-dose (D29 or D57/D01)	Seroconversion; n (%) (95% CI)	122 (77.7) (70.4; 84.0)	105 (66.9) (58.9; 74.2)	145 (92.4) (87.0; 96.0)	130 (82.8) (76.0; 88.4)
	Ratio of titers (GMTR) (95% CI)	13.8 (10.2; 18.8)	7.86 (5.89; 10.5)	32.7 (24.8; 43.1)	13.1 (10.2; 16.8)

Source: Modified from Table 11 of VAP00026 Clinical Study Report.

Reviewer's comment: I verified the secondary analyses based on the data submitted in the Standard Data Tabulation Model (SDTM) format, and my results were consistent with those reported by the Applicant.

6.1.11.3 Subpopulation Analyses

Analysis by age subgroup

Subgroup analysis to summarize post-vaccination HAI GMTs and SC rates by age subgroup (3 to 5 years and 6 to 8 years) for the PPAS are presented in Table 12 and Table 13.

For the RIV4 group, post-vaccination HAI GMTs in participants aged 6 to 8 years were higher than those from 3 to 5 years in all antigens. In particular, for the B/Yamagata strain, the GMTs increased almost three-fold (from 464 to 1185). Post-vaccination HAI GMTs in the IIV4 group were similar between the vaccine age subgroups in all antigens. GMTRs between the vaccine groups tended to be higher in participants 6 to 8 years. In particular, for the B/Victoria strain, the ratio increased almost two-fold, from 0.389 to 0.758.

Similar to post-vaccination HAI GMTs, participants in 3 to 5 years produced higher SC rates than those in 6 to 8 years in all antigens except for the A/H1N1 strain. The SC rates increased from 12.6% to 20.0 for the A/H3N2 strain, from -13.78% to -0.98% for the B/Victoria strain, and -1.47% to 13.1% for the B/Yamagata strain.

Table 12: Summary of geometric mean of HAI antibody titer at after vaccination (D29 or D57) by age group- Per-Protocol Analysis Set

		RIV4 (N = 160)			IIV4 (N = 158)			RIV4/IIV4	
Age group	Antigen/ strain	M	GMT	(95% CI)	M	GMT	(95% CI)	GMT Ratio	(95% CI)
3 to 5 yrs	A/H1N1	69	856	(559; 1311)	80	511	(349; 747)	1.68	(0.953; 2.95)
	A/H3N2	69	2052	(1374; 3066)	80	897	(643; 1253)	2.29	(1.37; 3.82)
	B/Victoria	69	264	(173; 404)	80	680	(491; 942)	0.389	(0.231; 0.656)
	B/Yamagata	69	464	(324; 666)	80	686	(517; 911)	0.677	(0.432; 1.06)
6 to 8 yrs	A/H1N1	90	1123	(835; 1511)	78	806	(563; 1155)	1.39	(0.880; 2.20)
	A/H3N2	90	2702	(2090; 3493)	78	881	(684; 1135)	3.07	(2.14; 4.39)
	B/Victoria	90	406	(303; 545)	78	536	(383; 749)	0.758	(0.489; 1.18)
	B/Yamagata	90	1185	(927; 1515)	78	731	(578; 925)	1.62	(1.15; 2.28)

Antigen/strain assessment for RIV4 and IIV4: A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
n: number of subjects experiencing the endpoint listed in the first 3 columns
M: number of participants with available data for the considered endpoint
The 2-sided 95% CI for a GM is based on the Student t-distribution.
Source: Modified from Table 2.43 under Module 1.11.3 of Clinical Information Amendment STN: 125285.553.0

Table 13: Number and percentage of participants with seroconversion of HAI antibody titer at D29 or D57 by age group - Per-Protocol Analysis Set

		RIV4 (N = 160)			IIV4 (N = 158)			RIV4 minus IIV4	
Age group	Antigen/ strain	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)
3 to 5 yrs	A/H1N1	63/69	91.3	(82.0; 96.7)	64/79	81.0	(70.6; 89.0)	10.3	(-1.19; 21.3)
	A/H3N2	62/69	89.9	(80.2; 95.8)	61/79	77.2	(66.4; 85.9)	12.6	(0.43; 24.2)
	B/Victoria	56/69	81.2	(69.9; 89.6)	75/79	94.9	(87.5; 98.6)	-13.78	(-24.98; -3.36)
	B/Yamagata	61/69	88.4	(78.4; 94.9)	71/79	89.9	(81.0; 95.5)	-1.47	(-12.29; 8.80)
6 to 8 yrs	A/H1N1	71/89	79.8	(69.9; 87.6)	58/78	74.4	(63.2; 83.6)	5.42	(-7.25; 18.2)
	A/H3N2	68/89	76.4	(66.2; 84.8)	44/78	56.4	(44.7; 67.6)	20.0	(5.67; 33.4)
	B/Victoria	79/89	88.8	(80.3; 94.5)	70/78	89.7	(80.8; 95.5)	-0.98	(-10.59; 9.06)
	B/Yamagata	79/89	88.8	(80.3; 94.5)	59/78	75.6	(64.6; 84.7)	13.1	(1.53; 24.8)

Antigen/strain assessment for RIV4 and IIV4: A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013 M: number of participants with available data for the considered endpoint
M: number of participants with available data for the considered endpoint
Seroconversion is defined as either a pre-dose titer < 1:10 at D01 and a post-dose titer >= 1:40 at D29 or a pre-dose titer >= 1:10 at D01 and a >= 4-fold increase in post-dose titer at D29
2-sided 95% CI for the single proportion (%) is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method without continuity correction.
Source: Modified from Table 2.44 under Module 1.11.3 of Clinical Information Amendment STN: 125285.553.0

Reviewer's comment:

The subgroup analyses by age subgroup in children 6 through 8 years of age showed a trend towards higher immune responses against some of the vaccine antigens, including B/Victoria, as compared to children 3 through 5 years of age. Due to the higher immune responses induced in participants aged 6 to 8 years compared to 3 to 5 years, CBER requested to do the same futility analysis by restricting the analyses and calculations of PPoS to participants in the age subgroup 6 through 8 years to see if the resulting PPoS met the criterion 20% to continue with the study enrollment.

In the Clinical Information Amendment of IND 15784.117 dated December 21, 2023, the applicant performed a post-hoc futility analysis and calculated PPoS to demonstrate noninferior HAI immune response of RIV4 vs IIV4 for all the 4 strains in all participants aged 6 to 8 years and the results are in Table 14. The overall PPoS was estimated at 23.2% which indicated a low probability of success for demonstrating the non-inferiority of RIV4 vs IIV4 in children 6-8 years. Specifically, while the PPoS from SC rates for the B/Victoria strain increased from 44.7% to 83.8%, the PPoS from GMTs increased from 0.9% to 29.5% when compared to the overall age groups (3 to 8 years).

Although it was greater than the threshold of 20%, the resulting PPoS of 23.2% was still low and close to the threshold. I defer to the clinical reviewer on regulatory decision regarding continuation of enrollment of Study VAP00026.

Table 14: Predictive Power of Overall Study Success, Predictive Power of GMTs, Predictive Power of Seroconversion Rates and Predictive Power of each antigen in children 6-8 years - Per-Protocol Analysis Set

	Strains	GMT ratio/Difference (%)	(95% CI)	PPoS (%)
	RIV4/IIV4			
GMT	A/H1N1	1.39	(0.880; 2.20)	99.2
	A/H3N2	3.07	(2.15; 4.39)	100
	B/Victoria	0.758	(0.489; 1.18)	29.5
	B/Yamagata	1.62	(1.15; 2.28)	100
Overall GMT	All Strains	-	-	29.3
Seroconversion	A/H1N1	5.42	(-7.25; 18.2)	94.3
	A/H3N2	20.0	(5.67; 33.4)	100
	B/Victoria	-0.98	(-10.59; 9.06)	83.8
	B/Yamagata	13.1	(1.53; 24.8)	100
Overall SC	All Strains	-	-	79.0
Overall Study		-	-	23.2

Antigen/strain assessment for RIV4 and IIV4: A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013.
For simulating data for RIV4, the seed 1545313 was used. For simulating data for IIV4 the seed 4878646 was used.
The seed used for IIV4 was determined by adding 3 to each digit included in the seed used for simulating the data of RIV4.
Source: Adapted from Table 1 from Clinical Information Amendment of IND 15784.117 dated December 21, 2023.

Analysis by race and sex

In both vaccination groups, the analysis by race and sex did not show meaningful differences between subgroups in terms of post vaccination immune responses, and thus the results are not described here.

6.1.11.4 Dropouts and/or Discontinuations

The proportions of subjects who withdrew from the study were small and similar between RIV4 and IIV4 groups. Therefore, missing data were not expected to have significant impact on the comparison of efficacy endpoints between the groups.

6.1.12 Safety Analyses

The safety overview after any vaccine injection is presented by vaccination group in the SafAS in Table 15.

Immediate Unsolicited AEs and ARs

None of the participants experienced any immediate unsolicited AE or AR within 30 minutes after any vaccination with RIV4 or IIV4.

Solicited Reactions

The percentage of participants who experienced at least 1 solicited reaction within 7 days after any vaccination consisted of 45.8% (82/179) of participants in RIV4 and 51.7% (93/180) of participants in IIV4.

Solicited Injection Site Reactions

The percentage of participants who experienced at least 1 solicited injection site reaction within 7 days after any vaccination consisted of 39.1% (70/179) of participants vaccinated with RIV4 and 42.2% (76/180) of participants vaccinated with IIV4.

Solicited Systemic Reactions

The percentage of participants who experienced at least 1 solicited systemic reaction within 7 days after any vaccination consisted of 27.9% (50/179) of participants vaccinated with RIV4 and 36.7% (66/180) of participants vaccinated with IIV4.

Overall, there were slightly more solicited reaction in the IIV4 group, especially in terms of solicited systemic reactions.

Unsolicited AEs

The percentage of participants who experienced at least 1 unsolicited AE within 28 days after any vaccination were similar between the vaccine groups: 24.3% (44/181) of participants in the RIV4 group and 26.0% (47/181) of participants in the IIV4 group.

Unsolicited ARs

The percentage of participants who experienced at least 1 unsolicited AR within 28 days after any vaccination consisted of 2.2% (4/181) of participants vaccinated with RIV4 and 1.1% (2/181) of participants vaccinated with IIV4.

MAAEs

The percentage of participants who experienced at least 1 MAAE within 28 days after any vaccination consisted of 9.9% (18/181) of participants vaccinated with RIV4 and 6.6% (12/181) of participants vaccinated with IIV4.

Deaths, AESIs, Discontinuations due to AEs, and SAEs

During the study, no death was reported and none of the participants experienced any AESIs or AEs leading to study discontinuation in any vaccination group.

One (0.6%) participant in the IIV4 group experienced an SAE during the study: 1 previously unvaccinated participant aged 6 years experienced hospitalization due to a Grade 3 bacterial infection. The event occurred 2 days after the 1st vaccination with IIV4 and lasted 7 days. The event resolved and was assessed as not related to the study vaccine and was considered as a MAAE. No SAEs were reported in the RIV4 group.

Reviewer's comment: The safety analyses were confirmed based on data submitted in the SDTM format, and the results were consistent with those reported by the Applicant.

Table 15: Safety overview after any vaccine injection - Safety Analysis Set

	RIV4 (N=181)			IIV4 (N=181)		
Period/Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 30 minutes after vaccine injection						
Immediate unsolicited AE	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
Immediate unsolicited AR	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
Solicited reaction within solicited period after vaccine injection	82/179	45.8	(38.4; 53.4)	93/180	51.7	(44.1; 59.2)
Solicited injection site reaction	70/179	39.1	(31.9; 46.7)	76/180	42.2	(34.9; 49.8)
Solicited systemic reaction	50/179	27.9	(21.5; 35.1)	66/180	36.7	(29.6; 44.2)
Within 28 days after vaccine injection						
Unsolicited AE	44/181	24.3	(18.3; 31.2)	47/181	26.0	(19.7; 33.0)
Unsolicited AR	4/181	2.2	(0.6; 5.6)	2/181	1.1	(0.1; 3.9)
AE leading to discontinuation	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
SAE	0/181	0	(0; 2.0)	1/181	0.6	(0; 3.0)
Death	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
AESI	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
MAAE	18/181	9.9	(6.0; 15.3)	12/181	6.6	(3.5; 11.3)
During 6-month follow-up period						
SAE	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
Death	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
AESI	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
MAAE	2/181	1.1	(0.1; 3.9)	2/181	1.1	(0.1; 3.9)
During the study						
SAE	0/181	0	(0; 2.0)	1/181	0.6	(0; 3.0)
Death	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
AESI	0/181	0	(0; 2.0)	0/181	0	(0; 2.0)
MAAE	19/181	10.5	(6.4; 15.9)	14/181	7.7	(4.3; 12.6)

n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
Source: Modified from Table 13 of VAP00026 Clinical Study Report.

6.2 VAP00027

Title: Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years

6.2.1 Objectives

Primary Immunogenicity Objective
To demonstrate the non-inferior hemagglutination inhibition (HAI) immune response of quadrivalent recombinant influenza vaccine (RIV4) for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years

Secondary Objectives

1. Immunogenicity: To summarize the HAI immune response induced by RIV4 in all participants
2. Safety: To assess the safety profile of RIV4 vaccine in all participants and by age group

6.2.2 Design Overview

VAP00027 was a Phase III, non-randomized, open-label, uncontrolled, multi-center study to assess the immunogenicity and safety of the RIV4 in participants 9 to 49 years of age in Europe and the US.

6.2.3 Population

The planned and actual number of participants in each analysis set of this report is presented overall and by age group in Table 16.

Table 16: VAP00027 study sample size

	9 to 17 years old	18 to 49 years old	All
Planned	667	667	1334
Enrolled	648	660	1308
FAS	626	634	1260
PPAS	609	606	1215
SafAS	641	658	1299

Source: Modified from Table S1 of VAP00027 Clinical Study Report.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects received the following experimental vaccine (Table 17).

Table 17: Study interventions, dose, mode of administration, and batch numbers

Intervention Name	RIV4 season/2022-2023/NH
Use	Experimental
IMP and NIMP	IMP
Type	Vaccine
Dose Formulation	Solution for injection in a pre-filled syringe
Dosage Level	0.5 mL per dose
Unit Dose Strength	45 µg of HA of each of the following strains per dose: • A/H1N1 strain: A/Wisconsin/588/2019 • A/H3N2 strain: A/Darwin/6/2021 • B/Victoria lineage strain: B/Austria/1359417/2021 • B/Yamagata lineage strain: B/Phuket/3073/2013
Route of Administration	IM injection
Batch Number	VA030496

Source: Modified from Table S2 of VAP00027 Clinical Study Report.

6.2.6 Sites and Centers

This study was conducted at 36 centers that enrolled participants in Europe and the United States.

6.2.7 Surveillance/Monitoring

Please refer to clinical review memo.

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

1. Individual HAI titer 28 days after last vaccination (Day [D]29)
2. Seroconversion, defined as:

   titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or

   titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D29

Non-inferiority of the age group 9-17 years as compared to 18-49 years after vaccination of both of age groups with RIV4 was conducted for post-vaccination GMTs and SC rates with a 1-sided Type I error rate of 0.025 for each strain. Since the primary objective included 8 endpoints (GMTs and SC rates for each of the 4 strains), all 8 NI hypotheses had to be rejected at 0.025 significance level, and thus no formal adjustment for multiplicity was necessary.

The primary analysis was conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains was demonstrated, then NI for SC was also tested.

Secondary Immunogenicity Endpoints

1. Individual HAI titer on D01 and 28 days after the last vaccination (D29)

2. Detectable HAI titer, i.e., with a titer ≥ 10 (1/dil) at D01 and 28 days after the last vaccination (D29)
3. Individual HAI titer ratio: 28 days after the last vaccination (D29) / D01
4. Seroconversion
5. Participants with titers ≥ 40 (1/dil) on D01 and 28 days after the last vaccination (D29)

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses

Non-inferiority of the age group 9-17 years as compared to 18-49 years after vaccination of both age groups with RIV4 was conducted for GMTs and SC rates.

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

The primary analysis was conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains was demonstrated, then NI of the SC rates was also tested.

Step1: Geometric Mean Titers

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H_0 needs to be rejected to demonstrate NI in GMTs.

$$H_0: GMT_{RIV4(9-17y)}/GMT_{RIV4(18-49y)} \leq 0.667$$
$$H_A: GMT_{RIV4(9-17y)}/GMT_{RIV4(18-49y)} > 0.667$$

where $GMT_{RIV4(9-17y)}$ and $GMT_{RIV4(18-49y)}$ denote the GMTs for participants aged 9-17 and 18-49 years old, respectively.

For calculation of GMTs, the log10 (data) was used for the statistical analysis. It was assumed that log10 transformation of the data follows a normal distribution.

Step 2: Seroconversion

For each of the 4 strains, the hypotheses are as follows. Each of the 4 individual H_0 needs to be rejected to demonstrate NI in SCs.

$$H_0: P_{RIV4(9-17y)} - P_{RIV4(18-49y)} \leq -10\%$$
$$H_A: P_{RIV4(9-17y)} - P_{RIV4(18-49y)} > -10\%$$

where $P_{RIV4(9-17y)}$ and $P_{RIV4(18-49y)}$ denote the seroconversion rates for participants aged 9-17 and 18-49 years old, respectively.

Non-inferiority was assessed on PPAS as the main analysis set and was planned to be confirmed on the FAS if the attrition rate from FAS to PPAS was greater than 10%.

Since the primary objective included 8 endpoints (GMTs and SC rates for each of the 4 strains), all 8 NI hypotheses had to be rejected at 0.025 significance level, and thus no formal adjustment for multiplicity was necessary.

For secondary immunogenicity analyses, there were no statistical hypotheses to be tested.

Sample size

Sample size calculation was based on a total of 1200 evaluable participants 9 to 49 years of age consisting of 600 children and adolescents 9 to 17 years of age (approximately 30% children 9 to 11 years of age) and 600 adults 18 to 49 years of age.

Assuming the same GMT for each strain across the age groups (9 to 17 years vs. 18 to 49 years) compared, and a standard deviation of log10 titers of 0.6 with a NI margin of 1.5, NI for GMTs was demonstrated with a power of at least 99.6%.

Assuming in each vaccine group the same expected SC rates (0.7, 0.5, 0.6, 0.5) 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 rate was demonstrated with a study power of approximately 80.10% (96.66%, 93.70%, 94.38% and 93.70% for each strain, respectively).

Hence, the overall study power was estimated to be 80.0% (80.0% = 99.6% [GMTs] x 80.10% [SC rate]).

Assuming an attrition rate of approximately 10% in this age group, a total of approximately 1334 participants 9 to 49 years of age was planned to be enrolled.

Subgroup analysis

Subgroup analyses were performed according to age subgroups (9-11, 12-17, 18-34 and 35-49 years of age), sex, race, previous influenza vaccination status (received a seasonal influenza vaccine in the last past influenza season or not) and baseline seropositivity status (seropositive and seronegative are defined as baseline antibody titer ≥ 1:10 or < 1:10), as appropriate according to number of participants in the respective subgroups. Subgroup analyses were performed on PPAS.

Populations for analyses

The following analysis sets were defined for analysis:

- Enrolled: All participants with data in the CRF.
- Safety Analysis Set (SafAS): Participants who have received one dose of the study vaccine. Safety data recorded for a vaccine received out of the protocol design were excluded from the analysis and listed separately.
- Full analysis set (FAS): Subset of participants who received one dose of the study vaccine and had a post-vaccination blood sample.
- Per-protocol analysis set (PPAS): Subset of the FAS. Participants presenting with at least one of the following criteria were 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 in the proper time window
    - Preparation and / or administration of vaccine was not done as per-protocol
    - Participant did not provide the post-dose serology sample at visit 2 in the proper time window ([D26, D39]) or a post-dose serology sample was not drawn
    - Participant received protocol-prohibited medications impacting or that may have an impact on the immune response
    - Any other deviation identified during the study conduct and identified as relevant by the clinical team during data review, i.e., indicated as excluding participants from this analysis set in the manual deviations dataset

Handling of missing data and outliers

Missing immunogenicity data were not imputed and no search for outliers were performed. All values of immunogenicity endpoints strictly under the lower limit of quantification (LLOQ) were treated as LLOQ/2, and all values above or equal to the upper limit of quantification (ULOQ) were treated as ULOQ.

For the analysis of the results of HAI performed in duplicate, the individual geometric mean of both values was computed for each blood sample and each strain, after managing extreme values as described above. The computed value was then considered the titer for that particular blood sample.

The derived endpoint fold-rise in the HAI immune response was driven by both baseline (D01) and post-baseline (D29) computed values as described above and was computed as individual ratio of 28 days after the last vaccination divided by D01. The fold-rise was missing if pre-vaccination (D01) or post-vaccination (D29) values was missing. Similarly, the seroconversion was missing if pre-vaccination (D01) or post-vaccination (D29) value was missing.

No replacement was done for safety missing data and outliers.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The number and percentage of participants included in each analysis population are provided in Table 18 for FAS and PPAS, and in Table 19 for SafAS.

A total of 1260 participants were included in the FAS consisting of 626 participants (96.6%) in the 9 to 17 years group and 634 participants (96.1%) in the 18 to 49 years group. A total of 1215 participants were included in the PPAS consisting of 609 participants (94.0%) in the 9 to 17 years group and 606 participants (91.8%) in the 18 to 49 years group.

Since the attrition rate from FAS to PPAS was lower than 10%, the statistical outputs in the FAS were not produced.

A total of 1299 participants were included in the SafAS after the injection consisting of 641 participants (98.9%) in the 9 to 17 years group and 658 participants (99.7%) in the 18 to 49 years group.

Table 18: Immunogenicity analysis sets by age group - study participants with data in CRF

	9 to 17 years (N=648)	**18 to 49 years (N=660)**	**All (N=1308)**
	n (%)	**n (%)**	**n (%)**
Full Analysis Set (FAS)	626 (96.6)	634 (96.1)	1260 (96.3)
Not injected	7 (1.1)	2 (0.3)	9 (0.7)
Did not provide a post-dose serology sample	22 (3.4)	26 (3.9)	48 (3.7)
Per-protocol analysis set (PPAS)	609 (94.0)	606 (91.8)	1215 (92.9)
Criterion for exclusion			
Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria	6 (0.9)	2 (0.3)	8 (0.6)
Preparation and / or administration of vaccine was not done as per-protocol	0	0	0
Participant did not provide the post-dose serology sample at visit 2 in the proper time window ([D26, D39]) or a post-dose serology sample was not drawn	36 (5.6)	42 (6.4)	78 (6.0)
Participant received protocol-prohibited medications impacting or that may have an impact on the immune response	4 (0.6)	14 (2.1)	18 (1.4)
Other deviations	0	0	0

n: number of study participants fulfilling the item listed
Note: a study participant may be associated with more than one criterion
Source: Adapted from Table 5 of VAP00027 Clinical Study Report.

Table 19: Safety analysis sets by age group - study participants with data in CRF

	9 to 17 years (N=648) n (%)	18 to 49 years (N=660) n (%)	All (N=1308) n (%)
Safety Analysis Set	641 (98.9)	658 (99.7)	1299 (99.3)
Solicited injection site safety assessed	618 (95.4)	635 (96.2)	1253 (95.8)
Solicited systemic safety assessed	615 (94.9)	635 (96.2)	1250 (95.6)

n: number of study participants experiencing the endpoint
Safety endpoints are considered assessed if at least one data point had been collected.
Unsolicited adverse events are never missing as all study participants had a 30-minute surveillance period after each injection
Source: Modified from Table 6 of VAP00027 Clinical Study Report.

6.1.10.1.1 Demographics

The demographic characteristics of randomized participants are summarized by age group in Table 20 for PPAS.

Overall, there were more females than males (653 females [53.7%] and 562 males [46.3%]) and the male/female ratio was 0.86. The imbalance was mostly driven by participants aged 18-49 years where the male/female ratio was 0.68 (246 males [40.6%] and 360 females [59.4%]). The overall mean age of participants was 23.5 years (±12.5). Most participants were White (77.4%), followed by Black or African American participants (18.9%), and most participants (87.0%) were of "Not Hispanic or Latino" ethnicity.

Reviewer's comment:

While an imbalance in male-to-female ratio (0.68) was observed in participants aged 18-49 years, subgroup analyses suggested no notable difference in seroconversion rates and titers between sex, and thus this imbalance is unlikely to affect the immunogenicity conclusions.

The demographic characteristics were generally similar between age groups (9-17 years and 18-49 years.

Table 20: Baseline demographic by age group - Per Protocol Analysis Set

	9 to 17 years (N=609)	18 to 49 years (N=606)	All (N=1215)
Sex: n (%)			
Male	316 (51.9)	246 (40.6)	562 (46.3)
Female	293 (48.1)	360 (59.4)	653 (53.7)
Missing	0	0	0
Sex ratio: Male/Female	1.08	0.68	0.86
Age (Year)			
M	609	606	1215
Mean (SD)	13.0 (2.48)	34.1 (9.20)	23.5 (12.5)
Min; Max	9.00; 17.0	18.0; 49.0	9.00; 49.0
Median	13.0	34.5	17.0
Q1; Q3	11.0; 15.0	27.0; 42.0	13.0; 34.0
Age subgroup n (%)			
9 to 11 years	186 (30.5)	-	186 (15.3)
12 to 17 years	423 (69.5)	-	423 (34.8)
18 to 34 years	-	303 (50.0)	303 (24.9)
35 to 49 years	-	303 (50.0)	303 (24.9)
Racial origin: n (%)			
American Indian or Alaska Native	4 (0.7)	0	4 (0.3)
Asian	1 (0.2)	6 (1.0)	7 (0.6)
Other Asian origin	1 (0.2)	4 (0.7)	5 (0.4)
Not reported	0	2 (0.3)	2 (0.2)
Black or African American	140 (23.0)	90 (14.9)	230 (18.9)
Native Hawaiian or Other Pacific Islander	1 (0.2)	2 (0.3)	3 (0.2)
White	447 (73.4)	493 (81.4)	940 (77.4)
Not Reported	0	2 (0.3)	2 (0.2)
Unknown	1 (0.2)	1 (0.2)	2 (0.2)
Multiple	15 (2.5)	12 (2.0)	27 (2.2)
Ethnicity: n (%)			
Hispanic or Latino	107 (17.6)	35 (5.8)	142 (11.7)
Not Hispanic or Latino	494 (81.1)	563 (92.9)	1057 (87.0)
Not reported	7 (1.1)	8 (1.3)	15 (1.2)
Unknown	1 (0.2)	0	1 (<0.1)

n: number of study participants fulfilling the item listed; Q1; Q3: first quartile; third quartile.
Source: Modified from Table 7 of VAP00027 Clinical Study Report.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoints

The primary objective of the study was to demonstrate non-inferiority of HAI immune response induced by RIV4 for the 4 strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) in participants aged 9 to 17 years versus participants aged 18 to 49 years. The NI data based on GMTs and SC rates at D29 after vaccination for the PPAS are presented in Table 21 and Table 22, respectively.

NI was demonstrated for all 8 endpoints included in the NI assessment (4 ratios of GMTs and 4 differences in SC rates) as the lower limit of the 95% CIs was higher than 0.667 for the ratios of GMTs and higher than -10% for the differences of SC rates for all 4 strains.

Reviewer's comment: I verified the primary analysis based on the data submitted in the Standard Data Tabulation Model (SDTM) format, and my results were consistent with those reported by the Applicant.

Table 21: Immunogenicity primary objective: Non-inferiority of immune response in terms of GMTs at D29 after vaccination of 9 to 17 years vs 18 to 49 years- Per-Protocol Analysis Set

	9 to 17 years (N = 609)			18 to 49 years (N = 606)			9 to 17 years/ 18 to 49 years		
Antigen/ strain	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**GMT Ratio**	**95% CI**	**Non-inferiority**
A/H1N1	609	1946	(1795; 2109)	606	982	(881; 1094)	1.98	(1.73; 2.27)	Y
A/H3N2	609	1975	(1771; 2202)	606	604	(531; 687)	3.27	(2.76; 3.87)	Y
B/Victoria	609	405	(362; 452)	606	258	(233; 285)	1.57	(1.35; 1.82)	Y
B/Yamagata	609	1941	(1779; 2118)	606	1593	(1477; 1717)	1.22	(1.09; 1.37)	Y

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013 M: number of participants with available data for the considered endpoint.
Non-inferiority is concluded if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (9 to 17 years/18 to 49 years) is > 0.667 for each strain
Source: Adapted from Table 8 of VAP00027 Clinical Study Report.

Table 22: Immunogenicity primary objective: Non-inferiority of immune response in terms of seroconversion rates after vaccination of 9 to 17 years vs 18 to 49 years- Per-Protocol Analysis Set

	9 to 17 years (N = 609)			18 to 49 years (N = 606)			9 to 17 years minus 18 to 49 years		
Antigen/ strain	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**Difference (%)**	**95% CI**	**Non-inferiority**
A/H1N1	477/609	78.3	(74.8; 81.5)	463/606	76.4	(72.8; 79.7)	1.92	(-2.78; 6.62)	Y
A/H3N2	527/609	86.5	(83.6; 89.1)	528/606	87.1	(84.2; 89.7)	-0.59	(-4.41; 3.23)	Y
B/Victoria	468/609	76.8	(73.3; 80.1)	445/605	73.6	(69.8; 77.0)	3.29	(-1.57; 8.14)	Y
B/Yamagata	470/609	77.2	(73.6; 80.5)	381/606	62.9	(58.9; 66.7)	14.3	(9.17; 19.3)	Y

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013 M: number of participants with available data for the considered endpoint.
Non-inferiority for SC rates is demonstrated if the lower limit of the 2-sided 95% CI is >-10% for the 4 strains
Source: Adapted from Table 9 of VAP00027 Clinical Study Report.

6.2.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objective was to summarize the HAI immune response induced by RIV4 in all participants.

HAI Antibody Titers

A summary of HAI Ab GMTs (1/dil) at D01 (baseline) and D29 (28 days post vaccination) for the 4 tested strains are presented overall and by age group in the PPAS in Table 23.

Compared to baseline, post-vaccination HAI Ab GMTs increased in both age groups and were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for all of the virus strains:

- A/H1N1 strain: 1946 (95% CI: 1795; 2109) and 982 (95% CI: 881; 1094)
- A/H3N2 strain: 1975 (95% CI: 1771; 2202) and 604 (95% CI: 531; 687)
- B/Victoria lineage strain: 405 (95% CI: 362; 452) and 258 (95% CI: 233; 285)
- B/Yamagata lineage strain: 1941 (95% CI: 1779; 2118) and 1593 (95% CI: 1477; 1717)

Table 23: Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by age group - Per-Protocol Analysis Set

		9 to 17 years (N=609)			18 to 49 years (N=606)			All (N = 1215)		
Strain	Time Point	M	GM	(95% CI)	M	GM	(95% CI)	M	GM	(95% CI)
A/H1N1	V01 (D01)	609	154	(137; 173)	606	74.9	(65.8; 85.1)	1215	107	(98.1; 117)
	V02 (D29)	609	1946	(1795; 2109)	606	982	(881; 1094)	1215	1383	(1290; 1484)
A/H3N2	V01 (D01)	609	111	(95.4; 128)	606	29.0	(25.7; 32.8)	1215	56.7	(51.2; 62.8)
	V02 (D29)	609	1975	(1771; 2202)	606	604	(531; 687)	1215	1094	(999; 1198)
B/Victoria	V01 (D01)	609	48.1	(43.0; 53.8)	605	37.3	(34.0; 40.9)	1214	42.4	(39.4; 45.6)
	V02 (D29)	609	405	(362; 452)	606	258	(233; 285)	1215	323	(300; 349)
B/Yamagata	V01 (D01)	609	272	(243; 305)	606	300	(269; 335)	1215	286	(264; 309)
	V02 (D29)	609	1941	(1779; 2118)	606	1593	(1477; 1717)	1215	1759	(1660; 1864)

Source: Modified from Table 10 of VAP00027 Clinical Study Report.

Individual HAI Antibody Titers Ratios, HAI Antibody Titer ≥ 40 and Detectable Titer ≥ 10, and Seroconversion Rates

Individual HAI Ab titers ratios D29/D01, the number and percentage of participants with HAI Ab titer ≥ 40 (1/dil) (i.e., seroprotection) and detectable titer ≥ 10 (1/dil) (i.e., seropositivity) at pre- and post-vaccination, and the number and percentage of participants with SC of HAI Ab titer at post-vaccination are presented for each strain overall and by age group in the PPAS in Table 24.

The post-vaccination HAI Ab GMT ratios (GMTRs) were similar in both age groups for all of the antigen strains.

Post-vaccination seroprotection rates increased for all 4 virus strains and were high in both age groups ranging from 95.0% to 100%. Similarly, seropositivity rates increased for all 4 virus strains and were very high in both age groups (≥ 99.5% in participants 9 to 17 years of age and ≥ 99.3% in participants 18 to 49 years of age).

The SC rates were similarly high in both age groups for all antigen strains except for B/Yamagata lineage strain where participants 9 to 17 years of age had higher SC rate than the rate from participants 18 to 49 years of age (77.2% [95% CI: 73.6; 80.5] and 62.9% [95% CI: 58.9; 66.7], respectively).

Table 24: Summary of HAI antibody response for each antigen - Per-Protocol Analysis Set

		9 to 17 years (N = 609)			
		A/H1N1	**A/H3N2**	**B/Victoria**	**B/Yamagata**
Pre-dose (D01)	M	609	609	609	609
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	154 (137; 173) 18 (3.0) (1.8; 4.6) 591 (97.0) (95.4; 98.2) 531 (87.2) (84.3; 89.7)	111 (95.4; 128) 66 (10.8) (8.5; 13.6) 543 (89.2) (86.4; 91.5) 455 (74.7) (71.1; 78.1)	48.1 (43.0; 53.8) 48 (7.9) (5.9; 10.3) 561 (92.1) (89.7; 94.1) 374 (61.4) (57.4; 65.3)	272 (243; 305) 13 (2.1) (1.1; 3.6) 596 (97.9) (96.4; 98.9) 567 (93.1) (90.8; 95.0)
Post-dose (D29)	M	609	609	609	609
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	1946 (1795; 2109) 0 (0; 0.6) 609 (100) (99.4; 100) 607 (99.7) (98.8; 100)	1975 (1771; 2202) 0 (0; 0.6) 609 (100) (99.4; 100) 603 (99.0) (97.9; 99.6)	405 (362; 452) 3 (0.5) (0.1; 1.4) 606 (99.5) (98.6; 99.9) 582 (95.6) (93.6; 97.1)	1941 (1779; 2118) 0 (0; 0.6) 609 (100) (99.4; 100) 606 (99.5) (98.6; 99.9)
Post-dose response based on pre-dose (D29/D01)	M	609	609	609	609
	GMTR (95% CI)	12.7 (11.1; 14.5)	17.9 (15.7; 20.3)	8.41 (7.55; 9.37)	7.13 (6.46; 7.87)
	Seroconversion n (%) (95% CI)	477 (78.3) (74.8; 81.5)	527 (86.5) (83.6; 89.1)	468 (76.8) (73.3; 80.1)	470 (77.2) (73.6; 80.5)

Source: Modified from Table 11 of VAP00027 Clinical Study Report.

Table 24: Summary of HAI antibody response for each antigen - Per-Protocol Analysis Set (continued)

		18 to 49 years (N = 606)			
		A/H1N1	**A/H3N2**	**B/Victoria**	**B/Yamagata**
Pre-dose (D01)	M	606	606	605	606
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	74.9 (65.8; 85.1) 62 (10.2) (7.9; 12.9) 544 (89.8) (87.1; 92.1) 435 (71.8) (68.0; 75.3)	29.0 (25.7; 32.8) 135 (22.3) (19.0; 25.8) 471 (77.7) (74.2; 81.0) 273 (45.0) (41.0; 49.1)	37.3 (34.0; 40.9) 50 (8.3) (6.2; 10.8) 555 (91.7) (89.2; 93.8) 362 (59.8) (55.8; 63.8)	300 (269; 335) 3 (0.5) (0.1; 1.4) 603 (99.5) (98.6; 99.9) 577 (95.2) (93.2; 96.8)
Post-dose (D29)	M	606	606	606	606
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	982 (881; 1094) 4 (0.7) (0.2; 1.7) 602 (99.3) (98.3; 99.8) 591 (97.5) (96.0; 98.6)	604 (531; 687) 2 (0.3) (0; 1.2) 604 (99.7) (98.8; 100) 576 (95.0) (93.0; 96.6)	258 (233; 285) 1 (0.2) (0; 0.9) 605 (99.8) (99.1; 100) 588 (97.0) (95.3; 98.2)	1593 (1477; 1717) 0 (0; 0.6) 606 (100) (99.4; 100) 606 (100) (99.4; 100)
Post-dose response based on pre-dose (D29/D01)	M	606	606	605	606
	GMTR (95% CI)	13.1 (11.4; 15.0)	20.8 (18.4; 23.6)	6.91 (6.25; 7.64)	5.31 (4.79; 5.88)
	Seroconversion n (%) (95% CI)	463 (76.4) (72.8; 79.7)	528 (87.1) (84.2; 89.7)	445 (73.6) (69.8; 77.0)	381 (62.9) (58.9; 66.7)

Source: Modified from Table 11 of VAP00027 Clinical Study Report.

Table 24: Summary of HAI antibody response for each antigen - Per-Protocol Analysis Set (continued)

		All (N = 1215)			
		A/H1N1	**A/H3N2**	**B/Victoria**	**B/Yamagata**
Pre-dose (D01)	M	1215	1215	1214	1215
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	107 (98.1; 117) 80 (6.6) (5.3; 8.1) 1135 (93.4) (91.9; 94.7) 966 (79.5) (77.1; 81.7)	56.7 (51.2; 62.8) 201 (16.5) (14.5; 18.8) 1014 (83.5) (81.2; 85.5) 728 (59.9) (57.1; 62.7)	42.4 (39.4; 45.6) 98 (8.1) (6.6; 9.7) 1116 (91.9) (90.3; 93.4) 736 (60.6) (57.8; 63.4)	286 (264; 309) 16 (1.3) (0.8; 2.1) 1199 (98.7) (97.9; 99.2) 1144 (94.2) (92.7; 95.4)
Post-dose (D29)	M	1215	1215	1215	1215
	Geometric Mean (95% CI) Participants with titers < 10 (95% CI) Participants with titers >= 10 (95% CI) Participants with titers >= 40 (95% CI)	1383 (1290; 1484) 4 (0.3) (0.1; 0.8) 1211 (99.7) (99.2; 99.9) 1198 (98.6) (97.8; 99.2)	1094 (999; 1198) 2 (0.2) (0; 0.6) 1213 (99.8) (99.4; 100) 1179 (97.0) (95.9; 97.9)	323 (300; 349) 4 (0.3) (0.1; 0.8) 1211 (99.7) (99.2; 99.9) 1170 (96.3) (95.1; 97.3)	1759 (1660; 1864) 0 (0; 0.3) 1215 (100) (99.7; 100) 1212 (99.8) (99.3; 99.9)
Post-dose response based on pre-dose (D29/D01)	M	1215	1215	1214	1215
	GMTR (95% CI)	12.9 (11.7; 14.2)	19.3 (17.6; 21.1)	7.63 (7.08; 8.21)	6.15 (5.73; 6.61)
	Seroconversion n (%) (95% CI)	 940 (77.4) (74.9; 79.7)	 1055 (86.8) (84.8; 88.7)	 913 (75.2) (72.7; 77.6)	 851 (70.0) (67.4; 72.6)

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013; n: number of participants experiencing the endpoint listed in the first 3 columns
M: number of participants with available data for the considered endpoint.
Seroconversion is defined as either a pre-dose titer < 1:10 at D01 and a post-dose titer >= 1:40 at D29 or a pre-dose titer >= 1:10 at D01 and a >= 4-fold increase in post-vaccination titer. GMTR: Ratio of the individual titers post-dose over pre-dose
The 2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method. The 2-sided 95% CI for a GM is based on the Student t-distribution
Source: Modified from Table 11 of VAP00027 Clinical Study Report.

Reviewer's comment: I verified the secondary analyses based on the data submitted in the Standard Data Tabulation Model (SDTM) format, and my results were consistent with those reported by the Applicant.

6.2.11.4 Dropouts and/or Discontinuations

The proportions of subjects who withdrew from the study were small and similar between the two age groups. Therefore, missing data were not expected to have significant impact on the comparison of efficacy endpoints between the groups.

6.2.12 Safety Analyses

The safety overview after any vaccine injection is presented by vaccination group in the SafAS in Table 25.

Immediate Unsolicited AEs and Ars

There was 1 participant (0.2%) in the 9 to 17 years group who reported at least 1 immediate unsolicited AE within 30 minutes of vaccination. This immediate unsolicited AE (epistaxis) was found to be Grade 1 intensity and not assessed as related to the vaccine by the Investigator.

Solicited Reactions

The percentage of participants who experienced at least 1 solicited reaction within 7 days after any vaccination consisted of 44.3% (274/618) of participants aged 9 to 17 years and 52.9% (336/635) of participants aged 18 to 49 years.

Solicited Injection Site Reactions

The percentage of participants who experienced at least 1 solicited injection site reaction within 7 days after any vaccination consisted of 35.6% (220/618) in the 9 to 17 years group and 40.8% (259/635) in the 18 to 49 years group. The most common solicited injection site adverse reaction was pain (34.4%), followed by erythema in the 9 to 17 years group, and pain (40.2%) followed by induration (3.3%) in the 18 to 49 years group.

Solicited Systemic Reactions

The percentage of participants who experienced at least 1 solicited systemic reaction within 7 days after any vaccination consisted of 29.6% (182/615) of participants aged 9 to 17 years and 36.2% (230/635) of participants aged 18 to 49 years. The most common solicited systemic adverse reaction was myalgia (19.3%), followed by headache (18.5%) and malaise (16.1%) in children 9 to 17 years of age, and headache (22.8%), myalgia (20.3%), and malaise (16.5%) in adolescents aged 18 to 49 years of age.

Overall, there were slightly more solicited reaction in the older age group (18 to 49 years).

Unsolicited AEs

The percentage of participants who experienced at least 1 unsolicited AE within 28 days after any vaccination were similar between the vaccine groups: 14.5% (93/641) of participants aged 9 to 17 years and 18.1% (119/658) of participants aged 18 to 49 years.

Unsolicited ARs

The percentage of participants who experienced at least 1 unsolicited AR within 28 days after any vaccination were similar between the vaccine groups: 4.7% (30/641) of participants aged 9 to 17 years and 4.0% (26/658) of participants aged 18 to 49 years. At least 1 unsolicited injection site adverse reaction was reported by 1.4% and 1.2% of participants and unsolicited systemic adverse reaction was reported by 3.3% and 2.9% of participants in the 9 to 17 years and 18 to 49 years age groups, respectively.

Deaths and AESIs

During the study, no death was reported and none of the participants experienced any AESIs in any age groups.

SAEs, and MAAEs, and Discontinuations due to AEs

- *In the 9 to 17 years group*

During the study, there were 3 participants (0.5%) who reported at least 1 SAE (1 participant [0.2%] within 28 days of vaccination and 2 participants [0.3%] during the 6-month follow-up) and 29 participants (4.5%) who reported at least 1 MAAE (27 participants [4.2%] within 28 days of vaccination and 3 participants [0.5%] during the 6-month follow-up). There were no SAEs considered as related to the vaccine.

Within 28 days of vaccination, there was no participant experiencing an AE leading to study discontinuation.

- *In the 18 to 49 years group*

During the study, there were 7 participants (1.1%) who reported at least 1 SAE (5 participants [0.8%] within 28 days of vaccination and 2 participants [0.3%] during the 6-month follow-up) and 37 participants (5.6%) who reported at least 1 MAAE (35 participants [5.3%] within 28 days of vaccination and 3 participants [0.5%] during the 6-month follow-up). There were no SAEs considered as related to the vaccine.

Within 28 days of vaccination, there were 2 participants experiencing an AE leading to study discontinuation.

Overall, the safety profile of RIV4 was comparable in participants aged 9 to 17 years and in participants aged 18 to 49 years, except that there were slightly less reported solicited reactions within 7 days of vaccination in 9 to 17 years group than in 18 to 49 years group.

Reviewer's comment: The safety analyses were confirmed based on data submitted in the SDTM format, and the results were consistent with those reported by the Applicant.

Table 25: Safety overview after any vaccine injection - Safety Analysis Set

Period/ Participants experiencing at least one:	9 to 17 years (N=641)			18 to 49 years (N=658)			All (N=1299)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Within 30 minutes after vaccine injection									
Immediate unsolicited AE	1/641	0.2	(0; 0.9)	0/658	0	(0; 0.6)	1/1299	<0.1	(0; 0.4)
Immediate unsolicited AR	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
Solicited reaction within solicited period after vaccine	274/618	44.3	(40.4; 48.4)	336/635	52.9	(48.9; 56.9)	610/1253	48.7	(45.9; 51.5)
Solicited injection site reaction	220/618	35.6	(31.8; 39.5)	259/635	40.8	(36.9; 44.7)	479/1253	38.2	(35.5; 41.0)
Injection site pain	212/617	34.4	(30.6; 38.3)	255/635	40.2	(36.3; 44.1)	467/1252	37.3	(34.6; 40.0)
Injection site erythema	28/618	4.5	(3.0; 6.5)	17/635	2.7	(1.6; 4.3)	45/1253	3.6	(2.6; 4.8)
Injection site swelling	23/618	3.7	(2.4; 5.5)	17/635	2.7	(1.6; 4.3)	40/1253	3.2	(2.3; 4.3)
Injection site induration	19/618	3.1	(1.9; 4.8)	21/635	3.3	(2.1; 5.0)	40/1253	3.2	(2.3; 4.3)
Injection site bruising	15/618	2.4	(1.4; 4.0)	7/635	1.1	(0.4; 2.3)	22/1253	1.8	(1.1; 2.6)
Solicited systemic reaction	182/615	29.6	(26.0; 33.4)	230/635	36.2	(32.5; 40.1)	412/1250	33.0	(30.4; 35.6)
Fever	17/608	2.8	(1.6; 4.4)	11/633	1.7	(0.9; 3.1)	28/1241	2.3	(1.5; 3.2)
Headache	114/615	18.5	(15.5; 21.8)	145/635	22.8	(19.6; 26.3)	259/1250	20.7	(18.5; 23.1)
Malaise	99/615	16.1	(13.3; 19.2)	105/635	16.5	(13.7; 19.7)	204/1250	16.3	(14.3; 18.5)
Myalgia	119/615	19.3	(16.3; 22.7)	129/635	20.3	(17.3; 23.7)	248/1250	19.8	(17.7; 22.2)
Chills	45/615	7.3	(5.4; 9.7)	40/635	6.3	(4.5; 8.5)	85/1250	6.8	(5.5; 8.3)
Within 28 days after vaccine injection									
Unsolicited AE	93/641	14.5	(11.9; 17.5)	119/658	18.1	(15.2; 21.2)	212/1299	16.3	(14.4; 18.4)
Unsolicited AR	30/641	4.7	(3.2; 6.6)	26/658	4.0	(2.6; 5.7)	56/1299	4.3	(3.3; 5.6)
Unsolicited injection site AR	9/641	1.4	(0.6; 2.6)	8/658	1.2	(0.5; 2.4)	17/1299	1.3	(0.8; 2.1)
Unsolicited systemic AR	21/641	3.3	(2.0; 5.0)	19/658	2.9	(1.7; 4.5)	40/1299	3.1	(2.2; 4.2)
AE leading to discontinuation	0/641	0	(0; 0.6)	2/658	0.3	(0; 1.1)	2/1299	0.2	(0; 0.6)
SAE	1/641	0.2	(0; 0.9)	5/658	0.8	(0.2; 1.8)	6/1299	0.5	(0.2; 1.0)
Death	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
AESI	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
MAAE	27/641	4.2	(2.8; 6.1)	35/658	5.3	(3.7; 7.3)	62/1299	4.8	(3.7; 6.1)
During 6-month follow-up period									
SAE	2/641	0.3	(0; 1.1)	2/658	0.3	(0; 1.1)	4/1299	0.3	(0.1; 0.8)
Death	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
AESI	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
MAAE	3/641	0.5	(0.1; 1.4)	3/658	0.5	(0.1; 1.3)	6/1299	0.5	(0.2; 1.0)
During the study									
SAE	3/641	0.5	(0.1; 1.4)	7/658	1.1	(0.4; 2.2)	10/1299	0.8	(0.4; 1.4)
Death	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
AESI	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
MAAE	29/641	4.5	(3.1; 6.4)	37/658	5.6	(4.0; 7.7)	66/1299	5.1	(4.0; 6.4)

n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
AR: Reactions related to study vaccine
Source: Modified from Table 14, Table 16, Table 17, and Table 8.38 of VAP00027 Clinical Study Report.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable since the populations enrolled in the two studies were mutually exclusive with respect to age range (3 to 8 years of age in VAP00026 and 9-17 years of age in VAP00027).

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable since the populations enrolled in the two studies were mutually exclusive with respect to age range (3 to 8 years of age in VAP00026 and 9-17 years of age in VAP00027).

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity

VAP00026

The study was terminated due to futility after having enrolled 26% (366 out of 1412) of planned participants during the 2022-2023 season. The primary immunogenicity objective to demonstrate the non-inferior HAI immune response of RIV4 vs IIV4 for the 4 strains in subjects aged 3 to 8 years based on GMTs and SC rates 28 days after the last vaccination on PPAS of subjects accumulated during the 2022-2023 season was not met.

- The NI criteria for HAI immune response of RIV4 versus licensed IIV4 based on GMTs and SC rates were met for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain
- The lower limits of the 2-sided 95% CIs of the GMTRs between RIV and IIV4 (GMT RIV4 / GMT IIV4) post vaccination were higher than 0.667 for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain, with a GMTR of 0.515 (95% CI: 0.397; 0.668)
- The lower limits of the 2-sided 95% CIs of the differences in SC rates (RIV4 - IIV4) were higher than -10% for A/H1N1, A/H3N2, and B/Yamagata lineage strains, but not for B/Victoria lineage strain with a difference in SC rates of -6.91% (95% CI: -14.02%; 0.10%)

The interim futility analysis indicated that the probability of the study success, based on the demonstration of the NI as defined in the primary objective, was estimated to be only 0.4%. This value was below the pre-defined futility threshold outlined in the FIC charter, which required that the probability exceeded 20% for enrollment in trial VAP00026 to continue.

VAP00027

The primary objective of NI of HAI immune response induced by RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by GMTs and SC rates at D29 was met. NI criteria were met for all 8 endpoints included in the NI assessment (4 ratios of GMTs and 4 differences in SC rates) as the lower limits of the 95% CIs were higher than 0.667 for the ratios of GMTs and higher than -10% for the differences of SC rates for all 4 strains on PPAS. The GMT ratios between groups were

- A/H1N1 strain: 1.98 (95% CI: 1.73; 2.27)
- A/H3N2 strain: 3.27 (95% CI: 2.76; 3.87)
- B/Victoria lineage strain: 1.57 (95% CI: 1.35; 1.82)
- B/Yamagata lineage strain: 1.22 (95% CI: 1.09; 1.37)

The differences in SC rates between groups were

- A/H1N1 strain: 1.92% (-2.78%; 6.62%)
- A/H3N2 strain: -0.59% (-4.41%; 3.23%)
- B/Victoria lineage strain: 3.29% (-1.57%; 8.14%)
- B/Yamagata lineage strain: 14.3% (9.17%; 19.3%)

Safety

No notable imbalance in reports of solicited reactions or unsolicited adverse events was observed in both the Studies VAP00026 and VAP00027.

10.2 Conclusions and Recommendations

Study VAP00026 failed to meet the primary objective to show the non-inferior HAI immune response of RIV4 versus licensed IIV4 in children aged 3 to 8 for all 4 strains according to the interim analysis. For Study VAP00027, the primary objective was met for all four strains by demonstrating NI of HAI immune response induced by RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age.

I defer to the clinical reviewers on the immunogenicity conclusions regarding extension of indication to individuals 9 to 17 years of age.