BLA Clinical Review Memorandum

Application Type	Efficacy Supplement to extend the indication to adolescents 9 through 17 years
STN	125285.613
CBER Received Date	May 31, 2024
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Division / Office	DCTR/OVRR
Priority Review	No
Reviewer Name	Cynthia Nolletti, MD
Review Completion Date / Stamped Date	March 19, 2025
Supervisory Concurrence	Meghan Ferris, MD, MPH Team Leader CRB2 Andrea Hulse, MD Chief, CRB2
Applicant	Sanofi Pasteur, Inc./Protein Sciences Corp
Proper Name	Quadrivalent Influenza Vaccine
Trade Name	Flublok Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5mL dose contains 45µg recombinant hemagglutinin (rHA), total 180µg, from each of the recommended influenza types and subtypes: • A/H1N1 • A/H3N2 • B/Yamagata • B/Victoria
Dosage Form and Route of Administration	Sterile solution for intramuscular (IM) injection supplied in single dose 0.5mL pre-filled syringes.
Dosing Regimen	A single 180mcg/0.5 mL dose IM
Indication(s) and Intended Population	Active immunization against disease caused by the influenza virus subtypes A and types B contained in the vaccine. For use in persons ≥9 years of age.
Orphan Designated	No

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GLOSSARY

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
BiMO	bioresearch monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, Manufacturing and Controls
COVID-19	coronavirus disease 2019
CRF	case report form
DER	deferral extension request
ESDR	early safety data review
FAS	full analysis set
FIC	Firewall Internal Committee
FSR	final study report
GBS	Guillain-Barre syndrome
GMT	geometric mean titer
HA	hemagglutinin
HD	high dose
HI	hemagglutination inhibition
IA	interim analysis
IIV3 or TIV	trivalent inactivated influenza vaccine
IIV4 or QIV	quadrivalent inactivated influenza vaccine
IM	intramuscular
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
LAIV	live-attenuated influenza vaccine
LL	lower limit (of confidence interval)
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NCT	National Clinical Trials
NH	Northern Hemisphere
NI	noninferior
NP	nucleoprotein
PeRC	Pediatric Review Committee
PI	package insert
PMR	postmarketing requirement
PPAS	per protocol analysis set
PPoS	predictive power of success
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PT	Preferred Term
RCT	randomized controlled trial
rHA	recombinant hemagglutinin
RIV3	trivalent recombinant hemagglutinin influenza vaccine (Flublok)

RIV4	quadrivalent recombinant hemagglutinin influenza vaccine (Flublok Quadrivalent)
rVE	relative vaccine efficacy
SafAS	safety analysis set
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SCR	seroconversion rate
SMT	Safety Management Team
SN	seroneutralization
SOC	System Organ Class
U.S.	United States
VE	vaccine efficacy
VRBPAC	Vaccine and Related Biological Products Advisory Committee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Flublok and Flublok Quadrivalent are trivalent and quadrivalent recombinant hemagglutinin influenza vaccines, respectively, (also referred to as RIV3 and RIV4 in this review) manufactured by Protein Sciences Corporation, a company owned by Sanofi Pasteur, Inc (both referred to as "the Applicant" in this review). On January 16, 2013, Flublok was approved for the active immunization of adults 18 through 49 years of age against disease caused by influenza subtypes A and type B contained in the vaccine. Approval was based on the demonstration of effectiveness in preventing culture-confirmed influenza illness and acceptable safety and was associated with two pediatric postmarketing requirements (PMRs) to study the vaccine in the pediatric population 3 through 17 years of age. On October 29, 2014, the indication for RIV3 was extended to adults 50 years of age and older under accelerated approval regulations, based on acceptable safety and immunogenicity data, with a PMR to conduct a study to confirm clinical benefit in this age group.

Flublok and Flublok Quadrivalent are manufactured by the same processes and have overlapping compositions. Clinical data generated from one formulation are relevant to the other. Because influenza vaccines were transitioning to quadrivalent formulations at the time RIV3 was approved, FDA agreed that the PMRs in adults ≥50 years of age and in the pediatric populations could be fulfilled using the RIV4 formulation. On October 7, 2016, Flublok Quadrivalent was approved for use in adults ≥18 years of age based on noninferior (NI) immunogenicity as compared with a United States (U.S.)-licensed quadrivalent inactivated influenza vaccine (IIV4), Fluarix Quadrivalent, and traditional approval of RIV3 and RIV4 was also granted in adults ≥50 years of age based on the demonstration of NI relative vaccine efficacy (rVE) of RIV4 as compared with IIV4. With the current supplement, the Applicant seeks to extend the indication for both RIV3 and RIV4 to adolescents 9 through 17 years of age based on data from Study VAP00027 (PMR #2). Because Study VAP00026 (PMR #1), conducted in children 3 through 8 years of age, was terminated early for futility, the Applicant does not seek an indication in this age group but has submitted a final clinical study report (FSR) in fulfillment of PMR #1.

VAP00027 was a Phase 3, non-randomized, open-label, uncontrolled, parallel group, multi-center study to assess the NI immunogenicity and safety of RIV4 in approximately 1334 healthy participants 9 through 49 years of age (667 children and adolescents 9 through 17 years and 667 adults 18 through 49 years) in Europe and the U.S. All participants were to receive a single 0.5 mL dose of RIV4, administered intramuscularly (IM), on Day 1. Blood for serologies were drawn prior to vaccination on Day 1 and at 28 days postvaccination. Safety assessments included collection of immediate reactions for 30 minutes postvaccination, solicited injection site and systemic reactions for 7 days postvaccination and non-serious unsolicited adverse events (AEs) for 28 days following vaccination. Serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), AEs leading to discontinuation, and pregnancy data were collected through six months postvaccination.

VAP00026 was a Phase 3, randomized, observer-blind, active-controlled, multicenter study conducted in the U.S. and Europe in children 3 through 8 years of age, to evaluate the safety and NI immunogenicity of RIV4 as compared with U.S.-licensed IIV4. The study planned to enroll a total of 1412 participants equally stratified between two age groups, 3 through 5 years and 6 through 8 years of age, with approximately equal numbers of participants who were previously unvaccinated or previously vaccinated against influenza. Participants were randomized 1:1 to receive RIV4 or IIV4, one or two 0.5 mL doses administered IM 28 days

apart, depending on whether they were previously vaccinated or previously unvaccinated against influenza, respectively.

Blood for serologies were drawn prior to vaccination on Day 1 (and Day 29 if previously unvaccinated) and at 28 days after the last vaccination (on Day 29 or Day 57). Safety assessments included collection of immediate reactions, solicited injection site and systemic reactions for 7 days following each vaccination, non-serious unsolicited AEs for 28 days following the last vaccination, and SAEs, MAAEs, AESIs and AEs leading to discontinuation through six months after the last vaccination. VAP00026 was terminated early due to futility, inability to reach the planned enrollment and a high likelihood of failure to meet the primary immunogenicity endpoints even if the targeted enrollment had been achieved.

Summary of Effectiveness

VAP00027

The primary objective of Study VAP00027 was to demonstrate the NI hemagglutination inhibition (HI) immune response induced by RIV4 against the four vaccine virus strains in participants 9 through 17 years of age as compared with participants 18 through 49 years of age. The primary immunogenicity endpoints for each of the four vaccine strains were: 1) individual HI titer 28 days after vaccination (Day 29) and 2) seroconversion, defined as an HI titer <1:10 prior to vaccination on Day 1 and a post-vaccination titer ≥1:40 at Day 29, or a pre-vaccination HI titer ≥1:10 on Day 1 and a ≥4-fold rise in titer at Day 29.

Noninferiority (NI) of RIV4 in participants 9 through 17 years of age as compared with adults 18 through 49 years of age was evaluated for geometric mean titers (GMTs) and seroconversion rates (SCRs). The primary analysis was conducted sequentially beginning with testing for NI of GMTs and, if successful for all 4 vaccine virus strains, followed by testing for NI of SCRs. Noninferiority for GMTs was demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) of the GMT ratio (RIV4 [9 through 17 years age group] divided by RIV4 [18 through 49 years age group] at 28 days after vaccination) was >0.667 for each of the 4 vaccine virus strains. Noninferiority for SCRs was demonstrated if the LL of the 2-sided 95% CI for the difference in SCRs (RIV4 [9 through 17 years age group] minus RIV4 [18 through 49 years age group] at 28 days after vaccination) was >-10% for all 4 vaccine virus strains. The primary endpoint was met if success criteria for NI of both GMTs and SCRs were met for all 4 vaccine virus strains.

The per protocol analysis set (PPAS) (a subset of participants who met all eligibility criteria, received one dose of study vaccine and provided a post-vaccination sample, and had no prespecified criteria that might impact the immune response) was used for the primary analysis of NI GMTs and SCRs, as measured by a validated HI assay based on egg-derived antigen. Post-vaccination GMT ratios and 95% CIs for each vaccine virus strain in the 9 through 17 years age group (n=609) as compared with the 18 through 49 years age group (n=606) were as follows: H1N1 = 1.98 (1.73, 2.27); H3N2 = 3.27 (2.76, 3.87); B/Victoria = 1.57 (1.35, 1.82); B/Yamagata = 1.22 (1.09, 1.37). Post-vaccination SCR differences and 95% CIs were as follows: H1N1 = 1.92 (-2.78, 6.62); H3N2 = -0.59 (-4.41, 3.23); 3.29 (-1.57, 8.14); 14.3 (9.17, 19.3). Success criteria for NI GMT ratios (LL of the 2-sided 95% CI must be >0.667) and for NI SCR differences (LL of the 2-sided 95% CI must be >-10%) were met for each of the four vaccine antigens. Thus, the primary immunogenicity endpoint was met.

VAP00026

The primary objective of Study VAP00026 was to demonstrate the NI HI immune response of RIV4 as compared with U.S.-licensed IIV4 for the four vaccine strains based on the egg-derived antigen in participants 3 through 8 years of age. The primary immunogenicity endpoints for each of the four vaccine strains were: 1) individual HI titer 28 days after the last vaccination (Day 29 in single-dose previously vaccinated participants or Day 57 in two-dose previously unvaccinated participants) and 2) seroconversion, defined as an HI titer <1:10 prior to vaccination on Day 1 and a post-vaccination titer ≥1:40 at Day 29 or Day 57, or a pre-vaccination HI titer ≥1:10 on Day 1 and a ≥4-fold rise in titer at Day 29 or Day 57. The primary NI analyses of GMT ratios and SCR differences were conducted on the PPAS and were evaluated according to the same pre-specified success criteria as were used in Study VAP00027.

Despite efforts to enhance enrollment, the Applicant was only able to recruit ~26% of the 1412 participants planned for enrollment. As a result, the protocol and statistical analysis plan (SAP) were amended to include an interim analysis (IA) of all included immunogenicity and safety data generated from ~368 recruited participants through 28 days after the last vaccination. The SAP prespecified that an unblinded group of statisticians would also calculate the predictive power of success (PPoS) for each of the 8 NI statistical tests included in the primary objective and for the overall study. The Applicant established an independent Firewall Internal Committee (FIC), comprised of senior members from clinical, safety and biostatistics divisions, to review the results of the interim analysis (IA) and recommend whether VAP00026 should continue or be terminated for futility or for safety reasons.

NI analyses of GMT ratios and SCR differences between RIV4 and IIV4 at 28 days after the last vaccination for all participants 3 through 8 years of age were performed on the PPAS. Post-vaccination GMT ratios and 95% CIs for each vaccine strain in the RIV4 group (n=160) as compared with the IIV4 group (n=158) were as follows: H1N1 = 1.28 (0.948, 1.73); H3N2 = 2.53 (1.93, 3.30); B/Victoria = 0.515 (0.397, 0.668); B/Yamagata = 1.02 (0.799, 1.30). Post-vaccination SCR differences and 95% CIs were as follows: H1N1 = 7.10 (-1.55, 15.7); H3N2 = 15.4 (5.80, 24.7); B/Victoria = -6.91 (-14.02, 0.10); B/Yamagata = 5.81 (-1.99, 13.6). Success criteria for NI GMT ratios and SCR differences were met for the H1N1, H3N2 and B/Yamagata strains but not for the B/Victoria strain. Because RIV4 did not meet the primary endpoint of NI GMTs and SCRs for all 4 vaccine antigens, Study VAP00026 did not meet the primary immunogenicity endpoint. Additionally, the PPoS was calculated as <1%, indicating that the probability of meeting the primary objective by the end of the study (i.e., assuming full enrollment) was very low, and the study was terminated for futility.

Summary of Safety

No new safety concerns were identified following review of safety data from Studies VAP00027 and VAP00026.

VAP00027

In Study VAP00027, the Safety Analysis Set (SafAS), defined as all participants who received one dose of vaccine, was comprised of 1,299 participants, including 641 and 658 in the 9 through 17 years and 18 through 49 years age groups, respectively. Overall, fewer participants 9 through 17 years of age experienced solicited local or systemic reactions (35.6% and 29.6%, respectively) as compared to participants 18 through 49 years of age (40.8% and 36.4%, respectively). Injection site pain was the most frequently reported solicited local reaction in participants 9 through 17 years and 18 through 49 years of age (34.4% and 40.2%, respectively). Other solicited injection site reactions occurred in <5% and <1% of participants in

the respective age groups. Percentages of solicited systemic events were similar between age groups. In participants 9 through 17 years of age, the most frequently reported solicited systemic reactions (>10%) were myalgia (19.3%), headache (18.5%) and malaise (16.1%). In participants 18 through 49 years of age, the most frequently reported solicited systemic reactions were headache (23.0%), myalgia (20.3%), and malaise (16.5%). Fever occurred in 2.8% and 1.7% of participants 9 through 17 years and 18 through 49 years, respectively. Most solicited injection site and systemic reactions were Grade 1 (mild) or Grade 2 (moderate) in severity and were short in duration.

Within 28 days after vaccination, unsolicited AEs were reported by fewer participants 9 through 17 years of age as compared with 18 through 49 years of age (14.5% vs 17.9%). No unusual patterns were identified. Most unsolicited AEs were mild to moderate (Grade 1 or 2) in intensity. A total of 24 (1.8%) of participants, 10 (1.6%) participants 9 through 17 years and 14 (2.1%) of participants 18 through 49 years of age, experienced severe (Grade 3) unsolicited AEs.

Within 180 days after vaccination, percentages of SAEs and MAAEs were low in both age groups, 0.5% and 4.5%, respectively, among participants 9 through 17 years of age and 1.1% and 5.6%, respectively, among participants 18 through 49 years of age. All SAEs were assessed as unrelated to study vaccination. No deaths or AESIs were reported during the study. Two participants, both in the age group 18 through 49 years, had AEs leading to discontinuation: one 45-year-old female had Grade 3 injection site erythema, induration, swelling and bruising and Grade 2 urticaria on Day 3 postvaccination; and one 29-year-old male had an intentional overdose on Day 8 postvaccination.

VAP00026

In Study VAP00026, the SafAS was comprised of 362 participants, including 181 participants in each treatment group. Overall, fewer participants in the RIV4 group experienced solicited local or systemic reactions after any vaccination (39.1% and 27.9%, respectively) as compared with participants in the IIV4 group (42.2% and 36.7%, respectively).

Solicited injection site reactions were reported by 32.9% and 44.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 40.7% and 43.8% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. The most commonly reported (>10%) solicited injection site reactions in the RIV4 or IIV4 groups, respectively, were pain (34.1% and 36.7%), erythema (13.5% and 16.8%), swelling (10.7% and 9.6%), and induration (9.6% and 10.7%). Percentages of injection site reactions in both treatment groups were generally higher in children 6 through 8 years of age as compared with children 3 through 5 years of age, respectively, with the largest imbalance observed for injection site pain: RIV4 40.0% versus 26.6% and IIV4 39.3% versus 34.1%. Most injection site reactions were Grade 1 (mild) or Grade 2 (moderate) in intensity and resolved spontaneously after 1-3 days. Grade 3 solicited injection site reactions occurred in 4.5% and 4.4% of RIV4 and IIV4 recipients, respectively, including 2.5% and 6.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 2.2% and 6.7% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. Among participants who received two doses of study vaccine (i.e., previously unvaccinated participants), percentages of solicited injection site pain and most other reactions were generally lower following the second vaccination as compared with the first.

Overall, solicited systemic reactions were reported by 27.9% and 36.7% of children 3 through 8 years of age in the RIV4 and IIV4 groups, respectively, including 30.4% and 26.0% of RIV4

recipients 3 through 5 years and 6 through 8 years of age, respectively, and 31.9% and 41.6% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. The most commonly reported (>10%) solicited systemic reactions following any vaccination in the RIV4 or IIV4 groups, respectively, were malaise (19.6% and 20.6%), myalgia (16.2% and 23.9%), and headache (12.8% and 16.7%). Percentages of solicited systemic reactions were generally higher in children 6 through 8 years of age as compared with children 3 through 5 years of age. Fever was reported in 4.5% and 7.2% of all RIV4 and IIV4 recipients, respectively, including in 5.1% and 4.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and in 6.6% and 7.9% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. Most solicited systemic reactions were Grade 1 (mild) or Grade 2 (moderate) in intensity and short in duration. Grade 3 solicited systemic reactions occurred in 3.9% and 5.0% of RIV4 and IIV4 recipients, respectively, including 2.5% and 5.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 2.2% and 7.9% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively.

Among participants who received two doses of study vaccine (i.e., previously unvaccinated participants), percentages of solicited systemic reactions were generally lower following the second vaccination as compared with the first. The percentages and severity of reactions between study groups and age subgroups showed patterns similar to those observed following any vaccination in the overall study population.

Within 28 days after vaccination, unsolicited AEs were reported by slightly fewer recipients of RIV4 as compared with IIV4 (24.3% vs 26.0%). No unusual patterns were observed. Within 180 days after vaccination, percentages of SAEs were low (0 and 0.6%, respectively) in both RIV4 and IIV4 groups. One SAE, bacterial infection, unspecified, occurred during the study and was assessed as unrelated to vaccination. RIV4 recipients reported more MAAEs as compared with IIV4 recipients (10.5% and 7.7%, respectively). No deaths, AESIs, or AEs leading to discontinuation occurred during the study.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The efficacy supplement included two clinical trials to evaluate the safety and immunogenicity of RIV4. Because VAP00026 enrolled only 26% of the planned study population of children 3 through 6 years of age (n=366) and was terminated for futility, the Applicant does not seek an indication in this population. Therefore, this demographic summary will not address Study VAP00026.

In Study VAP00027, the distributions of demographic and baseline characteristics were similar across the Per-Protocol, Safety and Enrolled Populations. In the PPAS and SafAS, the mean age of children and adolescents was 13.0 (SD ~2.48) years. The mean age of adults was 34.2 (9.20) years. Male and female participants comprised 52.1% and 47.9%, respectively, of participants 9 through 17 years of age and 40.1% and 59.9%, respectively, of participants 18 through 49 years of age in the SafAS. The majority of participants in both age groups were White, 73.4% and 72.1% of participants 9 through 17 years of age in the PPAS and SafAS, respectively, and 81.4% and 81.2% of participants 18 through 49 years of age, respectively. A total of 81.1%-81.4% of participants 9 through 17 years of age and 92.7%-92.9% participants 18 through 49 years of age in the PPAS and SafAS were non-Hispanic or non-Latino. Relative to U.S. population estimates for 2023, Black or African American participants were overrepresented (18.9%-19.6% of all participants 9 through 49 years of age versus 13.7% in the U.S.), and Asians (0.5%-0.6% of all participants versus 6.4%) and Hispanics or Latinos (11.4%-11.7% of all participants versus 19.5%) were underrepresented.

Immunogenicity – HI GMTs

Age subgroup analyses of HI GMTs conducted in the PPAS showed that, at 28 days post-vaccination, GMTs for the age subgroup 9 through 11 years as compared with 12 through 17 years were higher for the A/H3N2 strain, lower for the B/Victoria and B/Yamagata strains, and comparable for the A/H1N1 strain. Postvaccination Day 29 GMTs (95% CI) in participants 9 through 11 years and 12 through 17 years, respectively, were as follows:

- A/H1N1: 2101 (1786, 2472) vs 1881 (1717, 2062)
- A/H3N2: 2550 (2129, 3055) vs 1765 (1543, 2019)
- B/Victoria: 308 (248, 383) vs 456 (402, 517)
- B/Yamagata: 1339 (1101, 1627) vs 2286 (2094, 2496)

Subgroup analyses of post-vaccination GMTs conducted in the PPAS by sex and by race did not show any meaningful differences between male and female participants or among White and Black or African American participants. The numbers of participants of Asian, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander origin were too small for meaningful analyses. Subgroup analyses by ethnicity did not show meaningful differences in post-vaccination GMTs.

Subgroup analyses conducted in the PPAS by priming status showed that, among all participants 9 through 49 years of age, postvaccination GMTs [95% CIs] were higher in participants unvaccinated than in participants vaccinated in the previous season, respectively, for A/H1N1 (1630 [1496, 1776] vs 960 [855, 1077]) and B/Yamagata lineage (1889 [1757, 2030] vs 1502 [1366, 1651]) strains. There were no meaningful differences according to priming status for the A/H3N2 and B/Victoria strains. These trends were also observed within the two age groups 9 through 17 years and 18 through 49 years.

Subgroup analyses by baseline serostatus among all participants 9 through 49 years of age in the PPAS showed that postvaccination GMTs [95% CIs] were higher in baseline seropositive (HI titer ≥1:10) participants than in baseline seronegative (HI titer <1:10) participants for each strain. For the age group of participants 9 through 17 years of age, postvaccination GMTs in baseline seropositive were also higher as compared with baseline seronegative participants for the A/H3N2, B/Victoria and B/Yamagata strains. For the A/H1N1 strain, postvaccination GMTs in baseline seropositive participants (1989 [95% CI: 1839, 2152]) were higher than in baseline seronegative participants (941 [95% CI: 391, 2265]) but 95% CIs were overlapping.

Immunogenicity – Seroconversion Rates

Subgroup analyses by sex, White or Black/African American race, and ethnicity showed no meaningful differences in postvaccination SCRs among participants 9 through 17 years or 18 through 49 years of age. The numbers of participants in other racial subgroups were too small to draw meaningful conclusions.

Sub-analyses by priming status showed that for participants 9 through 49 years of age overall and within the age subgroups 9 through 17 years and 18 through 49 years, SCRs were higher in previously unvaccinated than previously vaccinated participants for the A/H1N1, B/Victoria, and B/Yamagata lineage strains. There were no meaningful differences in SCRs according to priming status for the A/H3N2 strain.

Sub-analyses by baseline serostatus, detectable HI titer ≥1:10 (“seropositive”) or undetectable (“seronegative”), among all participants 9 through 49 years of age or within age subgroups 9

through 17 years and 18 through 49 years in the PPAS, did not show meaningful differences in SCRs at 28 days postvaccination.

Safety

Subgroup analyses of the overview of safety were conducted on the SafAS according to age subgroups (9 through 11 years, 12 through 17 years, 18 through 34 years, and 35 through 49 years), sex, race, ethnicity, and previous influenza vaccination status.

The overall percentages of solicited and unsolicited AEs and long-term safety (SAEs, AESIs and MAAEs) were similar (with overlapping 95% CIs) across age subgroups except for the percentages of solicited injection site reactions within 7 days following vaccination which were slightly higher in participants 9 through 11 years of age as compared with participants 12 through 17 years of age (43.2% [95% CI: 36.0, 50.7] and 32.3% [95% CI: 27.9, 37.0], respectively).

Analyses by sex showed that among all participants 9 through 49 years of age, lower percentages of male participants reported any solicited injection site or systemic reactions within 7 days following vaccination as compared with female participants (42.3% [95% CI: 38.2, 46.4] versus 54.1% [50.3, 57.9], respectively). Solicited injection site reactions were reported in 32.2% [95% CI: 28.4, 36.2] of male participants and 43.4% [95% CI: 39.6, 47.2] of female participants, and solicited systemic reactions were reported in 28.8% [95% CI: 25.2, 32.7] of male participants and 36.4% [95% CI: 32.8, 40.2] of female participants. Unsolicited AEs were reported by lower percentages of male participants than in female participants 9 through 49 years of age (12.7% [95% CI: 10.1, 15.6] versus 19.4% [95% CI: 16.5, 22.5], respectively) with similar patterns observed within age subgroups. Lower percentages of male than female participants reported SAEs (0.3% [95% CI: 0, 1.2] vs 1.1% [95% CI: 0.5, 2.2]) and MAAEs (3.2% [95% CI: 1.9, 4.9] vs 6.7% [95% CI: 5.0, 8.8]).

Analyses by race in all participants 9 through 49 years of age showed that solicited injection site reactions and systemic reactions occurring within 7 days following vaccination were reported in higher percentages of White as compared with Black or African American participants (41.9% [95% CI: 38.8, 45.1] versus 24.5% [95% CI: 19.0, 30.5] and 35.3% [95% CI: 32.3, 38.4] versus 22.6% [95% CI: 17.3, 28.6], respectively). Similar trends between White and Black or African American participants were observed in the age subgroups 9 through 17 years and 18 through 49 years of age. Unsolicited AEs also occurred in higher percentages of White as compared with Black or African American participants (18.2% [95% CI: 15.8, 20.7] versus 10.2% [95% CI: 6.8, 14.6]). Numbers and percentages of SAEs and MAAEs were too small to make meaningful comparisons between White and Black or African American participants. The numbers of Asian (n=7), American Indian or Alaskan Native (n=6), Native Hawaiian or other Pacific Islander (n=4), and mixed origin (n=28) participants were too small and CIs too wide to draw meaning conclusions for these subgroups.

Analyses by ethnicity in all participants 9 through 49 years of age showed that solicited local injection site and systemic reactions occurring within 7 days following vaccination were reported in similar percentages (with overlapping 95% CIs) of Hispanic/Latino and non-Hispanic/non-Latino participants: solicited injection site reactions (36.8% [95% CI: 28.9, 45.2] and 38.5% [95% CI: 35.6, 41.5], respectively); solicited systemic reactions (37.5% [95% CI: 29.6, 45.9] and 32.3% [95% CI: 29.5, 35.1]. Percentages of solicited local and systemic reactions were also similar between Hispanic/Latino and non-Hispanic/non-Latino participants within the age subgroups 9 through 17 years and 18 through 49 years. Unsolicited AEs were reported by

similar percentages (with overlapping 95% CIs) of Hispanic/Latino and non-Hispanic/non-Latino participants 9 through 49 years of age (16.9% [95% CI: 11.2, 23.9] and 16.4% [95% CI: 14.3, 18.7], respectively) as well as within the age subgroups 9 through 17 years and 18 through 49 years. Numbers and percentages of SAEs and MAAEs were also similar but too small to draw meaningful conclusions.

Analyses of safety by priming status showed that solicited reactions within 7 days following vaccination were reported by a lower percentage of participants 9 through 49 years of age who were not vaccinated as compared to participants who were vaccinated in the previous season (44.9% [95% CI: 41.5, 48.3] and 56.6% [95% CI: 51.5, 61.6], respectively), primarily due to lower percentages of solicited injection site reactions in previously unvaccinated participants (34.0% [95% CI: 30.8, 37.2] versus 47.3% [95% CI: 42.2, 52.4], respectively). No meaningful differences between previously vaccinated and previously unvaccinated participants 9 through 49 years of age were observed for unsolicited AEs (16.3% [95% CI: 14.0, 18.9] and 16.1% [95% CI: 12.6, 20.1], respectively), SAEs (0.8% [95% CI: 0.3, 1.6] and 0.8% [95% 0.2, 2.2], respectively), or MAAEs (5.1% [95% CI: 3.8, 6.8] and 4.9% [95% CI: 3.0, 7.5], respectively).

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

On January 16, 2013, Flublok, a trivalent recombinant hemagglutinin influenza (RIV3) vaccine manufactured by Protein Sciences Corporation (PSC), was approved for use in adults 18 through 49 years of age for the active immunization against disease caused by influenza subtypes A and type B contained in the vaccine. On October 29, 2014, the indication was extended to adults 50 years of age and older under accelerated approval regulations (21 CFR 601 Subpart E), based on acceptable safety and immunogenicity data, with a PMR to conduct a study to confirm clinical benefit in this age group. In 2013, due to co-circulation of two influenza B virus lineages, the World Health Organization (WHO) and FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC) recommended the inclusion of a second influenza B vaccine virus antigen in influenza vaccines to provide coverage of both B lineages. Therefore, PSC began clinical development of a quadrivalent formulation (RIV4) with plans to transition manufacturing from Flublok to Flublok Quadrivalent. In accordance with these plans, and because RIV3 and RIV4 are manufactured by the same processes and have overlapping compositions, FDA agreed that the older adult confirmatory study and future pediatric PMRs could be conducted with the quadrivalent formulation containing 45 mcg hemagglutinin (HA) from the influenza virus strains A/H1N1, A/H3N2, B/Victoria lineage, and B/Yamagata lineage.

Flublok Quadrivalent was approved on October 7, 2016 and, since 2016, influenza vaccines available in the U.S. have included both trivalent (TIV or IIV3) and quadrivalent (QIV or IIV4) formulations. However, circulation of B/Yamagata lineage viruses has not been detected since March 2020 and, in the fall of 2023, both WHO and VRBPAC recommended that influenza vaccine manufacturers exclude the B/Yamagata lineage component from IIV4s and transition back to trivalent formulations. The Flublok pediatric PMRs were conducted with the RIV4 formulation. With this supplement, Sanofi Pasteur seeks to extend the indication for both RIV3 and RIV4 to adolescents 9 through 17 years of age based on data from Study VAP00027 (PMR #2). Because Study VAP00026 (PMR #1), conducted in children 3 through 8 years of age, was terminated early for futility, the Applicant does not seek an indication in this age group but has submitted a FSR in fulfillment of PMR #1.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an important infectious disease that causes considerable morbidity and mortality in the U.S. and throughout the world. From 2010 to 2023, the Centers for Disease Control and Prevention (CDC) estimated that influenza caused 9.3 to 41 million illnesses, 100,000-710,000 hospitalizations and 4,900-51,000 deaths. Complications, hospitalizations, and deaths from seasonal influenza disproportionately affect persons ≥65 years, children <5 years, especially those <2 years, and persons of any age with certain underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. Estimates of influenza-associated hospitalizations among children <1 year and 1 through 4 years of age during 1993-2008 were 151.0 and 38.8 per 100,000, respectively. Pediatric mortality due to influenza is <1 per 100,000 per person years. During the 10 most recent influenza seasons up to February 2023, the absolute number of pediatric deaths ranged from 1 (during the 2020-2021 coronavirus disease 2019 [COVID-19] pandemic) to 205 (2023-2024), with a higher number of 358 deaths during the 2009 H1N1 pandemic. Pediatric deaths from influenza may be underestimated because many cases are undiagnosed. The importance of vaccination is reflected in data showing that ~50% of reported deaths have occurred in otherwise healthy children and ~80% have occurred in children who were not fully vaccinated (CDC, 2023a; CDC, 2024a,b).

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and influenza B, cause most human disease. Influenza A is further categorized into subtypes based on two surface antigens, HA and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of influenza A based on combinations of 18 variants of HA and 11 variants of NA, but only subtypes H1N1, H2N2, and H3N2 circulate widely in humans. Influenza A is also isolated from non-human species including birds, horses, and swine. In contrast to influenza A, influenza B is comprised of single HA and NA subtypes and occurs almost exclusively in humans. Antibodies to the immunodominant influenza HA globular head epitopes are subtype and strain-specific and confer protection against future infection with antigenically similar strains, but not against another type or subtype.

Historically, influenza A/H3N2 strains have been associated with higher mortality as compared to the A/H1N1 or B strains. However, the B strain is known to cause serious disease in children. Although influenza B causes ~25% of all clinical disease, 34% of the 309 pediatric deaths reported to the CDC during 2004-2008 and 38% of 115 pediatric deaths reported during the 2010-2011 season were due to influenza B. One case series of autopsies on patients with fatal influenza B infections (including 32 mostly healthy pediatric patients <18 years) demonstrated that the influenza B infections were severe and rapidly progressive, and that 69% of 29 cases with available cardiac tissue were associated with myocardial injury. The authors also observed an age-related difference in complications of influenza B disease. While 82% of deaths in adults ≥18 years were associated with bacterial superinfection, most (90%) of the influenza B deaths in patients <18 years were associated with myocardial injury (McCullers, et al. 2012; Paddock, CD, et al. 2012).

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have co-circulated globally. Seasonal epidemics generally occur during the winter months and are caused by antigenic drift, new antigenic variants or viral strains that result from point mutations in the viral genome that occur during replication. Constant antigenic changes in the viral genome necessitate annual strain changes in the formulation of influenza vaccines for optimal protection. Neutralizing Ab against HA is the primary immune defense against infection with influenza. Although there is no established absolute immune correlate of protection, studies of egg-based influenza vaccines have shown that higher HI titers generally correlate with protection against illness as compared

with lower titers. Some studies have suggested that HI titers of 1:32 to 1:40 may protect against illness in approximately 50% of individuals (de Jong JC, et al., 2003; Fiore AE, et al., 2013; Fox JP, et al., 1982; Goodwin K, et al., 2006; Hobson D, et al., 1972, Treanor JJ, 2015).

The primary mode of controlling influenza disease is immunoprophylaxis. During the 2022-2023 influenza season, CDC estimated that influenza vaccination prevented 6.0 million influenza-related illnesses, 2.9 million healthcare visits, 65,000 hospitalizations, and 3,700 deaths. Because of the potential for serious and life-threatening influenza-related disease, CDC's Advisory Committee on Immunization Practices (ACIP) has, over the last decade, broadened its recommendations for immunoprophylaxis and now recommends influenza vaccination for all persons 6 months of age and older without known contraindications (CDC, 2023b).

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication

Six licensed antiviral agents are available in the U.S. for the treatment of influenza in persons with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive influenza, or are at higher risk for complications. Treatment of persons without severe infection or known risk factors for complications may also be considered if treatment can be initiated within 48 hours of onset or if infection with a novel influenza virus is suspected. Two older adamantane agents, amantadine and rimantadine, are active only against influenza A and are no longer recommended because of widespread resistance. One of three NA inhibitors, oseltamivir is an oral antiviral indicated for the treatment of influenza A and B in persons ≥14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Emergence of resistance during treatment with oseltamivir was a problem for seasonal H1N1 viruses prior to their replacement by the 2009 pandemic H1N1-like strains which are now in circulation and only rarely resistant. Currently, seasonal H3N2 and B strains are also rarely resistant to oseltamivir. Zanamivir, another NA inhibitor, is indicated for treatment of influenza in persons ≥7 years of age and for chemoprophylaxis in persons ≥5 years of age. It is administered as an orally inhaled powder and is associated with bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. It is rarely associated with resistance. The third NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of acute uncomplicated influenza A and B viral infection in persons 6 months of age and older. Adverse effects include diarrhea. Postmarketing reports for NAs have also described serious cutaneous reactions and sporadic transient neuropsychiatric events. Due to concerns for potential emergence of resistance and AEs, NA inhibitors are considered important adjuncts but are not substitutes for vaccination. The sixth antiviral agent for use against influenza is oral baloxavir marboxil, approved for treatment of acute uncomplicated influenza within 2 days of onset in otherwise healthy persons ≥5 years of age or in persons ≥12 years who are at higher risk of complications. Baloxavir is also indicated for post-exposure prophylaxis in persons ≥5 years of age. Emergence of resistance with prolonged use is a potential concern. (CDC, 2023c).

2.3 Safety and Efficacy of Pharmacologically Related Products

Licensed influenza vaccines in the U.S. include: standard dose trivalent and quadrivalent inactivated influenza vaccines (SD-IIV3 and SD-IIV4), a trivalent and quadrivalent recombinant influenza vaccine (RIV3 and RIV4), a trivalent and quadrivalent live-attenuated influenza vaccine (LAIV3 and LAIV4), a trivalent and quadrivalent high dose (HD) inactivated influenza vaccine (HD-IIV3 and HD-IIV4), and an adjuvanted trivalent and quadrivalent inactivated vaccine (aIIV3 and aIIV4). These vaccines are manufactured in eggs or cell culture. Not all licensed products are manufactured and distributed in any given influenza season and, as

mentioned in the introduction to Section 2 of this review, beginning in the 2024-2025 season, only trivalent formulations will be distributed in the U.S.. In the pediatric population, five IIV3 vaccines are available for use in persons 6 months and older [Afluria, Fluarix, Flucelvax, FluLaval, and Fluzone]. Of these, Flucelvax (ccIIV3) is manufactured in cell culture and the other four are manufactured in eggs. LAIV3 (FluMist) is approved in persons 2 years through 49 years of age. In adults, RIV3 (Flublok) is approved in adults ≥18 years of age. HD-IIV3 (Fluzone HD) and aIIV3 (Fluad) are approved for use in adults ≥65 years of age.

Estimates of influenza vaccine effectiveness vary considerably because effectiveness is dependent on many variables, e.g., antigenic match between the vaccine and circulating viruses in a particular season, age and immune status of the study population, study design (randomized controlled trials [RCTs] versus observational), method of diagnosis, and outcome measures (e.g., outpatient illness versus hospitalization or death). In previous seasons, RCTs of laboratory-confirmed influenza estimated vaccine efficacy (VE) in adults 18 through 64 years of age as approximately 60% (Olsterholm, et al., 2012). VE tends to be lower in the elderly and in immunocompromised patients. These populations are also at higher risk for severe disease and complications.

Children <2 years of age are among those at the highest risk for severe complications from influenza. According to CDC, influenza vaccination in children 6 months through 4 years during the 2022-2023 season prevented approximately 622,704 medical visits, 6479 hospitalizations, and 63 deaths. Studies in children who have not received a previous influenza vaccine have shown that receipt of two priming doses are more effective than a single dose. Because of heterogeneity among studies, RCTs in children have shown estimates of VE ranging from ~50% to 90%. Observational studies, conducted by CDC each year in several clinical trial networks across the U.S., use a test-negative design to mitigate against selection bias (CDC Influenza Pages, Burden of Disease and Vaccine Effectiveness). During the 2016-2017 influenza season, CDC estimated VE as 57% (95% CI: 43, 68) in children 6 months through 8 years of age and 36% (95% CI: 15, 52) in children 9 through 19 years. For the 2017-2018 season, estimated VE was 68% (95% CI: 55, 77) in children 6 months through 4 years and 32% (95% CI: 16, 44) in children 5 through 17 years. In a study of children <18 years admitted to intensive care units with acute respiratory illness during the 2019-2020 influenza season, the CDC estimated VE against critical illness as 63% (95% CI: 38, 78), similar across age groups. Effectiveness was 78% (95% CI: 41, 92) against antigenically similar (matched) A/H1N1 viruses, 47% (95% CI: -21, 77) against antigenically dissimilar (mismatched) A/H1N1 subclades, and 75% (95% CI: 37, 90) against mismatched B/Victoria viruses (Olson, et al., 2022). Circulation of influenza viruses decreased sharply with the emergence of the SARS-CoV-2 (COVID-19) pandemic in December 2019. Influenza activity increased following the COVID-19 pandemic and CDC estimated VE in persons of all ages as 46% for the 2022-2023 season. VE was highest in children 6 months through 4 years (53.6% [95% CI: 29.7, 70.7]) and lowest in persons ≥65 years (26.9% [95% CI: 9.5, 45.3]). During the 2024-2025 influenza season, CDC estimated VE against any influenza type or subtype in children and adolescents <18 years of age as ranging from 32% (95% CI: 1, 54) to 60% (95% CI: 56, 63) in the outpatient setting and ranging from 63% (95% CI: 41, 76) to 78% (95% CI: 60, 89). (Frutos, et al., 2025)

Seasonal IIVs licensed in the U.S. have a long history of safety. The most common AEs associated with IIVs are local injection site reactions, e.g., pain, erythema, and induration. These reactions generally occur in >10% of patients, are usually mild to moderate in intensity, and are relatively short in duration (24-48 hours). Systemic symptoms following vaccination, e.g., fever, arthralgia, myalgia, headache, are less common and, in RCTs, often occur at similar percentages as those observed in placebo recipients making causality uncertain.

Uncommon or rare AEs associated with influenza vaccines include neurologic events such as encephalitis, myelitis, and Guillain-Barré syndrome (GBS), and allergic or immediate hypersensitivity reactions, e.g., urticaria or angioedema. The incidence of anaphylaxis following IIV3 has been estimated as 1.35 cases per million doses (95% CI: 0.65, 2.47) (McNeil, et al., 2016; McNeil and DeStephano, 2018; DeStephano, et al., 2023). Evidence suggests that egg-based influenza vaccines are safe to administer to persons who are allergic to eggs, including individuals with a history of anaphylaxis (ACIP, 2024). Conversely, influenza vaccines manufactured without eggs, such as RIV3 and RIV4, have been associated with severe allergic reactions including among persons with previous allergic reactions to egg or to other influenza vaccines (Woo EJ, et al., 2015, 2017, and 2021).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

As of January 31, 2024, cumulative exposure to RIV3 and RIV4 in clinical trials is approximately 4,796 and 7,162 participants, respectively. Licensure of RIV3 in adults 18 through 49 years of age on 16 January 2013 was supported by a clinical trial (PSC04, n=4648) demonstrating VE as compared with placebo. On 29 October 2014, RIV3 received accelerated approval in adults ≥50 years of age based on NI immunogenicity as compared with Fluzone (studies PSC06 [n=602] and PSC03 [n=870]). The relative efficacy of RIV4 in adults ≥50 years of age, as compared with U.S.-licensed IIV4, was demonstrated in Study PSC12 (n=9003) and supported traditional approval in this population. Clinical studies in adults also include PSC01 (n=460), an early Phase 2 study of safety, immunogenicity, and efficacy in adults 18 through 49 years of age, PSC11 (n=2640) a postmarketing safety study of RIV3 in adults ≥50 years of age, and PSC16 (n=1350), a Phase 3 safety and immunogenicity study of RIV4 in adults 18 through 49 years of age. Clinical trial safety data are notable for one case of pleuropericarditis in a 47-year-old male in Study PSC04, that occurred 11 days following vaccination with RIV3. Because the etiology was undetermined, relatedness to RIV3 could not be excluded. Please see the clinical reviews of STN 125285/0, 125285/78 and 125285/194 for additional information regarding the clinical trial experience for RIV3 and RIV4 from studies supporting approval.

In addition to the two clinical trials submitted to this supplement, previous human experience with RIV3 and RIV4 in the pediatric population includes two clinical studies conducted in the U.S., PSC02 and PCS08. PSC02 was a Phase 1/2 dose-finding study conducted in 156 influenza vaccine-naïve children 6 through 59 months randomized to receive two doses of RIV3 or IIV3 (Fluzone) administered 28 days apart. Children were stratified into two age groups, 6 through 35 months and 36 through 59 months. The younger age group (n=115) was randomized 1:1:1 to receive RIV3 at 22.5 mcg or 45 mcg per antigen or IIV3 at 7.5 mcg per antigen. Children 36 through 59 months (n=41) were randomized 1:1 to receive RIV3 at 45 mcg per antigen or IIV3 at 15 mcg per antigen. In children 6 through 35 months of age, low postvaccination HI Ab responses to RIV3, particularly in seronegative children and against the influenza B strain, as compared with IIV3 formed the basis of a waiver to conduct additional studies in this age group. Responses in children 36 through 59 months were deemed sufficient to warrant further clinical evaluation under the Pediatric Research Equity Act (PREA). Please see the clinical review of the STN 125285/0 (Flublok original Biologics License Application [BLA] submission) and the Pediatric Study Plan (PSP) for Flublok Quadrivalent (IND 15784/2, dated October 29, 2013) for additional information. Study PSC08 was originally designed as a Phase 3 PREA PMR in children 6 through 17 years and was later revised as a Phase 2 exploratory immunogenicity and safety study. PSC08 was conducted in 219 children and adolescents 6 through 17 years of age randomized 1:1 to receive RIV4 or IIV4 (non-U.S.-licensed Fluarix Tetra) but was terminated early due to widespread circulation of influenza. Immunogenicity

results were limited by small sample sizes and wide 95% CIs but showed favorable trends towards NI immune responses as compared with IIV4 and supported conduct of a larger Phase 3 trial in this pediatric age population. For additional information, please see the clinical review of the PSC08 CSR (IND 15784/37). A third pediatric clinical non-IND clinical study (LIO-04-16) of the immunogenicity and safety of RIV4 in children 3 through 17 years of age was conducted in Mexico by PSC's business partner, Liomont Laboratories. However, as described later in this review (Section 2.5), the partnership was terminated, and the Applicant was unable to submit a study report for the Center for Biologics Evaluation and Research (CBER)'s review.

Flublok is approved in 37 countries worldwide. In adults 18 years of age and older, the cumulative postmarketing exposure to RIV3 and RIV4 is ~595,412 and ~37,434,227 recipients, respectively. Anaphylaxis is the only identified risk for RIV3 and RIV4. Although the vaccines do not contain egg proteins, allergic reactions requiring medical intervention have been reported following RIV3 and/or RIV4 (Woo, et al, 2015, 2017 and 2021). GBS is a potential risk for RIV3 and RIV4. The Applicant reports that four cases of GBS have been reported in the postmarketing experience for RIV4 but did not meet the Brighton Collaboration level 1 definition.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

January 16, 2013: Flublok was granted traditional approval in adults 18 through 49 years of age based on the demonstration of effectiveness in prevention of culture-confirmed influenza illness and an acceptable safety profile. Approval was associated with two pediatric PMRs, PSC08 in children and adolescents 6 through 17 years of age and PSC14 in children 3 through 5 years of age.

October 29, 2013: PSC submitted an Initial Pediatric Study Plan (iPSP) for RIV4 (IND 15784/2). PMR Study PSC14 was transitioned to a study of RIV4 and PMR Study PSC08 became an exploratory study to inform a new Phase 3 study (PSC17) in persons 6 through 17 years of age.

May 22, 2014: CBER issued an agreed iPSP letter to PSC to conduct a Phase 2 exploratory safety and immunogenicity study, PSC08, in children and adolescents 6 through 17 years of age and a Phase 3 safety and NI immunogenicity study, PSC17, in children and adolescents 6 through 17 years of age. The PMR PSC14, a safety and immunogenicity study in children 3 through 5 years of age, from the approval of Flublok in 2013, was still in place.

February 2, 2016: FDA issued a Release and Replace letter that released PSC from the original Phase 3 PREA PMR (PSC08) and replaced it with a revised exploratory Phase 2 study (PSC08) and a new Phase 3 study (PSC17) in children and adolescents 6 through 17 years of age.

March 9, 2016: The Pediatric Review Committee (PeRC) agreed with the final PSP for RIV4, to conduct PSC 14 and PSC17 in two age groups 3 through 5 years and 6 through 17 years, respectively. However, on March 22, 2016, PSC proposed replacing both NI immunogenicity studies (PSC14 and PSC17) with a single clinical endpoint study (PSC17) to be conducted in Mexico with Liomont Laboratories, a new business partner.

October 7, 2016: Approval of STN 125285/194, efficacy supplement for RIV4 in adults ≥18 years of age. The approval letter released PSC from PMR studies PSC17 and PSC 14 and replaced them with a revised single PMR (PSC17) to evaluate safety, immunogenicity and efficacy in children 3 years through 17 years of age. The FSR was due by June 30, 2020.

November 2017: PSC informed CBER of plans to conduct an immunogenicity study (LIO-04-16) in children 3 through 17 years of age in Mexico (with Liomont Laboratories) to inform the design of a new study of relative efficacy (VAP00004) that would fulfill regulatory requirements in both the U.S. and the EU.

May 7, 2020: STN 125285/433 – PSC/Sanofi submitted a Release and Replace request for PSC17.

July 15, 2020: STN 125285/433 – CBER issued a PMR Release and Replace letter releasing PSC/Sanofi Pasteur from the PSC17 PMR and replacing it with a new PMR to conduct a safety, immunogenicity, efficacy study (VAP00004) in children 3 through 17 years of age. The FSR was due on December 31, 2023.

December 31, 2020: Termination of the partnership between PSC and Liomont Laboratories. Results from Study LIO-04-16 were not available to Sanofi to inform and initiate the PMR Study VAP00004. The COVID-19 pandemic also prevented Sanofi from initiating the study.

June 29, 2021: IND 15784/90. Request for advice regarding release from the PMR VAP00004 and replacement with two new PMR immunobridging and safety studies, in children and adolescents 3 through 8 years of age (VAP00026) and 9 through 17 years of age (VAP00027). On September 24, 2021, CBER provided feedback and asked the Applicant to submit the proposal to STN 125285 for review by PeRC.

October 20, 2021: STN 125285/471 – Sanofi requested release from PMR VAP00004 and replacement with two new PMRs, VAP00026 and VAP00027.

April 5, 2022: PeRC agreed with Sanofi's 20 October 2021 release and replace request.

April 18, 2022: CBER issued a PMR Release and Replace letter. CBER's rationale for releasing the Applicant from the clinical efficacy Study VAP00004 was: "Due to the ongoing COVID-19 pandemic and low rates of influenza virus circulation during the last two seasons, conduct of an efficacy study of Flublok Quadrivalent is infeasible." The FSRs for the new PMRs VAP00027 and VAP00026 were due on December 31, 2023.

October 7, 2022: IND 15784/101. Submission of revised protocols VAP000026 and VAP000027.

April 17, 2023: IND 15784/111. Sanofi request for advice regarding an interim futility analysis for VAP00026 and a Deferral Extension Request (DER) for both VAP00026 and VAP00027 due to challenges in enrollment. CBER provided comments and requested additional information on June 7, 2023.

July 20, 2023: IND 15874/112. Sanofi submitted responses to our June 7, 2023 IR, a revised protocol for VAP00026, and an SAP including details of the futility analysis. CBER provided comments and requested additional information on August 22, 2024.

August 31, 2023: IND 15784/114. Sanofi responded to our IR regarding the SAP, futility analysis, and PPoS for protocol VAP00026.

September 29, 2023: STN 125285/533. Sanofi submitted a DER for PREA PMRs VAP00026 and VAP00027. The DER included key results, the futility analysis and PPoS for VAP00026.

Based on the futility analysis and recommendations from their FIC, Sanofi informed us that they had already terminated VAP00026 and no longer planned a second season of study.

November 7, 2023: PeRC agreed with CBER's recommendation to grant a DER for both VAP00026 and VAP00027 PREA PMRs.

November 13, 2023: CBER issued a Deferral Extension Granted letter for both PMRs due to: 1) delays involving study participants, sites, and/or management and 2) additional time required to prepare the study report and/or submission. New milestone dates for submission of FSRs were extended as follows:

- PMR #1 (VAP00026): from December 31, 2023 to June 30, 2024
- PMR #2 (VAP00027): from December 31, 2023 to May 31, 2024

November 20, 2023: CBER requested additional information on the feasibility of revising study VAP00026 to conduct a second season of study only in the older age subgroup of children 6 through 8 years of age.

December 21, 2023: IND 15784/117. In response to our November 20, 2023 IR, Sanofi reiterated persistent enrollment challenges, noted the low PPoS of 23.2% for meeting primary endpoints in this subgroup, and emphasized the statistical limitations of pursuing post hoc subgroup analyses. Moreover, the Applicant had already terminated the study. In response to the Applicant's request for our agreement with their plan not to seek an indication for Flublok in children 3 through 8 years of age, supervisors suggested the following response which was forwarded to the Applicant on March 29, 2024: "We acknowledge that you have terminated PREA PMR Study VAP00026 and plan to submit a FSR prior to June 30, 2024. After we have reviewed your FSR we will respond to your statement that you do not plan to seek an extension of indication for Flublok in children 3 to 8 years of age".

December 21, 2023: STN 125285/580. Prior Approval Supplement, a labeling supplement for the transition of distribution from RIV4 to RIV3 for the 2024-2025 influenza season. Approved March 4, 2024.

2.6 Other Relevant Background Information

Not applicable.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the protocol was written and conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, U.S. federal regulations, and local ethical and regulatory requirements. These requirements included IRB approval of the protocol and the informed consent of parents and guardians.

Bioresearch Monitoring (BiMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of two clinical study sites representing 13.5% and 8.7% of the total enrollment in Studies VAP00027 and VAP00026, respectively (sites #840010 and #8400013). Inspections at sites #8400010 and #8400013 found no deficiencies that would preclude approval. Please see the BiMO review for details.

3.3 Financial Disclosures

The Applicant provided a list of investigators for the clinical studies submitted to this supplemental Biologics License Application (sBLA) and certified that there were no clinical investigators with disclosable financial interests and/or arrangements. Disclosures for one site (7240018), VAP00026 and VAP00027, were partially incomplete because "yes/no" options for each statement were deleted rather than marked yes or no. The Applicant certified that it did not use the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The sBLA did not contain new Chemistry, Manufacturing and Controls (CMC) information. The CMC review team identified no concerns that would preclude approval, including an issue related to the shipment of blood samples for serologies from the clinical sites (both studies VAP00027 and VAP00026) to the Applicant's central laboratory. Some shipments did not include a temperature thermometer or the temperature indicator in the shipment had not been activated. In response to CMC's September 6, 2024 IR, the Applicant explained that all samples arrived frozen and in good condition and immunogenicity results were deemed reliable. Additionally, because some samples were observed as being hemolyzed at the clinical site, the Applicant conducted a performance assessment and concluded that hemolysis did not affect HI titers. The CMC review team found the Applicant's responses acceptable. After excluding participants with potential temperature excursions and hemolyzed blood samples, the Applicant also performed sensitivity analyses, obtained immunogenicity results consistent with the analyses performed on the original PPAS, and concluded that these events did not impact interpretation of the primary endpoint analyses in either study.

4.2 Assay Validation

The sBLA did not contain new assay validation information.

4.3 Nonclinical Pharmacology/Toxicology

The sBLA did not include new pharmacology/toxicology information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. However, prospective studies have not identified a specific HI titer that predicts protection against laboratory-confirmed influenza illness for either egg- or recombinant

hemagglutinin (rHA)-based vaccines (de Jong, et al, 2003; Patel, et al, 2023; Hobson, et al, 1972; Monto, et al, 2015, Treanor JJ, 2015).

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

Please see the discussion of termination of Study VAP00026 for futility in Sections 6.2.9 and 6.2.11 of this review as well as the statistical review of Study VAP00026. Regarding VAP00026, the statistical reviewer verified the Applicant's primary and secondary analyses and the interim futility analysis (which was conducted on immunogenicity data accumulated after enrolling 26% of the planned study population). The PPoS for achieving the primary objective if the study had been fully enrolled, was <1%, lower than the pre-defined threshold of 20% below which the FIC was to recommend termination for futility. The statistical reviewer verified the primary and secondary immunogenicity analyses for Study VAP00027 and confirmed that the safety analyses for both studies were consistent with the Applicant's report. The statistical review team identified no concerns regarding Study VAP00027 that would preclude approval in individuals 9 through 17 years of age.

4.6 Pharmacovigilance

The PVP reviewer identified no new safety concerns in the data submitted for the two pediatric studies or in postmarketing data and recommended routine pharmacovigilance for risk mitigation. Please see the PVP review for additional information.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The Applicant conducted two pivotal studies, VAP00026 and VAP00027, to support licensure of RIV4 in children and adolescents 3 through 8 years of age and 9 through 17 years of age, respectively. The reviewer evaluated study data for consistency with information included in the proposed package insert (PI). Study designs, endpoints and statistical methods were consistent with CBER guidance for data needed to support the licensure of influenza vaccines and with studies that have supported the licensure of other influenza vaccines in pediatric populations. Because the vaccines are manufactured by the same process and have overlapping compositions, clinical efficacy data for RIV3 are relevant to RIV4. Noninferior immune responses elicited by RIV4 in individuals 9 through 17 years of age as compared with adults 18 through 49 years of age were considered adequate to infer clinical benefit based on the clinical endpoint that supported the licensure of RIV3 in adults 18 through 49 years of age. Relative efficacy data for RIV4 as compared with IIV4 were also used to support licensure of RIV4 in adults ≥50 years of age and are supportive of inferred clinical benefit in the pediatric population 9 through 17 years of age. Because Study VAP00026 was terminated early for futility, the Applicant did not seek an indication in children 3 through 8 years of age. Nevertheless, immunogenicity data were reviewed to confirm the Applicant's conclusions regarding futility. Safety data from VAP00026 were reviewed to identify any safety concerns.

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

- STN 125285/613: May 31, 2024. Modules 1, 2 and 5, including datasets associated with the FSR for VAP00027.
- STN 125285/613.1 (sn0242): June 28, 2024. Modules 1 and 5, financial disclosures and HI assay validation methods.
- STN 125285/613.2 (sn0243): July 22,2024. Module 5, datasets for Study VAP00026.
- STN 125285/613.3 (sn0245): August 1, 2024. Response to July 26, 2024 IR. Module 5, VAP00026 and VAP00027 Analysis Data Reviewer's Guides updated with definitions for all flagged variables in ADaM datasets.
- STN 125285/613.5 (sn0248): August 7, 2024. Responses to July 26, 2024 request for subgroup analyses by age and ethnicity for VAP00026 and VAP00027 and to August 1, 2024 request for Style Sheets for ADaM define.xml.
- STN 125285/613.6 (sn0249): Response to August 20, 2024 IR regarding tables and datasets for VAP00027 and VAP00026 for Medical History and Concomitant Medications. Narrative of antipyretic use and analgesic use for VAP00026.
- STN 125285/613.7 (sn0252): Response to August 26, 2024 IR regarding futility analysis in children 6 through 8 years and comparative analysis to support the applicability of foreign studies to the U.S. population.
- STN 125285/613.8 (sn0253): Response to September 6, 2024 IR regarding VAP00027 Table 14 (Table 8.23), Overview of Safety (clarification of study periods), and for the number and percentage of participants missing all data for 7-day reactogenicity.
- STN 125285/613.9 (sn0255): Partial response to September 6, 2024 IR and September 10, 2024, items #3-#15, regarding the electronic datasets, electronic diary and shipping thermometers.
- STN 125285/613.10 (sn0256): Response to September 6, 2024 request for revised datasets for VAP00026 and VAP00027.
- STN 125285/613.11 (sn0259): Response to October 7, 2024 IR from data analyst and clinical reviewer regarding discrepancies in numbers of participants with solicited AEs in VAP00026 and request for algorithm used to generate VAP00026 Tables 14 and 15 (solicited AEs by severity grade).
- STN 125285/613.12 (sn0260): Response to October 16, 2024 request for updated draft PI following approval of labeling supplement STN 125285/610 on October 15, 2024 (addition of data from a pregnancy registry to Section 8).
- STN 125285/613.13 (sn0261): Response to November 7, 2024 IR regarding VAP00026 FSR Section 5.1.2.2, subanalyses of postvaccination HI titers according to prevaccination status.
- STN 125285/613.14 (sn0265): Response to January 16, 2025 IR regarding subgroup analyses of immunogenicity according to previous vaccination (priming) status and baseline serostatus.
- STN 125285/613.15 (sn0266): Partial response to February 7, 2025 data standards IR.
- STN 125285/613.16 (sn02XX): Final response to February 7, 2025 IR, revised datasets and associated CSR tables for VAP00026 and VAP00027.
- STN 125285/613.17 (sn0272): Revised draft Package Insert.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the two clinical studies submitted to the application.

Table 1. Overview of Clinical Trials

Study ID NCT# Season Location	Design	Population Enrolled	Objectives	Endpoints	Analysis Populations
VAP00027 NCT05513053 NH 2022/2023 USA, Czech Republic, Poland, Spain	Phase 3, non-randomized, open-label, uncontrolled, multicenter trial	Healthy adolescents 9-17 years and adults 18-49 years Total: 1308 9-17 yrs: 648 18-49 yrs: 660	Non-inferior immunogenicity, Safety	Co-primary: HI titer 28 days after the last vaccination, (GMT ratio) and SCR (SCR difference) for each strain. Secondary: %HI ≥1:40 and SCR Secondary: Frequency and severity of solicited AEs (reactogenicity, 7 days), unsolicited AEs (28 days), and SAEs, MAAEs, AESIs (180 days).	Per Protocol Total: 1215 9-17yrs: 609 18-49 yrs: 606 Safety Total: 1299 9-17 yrs: 641 18-49 yrs: 658
VAP00026 NCT05513391 NH 2022/2023 USA, Europe	Phase 3, randomized, observer blind, active controlled, multicenter trial	Healthy children 3-8 years Total: 366 RIV4: 183 IIV4: 183	Non-inferior immunogenicity Safety	Co-primary: HI titer 28 days after the last vaccination (GMT ratio) and SCR (SCR difference) for each strain. Secondary: %HI ≥1:40 and SCR Secondary: Frequency and severity of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), and SAEs/MAAEs/AESIs (180 days).	Per Protocol Total: 318 RIV4: 160 IIV4: 158 Safety Total: 362 RIV4: 181 IIV4: 181

Source: FDA-generated table
Abbreviations: NCT=National Clinical Trials; NH=Northern Hemisphere

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting

CBER did not identify issues that would have required the input of an independent panel of experts and determined that it was not necessary to publicly present the application at a Vaccine and Related Biologics Product Advisory Committee.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

"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"
Study ID: VAP00027
ClinicalTrials.gov identifier: NCT05513053.

6.1.1 Objectives

Primary Objective

To demonstrate the NI HI immune response of quadrivalent recombinant influenza vaccine (RIV4) for the four strains in participants 9 to 17 years of age vs participants 18 to 49 years of age.

Key Secondary Objectives

- Immunogenicity: To summarize the HI immune response induced by RIV4 in all participants.
- Safety: To describe the safety profile of RIV4 vaccine in all participants and by age group.

Exploratory Objective

- To describe the neutralizing Ab response in a subset of participants.

6.1.2 Design Overview

VAP00027 was a Phase 3, non-randomized, open-label, uncontrolled, parallel group, multi-center study to assess the NI immunogenicity and safety of RIV4 in approximately 1337 healthy participants 9 through 49 years of age (667 children and adolescents 9 through 17 years and 667 adults 18 through 49 years of age) in Europe and the U.S. All participants were to receive a single 0.5 mL dose of RIV4, administered IM, on Day 1. Blood for serologies were to be drawn prior to vaccination on Day 1 and at 28 days postvaccination. Safety assessments included collection of immediate reactions for 30 minutes postvaccination, solicited injection site and systemic reactions for 7 days following vaccination (Day 1 through Day 8), unsolicited AEs for 28 days following vaccination (from Day 1 through 29), and SAEs, MAAEs, AESIs and pregnancy data through 6 months postvaccination (Day 1 through Day 181). An independent internal Safety Management Team (SMT) was established to monitor the safety of the study. The SMT performed an Early Safety Data Review (ESDR) of 7-day safety data collected on the first 10% of participants 9 through 17 years of age prior to allowing initiation of vaccinations in the remainder of participants.

VAP00027 was initiated (first participant first visit) on October 27, 2022, and ended (last participant last visit) on October 27, 2023.

6.1.3 Population

Selected Inclusion Criteria

- Nine through 49 years of age
- Non-pregnant, non-lactating individuals
- Individuals of childbearing potential must agree to use effective contraception or abstinence from 4 weeks prior to the first study injection through at least 4 weeks after the last study injection.
- Signed informed consent and pediatric assent, according to local regulations

Selected Exclusion Criteria

- Known or suspected immunodeficiency or receipt of immunosuppressive therapies within six months of enrollment
- Known hypersensitivity to vaccine components
- History of GBS
- Thrombocytopenia, bleeding disorders, or any condition that, in the opinion of the investigator, could pose a health risk or interfere with study evaluations
- Receipt of any vaccine in the 4 weeks preceding the study intervention administration or planned receipt of any vaccine in the 4 weeks following the study intervention administration except for COVID-19 vaccination, which may have been received at least 2 weeks before study intervention
- Previous vaccination against influenza (in the 6 months prior to study intervention administration) with an investigational or marketed vaccine
- Receipt of immune globulins, blood or blood-derived products in the 3 months prior to enrollment

6.1.4 Study Treatments or Agents Mandated by the Protocol

RIV4 solution for injection was supplied in pre-filled syringes containing a single 0.5 mL dose of the NH 2022-2023 season formulation, 45 mcg of HA from four influenza virus strains:

- 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

Excipients and diluent per 0.5 mL dose included: sodium chloride 4.4 mg; monobasic sodium phosphate 0.2 mg; dibasic sodium phosphate 0.5 mg; polysorbate 20 (Tween 20) 27.5 µg; octylphenol ethoxylate (Triton X-100) ≤100 µg; and water for injection.

Batch number: VA030496

6.1.5 Directions for Use

All study participants were to receive a single 0.5 mL dose of RIV4 on Study Day 1, administered IM into the deltoid region of the upper arm.

6.1.6 Sites and Centers

VAP00027 was conducted at 36 sites across the U.S. and Europe. Study sites and the principal investigator for each site are presented in Table 2. Of a total 1308 participants enrolled, study sites in the U.S., Poland, Spain and the Czech Republic included 82.1%, 6.9%, 6.2% and 4.7%, respectively. Please see Table 8.3 and Appendix 16.1.5 of the FSR for additional information.

Table 2. Study Sites, Investigators, and Number of Enrolled Participants*, Study VAP00027**

Site	Investigator	Location	#Enrolled*	Country Total n (%)
2030001	Daniel Drazan	Czech Republic	62	62 (4.74)
6160008	Agnieszka Zielinska	Poland	0	-
6160001	Ernest Kuchar	Poland	0	-
6160003	Oleg Warszalewski	Poland	7	-
6160004	Marek Konieczny	Poland	27	-
6160005	Barbara Pajec	Poland	24	-
6160006	Bernadetta Majorek-Olechowska	Poland	6	-
6160007	Andrzej Galaj	Poland	10	-
6160010	Piotr Korbal	Poland	4	-
6160011	Anna Ploszczuk	Poland	0	-
6160012	Tomasz Zajac	Poland	13	91 (6.95)
7240004	Pablo Rojo	Spain	0	-
7240001	Silvina Laura Natalini Martinez	Spain	42	-
7240002	Ignacio De Los Santos Gil	Spain	0	-
7240003	Belen Ruiz Antoran	Spain	0	-
7240005	Manuel Ramon Baca Cots	Spain	2	-
7240006	Silvia Narejos Perez	Spain	1	-
7240007	Ignacio Salamanca de la Cueva	Spain	15	-
7240008	Maria del Mar Martinez Colls	Spain	0	-
7240010	Victor Del Campo Perez	Spain	0	-
7240013	Maria Garces-Sanchez	Spain	5	-
7240014	Cristina Calvo Rey	Spain	1	-
7240016	Francisco Gimenez Sanchez	Spain	0	-
7240017	Federico Martinon-Torres	Spain	0	-
7240018	Jose Garcia Sicilia Lopez	Spain	15	81 (6.19)
8400001	Todd Bertoch	UT, USA	104	-
8400003	Donald Brandon	CA, USA	64	-
8400004	Laurence Chu	TX, USA	34	-
8400005	Rodrigo Garcia	SC, USA	29	-
8400006	Frank Eder	VT, USA	25	-
8400007	David Ensz	IA, USA	39	-
8400009	Brandon Essink	NE, USA	113	-
8400010	Daniel Finn	KY, USA	94	-
8400011	Charles Harper	NE, USA	44	-
8400012	Scott Striplin/Robert Jeanfreau	LA, USA	90	-
8400013	Jay Meyer	NE, USA	83	-
8400014	Abraham Moskow	SC, USA	63	-
8400015	Banu Myneni	VA, USA	10	-
8400016	Suchet Patel	NY, USA	18	-
8400017	James Peterson	UT, USA	67	-
8400020	Julie Shepard	OH, USA	38	-
8400021	Stacy Slechta	KS, USA	63	-
8400022	Bruce Etheridge	SC, USA	58	-
8400023	Max Hale	AL, USA	14	-
8400024	Ronald Orso	AL, USA	2	-
8400025	Kevin Rouse	AR, USA	22	1074 (82.11)
Total	-	-	1308	1308 (100)

Source: Adapted from STN 125285.613, VAP00027 FSR, Table 8.3, Appendix 16.1.5 and electronic datasets.
*Number of participants in the Enrolled Analysis Set.
**ClinicalTrials.gov identifier: NCT05513053

Applicability of Data from Foreign Study Sites

In response to our request for comparative analyses of demographic and baseline characteristics, safety, and immunogenicity by country to support the applicability of data from foreign study sites to the U.S. population and practice of medicine, the Applicant indicated that, because 82% of participants in Study VAP00027 were from the U.S., the study was highly representative of the U.S. population. Sub-analyses of demographic and baseline characteristics, safety and immunogenicity for the Czech Republic, Poland, and Spain were generally similar as compared with analyses limited to U.S. participants. In the Full Analysis Set (FAS), percentages of male and female participants were similar across countries. Relative to other countries, the U.S. and Spain had more participants 12-17 years of age (36.2% and 31.6%, respectively) than 9-11 years of age (13.9% and 16.5%, respectively) and Spain had more participants 35-49 years of age (41.8%) relative to the other 3 countries (21.4%-27.4%). In the U.S., Black or African American participants comprised 23.3% of the overall study population as compared with no participants of Black or African American origin in the other countries. Spain and the U.S. were the only countries with Latino or Hispanic participants (22.8% and 12.5%, respectively).

Safety analyses among participants 9 through 18 years of age showed similar trends across countries except that Spain had a higher percentage of participants who reported any solicited injection site reaction as compared to the U.S., 60.5% (95% CI: 43.4, 76.0) vs 33.2% (95% CI: 29.1, 37.5). Analyses of immunogenicity did not show clear or consistent differences among countries by vaccine strain or overall. Please see STN 125285/613.7, VAP00027 FSR, Appendix 15 Addendum, for additional information.

> ***Reviewer Comment:*** *Descriptive comparative analyses between the U.S. and non-U.S. countries showed mostly similar results and, because the percentages of participants from non-U.S. countries were much lower as compared with the U.S., suggest that the overall study population adequately represented the U.S. population.*

6.1.7 Surveillance/Monitoring

Informed consent was obtained prior to performing study procedures. For participants 9 through 17 years of age, parents or legal representatives were interviewed to provide or clarify answers to questions and were provided with instructions for completing diaries. Screening included a complete medical history and physical examination, concomitant medications, and a urine pregnancy test prior to vaccination on Day 1/Visit 1. Participants were observed for immediate hypersensitivity reactions and other AEs for 30 minutes following vaccination. Solicited AEs were actively and systematically collected for 7 days following vaccination via a paper or electronic diary. Unsolicited AEs, serious and non-serious, were recorded passively in the diary for 28 days postvaccination. Diaries were reviewed with study staff and collected at the Day 29 visit. A new Memory Aid was distributed on Day 29 to record any additional Unsolicited AEs, SAEs, AESIs and/or MAAEs that occurred over the remainder of the 6-month follow-up period. The Memory Aid was collected at the final study visit on Day 181.

Definitions of AEs and SAEs and reporting requirements were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization.

Solicited injection site reactions included: pain and measured erythema, swelling, induration, and bruising. Solicited systemic reactions included fever (oral temperature measurement),

headache, malaise, myalgia, and chills. Grading scales for recording solicited local and systemic reactions are presented in Tables 3, 4, and 5.

Table 3. Solicited Injection Site Reactions: Severity Grading Scales, Children 9 Through 11 Years of Age, Study VAP00027

CRF Term (MedDRA LLT)	Injection Site Pain	Injection Site Erythema	Injection Site Swelling	Injection Site Induration	Injection Site Bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Intensity scale per CRF*	Grade 1: Easily tolerated Grade 2: discomfort interferes with normal behavior or activities Grade 3: incapacitating, unable to perform usual activities	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm
Intensity scale per Diary card	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	n/a	n/a	n/a	n/a

Source: Modified from STN 125285.613, Module 5, FSR Appendix 1, Protocol VAP00027, Appendix 10.2.5.
Abbreviations: MedDRA LLT=Medical Dictionary of Regulatory Activities, lower-level term; CRF=case report form; mm=millimeters; n/a=not applicable.
*For pain, the scale was provided in the CRF and the intensity transcribed from the diary card. For measured injection site reactions (e.g., erythema and swelling), the classification as Grades 1, 2, or 3 were to be applied at the time of statistical analysis. The actual size of the reaction was to be reported in the CRF.

Table 4. Solicited Injection Site Reactions: Severity Grading Scales, Adolescents and Adults ≥12 Years of Age, Study VAP00027

CRF Term (MedDRA LLT)	Injection Site Pain	Injection Site Erythema	Injection Site Swelling	Injection Site Induration	Injection Site Bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Intensity scale per CRF*	Grade 1: usually transient, may require only minimal therapeutic intervention; does not generally interfere with activities of daily living (ADL) Grade 2: usually alleviated with additional therapeutic intervention;	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm	Grade 1: >0 to <25 mm Grade 2: ≥25 to <50 mm Grade 3: ≥50 mm

CRF Term (MedDRA LLT)	Injection Site Pain	Injection Site Erythema	Injection Site Swelling	Injection Site Induration	Injection Site Bruising
	interferes with ADL, causing discomfort but poses no significant or permanent risk of harm Grade 3: interrupts usual ADL or significantly affects clinical status, or may require intensive therapeutic intervention.				
Intensity scale per Diary card*	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	n/a	n/a	n/a	n/a

Source: Modified from STN 125285.613, Module 5, FSR Appendix 1, Protocol VAP00027, Appendix 10.2.5, Assessment of Intensity.
Abbreviations: MedDRA LLT=Medical Dictionary of Regulatory Activities, lower level term; CRF=case report form; mm=millimeter; n/a=not applicable.
*For pain, the scale was provided in the CRF and the intensity transcribed from the diary card. For measured injection site reactions (e.g., erythema and swelling), the classification as Grades 1, 2, or 3 were to be applied at the time of statistical analysis. The actual size of the reaction was to be reported in the CRF.

Table 5. Solicited Systemic Reactions: Severity Grading Scales, Participants ≥9 Years of Age, Study VAP00027

CRF Term (MedDRA LLT)*	Grade 1	Grade 2	Grade 3
Headache, Malaise, Myalgia, Chills	CRF: Usually transient, may require only minimal therapeutic intervention; does not generally interfere with usual ADLs Diary card: No interference with activity	CRF: Usually alleviated with additional therapeutic intervention; interferes with usual ADLs, causing discomfort but poses no significant or permanent risk of harm. Diary card: Some interference with activity	CRF: Interrupts usual ADLs, or significantly affects clinical status, or may require intensive therapeutic intervention. Diary card: Significant, prevents daily activity
Fever (measured temperature)**	≥38.0°C to ≤38.4°C, or ≥100.4°F to ≤101.1°F	≥38.5°C to ≤38.9°C, or ≥101.2°F to ≤102.0°F	≥39.0°C or ≥102.1°F

Source: Modified from STN 125285.613, Module 5, FSR Appendix 1, Protocol VAP00027, Appendix 10.2.5.
Abbreviations: MedDRA LLT=Medical Dictionary of Regulatory Activities, lower level term; CRF=case report form.
*Corresponding Diary Card terms: headache=headache; malaise=feeling unwell; myalgia=muscle aches and pains; chills=chills; fever=temperature.
**For all reactions (except fever), the scale was provided in the CRF and the intensity transcribed from the diary card. For fever, the body temperature was to be recorded, and the classification as Grade 1, 2, or 3 assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale. The preferred route for measurement of body temperature was oral.

The severity grading scale for unsolicited AEs is presented in Table 6.

Table 6. Unsolicited Adverse Events: Severity Grading Scales, Participants ≥9 Years of Age, Study VAP00027

Unsolicited Adverse Event	Grade 1	Grade 2	Grade 3
MedDRA LLT	CRF: Usually transient, may require only minimal therapeutic intervention; does not generally interfere with usual ADLs Diary card: No interference with activity	CRF: Usually alleviated with additional therapeutic intervention; interferes with usual ADLs, causing discomfort but poses no significant or permanent risk of harm. Diary card: Some interference with activity	CRF: Interrupts usual ADLs, or significantly affects clinical status, or may require intensive therapeutic intervention. Diary card: Significant, prevents daily activity

Source: STN 125285.613, Module 5, VAP 00027 FSR Appendix 1, Protocol VAP00027, Appendix 10.2.5.1.2, Unsolicited AE Intensity Grading Scale.
Abbreviations: MedDRA LLT=Medical Dictionary of Regulatory Activities, lower-level term; CRF=case report form; ADL=activities of daily living.

Adverse Events of Special Interest (AESIs)

The protocol and SAP defined AESIs consistent with the Council for International Organizations of Medical Sciences (CIOMS) Working Group definition, as serious or non-serious AEs of scientific and medical concern specific to the study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Applicant can be appropriate and for which further investigation may be warranted to characterize the event and the safety profile of the product. The protocol specified that AESIs would be captured as SAEs and included: new onset of GBS, encephalitis/myelitis, including transverse myelitis, Bell's palsy, optic neuritis, thrombocytopenia, vasculitis, and anaphylaxis.

Assessment of Relatedness of AEs:

All solicited and unsolicited injection site reactions and all solicited systemic events were considered related to study injections. Relatedness of non-serious AEs were to be assessed by the investigator. SAEs and AESIs were assessed by both the investigator and the Applicant. The Applicant assessment was to be recorded only in the Applicant's Global Pharmacovigilance database.

Definitions of relatedness were pre-specified as follows:

- Not related: The AE is clearly or most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination.
- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

The primary immunogenicity endpoints were:

- Individual HI titer 28 days after vaccination (Day 29)

- Seroconversion, defined as an HI titer <1:10 prior to vaccination on Day 1 and a post-vaccination titer ≥1:40 at Day 29, or a pre-vaccination HI titer ≥1:10 on Day 1 and a ≥4-fold rise in titer at Day 29.

Immunogenicity parameters were calculated for each study group with 95% CIs.

The noninferiority of RIV4 in participants 9 through 17 years of age as compared with adults 18 through 49 years of age was evaluated for GMTs and SCRs. The primary analysis was conducted sequentially, beginning with testing for NI of GMTs and, if successful for all 4 vaccine virus strains, was followed by testing for NI of SCRs.

Noninferiority for GMTs was demonstrated if the LL of the 2-sided 95% CI of the GMT ratio (RIV4 [9 through 17 years] divided by RIV4 [18 through 49 years] at 28 days after vaccination) was >0.667 for each of the 4 vaccine virus strains.

Noninferiority for SCRs was demonstrated if the LL of the 2-sided 95% CI for the difference in SCRs (RIV4 [9 through 17 years] minus RIV4 [18 through 49 years] at 28 days after vaccination) was >-10% for all 4 vaccine virus strains.

The primary endpoint was met if success criteria for NI of both GMTs and SCRs were met for all 4 vaccine virus strains. The PPAS was used for the primary analysis of NI GMTs and SCRs.

Please see the statistical review and the FSR (synopsis, Appendix 1, protocol Section 9, and Appendix 10, SAP) for detailed statistical methodology.

> ***Reviewer Comment:*** *Success criteria for establishing the noninferiority of RIV4 in adolescents relative to the adult comparator group followed FDA Guidance for Industry: Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines, May 2007.*

Secondary Immunogenicity Endpoints

- Individual HI titer prior to vaccination on Day 1 and at 28 days after vaccination (Day 29)
- Detectable HI titer, i.e., ≥1:10 at Day 1 and at 28 days after vaccination
- Individual HI titer ratio: 28 days after vaccination Day 29 / Day 1
- Participants with an HI titer ≥1:40 on Day 1 and at 28 days after vaccination
- Seroconversion at 28 days after vaccination

Secondary immunogenicity parameters were calculated with 95% CIs using descriptive statistics for each study group and age subgroup. Analyses were to be performed on the PPAS provided that the attrition rate from FAS to PPAS was not greater than 10%.

Secondary Safety Endpoints

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after vaccination
- Occurrence of solicited injection site reactions and systemic reactions for 7 days following vaccination, Day 1 up to Day 8), pre-specified in the participant paper or eDiary and in the Case Report Form (CRF).
- Occurrence of unsolicited AEs up to 28 days after vaccination
- Occurrence of MAAEs up to 28 days after vaccination
- Occurrence of SAEs (including AESIs) throughout the study
- Occurrence of AESIs throughout the study

Reviewer Comment: *Although the occurrence of MAAEs up to 28 days postvaccination was a prespecified secondary endpoint, MAAEs were collected through the end of the study and, according to the SAP, analyzed within 28 days after vaccination, from Day 29 to Day 180 after vaccination, and within 180 days after vaccination.*

Unsolicited AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. All safety analyses were descriptive. For solicited reactions, denominators for percentages were the total number of participants who had non-missing data for the endpoint considered. For unsolicited AEs, the denominator was the total number of participants who were vaccinated. The SafAS was the analysis population for safety data.

Exploratory Endpoints

Exploratory endpoints included individual seroneutralization (SN) Ab titers, fold increases, participants with SN Ab titers ≥1:40 at 28 days postvaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the SAP.

The study planned to enroll approximately 1334 participants 9 through 49 years of age (667 participants 9 through 17 years and 667 adults 18 through 49 years of age). To limit bias and allow extrapolation of results, at least 30% of participants 9 through 17 years of age were to be in the 9-11 years age subgroup and the percentage of adults older than 35 years of age was limited to 50%.

Approximately 1200 evaluable participants 9 through 49 years of age (600 persons 9 through 17 years of age [of which ~30% were 9-11 years] and 600 adults 18 through 49 years of age) were planned for the evaluation of immunogenicity. The sample size was calculated to demonstrate NI GMTs with a NI margin of 1.5 and a power of at least 99.6% and NI SCRs with an NI margin of 10% and a power of ~80.10% for 4 vaccine virus strains. The overall study power for demonstrating NI GMTs and SCRs for all 4 vaccine virus strains was estimated as 80.0%.

To demonstrate NI for a total of 8 co-primary GMT and SCR endpoints with an overall power of 80% and type 2 error rate of 20%, and to allow for an attrition rate of ~10%, a total sample size of 1334 participants 9 through 49 years of age was planned for enrollment.

No adjustment was made for multiple comparisons because the sample size and power were calculated based on sequential analyses of eight co-primary endpoints. This was acceptable to the statistical reviewer and review team.

The study was unblinded because the primary objective was to demonstrate NI immunogenicity of RIV4 between participants 9 through 17 years of age and 18 through 49 years of age.

Missing data were not imputed.

The SAP, version 2.0, dated December 6, 2023, pre-specified an IA of immunogenicity and safety on data collected within 28 days following vaccination (through Day 29). A final database lock and final analysis was to be performed after SN data and 6-month follow-up safety data were collected. No adjustment for multiplicity was necessary for the IA because interim

immunogenicity data represented the final analysis of the primary immunogenicity endpoint. All planned analyses following the IA were descriptive.

Changes in the Conduct of the Study or Planned Analyses

- The blood visit window was increased at the statistical analysis level to address operational constraints while maintaining clinical relevance of the readouts. According to the SAP, the Day 29 blood draw window was (-2, 7+) and the PPAS included serology samples drawn from Day 26 to Day 39.
- Recruitment of children and adolescents 9 through 17 years of age was more challenging than recruitment of adults 18 through 49 years of age. Therefore, the last adult was enrolled on January 5, 2023 whereas the last participant 9 through 17 years of age was enrolled on April 28, 2023. To evaluate the impact of the delay in recruitment of participants 9 through 17 years of age, the Applicant performed a complementary analysis of immunogenicity on data collected during the period when participants in both age groups were enrolled (up to January 5, 2023).
- No changes were made after the database lock for the primary endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- Enrolled: All participants with data in the CRF.
- SafAS: Participants who received one dose of study vaccine. Safety data recorded for a vaccine received outside the protocol were to be excluded from the analysis and listed separately.
- FAS: Subset of participants who received one dose of study vaccine and had a post-vaccination blood sample. The analysis of the immune response by the SN assay was performed on participants from FAS who were randomized in the exploratory subset (FAS-SN).
- 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 not done per-protocol
    - Participant did not provide the post-dose serology sample at Visit 2 in the proper time window (Day 26 to Day 39) or a post-dose serology sample was not drawn
    - Participant received a protocol-prohibited medication impacting or that may have had 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.
    - Analysis of the SN response was to be performed on participants in the PPAS who were randomized in the exploratory subset (PPAS-SN).

The number of participants in each analysis set are presented in Table 7 below.

Table 7. Analysis Populations – Enrolled Population, Study VAP00027*

Population	9 to 17 years n (%) N=648	18 to 49 years n (%) N=660	All n (%) N=1308
Planned	667	667	1334
Enrolled	648 (100)	660 (100)	1308 (100)
Full Analysis Set	626 (96.6)	634 (96.1)	1260 (96.3)
Per Protocol Analysis Set	609 (94.0)	606 (91.8)	1215 (92.9)
Safety Analysis Set	641 (98.9)	658 (99.7)	1299 (99.3)
Solicited injection site assessed	618 (95.4)	635 (96.2)	1253 (95.8)
Solicited systemic safety assessed	615 (94.9)	635 (96.2)	1250 (95.6)

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables S1, 5, 6, 8.2, 8.10 and 8.13, and evaluation of the electronic datasets.
Abbreviations: FAS=full analysis set; PPAS=per-protocol analysis set; SafAS=safety analysis set.
*ClinicalTrials.gov identifier: NCT05513053

In accordance with the SAP, because the attrition rate from the FAS to the PPAS was <10%, immunogenicity analyses were performed on the PPAS and not on the FAS.

6.1.10.1.1 Demographics

Table 8 presents demographic and baseline characteristics of the main analysis populations, the PPAS and SafAS, according to age group. The distributions of characteristics were similar across the PPAS, SafAS, and Enrolled Populations (data for the Enrolled Population are not shown but are located in FSR Table 8.14). In the PPAS and SafAS, the mean age of children and adolescents was 13.0 (SD 2.48) years. The mean age of adults was 34.2 (SD 9.20) years. As specified by the protocol, at least 30% (actual 30.9%) of enrolled participants 9 through 17 years of age were in the 9-11 years subgroup and the percentage of adults above 35 years of age was limited to 50% (actual 50.6%). Within each age group (9 through 17 years and 18 through 49 years), the percentages of males and females were balanced. The majority of participants in both age groups were White (77.4%-76.7%) and non-Hispanic or Latino (87.0%-87.1%). Relative to U.S. population estimates for 2023, Black or African American participants were overrepresented and Asians and Hispanics or Latinos were underrepresented.

Table 8. Demographic and Baseline Characteristics (PPAS and SafAS)*, Study VAP00027

Characteristic	PPAS 9-17 yrs N=609	PPAS 18-49 yrs N=606	PPAS 9-49 yrs N=1215	SafAS 9-17 yrs N=641	SafAS 18-49 yrs N=658	SafAS 9-49 yrs N=1299	U.S. Census 2023*
Sex, %	-	-	-	-	-	-	-
Male	51.9	40.6	46.3	52.1	40.1	46.0	49.5
Female	48.1	59.4	53.7	47.9	59.9	54.0	50.5
Mean Age (year) (SD)	13.0 (2.48)	34.1 (9.20)	23.5 (12.5)	13.0 (2.49)	34.3 (9.20)	23.8 (12.6)	-
Age subgroup %	-	-	-	-	-	-	-
9-11 yrs	30.5	-	15.3	30.7	-	15.2	-
12-17 yrs	69.5	-	34.8	69.3	-	34.2	-
18-34 yrs	-	50.0	24.9	-	49.4	25.0	-
35-49 yrs	-	50.0	24.9	-	50.6	25.6	-
Race, %	-	-	-	-	-	-	-
American Indian or Alaskan Native	0.7	0	0.3	0.8	0.2	0.5	1.3
Asian	0.2	1.0	0.6	0.2	0.9	0.5	6.4
Black or African American	23.0	14.9	18.9	24.3	14.9	19.6	13.7

Characteristic	PPAS 9-17 yrs N=609	PPAS 18-49 yrs N=606	PPAS 9-49 yrs N=1215	SafAS 9-17 yrs N=641	SafAS 18-49 yrs N=658	SafAS 9-49 yrs N=1299	U.S. Census 2023*
Native Hawaiian or Pacific Islander	0.2	0.3	0.2	0.2	0.5	0.3	0.3
White	73.4	81.4	77.4	72.1	81.2	76.7	75.3
Not reported	0	0.3	0.2	0	0.3	0.2	-
Unknown	0.2	0.2	0.2	0.2	0.2	0.2	-
Multiple	2.5	2.0	2.2	2.3	2.0	2.2	3.1
Ethnicity, %	-	-	-	-	-	-	-
Hispanic or Latino	17.6	5.8	11.7	17.2	5.8	11.4	19.5
Not Hispanic or Latino	81.1	92.9	87.0	81.4	92.7	87.1	58.4*
Not reported	1.1	1.3	1.2	1.2	1.5	1.4	-
Unknown	0.2	0	<0.1	0.2	0	<0.1	-

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR Tables 7, 8.14 (Enrolled Population), 8.16 (PPAS), and 8.19 (SafAS).
Abbreviations: FSR=final study report; PPAS=per-protocol analysis set; SafAS=safety analysis set.
*U.S. 2020 Census and Quick Facts census estimates for 2023 available at: https://www.census.gov/en.html and https://www.census.gov/quickfacts/, respectively. U.S. Population as of July 1, 2023 was estimated as 334,914,895. Not Hispanic or Latino 2023 estimate is based on the white alone subset.
*ClinicalTrials.gov identifier: NCT05513053

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

A total of 188 (29.0%) enrolled participants in the 9 to 17 years age group and 205 (31.1%) participants in the 18 to 49 years age group were vaccinated with the 2021-2022 seasonal influenza vaccines. Another 2.9% and 1.2%, respectively, reported having laboratory-confirmed influenza illness in the prior influenza season.

> ***Reviewer Comment:*** *The SAP defined previous vaccination status as having received a seasonal influenza vaccine in the last past influenza season or not.*

Medical History

Of a total of 1308 enrolled participants, 778 (59.5%) reported at least one past and current significant medical history: 338 (52.2%) participants in the 9 to 17 years group and 440 (66.7%) participants in the 18 to 49 years group. A total of 701 (53.6%) participants reported ongoing medical conditions at inclusion: 308 (47.5%) in the 9 to 17 years group and 393 (59.5%) in the 18 to 49 years group. The most common (>5%) pre-existing and ongoing medical conditions reported by participants in either age group 9 through 17 years or 18 through 49 years, respectively, as categorized by MedDRA System Organ Class (SOC), were: gastrointestinal disorders (3.7% and 12.3%), immune system disorders (15.9% and 23.3%), infections and infestations (5.8% and 6.2%), metabolism and nutrition disorders (4.7% and 9.9%), musculoskeletal and connective tissue disorders (2.8% and 9.4%), nervous system disorders (6.2% and 11.1%), psychiatric disorders (21.4% and 27.4%), respiratory, thoracic and mediastinal disorders (12.6% and 10.0%), skin and subcutaneous disorders (7.5% and 6.7%), surgical and medical procedures (2.7% and 11.4%), and vascular disorders (0.2% and 9.0%).

The most common (>5%) pre-existing and ongoing conditions in either age group 9 through 17 years or 18 through 49 years, respectively, as categorized by MedDRA Preferred Term (PT), were: drug hypersensitivity (2.3% and 7.9%), seasonal allergy (11.9% and 12.9%), anxiety (6.2% and 15.2%), attention deficit and hypersensitivity disorder (15.1% and 5.6%), depression

(4.5% and 15.8%), asthma (8.6% and 7.0%), and hypertension (0.2% and 8.2%). Obesity was similar between the age groups, 2.3% and 2.7%.

> ***Reviewer Comment:*** *The observed differences in underlying medical conditions were expected given differences in the ages of the two study groups. No large differences in immunocompromising or other conditions that might impact immune responses to vaccination were apparent.*

Concomitant Medications

Reportable concomitant medications were those medications taken prior to vaccination or during the study that may have had an impact on safety (e.g., reducing the intensity or frequency of an AE) and/or immunogenicity (e.g., immunosuppressive or immunomodulating agents). Of 1308 participants in the Enrolled Population, a total of 335 (25.6%) participants reported taking at least one reportable concomitant medication, 18.4% in the 9 to 17 years age group and 32.7% in the 18 to 49 years age group. Concomitant prophylactic medications (e.g., antipyretics, analgesics, or non-steroidal anti-inflammatory drugs) were reported in 10 (1.5%) participants in the 9 to 17 years age group and 24 (3.6%) participants in the 18 to 49 years age group. Prohibited medications (e.g., corticosteroids) were reported in 4 (0.6%) participants in the 9 to 17 years age group and 14 (2.1%) participants in the 18 to 49 years age group.

> ***Reviewer Comment:*** *Summary tables of concomitant medications and the electronic datasets were reviewed. As might be expected, a higher percentage of adults reported concomitant medication use. However, overall use and differences in the use of antipyretics, non-steroidal anti-inflammatory drugs, corticosteroids and immunomodulators were low and unlikely to have significantly impacted the evaluation of immunogenicity or safety assessments.*

6.1.10.1.3 Subject Disposition

Table 9 presents the disposition of participants and analysis populations.

Table 9. Disposition of Participants by Age Group – Enrolled Population, Study VAP00027*

Disposition	9-17 years n (%) N=648	18-49 years n (%) N=660	All n (%) N=1308
Enrolled	648 (100)	660 (100)	1308 (100)
Not vaccinated	7 (1.0)	2 (0.3)	9 (0.7)
Screen failures	5	1	6
Withdrew consent	2	1	3
Vaccinated	641 (98.9)	658 (99.7)	1299 (99.3)
Early termination/Discontinued	19 (2.9)	24 (3.6)	43 (3.3)
AE	0	2 (0.3)	2 (0.2)
Protocol deviation	6 (0.9)	3 (0.5)	9 (0.7)
Withdrawal by subject	2 (0.3)	9 (1.4)	11 (0.8)
Withdrawal by parent or guardian	2 (0.3)	0	2 (0.2)
Lost to follow-up	9 (1.4)	10 (1.5)*	19 (1.4)*
Completed Active Phase Day 29	629 (97.1)	636 (96.3)*	1265 (96.7)*
Completed 6-month follow-up	611 (94.3)	613 (92.9)	1224 (93.6)
Did not complete 6-month follow-up	33 (5.1)	46 (7.0)	79 (6.0)

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR Figure 2, Tables 8.2 and 8.9.
Abbreviations: n=number of participants with specific disposition in the age group; N=denominator for enrolled population in the age group; NCT=National Clinical Trial.
*ClinicalTrials.gov identifier: NCT05513053

**One participant in the 18 through 49 age group was mistakenly counted as lost to follow up during the active phase despite completion of V02 assessments and active phase. This participant was lost-to-follow up at the time of the 6-month follow-up. The table above reflects the actual disposition described in the FSR Section 4.1 and presented in FSR Figure 2. FSR Table 8.9 reflects the uncorrected additional participant 18 through 49 years of age mistakenly counted as lost-to-follow-up during the active phase.

Of a total 1308 participants enrolled, 98.9% and 99.7% of age groups 9 through 17 years and 18 through 49 years were vaccinated. A total of 2.9% and 3.6% of participants in the respective age groups discontinued before completing the active phase of the study (Visit 2/Day 29 follow-up). The primary reason for early termination was lost-to-follow-up, 1.4% and 1.5%, respectively. Two participants, both in the 18 through 49 years age group, discontinued early due to AEs. Please see Section 6.1.12.7 of this review for additional information. Of 1308 enrolled participants, 93.6% completed the 6-month follow-up visit (94.3% and 92.9% of participants in the 9 through 17 years and 18 through 49 years age groups, respectively).

> ***Reviewer Comment:*** *Evaluation of the electronic datasets confirmed the Applicant's report of analysis populations and participant disposition. Overall, 6.4% of participants discontinued the study, approximately half of whom (3.3%) discontinued during the active phase of the study. The overall percentage of participants who terminated early (3.3%) was relatively low, without a large imbalance between the two age groups, and was unlikely to have significantly impacted the interpretation of immunogenicity or safety results.*

Table 10 presents the numbers and percentages of participants with major protocol deviations.

Table 10. Major Protocol Deviations – Enrolled Population, Study VAP00027*

Deviation	9-17 years n (%) N=648	18-49 years n (%) N=660	Total
At least one major deviation	69 (10.6)	86 (13.0)	155 (11.9)
For participants 12 to 49 years of age: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion	0	1 (0.2)	1 (<0.1)
IRT assignment performed prior to participant visit	3 (0.5)	2 (0.3)	5 (0.4)
Lost, nonexistent, missing or incomplete source data	7 (1.1)	2 (0.3)	9 (0.7)
Missing or not provided safety participant's diary/eDiary card	0	1 (0.2)	1 (<0.1)
Other deviation related to Assessments and Procedures	0	3 (0.5)	3 (0.2)
Participant assigned to two participant ID numbers by IRT	0	2 (0.3)	2 (0.2)
Planned sample (blood) not performed within the protocol-specified time window	24 (3.7)	30 (4.5)	54 (4.1)
Planned sample (blood) not performed	10 (1.5)	10 (1.5)	20 (1.5)
Protocol prohibited therapy/medication/vaccine/ administered	4 (0.6)	14 (2.1)	18 (1.4)
Study physical visit, phone call or safety contact not performed	28 (4.3)	33 (5.0)	61 (4.7)

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR Tables 4 and 8.12, and evaluation of electronic datasets.
Abbreviations: IRT=interactive response technology used to assign participant to age group and ID number;
*ClinicalTrials.gov identifier: NCT05513053

A total of 155 participants (11.9%) had at least one major protocol deviation: 69 participants (10.6%) and 86 participants (13.0%) in the 9 to 17 years age group and in the 18 to 49 years age group, respectively. The most frequently reported major protocol deviations were: "Study physical visit, phone call or safety contact not performed" (4.7%), "Planned sample (blood) not

performed within the protocol-specified time window" (4.1%), and "Planned sample (blood) not performed" (1.5%).

> ***Reviewer Comment:*** *Evaluation of the electronic datasets was consistent with the Applicant's report. Major protocol deviations were relatively high in frequency (>10%) in both age groups although no single category of deviation was likely to have a large impact on the primary immunogenicity analyses.*

The number and percentage of participants with at least one protocol deviation leading to exclusion from the FAS and/or the PPAS are presented in Table 11.

Table 11. Immunogenicity Analysis Sets and Criteria for Exclusion, Study VAP00027*

Analysis Set and Reasons for Exclusion	9-17 yrs n (%) N=648	18-49 yrs n (%) N=660	All n (%) N=1308
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 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)
Participant did not meet all inclusion criteria or met at least one exclusion criterion	6 (0.9)	2 (0.3)	8 (0.6)
Preparation and/or administration of vaccine not done per protocol	0	0	0
Participant did not provide post-dose serology sample at visit 2 in proper 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

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables 4, 5, 8.10, and 8.12, and evaluation of the electronic datasets.
Abbreviations: N=number in the Enrolled Population; n=number in the analysis set or fulfilling the exclusion criterion listed, FSR=Final Study Report; yrs=years.
*ClinicalTrials.gov identifier: NCT05513053

Failure to draw the post-dose serology sample or to collect the sample in the protocol-specified time window was the most common protocol deviation leading to exclusion from the PPAS, affecting a total of 78 participants (6.0%), followed by receipt of protocol-prohibited medications impacting or that may have had an impact on the immune response, affecting a total of 18 participants (1.4%), and failure to meet all protocol-specified inclusion criteria or meeting at least one protocol exclusion criterion, affecting a total of 8 participants (0.6%).

> ***Reviewer Comments:*** *Major protocol deviations leading to exclusion from the PPAS were relatively low in frequency in both age groups and unlikely to have had a substantial impact on the primary immunogenicity endpoints.*
>
> *Review of the SDTM CO dataset included 6,401 rows (representing 677 participants) who had comments related to issues with the temperature of serology samples. For example, entries such as "temperature indicator not present in shipment" or "not activated" or "does not conform" affected at least 6320 samples from 662 participants. At least another 60 samples were hemolyzed. These issues also affected samples from VAP00026 and were not reported as deviations or otherwise mentioned in the body of the FSR. On 06 September*

2024, an IR was forwarded to the Applicant requesting an explanation for these events and how they may have impacted the reliability of the immunogenicity results as measured by the HI assay and as reported in the FSR. The Applicant's response (STN 125285/613.9) indicated that all specimens were received frozen and in good condition without evidence of a temperature excursion (i.e., had not thawed). Regarding hemolysis, the Applicant stated that, for some samples, hemolysis occurred at the study site between the time of blood draw and sample decantation after centrifugation. Based on a performance assessment of the HI assay, the Applicant concluded that hemolysis of the samples is not expected to affect HI assay results. Neither the thermometer nor the hemolysis issues were considered protocol deviations. The Applicant also performed sensitivity analyses of the primary immunogenicity objective by excluding all participants who had comments related to malfunctioning shipment thermometers or hemolyzed blood samples and found no statistically significant changes in the results of NI GMTs and SCRs. The results of the sensitivity analyses (STN 125285/613.9, Appendix 1, Tables 1 and 2) were reviewed. This reviewer agrees that the sensitivity analyses do not change the interpretation of the primary endpoint analyses. The CMC review team found the Applicant's responses acceptable and agreed that the thermometer malfunctions and hemolyzed serology samples did not impact interpretation of HI titer results. Please see the CMC review for further information.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The immunogenicity of the study vaccine was assessed at 28 days after vaccination by measuring HI Ab titers to the four virus strains included in the vaccines. Tables 12 and 13 present results of postvaccination HI GMTs, SCRs, and analyses of NI for adjusted GMT ratios and SCR differences for each vaccine virus strain in the 9 through 17 years age group as compared with the 18 through 49 years age group in the PPAS.

Table 12. HI Antibody GMTs and Primary Analysis of Noninferior GMT Ratios at 28 Days after Vaccination with Flublok Quadrivalent in Participants 9 through 17 Years of Age Versus 18 through 49 Years of Age, Per Protocol Analysis Set, Study VAP00027*

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

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables 8 and 8.54
Abbreviations: HI=hemagglutination inhibition; GMT=geometric mean titer; 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 GMT=geometric mean titer; CI=confidence interval; NI=noninferiority; Y=yes
*ClinicalTrials.gov identifier: NCT05513053
**Noninferiority criteria for GMT ratio: lower limit of the 2-sided 95% CI for the GMT ratio 9 through 17 years / 18 through 49 years must be >0.667 for all 4 antigen strains.

Table 13. HI Antibody Seroconversion Rates and Primary Analysis of Noninferior Seroconversion Rates at 28 Days after Vaccination with Flublok Quadrivalent in Participants 9 through 17 Years of Age Versus 18 through 49 Years of Age, Per Protocol Analysis Set, Study VAP00027*

Antigen Strain	SCR % (95% CI) 9-17 years N=609	SCR % (95% CI) 18-49 years N=606	SCR % Difference	95% CI	NI Criteria Met?**
A/H1N1	78.3 (74.8, 81.5)	76.4 (72.8, 79.7)	1.92	(-2.78, 6.62)	Y
A/H3N2	86.5 (83.6, 89.1)	87.1 (84.2, 89.7)	-0.59	(-4.41, 3.23)	Y
B/Victoria	76.8 (73.3, 80.1)	73.6 (69.8, 77.0)	3.29	(-1.57, 8.14)	Y
B/Yamagata	77.2 (73.6, 80.5)	62.9 (58.9, 66.7)	14.3	(9.17, 19.3)	Y

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables 9 and 8.56
Abbreviations: HI=hemagglutination inhibition; SCR=seroconversion rate; 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; CI=confidence interval; NI=noninferiority; Y=yes
*ClinicalTrials.gov identifier: NCT05513053
**Noninferiority criteria for SCR difference: lower limit of the 2-sided 95% CI for the SCR difference 9 through 17 years minus 18 through 49 years must be >-10% for all 4 antigen strains.

Success criteria for NI GMT ratios (LL of the 2-sided 95% CI must be >0.667) and for NI SCR differences (LL of the 2-sided 95% CI must be >-10%) were met for each of the four vaccine antigens. Therefore, the study met the primary immunogenicity endpoint.

> ***Reviewer Comment:*** *Due to temperature excursions and hemolysis of serology samples described in Section 6.1.10.1.3 of this review, the Applicant performed sensitivity analyses. After excluding participants whose blood samples did not include an activated temperature thermometer and those that were hemolyzed from the PPAS (9 through 17 years n=291; 18 through 49 years n=297), the Applicant performed sensitivity analyses of NI immune responses as measured by GMT ratios and SCR differences. Although sample sizes were much smaller and 95% CIs wider, results were consistent with the analyses performed on the original PPAS and did not impact interpretation of the primary endpoint analyses.*

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objective was to summarize HI immune response induced by RIV4 in each participant and by age group in terms of HI titers, GMTs, and SCRs at prior to vaccination on Day 1 and at 28 days postvaccination (Day 29).

HI Antibody Titers

Evaluation of HI GMTs at baseline (Day 1) and Day 29 was conducted on the PPAS overall and by age group. At baseline, GMTs were higher in participants 9 through 17 years of age than in participants 18 through 49 years of age for the A/H1N1 (154 [95% CI: 137, 173] vs 74.9 [95% CI: 65.8, 85.1]), A/H3N2 (111 [95% CI: 95.4, 128] vs 29.0 [95% CI: 25.7, 32.8], and B/Victoria lineage (48.1 [95% CI: 43.0, 53.8] vs 37.3 [95% CI: 34.0, 40.9]) strains, and were similar in both age groups for B/Yamagata lineage strain (272 [95% CI: 243, 305] and 300 [95% CI: 269, 335], respectively).

At Day 29, the HI GMTs increased in both age groups and were higher in participants 9 through 17 years of age than in participants 18 through 49 years of age, respectively, for each virus strain:

- A/H1N1 strain: 1946 (95% CI: 1795, 2109) vs 982 (95% CI: 881, 1094)
- A/H3N2 strain: 1975 (95% CI: 1771, 2202) vs 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) vs 1593 (95% CI: 1477, 1717)

Postvaccination HI titers ≥1:40 at Day 29

The number and percentage of participants in the PPAS who were seropositive (detectable HI titer ≥1:10) and with HI titers ≥1:40 (%HI ≥1:40) at Day 1 and Day 29 are presented in Table 11 of the FSR.

At baseline, the percentages of participants with HI titer ≥1:10 were higher in participants 9 through 17 years of age than in participants 18 through 49 years of age for the A/H1N1 and A/H3N2 strains and were similar in both age groups for B/Victoria and B/Yamagata strains.

At baseline, the %HI ≥1:40 was higher in participants 9 through 17 years of age than in participants 18 through 49 years of age for the A/H1N1 and A/H3N2 strains and were similar in both age groups for the B/Victoria and B/Yamagata strains.

At Day 29, the %HI titer ≥1:40 increased for all 4 virus strains and were high in both age groups (≥95.6% in participants 9 through 17 years of age and ≥95.0% in participants 18 through 49 years of age). Table 14 below shows the percentages of participants with postvaccination HI titers ≥1:40 by age group and virus strain.

Table 14. Percentages of Participants with HI titers ≥1:40 at 28 Days Postvaccination by Age Group and Vaccine Antigen Strain, Per Protocol Analysis Set, Study VAP00027*

Antigen Strain	9-17 years Day 29 %HI ≥1:40 (95% CI) N=609	18-49 years Day 29 %HI ≥1:40 (95% CI) N=606
A/H1N1	99.7 (98.8, 100)	97.5 (96.0, 98.6)
A/H3N2	99.0 (97.9, 99.6)	95.0 (93.0, 96.6)
B/Victoria	95.6 (93.6, 97.1)	97.0 (95.3, 98.2)
B/Yamagata	99.5 (98.6, 99.9)	100 (99.4, 100)

Source: STN 125285/613, Module 5, VAP00027 FSR, Tables 11 and 8.62
Abbreviations: HI=hemagglutination inhibition; 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; CI=confidence interval
*ClinicalTrials.gov identifier: NCT05513053

Seroconversion Rates

HI titer SCRs at Day 29 have been presented in Table 13, Section 6.1.11.1, Analyses of the Primary Endpoint, of this review. SCRs were similar in both age groups for A/H1N1, A/H3N2, and B/Victoria lineage strains and were higher in participants 9 through 17 years of age than in participants 18 than 49 years of age for the B/Yamagata lineage strain.

> ***Reviewer Comment:*** *In both age groups, postvaccination HI GMTs against the B/Victoria strain were notably lower as compared with the other vaccine strains. However, in participants 9 through 17 years, the LL of the 95% CI for the secondary endpoints of % HI*

≥1:40 and SCR for each strain at 28 days postvaccination were >70% and >40%, respectively, for all strains including B/Victoria.

6.1.11.3 Subpopulation Analyses

HI Antibody Titers

Age subgroup analyses conducted in the PPAS showed that, at 28 days postvaccination, GMTs for the age subgroup 9 through 11 years as compared with 12 through 17 years were higher for the A/H3N2 strain, lower for the B/Victoria and B/Yamagata strains, and comparable for the A/H1N1 strain. Postvaccination Day 29 GMTs (95% CI) in participants 9 through 11 years and 12 through 17 years, respectively, were as follows:

- A/H1N1: 2101 (1786, 2472) vs 1881 (1717, 2062)
- A/H3N2: 2550 (2129, 3055) vs 1765 (1543, 2019)
- B/Victoria: 308 (248, 383) vs 456 (402, 517)
- B/Yamagata: 1339 (1101, 1627) vs 2286 (2094, 2496)

Reviewer Comment: *The trend for lower Ab responses to the B strains could possibly be explained by lower rates of previous exposure to influenza B, particularly in younger individuals. However, information regarding prior influenza infection in the study population is unavailable. Additionally, multiple factors may influence the immune response and vaccine effectiveness, e.g., priming by prior exposures or vaccination, antigenic distance between vaccine antigen and prior exposures, preferential boosting dependent on prior exposure ("original antigenic sin"), inherent differences in vaccine antigens, differences in vaccine platforms resulting in mutations and/or glycosylation that impact immunogenicity, and cellular responses that may affect recall Ab responses upon subsequent exposure. The explanation for lower responses to the B strains in this study is not clear and may be multifactorial (Belongia EA, et al, 2017; Khurana S, et al, 2019; Patel MM, et al, 2023).*

Subgroup analyses of postvaccination GMTs conducted in the PPAS by sex did not show meaningful differences between male and female participants. In male and female participants 9 through 17 years of age, respectively, GMTs (95% CIs) at Day 29 for each vaccine strain were as follows:

- A/H1N1: 1908 (1696, 2147) vs 1998 (1781, 2218)
- A/H3N2: 1994 (1702, 2335) vs 1955 (1682, 2272)
- B/Victoria: 386 (331, 451) vs 425 (363, 498)
- B/Yamagata: 1972 (1748, 2225) vs 1909 (1682, 2167).

Postvaccination (Day 29) GMTs in adults 18 through 49 years of age showed similar patterns, i.e., lowest for the B/Victoria strain, but were overall lower than in the younger age cohort.

Subgroup analyses by race conducted in the PPAS did not show meaningful differences in postvaccination GMTs. Among White and Black/African American participants 9 through 17 years of age, respectively, GMTs (95% CIs) at Day 29 were as follows:

- A/H1N1: 1907 (1731, 2100) vs 2079 (1778, 2431)
- A/H3N2: 1851 (1621, 2114) vs 2400 (1982, 2907)
- B/Victoria: 399 (351, 454) vs 418 (334, 523)
- B/ Yamagata: 1907 (1731, 2100) vs 2039 (1664, 2497)

Numbers of participants of Asian, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander origin were too small for meaningful analyses.

Subgroup analyses by ethnicity conducted in the PPAS among participants 9 through 49 years of age, overall or within age subgroups 9 through 17 years and 18 through 49 years, did not show meaningful differences in postvaccination GMTs. Among Hispanic/Latino and non-Hispanic/non-Latino participants 9 through 17 years of age, respectively, GMTs (95% CIs) at Day 29 were as follows:

- A/H1N1: 1840 (1527, 2217) vs 1977 (1807, 2165)
- A/H3N2: 2122 (1665, 2704) vs 1950 (1725, 2204)
- B/Victoria: 404 (307, 532) vs 403 (357, 456)
- B/ Yamagata: 2191 (1863, 2578) vs 1885 (1704, 2086)

Subgroup analyses conducted in the PPAS by priming status showed that, among all participants 9 through 49 years of age, postvaccination GMTs [95% CIs] were higher in participants unvaccinated than in participants vaccinated in the previous season, respectively, for A/H1N1 (1630 [1496, 1776] vs 960 [855, 1077]) and B/Yamagata lineage (1889 [1757, 2030] vs 1502 [1366, 1651]) strains. There were no meaningful differences according to priming status for the A/H3N2 and B/Victoria strains. These trends were also observed within the two age groups. Postvaccination GMTs in previously unvaccinated and previously vaccinated participants 9 through 17 years of age, respectively, are shown below:

- A/H1N1: 2276 (2072, 2501) vs 1351 (1169, 1561)
- A/H3N2: 2054 (1804, 2339) vs 1838 (1502, 2250)
- B/Victoria: 399 (348, 457) vs 422 (348, 512)
- B/Yamagata: 1995 (1785, 2229) vs 1803 (1575, 2064)

Subgroup analyses by baseline serostatus among all participants 9 through 49 years of age in the PPAS showed that postvaccination GMTs [95% CIs] were higher in baseline seropositive (HI titer ≥1:10) participants than in baseline seronegative (HI titer <1:10) participants, respectively, for each strain: A/H1N1 (1550 [1453, 1652] vs 276 [181, 421]); A/H3N2 (1573 [1448, 1709] vs 175 [140, 218]); B/Victoria (364 [338, 392] vs 83.5 [63.1, 110]); and B/Yamagata (1819 [1721, 1922] vs 141 [58.5, 337]). Postvaccination GMTs (95% CI) in baseline seropositive and seronegative participants 9 through 17 years of age, respectively, were as follows:

- A/H1N1: 1989 (1839, 2152) vs 941 (391, 2265)
- A/H3N2: 2518 (2289, 2770) vs 268 (184, 390)
- B/Victoria: 471 (424, 524) vs 68.3 (45.1, 103)
- B/Yamagata: 2076 (1918, 2248) vs 89.0 (37.3, 212)

> ***Reviewer Comment:*** *As compared with previous vaccination history which only captured whether participants received a seasonal influenza vaccination in the last influenza season and, somewhat unexpectedly, showed that previous vaccination was not associated with higher postvaccination GMTs than in previously unvaccinated participants, sub-analyses of immunogenicity according to baseline serostatus did show that seropositive status at baseline was associated with higher postvaccination GMTs. A possible explanation for the disparate results may be that, for the study period, serostatus provided a more accurate picture of the effect of priming on postvaccination GMTs by reflecting a cumulative effect of previous exposures to natural infection and vaccinations.*

Seroconversion Rates

Subgroup analyses of SCRs are described in detail in Section 5.1.2.4 and Appendix 15 Tables 7, 11, 15, 19 and 23 of the FSR.

Analyses of SCRs at Day 29 according to age subgroups (9-11 years of age, 12-17 years of age, 18-34 years of age, and 35-49 years of age) showed no meaningful differences in SCRs among the four age subgroups for the A/H1N1, A/H3N2, B/Victoria lineage strains. The B/Yamagata strain showed a trend toward higher SCRs in participants 9 through 11 years and 12 through 17 years of age as compared with the adult age subgroups. SCRs [95% CIs] at Day 29 between the age subgroups 9 through 11 years and 12 through 17 years, respectively, were comparable and were as follows:

- A/H1N1: 83.9 [77.8, 88.8] vs 75.9 [71.5, 79.9]
- A/H3N2: 86.6 [80.8, 91.1] vs 86.5 [82.9, 89.6]
- B/Victoria: 76.9 [70.2, 82.7] vs 76.8 [72.5, 80.8]
- B/Yamagata: 81.7 [75.4, 87.0] vs 75.2 [70.8, 79.2]

Subgroup analyses of SCRs by sex showed no meaningful differences in either age subgroup. For participants 9 through 17 years of age in the PPAS, SCRs (95% CIs) in males and females, respectively, according to vaccine strain were as follows:

- A/H1N1: 76.6 (71.5, 81.1) vs 80.2 (75.2, 84.6)
- A/H3N2: 85.4 (81.1, 89.1) vs 87.7 (83.4, 91.2)
- B/Victoria: 75.9 (70.8, 80.6) vs 77.8 (72.6, 82.4)
- B/Yamagata: 76.9 (71.9, 81.4) vs 77.5 (72.3, 82.1).

Subgroup analyses of SCRs by race, overall and within both age groups, did not show meaningful differences between White and Black or African American participants. The numbers of participants in other racial subgroups were too small to draw meaningful conclusions. For participants 9 through 17 years of age in the PPAS, SCRs (95% CIs) in White and Black/African American subgroups, respectively, were as follows:

- A/H1N1: 77.4 (73.2, 81.2) vs 80.0 (72.4, 86.3)
- A/H3N2: 86.6 (83.1, 89.6) vs 85.7 (78.8, 91.1)
- B/Victoria: 74.3 (70.0, 78.3) vs 84.3 (77.2, 89.9)
- B/Yamagata: 75.4 (71.1, 79.3) vs 80.7 (73.2, 86.9)

Subgroup analyses by ethnicity conducted in the PPAS among participants 9 through 17 years and 18 through 49 years of age, did not show meaningful differences in postvaccination SCRs. Among Hispanic/Latino and non-Hispanic/non-Latino participants 9 through 17 years of age, respectively, SCRs (95% CIs) at Day 29 were as follows:

- A/H1N1: 69.2 (59.5, 77.7) vs 80.8 (77.0, 84.2)
- A/H3N2: 84.1 (75.8, 90.5) vs 87.2 (84.0, 90.1)
- B/Victoria: 73.8 (64.4, 81.9) vs 77.5 (73.6, 81.1)
- B/ Yamagata: 75.7 (66.5, 83.5) vs 77.7 (73.8, 81.3)

Analyses by priming status showed that for participants 9 through 49 years of age overall and within the age subgroups 9 through 17 years and 18 through 49 years, SCRs were higher in previously unvaccinated than previously vaccinated participants for the A/H1N1, B/Victoria, and B/Yamagata lineage strains. There were no meaningful differences in SCRs according to priming status for the A/H3N2 strain. For participants 9 through 17 years of age in the PPAS, SCRs (95% CIs) in previously unvaccinated and vaccinated participants, respectively, were as follows:

- A/H1N1: 85.2 (81.4, 88.4) vs 62.8 (55.3, 69.9)
- A/H3N2: 86.6 (83.0, 89.7) vs 86.1 (80.2, 90.8)
- B/Victoria: 81.9 (77.9, 85.4) vs 64.4 (57.0, 71.4)
- B/Yamagata: 84.5 (80.7, 87.8) vs 59.4 (51.9, 66.7)

Analyses by baseline serostatus, detectable HI titer ≥1:10 ("seropositive") or undetectable ("seronegative"), among all participants 9 through 49 years of age or within age subgroups 9 through 17 years and 18 through 49 years in the PPAS, did not show meaningful differences in SCRs at 28 days postvaccination. For participants 9 through 17 years of age in the PPAS, SCRs (95% CIs) in baseline seropositive and seronegative participants, respectively, were as follows:

- A/H1N1: 77.8 (74.3, 81.1) vs 94.4 (72.7, 99.9)
- A/H3N2: 85.6 (82.4, 88.5) vs 93.9 (85.2, 98.3)
- B/Victoria: 77.4 (73.7, 80.8) vs 70.8 (55.9, 83.0)
- B/Yamagata: 77.0 (73.4, 80.3) vs 84.6 (54.6, 98.1)

Reviewer Comments: *SCRs showed a general trend to be higher in previously unvaccinated participants as compared to previously vaccinated participants. This could be due to lower HI titers at baseline in the unprimed group, making it easier to achieve a 4-fold rise in titer to at least 1:40. If we apply the same reasoning to serostatus, we might expect participants who were seronegative at baseline to have higher SCRs as compared with baseline seropositive participants. However, sub-analyses of SCRs did not show meaningful differences according to baseline serostatus. As mentioned earlier in this review, other factors such as repeated vaccinations and antigenic distance from prior vaccinations, not evaluated in this study, may influence the immune response. Overall, subgroup analyses of GMTs and SCRs by priming status and baseline serostatus do not show clear patterns or allow us to draw meaningful conclusions.*

In response to our request for comment regarding the low immune responses observed to the B/Victoria vaccine strain, the Applicant stated that, while immunity to influenza B viruses remains understudied, it is generally recognized that immune responses to influenza B viruses are less robust than to influenza A viruses and that lower responses to B/Victoria as compared with the B/Yamagata lineage have been observed in the past, especially in younger age groups. One explanation may relate to inherent properties of B/Victoria antigens that make them less effective in priming immune responses than other lineages. Another explanation is the priming effect of previous exposures that boost immune responses following subsequent exposures. Studies have shown that prior vaccination with a specific strain or antigen results in preferential boosting of that antigen and lower responses to a different antigen with subsequent vaccinations (a phenomenon known as "original antigenic sin"). The Applicant also noted that HI assays vary in sensitivity and may be less sensitive in detecting antibodies against influenza B as compared with influenza A, but did not offer this as an explanation for the lower responses to the B/Victoria versus the B/Yamagata strain observed in Study VAP00027. Regarding Study VAP00027, the Applicant also noted that no differences in GMT responses were observed according to previous vaccination (priming) status whereas postvaccination GMTs were higher in baseline seropositive participants. The Applicant attributed the similarity between HI Ab responses in participants 9 through 17 years and 18 through 49 years of age (noninferiority) to the maturity of the immune system in those age groups as compared with younger children. Low responses to the B/Victoria strain could not be attributed to sex, race, or ethnicity. Factors such as host genetic makeup, obesity, or other underlying conditions were not evaluated in Study VAP00027.

6.1.11.4 Dropouts and/or Discontinuations

Please see Section 6.1.9, Statistical Considerations, and Section 6.1.10.1.3, Subject Disposition, of this review. Dropouts were not replaced. Missing data were not imputed. Overall, of a total of 1308 enrolled participants, 96.7% completed the active phase of the study (Day 29) and 3.3% terminated early, most due to lost-to-follow-up (1.4%). Early discontinuation rates were similar between participants 9 through 17 years and 18 through 49 years of age (2.9% and 3.6%, respectively) and were unlikely to introduce bias or impact interpretation of immunogenicity results. A total of 78 (6.0%) of enrolled participants (5.6% of those 9 through 17 years and 6.4% of those 18 through 49 years of age) were excluded from the PPAS due to not providing the post-dose serology sample or to not providing a sample in the proper time window.

6.1.11.5 Exploratory and Post Hoc Analyses

Results of neutralizing Ab responses are presented in Section 5.1.3 of the FSR and showed similar patterns as observed for HI Ab responses. SN responses were similar between participants 9 through 17 years and 18 through 49 years of age.

6.1.12 Safety Analyses

6.1.12.1 Methods

The SafAS, defined as all participants who received one dose of vaccine, was used to summarize all safety data. The SafAS was comprised of 1,299 participants, including 641 and 658 in the 9 through 17 years and 18 through 49 years age groups, respectively. Denominators for the SafAS were used to calculate percentages of unsolicited AEs, SAEs, AESIs and MAAEs. Within the SafAS, denominators used to calculate percentages of solicited AEs were the number of participants with non-missing data for the relevant endpoint. Overall, 1253 (95.8%) of enrolled participants (618 [95.4%] of those 9 through 17 years and 635 [96.2%] of those 18 through 49 years of age) provided any solicited AE data within the solicited AE period. Please see Section 6.1.7 of this review for additional information regarding methods used to collect and assess safety data for Study VAP00027.

Unsolicited AEs occurring within 28 days after vaccination were pre-specified in the Section 4.2.1.2.3 of the SAP as AEs that occurred with a time of onset between Day 1 and Day 29 and/or missing. An AE with missing time of onset was also considered to have occurred just after vaccination. SAEs, AESIs and MAAEs were analyzed as occurring within 28 days after vaccination, from Day 29 to 180 days after vaccination (Day 181), and within 180 days after vaccination (Day 181).

6.1.12.2 Overview of Adverse Events

Table 15 presents an overview of AEs reported in Study VAP00027.

Table 15. Solicited and Unsolicited Adverse Events Reported through Day 29 and Long-Term Safety through Day 181, SafAS, Study VAP00027*

Adverse Event	9-17 years % N=641	18-49 years % N=658	All % N=1299
Immediate unsolicited AE within 30 minutes after vaccination	0.2	0	<0.1
Immediate unsolicited adverse reaction	0	0	0
Any solicited reaction**	44.3	53.1	48.8
Grade 3 solicited reaction**	6.5	4.6	5.5
Missing all solicited AE data	3.6	3.5	3.5

Adverse Event	9-17 years % N=641	18-49 years % N=658	All % N=1299
Any solicited injection site reaction**	35.6	40.8	38.2
Grade 3 solicited injection site reaction**	3.1	1.4	2.2
Missing all solicited injection site reaction data	3.6	3.5	3.5
Any solicited systemic reaction**	29.6	36.4	33.0
Grade 3 solicited systemic reaction**	4.6	3.1	3.8
Missing all solicited systemic reaction data	4.1	3.5	3.8
Within 28 days after vaccination	--	--	--
Unsolicited AE	14.5	17.9	16.2
Unsolicited AR	4.7	3.8	4.2
AE leading to discontinuation	0	0.3	0.2
SAE	0.2	0.8	0.5
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	4.2	5.3	4.8
During 6-month follow-up period***	--	--	--
SAE	0.3	0.3	0.3
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	0.5	0.5	0.5
AE leading to discontinuation	0	0	0
During the study***	--	--	--
SAE	0.5	1.1	0.8
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	4.5	5.6	5.1
AE leading to discontinuation	0	0.3	0.2

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables 14, 15, 8.23, 8.24 and evaluation of the electronic datasets, and Amendment 125285/613.8, and Amendment 125285/613.16 FSR Tables 8.23 and 8.24.
Abbreviations: SafAS=safety analysis set; AE=adverse event; AR=adverse reaction; SAE=serious adverse event; AESI=adverse event of special interest; MAAE=medically attended adverse event.
*ClinicalTrials.gov identifier: NCT05513053
**Solicited injection site and systemic adverse reactions were all considered related to study vaccine and were collected during the 7 days following vaccination (Day 1 through Day 8). Denominators for Solicited Adverse Reactions safety subsets were used to calculate the percentages of solicited ARs and represented the number of participants who had non-missing data for the relevant endpoint. Non-missing data for solicited reactions included any of the following reactions: None/No presence; Grade 1; Grade 2; and Grade 3. Denominators for both analysis sets for Any Solicited Adverse Reaction and Any Solicited Injection Site Reaction were: Overall n=1253; 9 through 17 yrs n=618; and 18 through 49 yrs n=635. Denominators for the analysis set for Any Solicited Systemic Adverse Reaction were: Overall n=1250; 9 through 17 yrs n=615; 17-49 yrs n=635.
***For long-term safety (SAEs, AESIs, and MAAEs), numbers and percentages of participants with events collected during the 6-month follow-up period represents the interval from Day 29 through the end of the study (Day 181). The period labeled "during the study" represent the number and percentages of participants with events collected within 28 days following vaccination and during the 6-month follow-up period (Day 1 through Day 181). Two participants (ID (b) (6) and (b) (6)) had unique MAAEs in both periods Day 1-Day28 and Day 29-Day 181.

> ***Reviewer Comment:*** *In amendment STN 125285/613.8, the Applicant clarified that, although "6-month follow-up" is defined in the protocol study design, SAP, dataset epoch and Reviewer Guides, and dataset define.xml files, as including Day 1 through Day 181, in FSR Tables 14 and 8.23 (and Table 15 above), "During the 6-month follow-up period" represents Day 29 through Day 181 and "During the Study" represents Day 1 through Day 181.*

Overall, fewer participants 9 through 17 years of age experienced solicited local or systemic reactions (35.6% and 29.6%, respectively) as compared with participants 18 through 49 years of age (40.8% and 36.4%, respectively). Within 28 days after vaccination, unsolicited AEs were

also reported by fewer participants 9 through 17 years of age as compared to 18 through 49 years of age (14.5% vs 17.9%). Within 180 days after vaccination, percentages of SAEs and MAAEs were low (0.8% and 5.1%, respectively) across both age groups. No deaths or AESIs were reported during the study. Two participants, both in the age group 18 through 49 years, had AEs leading to discontinuation: one 45-year-old female had Grade 3 injection site erythema, induration, swelling and bruising and Grade 2 urticaria on Day 3 postvaccination; and one 29-year-old male had an intentional overdose on Day 8 postvaccination.

> ***Reviewer Comment:*** *Evaluation of the electronic datasets yielded numbers and percentages of solicited AEs, unsolicited AEs, and SAEs consistent with the Applicant's report.*

Solicited Local Injection Site Reactions

Table 16 summarizes the percentages of solicited local injection site reactions reported in the seven days following vaccination (Day 1 through Day 8) by age, overall, and Grade 3 severity.

Table 16. Percentages of Solicited Local Injection Site Reactions within 7 Days following Vaccination by Age Group, SafAS, Study VAP00027*

Solicited Injection Site Reaction	9-17 yrs Any N=641 %	9-17 yrs Grade 3 N=641 %	18-49 yrs Any N=658 %	18-49 yrs Grade 3 N=658 %	All Any N=1299 %	All Grade 3 N=1299 %
Pain	34.4	0.8	40.2	0.3	37.3	0.6
Erythema	4.5	1.1	2.7	0.5	3.6	0.8
Swelling	3.7	1.5	2.7	0.5	3.2	1.0
Induration	3.1	0.8	3.3	0.8	3.2	0.8
Bruising	2.4	0.5	1.1	0.5	1.8	0.5

Source: Modified from STN 125285.613, Module 5, VAP00027 FSR, Tables 16 and 8.27 and Amendment 125285/613.16 FSR Tables 8.25.
Abbreviations: SafAS=Safety Analysis Set; All=All participants with any non-missing data for solicited injection site reactions; Any=any participant with non-missing data for the specified injection site reaction;
*ClinicalTrials.gov identifier: NCT05513053
Grade 3 pain (9 to 11 years): Incapacitating, unable to perform usual activities; significant; prevents daily activity. Grade 3 erythema, swelling, induration and bruising (9 to 11 years): ≥50 mm
Grade 3 pain (≥12 years): Defined as significant; intensive therapeutic intervention; prevents daily activity
Grade 3 erythema, swelling, induration and bruising (≥12 years): ≥100 mm
Denominators for Solicited Adverse Reactions safety subsets were used to calculate the percentages of solicited ARs and represented the number of participants who had non-missing data for the relevant endpoint. Non-missing data for solicited reactions included any of the following reactions: None/No presence; Grade 1; Grade 2; and Grade 3. Denominators for 9 through 17 years: Any injection site reaction=618; pain=617; erythema, swelling, induration and bruising=618. Denominators for 18 through 49 years: Any injection site reaction, pain, erythema, swelling, induration and bruising=635. Denominators for All (9 through 49 years): Any injection site reaction, erythema, swelling, induration, and bruising=1253; injection site pain=1252.

A total of 1253 participants (618 and 635 participants 9 through 17 years and 18 through 49 years of age, respectively) provided data for solicited injection site reactions. Injection site pain was the most frequently reported solicited local reaction in participants 9 through 17 years and 18 through 49 years of age (34.4% and 40.2%, respectively). Other solicited injection site reactions occurred in <5% and <1% of participants in the respective age groups. Most reactions were Grade 1 (mild) or Grade 2 (moderate) in severity, began within four days following vaccination, and resolved spontaneously within 1-3 days. Grade 3 reactions occurred in ≤1.5% of participants 9 through 17 years of age and in <1% of adults 18 through 49 years of age.

Solicited Systemic Adverse Reactions

Table 17 summarizes the percentages of solicited systemic adverse reactions reported in the seven days following vaccination (Day 1 through Day 8) by age, overall, and Grade 3 severity.

Table 17. Percentages of Solicited Systemic Adverse Reactions within 7 Days following Vaccination by Age Group, SafAS, Study VAP00027*

Solicited Systemic Adverse Reaction	9-17 yrs Any N=641 %	9-17 yrs Grade 3 N=641 %	18-49 yrs Any N=658 %	18-49 yrs Grade 3 N=658 %	All Any N=1299 %	All Grade 3 N=1299 %
Myalgia	19.3	1.5	20.3	0.9	19.8	1.2
Headache	18.5	2.6	23.0	1.3	20.8	1.9
Malaise	16.1	2.6	16.5	1.6	16.3	2.1
Chills	7.3	0.7	6.3	0.6	6.8	0.6
Fever	2.8	1.0	1.7	0.5	2.3	0.7

Source: Modified from STN 125285.613, Module 5, VAP00027 FSR, Tables 17 and 8.33, and Amendment 125285/613.16 FSR Table 8.25 and 8.33.
Abbreviations: SafAS=Safety Analysis Set; All=All participants with any non-missing data for solicited systemic adverse reactions; Any=any participant with non-missing data for the specified systemic adverse reaction;
*ClinicalTrials.gov identifier: NCT05513053
Grade 3 myalgia, headache, malaise and chills: Defined as significant; intensive therapeutic intervention; prevents daily activity.
Grade 3 fever: ≥101.2℉ (≥39.0℃)
Denominators for Solicited Adverse Reactions safety subsets were used to calculate the percentages of solicited ARs and represented the number of participants who had non-missing data for the relevant endpoint. Non-missing data for solicited reactions included any of the following reactions: None/No presence; Grade 1; Grade 2; and Grade 3. Denominators for 9 through 17 years: Any systemic adverse reaction, myalgia, headache, malaise, and chills=615; fever=608. Denominators for 18 through 49 years: Any systemic adverse reaction, myalgia, headache, malaise, and chills=635; fever=633. Denominators for All (9-49 years): Any systemic adverse reaction, myalgia, headache, malaise, and chills=1250; fever=1241.

A total of 1250 participants (615 and 635 participants 9 through 17 years and 18 through 49 years of age, respectively) provided data for solicited systemic adverse reactions. Percentages of events were similar between age groups. In participants 9 through 17 years of age, the most frequently reported solicited systemic reactions (>10%) were myalgia (19.3%), headache (18.5%) and malaise (16.1%). In participants 18 through 49 years of age, the most frequently reported solicited systemic reactions were headache (23.0%), myalgia (20.3%), and malaise (16.5%). Fever occurred in 2.8% and 1.7% of participants 9 through 17 years and 18 through 49 years of age, respectively. Most reactions were Grade 1 (mild) or Grade 2 (moderate) in severity, began within 4 days following vaccination, and resolved spontaneously within 1-3 days.

A total of 28 participants (4.6%) 9 through 17 years of age reported at least 1 Grade 3 solicited systemic reaction within 7 days following vaccination, predominantly headache and malaise, each reported by 16 participants (2.6%). A total of 20 participants (3.1%) 18 through 49 years of age reported at least 1 Grade 3 solicited systemic reaction within 7 days following vaccination, predominantly malaise (1.6%) and headache (1.3%). Grade 3 fever occurred in 6 (1.0%) and 3 (0.5%) participants 9 through 17 years and 18 through 49 years of age, respectively.

> ***Reviewer Comments:*** *As noted in Section 6.1.10.1.2 of this review, the use of concomitant prophylactic medications (e.g., antipyretics, analgesics, or non-steroidal anti-inflammatory drugs) was low in both age groups and was unlikely to have had a large impact on interpretation of solicited reactogenicity data.*
>
> *Percentages of solicited AEs appeared acceptable in both age groups and were similar to rates observed following vaccination with other approved influenza vaccines. Evaluation of the electronic datasets for numbers of participants who reported any solicited AE and Grade 3 solicited AEs according to specific parameters and age group was consistent with the Applicant's report. The datasets confirmed that a total of 46 (3.5%) participants in the* SafAS *had no solicited AE data recorded in the e-Diary or CRF and were reported as missing all solicited AE data for the 7-day solicited AE period.*

Unsolicited Adverse Events (Day 1 through Day 29)

Unsolicited AEs that began following exposure to study treatment were included in the analyses of unsolicited AEs. AEs were coded according to MedDRA PT and SOC, version 26.1. Please see Table 15 at the beginning of Section 6.1.12.2 for an overview of unsolicited AEs and FSR Tables 18, 19, 8.39, 8.40, 8.41, 8.42 and 8.43 for detailed summaries of AEs by PTs and SOCs reported in each age group.

Immediate Unsolicited Adverse Events

One participant in the SafAS (<0.1%) experienced an unsolicited AE in the 30 minutes following vaccination. The participant, in the 9 through 17 years age group, had a Grade 1 (mild) AE of epistaxis that was assessed as not related to study vaccine by the investigator.

Unsolicited Adverse Events with 28 Days

Unsolicited AEs experienced by ≥1% of participants in either age group within 28 days following study injection are presented in Table 18 according to MedDRA SOC and PT.

Table 18. Percentages of Unsolicited Adverse Events Occurring in ≥1% of Participants Within 28 Days Following Vaccination by Age Group and MedDRA System Organ Class and Preferred Term, SafAS, Study VAP00027*

Unsolicited AE	9-17 yrs n (%) N=641	18-49 yrs n (%) N=658	All n (%) N=1299
Any unsolicited AE	93 (14.5)	118 (17.9)	211 (16.2)
Gastrointestinal disorders	16 (2.5)	13 (2.0)	29 (2.2)
Diarrhea	3 (0.5)	8 (1.2)	11 (0.8)
General disorders and administration site conditions	14 (2.2)	11 (1.7)	25 (1.9)
Infections and infestations	31 (4.8)	49 (7.4)	80 (6.2)
Upper respiratory tract infection	7 (1.1)	22 (3.3)	29 (2.2)
Nervous system disorders	4 (0.6)	14 (2.1)	18 (1.4)
Headache	2 (0.3)	7 (1.1)	9 (0.7)
Respiratory, thoracic and mediastinal disorders	26 (4.1)	29 (4.4)	55 (4.2)
Cough	11 (1.7)	8 (1.2)	19 (1.5)
Nasal congestion	5 (0.8)	11 (1.7)	16 (1.2)
Oropharyngeal pain	10 (1.6)	11 (1.7)	21 (1.6)
Rhinorrhea	7 (1.1)	8 (1.2)	15 (1.2)

Source: Modified from STN 125285.613, Module 5, VAP00027 FSR, Tables 18 and 8.39 and Amendment 125285/613.16 FSR Table 8.39.
*ClinicalTrials.gov identifier: NCT05513053
Abbreviations: SafAS=Safety Analysis Set; All=All participants 9 through 49 years of age in the SafAS; AE=adverse event; Any=any occurrence of an unsolicited AE from Day 1 through Day 29.

A total of 211 participants (16.2%), including 93 (14.5%) participants 9 through 17 years and 118 (17.9%) adults 18 through 49 years of age, reported a total of 322 unsolicited AEs in the 28 days following vaccination. The most frequently (≥1%) reported events in the 9 through 17 years and 18 through 49 years age groups, respectively, as categorized by SOC were: gastrointestinal disorders (2.5% vs 2.0%), general disorders and administration site conditions (2.2% vs 1.7%), infections and infestations (4.8% vs 7.4%), nervous system disorders (0.6% vs 2.1%), and respiratory, thoracic and mediastinal disorders (4.1% vs 4.4%). The most frequently (≥1%) reported AEs as categorized by PT were: diarrhea (0.5% vs 1.2%), upper respiratory tract infection (1.1% vs 3.3%), headache (0.3% vs 1.1%), nasal congestion (0.8% vs 1.7%), oropharyngeal pain (1.6% vs 1.7%), and rhinorrhea (1.1% vs 1.2%).

Severe (Grade 3) Unsolicited Adverse Events

Most unsolicited AEs were mild to moderate in intensity (Grade 1 or 2). A total of 24 (1.8%) participants, 10 (1.6%) participants 9 through 17 years of age and 14 (2.1%) participants 18 through 49 years of age, experienced a total of 35 severe (Grade 3) unsolicited AEs. The Grade 3 unsolicited AEs reported most frequently (≥1%) were 20 AEs categorized in the MedDRA SOC of General Disorders and Administration Site Conditions, reported by 20 participants (9 [1.4%] and 11 [1.7%] participants 9 through 17 years and 18 through 49 years of age, respectively). All were considered related to study injection. Of the 14 Grade 3 unsolicited AEs considered not related to study injection, 4 events occurred in 3 (0.5%) participants 9 through 17 years of age, including influenza, upper respiratory tract infection, and suicidal ideation (which occurred on two separate occasions). Ten Grade 3 unsolicited AEs considered not related to study injection occurred in 10 (1.5%) participants 18 through 49 years of age, including gastroenteritis, pharyngitis streptococcal, influenza, viral infection, intentional overdose, overdose, gastric cancer recurrent, seizure, major depression, and acute respiratory failure.

Within 28 days of vaccination, among all participants, a total of 8 (0.6%) reported 10 AEs for which the severity grade was missing. Of the 4 participants with AEs occurring within 7 days following vaccination, 3 appeared related to the injection site (pruritus and rash). The other events appeared unrelated to vaccination. Viewed another way, 13 (3.81%) of all 341 AEs categorized as unsolicited and reported during the entire study period had missing data for severity grade and 10 (3.08%) of 324 AEs categorized as unsolicited and reported within 28 days of vaccination had data missing for severity grade.

A total of 55 (4.2%) participants, including 30 (4.7%) participants 9 through 17 years of age and 25 (3.8%) participants 18 through 49 years of age, had unsolicited AEs assessed by the investigator as related to study vaccine, also called adverse reactions (ARs). Most ARs were categorized as general disorders and administration site conditions, occurring in 1.7% and 1.1% of participants 9 through 17 years of age and 18 through 49 years of age, respectively, or as respiratory, thoracic and mediastinal disorders, occurring in 1.7% and 1.5%, respectively. Of the 55 participants assessed as having related AEs, 7 (1.1%) participants 9 through 17 years of age and 6 (0.9%) participants 18 through 49 years of age had a total of 21 related AEs assessed as severe (Grade 3) in intensity. Of the 21 unsolicited AEs assessed as Grade 3 and related, 20 events were injection site reactions (e.g., bruising, induration, swelling and/or erythema), 1 event was nausea. One 45-year-old participant with related Grade 3 injection site bruising, redness, induration, and swelling on Day 3 also had Grade 2 hives (urticaria) on Day 2, assessed as related by the investigator, and was discontinued (see Section 6.1.12.7 of this review). One 10-year-old participant had a Grade 2 unsolicited AE of exacerbation of asthma on Day 2 postvaccination, assessed as related, and recovered after 3 days. No ARs were assessed as serious.

> ***Reviewer Comment:*** *The Applicant provided brief descriptions of Grade 3 unsolicited AEs and more extensive narratives for those which were also assessed as serious (described later in this review). Evaluation of the electronic datasets showed that the types, percentages, intensities, and assessment of relatedness of unsolicited AEs, including Grade 3 AEs, were consistent with the Applicant's report.*

Among participants 9 through 17 years of age, 5.9% had unsolicited AEs that began within 4 days of vaccination (Day 1 through Day 4) and 4.1% had AEs with an onset on Day 16 or later. Time of onset showed similar patterns in participants 18 through 49 years of age. Among

participants 9 through 17 years of age, the duration of unsolicited AEs was 1-3 days (5.6%), 4-7 days (3.9%), or ≥8 days (4.2%). A larger percentage (7.3%) of participants 18 through 49 years of age had unsolicited AEs ≥8 days in duration but duration of AEs was otherwise comparable to the younger age group.

Medically Attended Adverse Events (MAAEs)

A total of 66 (5.1%) participants, 29 (4.5%) of participants 9 through 17 years and 37 (5.6%) of participants 18 through 49 years of age reported MAAEs during the study. Most participants, 4.2% and 5.3% in the respective age groups, reported MAAEs within 28 days of vaccination. No MAAEs were considered related to study vaccine by either the investigator or the Applicant.

> ***Reviewer Comment:*** *MAAEs were reviewed and appeared unrelated to study vaccination. A total of 46 of 86 MAAEs (occurring in 40 of 66 participants overall), were categorized in the SOC of Infections and Infestations. Evaluation of the electronic dataset was consistent with the Applicant's report.*

Subgroup Analyses of Safety

Subgroup analyses of the overview of safety were conducted on the SafAS according to age subgroups (9-11 years, 12-17 years, 18-34 years, and 35-49 years), sex, race, ethnicity, and previous influenza vaccination status.

The overall percentages of solicited and unsolicited AEs and long-term safety (SAEs, AESIs and MAAEs) were similar (with overlapping 95% CIs) across age subgroups except for the percentages of solicited injection site reactions within 7 days following vaccination which were slightly higher in participants 9 through 11 years of age as compared to participants 12 through 17 years of age (43.2% [95% CI: 36.0, 50.7] and 32.3% [95% CI: 27.9, 37.0], respectively).

Analyses by sex showed that among all participants 9 through 49 years of age, lower percentages of male participants reported any solicited injection site or systemic reactions within 7 days following vaccination as compared with female participants (42.3% [95% CI: 38.2, 46.4] versus 54.1% [50.3, 57.9], respectively). Solicited injection site reactions were reported in 32.2% [95% CI: 28.4, 36.2] of male participants and 43.4% [95% CI: 39.6, 47.2] of female participants, and solicited systemic reactions were reported in 28.8% [95% CI: 25.2, 32.7] of male participants and 36.4% [95% CI: 32.8, 40.2] of female participants. Similar patterns were observed within each age subgroup of participants 9 through 17 years of age and 18 through 49 years of age. Unsolicited AEs were reported by lower percentages of male participants than in female participants 9 through 49 years of age (12.7% [95% CI: 10.1, 15.6] versus 19.4% [95% CI: 16.5, 22.5], respectively) with similar patterns observed within age subgroups. Lower percentages of male than female participants reported SAEs (0.3% [95% CI: 0, 1.2] vs 1.1% [95% CI: 0.5, 2.2]) and MAAEs (3.2% [95% CI: 1.9, 4.9] vs 6.7% [95% CI: 5.0, 8.8]).

Analyses by race in all participants 9 through 49 years of age showed that all solicited reactions within 7 days following vaccination were reported in higher percentages of White participants than in Black or African American participants (53.0% [95% CI: 49.8, 56.2] and 31.0% [95% CI: 25.1, 37.4], respectively). Solicited injection site reactions and systemic reactions were also reported in higher percentages of White as compared with Black or African American participants (41.9% [95% CI: 38.8, 45.1] versus 24.5% [95% CI: 19.0, 30.5] and 35.3% [95% CI: 32.3, 38.4] versus 22.6% [95% CI: 17.3, 28.6], respectively). Similar trends in higher percentages of solicited local and systemic reactions in White participants as compared with Black or African American participants were observed in the age subgroups 9 through 17 years

and 18 through 49 years of age. Unsolicited AEs also occurred in higher percentages of White as compared with Black or African American participants (18.2% [95% CI: 15.8, 20.7] versus 10.2% [95% CI: 6.8, 14.6]). Numbers and percentages of SAEs (0.9% [95% CI: 0.4, 1.7] and 0 [95% CI: 0, 1.4] and MAAEs (5.6% [95% CI: 4.3, 7.2] and 2.8% [95% CI: 1.1, 5.6] reported in White and Black or African American participants, respectively, were too small to make meaningful comparisons. The numbers of Asian (n=7), American Indian or Alaskan Native (n=6), Native Hawaiian or other Pacific Islander (n=4), and mixed origin (n=28) participants were too small and CIs too wide to draw meaning conclusions for these racial subgroups.

Analyses by ethnicity in all participants 9 through 49 years of age showed that all solicited reactions within 7 days following vaccination were reported in similar percentages (with overlapping 95% CIs) of Hispanic/Latino and non-Hispanic/non-Latino participants (50.0% [95% CI: 41.6, 58.4] and 48.5% [95% CI: 45.5, 51.5], respectively). The percentages of participants who reported solicited injection site reactions (36.8% [95% CI: 28.9, 45.2] and 38.5% [95% CI: 35.6, 41.5], respectively) and solicited systemic reactions (37.5% [95% CI: 29.6, 45.9] and 32.3% [95% CI: 29.5, 35.1], respectively) were also similar. Percentages of solicited local and systemic reactions were also similar between Hispanic/Latino and non-Hispanic/non-Latino participants within the age subgroups 9 through 17 years and 18 through 49 years. Unsolicited AEs were reported by similar percentages (with overlapping 95% CIs) of Hispanic/Latino and non-Hispanic/non-Latino participants 9 through 49 years of age (16.9% [95% CI: 11.2, 23.9] and 16.4% [95% CI: 14.3, 18.7], respectively) as well as within the age subgroups 9 through 17 years and 18 through 49 years. Numbers and percentages of SAEs (0.7% [95% CI: 0, 3.7] and 0.8% [95% CI: 0.4, 1.5] and MAAEs 4.7% [95% CI: 1.9, 9.5] and 5.1% [95% CI: 3.9, 6.6] reported by Hispanic/Latino and non-Hispanic/non-Latinos, respectively, during the study were also similar but too small to draw meaningful conclusions.

Analyses by priming status showed that solicited reactions within 7 days following vaccination were reported by a lower percentage of participants 9 through 49 years of age who were not vaccinated as compared with participants who were vaccinated in the previous season (44.9% [95% CI: 41.5, 48.3] and 56.6% [95% CI: 51.5, 61.6], respectively), primarily due to lower percentages of solicited injection site reactions in previously unvaccinated participants (34.0% [95% CI: 30.8, 37.2] versus 47.3% [95% CI: 42.2, 52.4], respectively). No meaningful differences between previously vaccinated and previously unvaccinated participants 9 through 49 years of age were observed for unsolicited AEs (16.3% [95% CI: 14.0, 18.9] and 16.1% [95% CI: 12.6, 20.1], respectively), SAEs (0.8% [95% CI: 0.3, 1.6] and 0.8% [95% 0.2, 2.2], respectively), or MAAEs (5.1% [95% CI: 3.8, 6.8] and 4.9% [95% CI: 3.0, 7.5], respectively).

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 10 (0.8%) participants experienced a total of 13 SAEs, all nonfatal, during the study, 6 (0.5%) within 28 days of vaccination and 4 (0.3%) during the 6-month follow-up period. Four SAEs occurred in 3 (0.5%) participants 9 through 17 years of age and 9 SAEs occurred in 7 (1.1%) participants 18 through 49 years of age. No SAEs were assessed as related to study vaccine. Table 19 summarizes all SAEs reported during the study according to age group, MedDRA SOC, and PT. Table 20 summarizes all SAEs by subject, age, onset, seriousness criterion, severity, relatedness, and outcome.

Table 19. Frequency of Serious Adverse Events, from Day 1 through Day 181, by Age Group and MedDRA System Organ Class and Preferred Term, SafAS, Study VAP00027*

Serious Adverse Event	9-17 yrs N=641 n (%)	18-49 yrs N=658 n (%)	All N=1299 n (%)
Any SAE	3 (0.5)	7 (1.1)	10 (0.8)
Any Related SAE	0	0	0
Gastrointestinal disorders	0	1 (0.2)	1 (<0.1)
Obstructive pancreatitis	0	1 (0.2)	1 (<0.1)
Infections and infestations	0	1 (0.2)	1 (<0.1)
Kidney infection	0	1 (0.2)	1 (<0.1)
Injury, poisoning and procedural complications	1 (0.2)	2 (0.3)	3 (0.2)
Intentional overdose	0	1 (0.2)	1 (<0.1)
Overdose	0	1 (0.2)	1 (<0.1)
Spinal fracture	1 (0.2)	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.2)	1 (<0.1)
Gastric cancer recurrent	0	1 (0.2)	1 (<0.1)
Nervous system disorders	0	1 (0.2)	1 (<0.1)
Seizure	0	1 (0.2)	1 (<0.1)
Psychiatric disorders	2 (0.3)	2 (0.3)	4 (0.3)
Major depression	0	1 (0.2)	1 (<0.1)
Suicidal ideation	2 (0.3)	1 (0.2)	3 (0.2)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (<0.1)
Acute respiratory failure	0	1 (0.2)	1 (<0.1)

Source: Modified from STN 125285/613, Module 5, VAP00027 FSR, Tables 20, 8.46, 8.47 and evaluation of the electronic datasets.
Abbreviations: SafAS=safety analysis set; SAE=serious adverse event
*ClinicalTrials.gov identifier: NCT05513053

Table 20. SAEs Day 1 through Day 181 by Subject, Age/Sex, Onset, Seriousness, Severity, Relatedness and Outcome, SafAS, Study VAP00027*

Subject	Age/ Sex	Preferred Term(s)	Onset Day[1]	Serious Criterion[2]	Severity Grade[3]	Related[4]	Outcome[5]
(b) (6)	16/F	Spinal fracture	124	H	3	No	Not Rec
	16/M	Suicidal ideation	12	O	3	No	Not Rec
	16/M	Suicidal ideation	18	H+O	3	No	Not Rec
	13/F	Suicidal ideation	31	H	3	No	Rec
	29/M	Major depression	3	H	3	No	Rec
	29/M	Intentional overdose	8	H	3	No	Rec
	38/F	Gastric cancer recurrent	missing	H	3	No	Not Rec
	26/F	Suicidal ideation	22	H	2	No	Rec
	38/F	Seizure	8	H	3	No	Rec
	28/F	Acute respiratory failure	5	H+L	3	No	Rec
	28/F	Overdose	5	H+L	3	No	Rec
	32/F	Kidney infection	134	H	3	No	Rec
	33/F	Obstructive pancreatitis	166	H	3	No	Rec

Source: Adapted from STN 125285/613, Module 5, VAP00027 FSR, Tables 20, 8.44, 8.45, 8.46, 8.47, 8.48, 8.49, Appendix 14 case narratives, and the electronic datasets.
Abbreviations: SafAS=safety analysis set; M=male; F=female
Notes:
*ClinicalTrials.gov identifier: NCT05513053.
[1]Onset Day = Study Day number relative to vaccination Study Day 1.

[2]Seriousness criterion: H=hospitalization; L=life-threatening; O=other medically important event;
[3]Severity Grade: 1=mild; 2=moderate; 3=severe.
[4]Related: "Yes" signifies investigator assessment of "related" to study vaccine. "No" signifies investigator assessment of "not related" to study vaccine. Applicant concurred with investigator assessments.
[5]Outcome: Rec=recovered or resolved; Not Rec=not recovered or not resolved

Reviewer Comment: *Case narratives were reviewed. SAEs of interest included 1 case of seizures and 5 participants with suicidal ideation, major depression, drug overdose, and/or acute respiratory failure resulting in hospitalization. This reviewer agrees with the investigator assessments that the SAEs were related to underlying medical conditions and illicit or recreational drug use and not to the investigational vaccines.*

6.1.12.5 Adverse Events of Special Interest (AESIs)

No AESIs were reported during the study.

Pregnancy

One pregnancy was reported during the study, with no AEs or complications. Participant ID (b) (6) was a 36-year-old female whose relevant medical history included two prior pregnancies resulting in live births without complications and one elective termination for trisomy 18. She received RIV4 on (b) (6), and became pregnant ~2 months postvaccination. Prenatal tests were unremarkable. On (b) (6), at 39 weeks gestation and 335 days postvaccination, she delivered a healthy live female infant without reported defects or complications.

6.1.12.6 Clinical Test Results

Clinical safety laboratories were not collected in this study. Laboratory or vital sign abnormalities obtained in the evaluation of serious, severe, or otherwise significant AEs are described in Sections 6.1.12.3 and 6.1.12.4. Evaluation of electronic datasets revealed no episodes of hypotension or anaphylaxis in the 30 minutes post-vaccination.

6.1.12.7 Dropouts and/or Discontinuations

A total of 2 (0.2%) participants, both in the 18 through 49 years age group (0.3%), had AEs leading to discontinuation during the study. Participant ID (b) (6) had an SAE of intentional overdose and is described in Section 6.1.12.4 of this review. Participant ID (b) (6) was discontinued due to non-serious AEs of Grade 2 (moderate) urticaria, that began one day following vaccination (Study Day 2), and injection site bruising, erythema, induration and swelling, all Grade 3 (severe), that began 2 days following vaccination (Study Day 3). She also had Grade 2 injection site pain, headache, malaise, myalgia, chills and temperature of 100.4ºF on Study Day 3.

6.1.13 Study Summary and Conclusions

Immunogenicity Conclusions

Vaccination of participants 9 through 17 years of age with RIV4 induced a NI immune response as compared with adults 18 through 49 years of age and met prespecified co-primary endpoints of GMT ratios and SCR differences for all four vaccine virus antigens, as measured by anti-HI antibodies at 28 days postvaccination.

At baseline, the percentages of participants with both HI titers ≥1:10 and HI titers ≥1:40 were higher in participants 9 through 17 years of age than in participants 18 through 49 years of age for the A/H1N1 and A/H3N2 strains and were similar in both age groups for the B/Victoria and

B/Yamagata strains. At Day 29, the percentages of participants with HI titers ≥1:40 increased for all 4 virus strains and were high in both age groups (≥95.6% in participants 9 through 17 years of age and ≥95.0% in participants 18 through 49 years of age). In both age groups, fold-rises in GMTs were highest against the A/H3N2 strain and lowest against the B strains.

Sub-analyses of immune responses according to age subgroups, sex, race, ethnicity, baseline serostatus, and previous vaccination status generally followed patterns observed in the overall Per Protocol population. No large or clinically meaningful differences were observed between subgroups. Subgroup analyses were limited by relatively small sample sizes and the descriptive nature of the analyses.

Exploratory analyses of immune responses as measured by the SN assay (data not shown in this review) showed immune responses to all four vaccine antigens and were comparable between participants 9 through 17 years of age and 18 through 49 years of age.

Safety

Overall, vaccination with RIV4 in participants 9 through 17 years of age and 18 through 49 years of age was associated with acceptable safety data. No unusual patterns of AEs or safety concerns were identified in either group.

Participants 9 through 17 years of age, as compared with adults 18 through 49 years of age, showed trends toward lower percentages of solicited injection site reactions (35.6% versus 40.8%) and solicited systemic reactions (29.6% versus 36.2%) in the 7 days following vaccination.

The frequency of unsolicited AEs occurring within 28 days after vaccination was slightly lower in participants 9 through 17 years of age as compared with 18 through 49 years of age (14.5% versus 18.1%). The percentages of SAEs (<1%) and MAAEs (<5%) were low in both age groups and no events were considered related to study vaccine. No deaths or AESIs were reported during the study.

Subgroup analyses of safety according to additional age subgroups, sex, race, ethnicity, and previous influenza vaccination status showed trends toward higher percentages of solicited injection site reactions in participants 9 through 11 years of age as compared with participants 12 through 17 years of age. Solicited injection site and systemic reactions were reported by higher percentages of females as compared with males, White as compared with Black or African American participants, and in participants vaccinated in the previous season as compared with previously unvaccinated participants. The percentages of solicited injection site and systemic reactions were similar between Hispanic/Latino and non-Hispanic/non-Latino participants. Subgroup analyses of Unsolicited AEs showed trends toward overall higher percentages in females and White participants but no meaningful differences in the percentages of events overall between Hispanic/Latino and non-Hispanic/non-Latino participants. Numbers and percentages of participants who experienced SAEs and MAAEs were too small to draw definitive conclusions. Overall, subgroup comparisons were limited by small sample sizes and the descriptive nature of the analyses do not allow us to draw firm conclusions from the observed trends.

6.2 Trial #2

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

Study ID: VAP00026

ClinicalTrials.gov identifier: NCT05513391

6.2.1 Objectives (Primary, Secondary, etc.)

Primary Objective

To demonstrate the NI HI immune response of RIV4 versus licensed IIV4 for the 4 strains based on the egg-derived antigen in all participants 3 to 8 years of age.

Key Secondary Objectives

- To summarize the HI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg-derived antigen in participants 3 to 8 years of age.
- To assess the safety profile of each vaccine in all participants and by age group.

6.2.2 Design Overview

VAP00026 was a Phase 3, randomized, observer-blind, active-controlled, multicenter study conducted in the U.S. and Europe in children 3 through 8 years of age, to evaluate the safety and NI immunogenicity of RIV4 as compared to U.S.-licensed IIV4 for the four strains included in the vaccine, as measured by the HI assay using egg-derived antigens. The study planned to enroll a total of 1412 participants equally stratified between two age groups, 3 through 5 years and 6 through 8 years, with approximately equal numbers of participants who were previously unvaccinated and previously vaccinated against influenza. Participants were randomized 1:1 to receive RIV4 or IIV4, one or two 0.5 mL doses, administered IM 28 days apart, depending on whether they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively.

Blood for serologies were drawn prior to vaccination on Day 1 and at 28 days after the last vaccination (on Day 29 or Day 57). Safety assessments included a 30-minute observation period postvaccination for immediate reactions, solicited injection site and systemic reactions for 7 days following each vaccination (Day 1 through Day 8 and/or Day 29 through Day 36), unsolicited AEs for 28 days following each vaccination (from Day 1 to 29 or 57), and SAEs, MAAEs and AESIs from Day 1 to Day 181 (end of study at six months). An independent internal SMT was established to perform an ESDR of 7-day safety data collected on the first 10% of participants 3 through 8 years of age prior to allowing the remainder of participants to begin vaccinations.

VAP00026 was initiated (first participant first visit) on November 10, 2022 and ended (last participant last visit) on May 22, 2023. Due to challenges in enrollment, the study was modified to include an IA for futility by the FIC to review safety and assess the likelihood of study success. The futility analysis was performed after ~25% of the targeted enrollment population had been enrolled and vaccinated. Please see Section 6.2.9 of this review for additional information.

Following the futility analysis and upon recommendation by the FIC, the study was terminated early on December 7, 2023. Analyses presented in the FSR are based on a database lock point dated December 21, 2023.

6.2.3 Population

Selected Inclusion Criteria

- Age 3 through 8 years on the day of inclusion
- Assent signed and dated by the participant and Informed Consent Form (ICF) signed and dated by the parent(s) or other legal representative
- Participant and parent/legal representative able to attend all scheduled visits and comply with all study procedures

Selected Exclusion Criteria

- Known or suspected immunodeficiency or receipt of immunosuppressive therapies within six months of enrollment
- Known hypersensitivity to vaccine components
- Moderate or severe acute illness or infection (as determined by the investigator) or febrile illness (temperature ≥38.0°C [≥100.4°F]) on the day of study injection. A prospective participant should not be included in the study until the condition resolved or the febrile event subsided.
- History of GBS
- Thrombocytopenia, bleeding disorders, or any condition that, in the opinion of the investigator, could pose a health risk or interfere with study evaluations.
- Receipt of any vaccine in the 4 weeks preceding the study intervention administration or planned receipt of any vaccine in the 4 weeks following the study intervention administration except for COVID-19 vaccination, which may have been received at least 2 weeks before study intervention.
- Previous vaccination against influenza (in the 6 months prior to study intervention administration) with an investigational or marketed vaccine
- Receipt of immune globulins, blood or blood-derived products in the 3 months prior to enrollment

6.2.4 Study Treatments or Agents Mandated by the Protocol

RIV4 solution for injection was supplied in pre-filled syringes containing a single 0.5 mL dose of the NH 2022-2023 season formulation (recommended for cell-culture-based vaccines), 45 mcg of HA from four influenza virus strains:

- 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

Excipients and diluent per 0.5 mL dose included: sodium chloride 4.4 mg; monobasic sodium phosphate 0.2 mg; dibasic sodium phosphate 0.5 mg; polysorbate 20 (Tween 20) 27.5 µg; octylphenol ethoxylate (Triton X-100) ≤100 µg; and water for injection.

Batch number: VA030631

IIV4 suspension for injection was supplied in pre-filled syringes containing a single 0.5 mL dose of the NH 2022-2023 formulation (recommended for egg-based vaccines), 15 mcg of HA from four influenza virus strains:

- A/H1N1 strain: A/Victoria/2570/2019
- A/H3N2 strain: A/Darwin/6/2021
- B/Victoria lineage strain: B/Austria/1359417/2021
- B/Yamagata lineage strain: B/Phuket/3073/2013

Excipients and diluent per 0.5 mL dose included: octylphenol-10 (Triton X-100) ≤0.115 mg; α-tocopheryl hydrogen succinate ≤0.135 mg; polysorbate 80 (Tween 80) ≤0.550 mg.

Batch number: VA030754

6.2.5 Directions for Use

All study participants were to receive a single 0.5 mL dose of blinded study vaccine on Study Day 1 and, if previously unvaccinated, a second dose on Day 29, administered IM into the deltoid region of the upper arm.

6.2.6 Sites and Centers

VAP00026 was conducted at 31 sites across the U.S. and Europe. Study sites and the principal investigator for each site are presented in Table 21. Of a total of 366 randomized participants enrolled, study sites in the U.S., Poland, and Spain included 69.7%, 19.4%, and 10.9%, respectively. Please see Table 8.4 and Appendix 5 of the FSR for additional information.

Table 21. Study Sites, Investigators, and Number of Randomized Participants*, Study VAP00026**

Site	Investigator	Location	# Randomized*	Country Total n (%)
6160001	Ernest Kuchar	Poland	2	--
6160003	Oleg Warszalewski	Poland	20	--
6160005	Barbara Pajec	Poland	16	--
6160006	Bernadetta Majorek-Olechowska	Poland	7	--
6160007	Andrzej Galaj	Poland	4	--
6160010	Piotr Korbal	Poland	12	--
6160012	Tomasz Zajac	Poland	10	71 (19.4)
7240001	Silvina Laura Natalini Martinez	Spain	14	--
7240004	Pablo Rojo Conejo	Spain	2	--
7240005	Manuel Ramon Baca Cots	Spain	2	--
7240007	Ignacio Salamanca de la Cueva	Spain	5	--
7240014	Cristina Calvo Rey	Spain	4	--
7240018	Jose Garcia Sicilia Lopez	Spain	13	40 (10.9)
8400001	Todd Bertoch	USA	37	--
8400003	Donald Brandon	USA	8	--
8400005	Rodrigo Garcia	USA	7	--
8400006	Frank Eder	USA	9	--
8400007	David Ensz	USA	8	--
8400009	Brandon Essink	USA	39	--
8400010	Daniel Finn	USA	24	--
8400012	Scott Striplin / Robert Jeanfreau	USA	22	--
8400013	Jay Meyer	USA	8	--
8400014	Abraham Moskow	USA	7	--
8400016	Suchet Patel	USA	1	--

Site	Investigator	Location	# Randomized*	Country Total n (%)
8400017	James Peterson	USA	11	--
8400020	Julie Shepard	USA	34	--
8400021	Stacy Slechta	USA	13	--
8400022	Bruce Etheridge	USA	1	--
8400023	Max Hale	USA	2	--
8400025	Kevin Rouse	USA	10	--
8400027	Peter Silas	USA	14	255 (69.7)
Total	**-**	**-**	**366**	**366 (100)**

Source: Adapted from STN 125285.613, VAP00026 FSR, Table 8.4, Appendix 5 and electronic datasets.
*Number of participants in the Randomized Population.
**ClinicalTrials.gov identifier: NCT05513391

Applicability of Data from Foreign Study Sites

In response to our request for comparative analyses of data by country to support the applicability of data from foreign study sites to the U.S. population and practice of medicine, the Applicant indicated that, because 70% of participants in Study VAP00026 were from the U.S., the study was highly representative of the U.S. population. Sub-analyses of demographic and baseline characteristics, safety and immunogenicity for Poland and Spain were generally similar as compared with analyses limited to U.S. participants. In the FAS, percentages of male and female participants and mean ages of participants were similar across countries. In the U.S. Black or African American participants 3 through 8 years of age comprised 24.2% (RIV4) to 25.4% (IIV4) of the overall study population as compared with no participants of Black or African American origin in the other countries. Spain and the U.S. were the only countries with Latino or Hispanic participants and percentages differed between study vaccine groups. The percentage of Latino or Hispanic participants in the IIV4 and RIV4 groups in Spain were 54.2% and 25.0%, respectively, and in the U.S., 13.6% and 10.0%, respectively.

Safety analyses showed that, among recipients of RIV4, 3 through 8 years of age, the percentage of participants in Spain (68.8% [95% CI: 41.3, 89.0]) who reported solicited injection site reactions was higher than in Poland (41.0% [95% CI: 25.6, 57.9]) or the U.S. (34.7% [95% CI: 26.4, 43.7]). Solicited systemic reactions were also higher among recipients of RIV4 in Spain (43.8% [95% CI: 19.8, 70.1]) as compared with participants in Poland (28.2% [95% CI: 15.0, 44.9]) and the U.S. (25.8% [95% CI: 18.4, 34.4]). Similar trends were observed across countries in the IIV4 group. The percentage of participants who reported unsolicited AEs within 28 days of vaccination also showed a trend to be higher in Spain as compared with Poland and the U.S. for RIV4: 31.3% ([95% CI: 11.0, 58.7]) versus (20.5% (95% CI: 9.3, 36.5)] and 24.6% (95% CI: 17.4, 33.1]), respectively. Analyses of immunogenicity did not show clear or consistent differences among countries by vaccine strain or overall. Please see STN 125285/613.7, VAP00026 FSR, Appendix 15 Addendum, for additional information.

> ***Reviewer Comment:*** *The numbers and percentages of participants from non-U.S. countries were lower as compared with the U.S. Descriptive comparative analyses showed mostly similar results with wide and overlapping 95% CIs with a trend toward more solicited reactions among Spanish participants. Interpretation of results from VAP00026 was limited by early termination and a small sample size. However, sub-analyses by country suggest that the study population adequately represented the U.S. population.*

6.2.7 Surveillance/Monitoring

Informed consent and, where applicable according to local regulations, assent were obtained from participants and parents or their legal representative prior to enrollment. Screening occurred on Day 1/Visit 1 and included review of eligibility criteria, complete medical history and physical examination, concomitant medications, influenza vaccination history, and collection of blood for prevaccination serologies. Eligible participants were enrolled, randomized, and vaccinated on Day 1, and, if previously unvaccinated, were vaccinated with a second dose on Day 29. Participants were observed for immediate hypersensitivity reactions and other AEs for 30 minutes following each vaccination. Solicited AEs were actively and systematically collected for seven days following each vaccination (Day 1 through Day 8; Day 29 through Day 36) via a paper or electronic diary. A follow-up telephone call with study staff occurred at Day 9 and, if applicable, Day 37 to review instructions, AEs and address concerns. Unsolicited AEs, serious and non-serious, were also recorded passively in the Diary for 28 days after each vaccination. Diaries were reviewed with study staff and collected at the Day 29 and, if applicable, Day 57 visit. For previously vaccinated participants who received a single dose, a blood sample for serologies was collected at Day 29 and a new Memory Aid was distributed to record any additional Unsolicited AEs, SAEs, AESIs and/or MAAEs that occurred over the remainder of the 6-month follow-up period. For single dose participants, the Memory Aid was collected at the final study visit on Day 181. For previously unvaccinated participants who were to receive two doses, the Day 29 visit included review of eligibility and the first diary card, and a targeted physical examination prior to the second vaccination. A second diary was distributed for collection of solicited AEs for 7 days and unsolicited for 28 days postvaccination. Participants returned to the study site at Day 57 to review the second diary, provide a blood sample for serologies, and receive a Memory Aid for collection of additional AEs, SAEs, AESIs and MAAEs through the 6-month follow-up period (to Day 209).

Definitions of AEs and SAEs and reporting requirements were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization.

Assessment of the Intensity of Adverse Events

Solicited injection site reactions included: pain and measured erythema, swelling, induration, and bruising. Solicited systemic reactions included fever (oral temperature measurement), headache, malaise, myalgia, and chills. Grading scales for recording the intensity of solicited injection site reactions were identical to those used for participants 9 through 11 years of age in Study VAP00027 (Section 6.1.7, Table 3). Grading scales for recording the intensity of solicited systemic reactions and for all other unsolicited AEs were identical to those used for participants ≥9 years of age in Study VAP00027 (Section 6.1.7, Tables 5 and 6, respectively). Source tables are found in the FSR for VAP00026, Appendix 1, Protocol, Appendix 10.2.5, Assessment of Intensity.

Adverse Events of Special Interest (AESIs)

The protocol and SAP defined AESIs consistent with the CIOMS Working Group definition. AESIs were also captured as SAEs and included the same terms as in Study VAP00027, listed in Section 6.1.7 of this review.

Assessment of Relatedness of AEs:

Criteria for the assessment of relatedness of AEs were identical to those specified for Study VAP00027. Please see Section 6.1.7 of this review and the FSR for VAP00026, Appendix 1, Protocol Appendix 10.2.3, Assessment of Causal Relationship.

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

Eight co-primary immunogenicity endpoints (GMTs and SCRs for each of four vaccine strains) were prespecified:

- Individual HI titer 28 days after last vaccination (Day 29 or Day 57)
- Seroconversion, defined as a post-vaccination HI titer to at least 1:40 as in Study VAP00027, at Day 29 (previously vaccinated, single dose participants) or Day 57 (previously unvaccinated, two-dose participants)

The primary NI analyses were to be conducted on the PPAS regardless of previous vaccination status and evaluated according to the following pre-specified success criteria:

- For each strain, NI GMTs would be demonstrated if the LL of the 2-sided 95% CI for the GMT ratio, (GMT RIV4 / GMT IIV4) was >0.667.
- For each strain, NI SCRs would be demonstrated if the LL of the 2-sided 95% CI for the difference in SCRs (SCR RIV4 – SCR IIV4) >-10%.

Secondary Immunogenicity Endpoints

- Individual HI titer on Day 1 and 28 days after the last vaccination (D29 or D57)
- Detectable HI titer (≥1:10) at Day 1 and 28 days after the last vaccination
- Individual HI titer ratio: 28 days after the last vaccination (D29 or D57) / D01
- Seroconversion at 28 days after the last vaccination
- Participants with HI titers ≥1:40 on Day 1 and 28 days after the last vaccination

Safety Endpoints

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence of pre-specified solicited injection site reactions and systemic reactions occurring up to 8 days after each vaccination
- Occurrence of unsolicited AEs up to 28 days after each vaccination
- Occurrence of MAAEs up to 28 days after each vaccination
- Occurrence of SAEs (including AESIs) throughout the study
- Occurrence of AESIs throughout the study

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the SAP.

For the primary NI analysis, the NI of postvaccination GMTs (GMT ratios) and SCR between RIV4 and IIV4 treatment groups for each vaccine strain was evaluated using a 1-sided Type I error rate of 0.025 for each comparison. The primary analysis was conducted sequentially beginning with testing for NI of GMTs. If NI of GMTs was demonstrated for the four strains, then NI for SC was also tested. Because all 8 NI hypotheses had to be rejected at 0.025 significance level, no formal adjustment for multiplicity was necessary. GMTs were adjusted for baseline HI titer, prevaccination status, age subgroup, season, and treatment group.

The sample size was calculated to provide an overall study power of >80% and an overall type II error <20% for the 8 NI tests.

Immunogenicity analyses were to be conducted on the FAS in addition to the PPAS only if the attrition rate was >10%.

Descriptive statistics were used to analyze safety endpoints.

Missing data were not imputed for immunogenicity or safety analyses.

Interim Analysis for Futility

Despite efforts to enhance enrollment, the Applicant was only able to recruit ~26% of the 1412 participants planned for enrollment by the end of the Northern Hemisphere (NH) 2022-2023 recruitment period. As a result, the protocol and SAP were amended to include an IA of data generated from ~368 recruited participants. The IA was to summarize all included immunogenicity and safety data through 28 days after the last vaccination (Day 29 or Day 57 as applicable). In addition, the IA would include listings of all available data collected after the Day 29 and Day 57 timepoints for SAEs, Grade 3 adverse reactions, and AEs leading to discontinuation.

The SAP specified that an unblinded group of statisticians would evaluate safety and calculate the PPoS for each of the 8 NI statistical tests included in the primary objective and for the overall study. An independent FIC, comprised of senior members from clinical, safety and biostatistics divisions, was established to review the results of the IA and recommend whether VAP00026 should continue or be terminated for futility or for safety reasons.

An FIC recommendation to terminate the study would be based on the following criteria:

- The overall PPoS of the 4 GMTs and 4 SC NI statistical tests, based on a guidance of PPoS of less or equal 20%, also considering the trend across the different PPoS calculated:
    - The individual PPoS to meet NI for each vaccine strain and each parameter (GMT and SCR)
    - The overall PPoS of the 4 GMTs NI statistical tests
    - The overall PPoS of the 4 SC NI statistical tests
- RIV4 immunogenicity results relative to IIV4 in each age, priming status and baseline serological status subgroup would also inform the decision.
- Safety results.

The PPoS was defined as the probability that the final study result would be successful given the data observed at the time of the IA. The PPoS was based on simulations conducted first on GMTs and then on SCRs for each vaccine strain, and included age subgroup and previous vaccination status subsets, specified in Section 3.5.2.1 of the SAP. The overall PPoS for NI of GMTs and SCRs were calculated by multiplying the individual PPoS for NI of GMTs and SCRs, respectively. The overall study PPoS was calculated by multiplying the 8 individual PPoS for NI of GMTs and SCRs.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- Randomized: all participants randomized by study interactive response technology (IRT) to one of the study groups

- SafAS: Received at least one dose of the study vaccine; analyzed after each dose according to the vaccine actually received, and after any dose according to the vaccine received at the first dose. Safety data recorded for a vaccine received out of the protocol were excluded from the analysis and listed separately.
- FAS: Subset of randomized participants who received at least one dose of study vaccine and had a post-vaccination blood sample; analyzed according to treatment assigned at randomization
- PPAS: Subset of participants in the FAS; participants with one or more of the following criteria were excluded from the PPAS:
    - Did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
    - Did not complete the vaccination schedule
    - Received a vaccine other than the one they were randomized to receive
    - Preparation and/or administration of vaccine not performed per-protocol
    - Did not receive vaccine in the proper time window
    - Did not provide the post-dose serology sample at Visit 2 or at Visit 3 in the proper time window (-2 to +7 days after the respective vaccination) or a post-dose serology sample was not drawn at Visit 2 or Visit 3
    - Received protocol-prohibited medications impacting or that may have an impact on the immune response
- Seroneutralization exploratory subsets: Analyses of the immune response by SN assay were performed on the participants from the FAS and/or PPAS who were randomized in the exploratory subsets FAS-SN and/or PPAS-SN.

Table 22 presents the number and percentage of participants in the analysis sets.

Table 22. Analysis Sets by Randomized Groups, Randomized Population, Study VAP00026*

Analysis Set	RIV4 n (%) N=183	IIV4 n (%) N=183	All n (%) N=366
Randomized	183 (100)	183 (100)	366 (100)
Full Analysis Set (FAS)	171 (93.4)	169 (92.3)	340 (92.9)
Per-Protocol Analysis Set (PPAS)	160 (87.4)	158 (86.3)	318 (86.9)
Previously vaccinated**	97 (92.4)	96 (91.4)	193 (91.9)
Previously unvaccinated**	63 (80.8)	62 (79.5)	125 (80.1)
Safety Analysis Set (SafAS)	181 (98.9)	181 (98.9)	362 (98.9)
3 through 5 years**	81 (98.8)	91 (97.8)	172 (98.3)
6 through 8 years**	100 (99.0)	90 (100)	190 (99.5)

Source: Modified from STN 125285/613, Module 5, FSR VAP00026, Tables 6, 7, 8.11, and 8.14, and evaluation of the electronic datasets.
*ClinicalTrials.gov identifier: NCT05513391
**Denominators for PPAS previously vaccinated: RIV4=105; IIV4=105; All=210. **Denominators for PPAS previously unvaccinated: RIV4=78; IIV4=78; All=156.
**Denominators for SafAS 3 through 5 years: RIV4=82; IIV4=93; All= 175.
**Denominators for SafAS 6 through 8 years: RIV4=101; IIV4=90; All=191.

6.2.10.1.1 Demographics

A total of 366 participants were randomized in the study, including 178 (48.6%) male and 188 (51.4%) female participants, with similar percentages across treatment and age subgroups. Of 366 randomized participants, 175 (47.8%) were 3 through 5 years of age and 191 (52.2%) were 6 through 8 years of age. The mean age of all participants was 5.60 (SD 1.68) years and was

similar between treatment groups. The mean ages of children 3 through 5 years and 6 through 8 years of age were 4.07 (SD 0.83) and 7.01 (SD 0.83), respectively.

Among all participants, racial origin was mostly White (76.5%) followed by Black or African American (17.5%), and mixed (4.6%). No participants were Asian, 1 (0.3) was Hawaiian or other Pacific Islander, and 3 (0.8) were American Indian or Alaskan Native. An imbalance between treatment groups was observed for participants of mixed origin, 2.2% and 7.1% among RIV4 and IIV4 participants, respectively. Some imbalances of racial origin between treatment groups were also observed within age subgroups. Among children 3 through 5 years of age who received RIV4 or IIV4, respectively, 84.1% and 73.1% were White, 9.8% and 18.3% were Black or African American, and 3.7% and 8.6% were of mixed racial origin. Among children 6 through 8 years of age, racial origin was more balanced between treatment groups except for children of mixed origin (RIV4 1.0% and IIV4 5.6%).

Among all participants, most (86.6%) were non-Hispanic or non-Latino in ethnicity as compared with 58.4% of Whites in the U.S. population.

The Applicant's summaries of baseline demographic characteristics of the FAS and PPAS populations (Tables 8.16 and 8.17 of the FSR) showed similar distributions as for the Randomized Population.

> ***Reviewer Comment:*** *Relative to the U.S. population, Black and African American participants were somewhat overrepresented and Asian participants were underrepresented. Participants of Hispanic/Latino ethnicity (13.1% of all participants) were also underrepresented. The effect of racial origin or ethnicity on immune responses or on adverse reactions is not established and the impact imbalances of demographic characteristics may have had on study outcomes is unknown.*
>
> *Evaluation of the electronic datasets was consistent with the Applicant's report of baseline demographic characteristics.*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

Of the total 366 randomized participants, 210 (57.4%) and 156 (42.6%) were previously vaccinated and unvaccinated against influenza, respectively. Within each priming status group, participants 3 to 8 years of age were balanced between treatment groups (RIV4 and IIV4 each 50%). Of a total 109 (29.8%) participants who had received a seasonal influenza vaccine in the last season (NH 2021-2022), 29.0% and 30.6% were randomized to receive RIV4 and IIV4, respectively.

> ***Reviewer Comment:*** *Influenza vaccine priming status was balanced between treatment groups.*

Medical History

Of a total of 366 randomized participants, 160 (43.7%) reported at least one past and/or current significant medical history: 83 (45.4%) participants in the RIV4 group and 77 (42.1%) participants in the IIV4 group. A total of 138 (37.7%) participants reported ongoing medical conditions at inclusion: 70 (38.3%) in the RIV4 group and 68 (37.2%) in the IIV4 group. In response to a request for information, the Applicant provided tabular summaries and datasets of

medical history for the 362 participants in the SafAS of which 83 (45.9%) and 76 (42.0%) of participants in the RIV4 and IIV4 groups, respectively, reported having any pre-existing or ongoing medical condition, with similar distributions within age subgroups.

The most common (>5%) pre-existing and ongoing medical conditions reported by participants in either the RIV4 or IIV4 groups, respectively, were those in the following MedDRA SOCs: gastrointestinal disorders (9.9% and 6.6%), immune system disorders (13.8% and 15.5%), infections and infestations (7.7% and 9.4%), metabolism and nutrition disorders (5.5% and 3.9%), nervous system disorders (6.6% and 6.1%), psychiatric disorders (8.8% and 12.7%), respiratory, thoracic and mediastinal disorders (13.3% and 12.7%), and skin and subcutaneous disorders (8.3% and 7.2%).

The most common (>5%) pre-existing and ongoing conditions in either the RIV4 or IIV4 groups, respectively, as categorized by MedDRA PT were: constipation (5.0% in both groups), seasonal allergy (9.9% and 12.2%), attention deficit and hypersensitivity disorder (4.4% and 7.7%), asthma (8.3% in both groups), and eczema (7.2% and 3.3%). Obesity was 2.2% in both treatment groups.

> ***Reviewer Comment:*** *Evaluation of medical conditions as categorized by MedDRA SOC and PT revealed no large imbalances between treatment groups.*

Concomitant Medications

A total of 94 (25.7%) of 366 randomized participants had reportable concomitant medication use during the study, including 26.7% of 210 previously vaccinated and 24.4% of 156 previously unvaccinated participants. Overall, only 1 (0.5%) participant in each treatment group took medications considered by the Applicant as prophylactic. A total of 3 (1.6%) participants in the RIV4 group and 2 (1.1%) participants in the IIV4 group took medications considered by the Applicant as prohibited. Among recipients of RIV4, prohibited medications included other licensed vaccines (e.g., DTAP, hepatitis, varicella, MMR). Among recipients of IIV4, prohibited medications included acetaminophen and ibuprofen.

Evaluation of antipyretic and analgesic use within 7 days of any vaccination showed that a total of 13 (7.2%) and 24 (13.3%) of participants in the RIV4 and IIV4 groups, respectively, reported use of these medications, primarily after the first vaccination (6.6% and 11.6%, respectively). For each treatment group, the percentages of participants who reported antipyretic or analgesic use within each age subgroup were similar.

> ***Reviewer Comment:*** *Evaluation of the Applicant's summary tables and datasets (submitted to STN 125285/613.6) did not reveal large imbalances of concomitant medications likely impact the assessments of immunogenicity or safety.*

6.2.10.1.3 Subject Disposition

Table 23 presents the disposition of participants. A total of 366 of 1412 (25.9%) participants originally planned for enrollment were enrolled, stratified by age subgroup and previous influenza vaccination status, and randomized to receive RIV4 or IIV4 (183 participants per treatment group). Among all randomized participants, 181 (98.9%) in each treatment group were vaccinated. Of previously vaccinated participants (single dose), a total of 207 (98.6%) were vaccinated and 205 (97.6%) completed the active phase of the study on Day 29. Of previously unvaccinated participants (two doses), a total of 151 (96.8%) received both vaccinations and 149 (95.5%) completed the active phase of the study at Day 57. Among

participants randomized to receive RIV4, a total of 6 vaccinated participants terminated prior to completing the active phase of the study. Of these, 2 participants randomized to receive RIV4 were not vaccinated (screen failures), one due to an AE of syncope after blood draw and one due to withdrawal of consent during the blood draw. An additional 4 participants terminated after the first or second vaccination due to withdrawal of consent. Among participants randomized to receive IIV4, a total of 6 participants terminated prior to completing the active phase of the study. Two participants were not vaccinated (screen failures), one due to a protocol deviation and to withdrawal of consent. Another 4 participants terminated after vaccinations, 2 withdrew consent, and 2 were lost to follow-up. Among all participants, a total of 347 (94.8%), 172 (94.0%) and 175 (95.6%) of participants randomized to receive RIV4 or IIV4, respectively, completed the 6-month follow-up period.

Table 23. Disposition of Participants by Previous Vaccination Status, Age Group, Treatment Group, Randomized Population, Study VAP00026*

Disposition by Previous Vaccination Status	RIV4 n/M(%) N=183	IIV4 n/M(%) N=183	All n/M(%) N=366
All	--	--	--
Planned	706 (n/a)	706 (n/a)	1412 (n/a)
Randomized	183/183 (100)	183 (100)	366 (100)
Randomized 3-5 yrs	82/183 (44.8)	93/183 (50.8)	175/366 (47.8)
Randomized 6-8 yrs	101/183 (55.2)	90/183 (49.2)	191/366 (52.2)
Vaccinated D1	181 (98.9)	181 (98.9)	362/366 (98.9)
Completed Active Phase	177/183 (96.7)	177/183 (96.7)	354/366 (96.7)
Early termination	6/183 (3.3)	6/183 (3.3)	12/366 (3.3)
Reason-adverse event	1/183 (0.5)	0	1/366 (0.3)
Reason-protocol deviation	0	1/183 (0.5)	1/366 (0.3)
Reason-withdrawal by subject	3/183 (1.6)	1/183 (0.5)	4/366 (1.1)
Reason-withdrawal by parent/guardian	2/183 (1.1)	2/183 (1.1)	4/366 (1.1)
Reason-lost to follow-up	0	2/183 (1.1)	2/366 (0.5)
Completed 6-month follow-up	172/183 (94.0)	175/183 (95.6)	347/366 (94.8)
Did not complete 6-month follow-up	11/183 (6.0)	8/183 (4.4)	19/366 (5.2)
Previously vaccinated	--	--	--
Planned	353 (n/a)	353 (n/a)	706 (n/a)
Randomized	105/105 (100)	105/105 (100)	210/210 (100)
Randomized 3-5 yrs	43/105 (41.0)	49/105 (46.7)	92/210 (43.8)
Randomized 6-8 yrs	62/105 (59.0)	56/105 (53.3)	118/210 (56.2)
Vaccinated D1	104/105 (99.0)	103/105 (98.1)	207/210 (98.6)
Discontinued-VW	2	1	3
Discontinued-PD	0	1	1
Discontinued-AE	1	0	1
Completed Active Phase D29	102/105 (97.1)	103/105 (98.1)	205/210 (97.6)
Completed 6-month follow-up	98/105 (93.3)	102/105 (97.1)	200/210 (95.2)
Previously unvaccinated	--	--	--
Planned	353 (n/a)	353 (n/a)	706 (n/a)
Randomized	78/78 (100)	78/78 (100)	156/156 (100)
Randomized 3-5 yrs	39/78 (50.0)	44/78 (56.4)	83/156 (53.2)
Randomized 6-8 yrs	39/78 (50.0)	34/78 (43.6)	73/156 (46.8)
Vaccinated D1	77/78 (98.7)	78/78 (100)	155/156 (99.4)
Discontinued-VW	2	2	4
Vaccinated D29	75/78 (96.2)	76/78 (97.4)	151/156 (96.8)
Discontinued-VW	1	0	1
Discontinued-FU	0	2	2

Disposition by Previous Vaccination Status	RIV4 n/M(%) N=183	IIV4 n/M(%) N=183	All n/M(%) N=366
Completed Active Phase D57	75/78 (96.2)	74/78 (94.9)	149/156 (95.5)
Completed 6-month follow-up	74/78 (94.9)	73/78 (93.6)	147/156 (94.2)

Source: Modified from STN 125285/613, Module 5, FSR VAP00026, Figure 3, Tables 4, 8.2, 8.3, 8.10, and evaluation of the electronic datasets.
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; n=number of participants fulfilling the item listed; M=number of participants with available data for the corresponding randomized group; D1=Day 1; D29=Day 29 time point for first vaccination; D57=Day 57 timepoint for second vaccination; VW=voluntary withdrawal; PD=protocol deviation; AE=adverse event; FU=follow-up.
*ClinicalTrials.gov identifier: NCT05513391

Major protocol deviations are summarized in Table 24 below.

Table 24. Major and Critical Protocol Deviations, Randomized Population, Study VAP00026*

Deviation	RIV4 (%) N=183	IIV4 (%) N=183	All (%) N=366
Participants with at least one major or critical deviation	20.8	19.1	19.7
Participants with at least one major deviation	20.8	18.6	19.7
Assessment (Diary) not performed	1.1	0	0.5
IMP administered but not within protocol-specified time window	3.3	3.3	3.3
IMP dispensed without IRT allocation at re-supply visit	0	0.5	0.3
IMP not administered	1.1	1.1	1.1
Blood sample not performed within protocol-specified time window	2.2	5.5	3.8
Blood sample not performed	5.5	5.5	5.5
Previous vaccination against influenza in the previous 6 months with an investigational or marketed vaccine	0	0.5	0.3
Protocol-prohibited therapy, medication, or vaccine administered	1.6	1.1	1.4
Randomization not performed in sequence as defined in protocol	0.5	0	0.3
Receipt of any vaccine in the 4 weeks preceding first study intervention administration or planned receipt of any vaccine in the 4 weeks following study intervention administration	0.5	0	0.3
Informed consent/assent form not obtained before intervention(s) performed as specified in protocol	0.5	1.1	0.8
Informed consent/assent not obtained for amendment requiring re-consent	0.5	0	0.3
Informed consent/assent obtained with a misconduct in consent process or documentation	0	0.5	0.3
Study physical visit, phone call or safety contact not performed	2.7	3.3	3.0
Wrong randomization stratum	3.3	1.1	2.2
Study participants with at least one critical protocol deviation	0	1.1	0.5
Informed consent/assent form obtained with a misconduct in consent process or documentation	0	1.1	0.5

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR Tables 5 and 8.13, and evaluation of the electronic datasets.
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=quadrivalent inactivated influenza vaccine; N=denominator; IMP=investigational medicinal product
*ClinicalTrials.gov identifier: NCT05513391

A total of 72 of 366 randomized participants (19.7%) had at least one major protocol deviation: 38 participants (20.8%) and 34 participants (18.6%) in the RIV4 and IIV4 groups, respectively. The most frequently reported major protocol deviations were: “Planned sample (blood) not performed” deviation (5.5% in each group), “Planned sample (blood) not performed within the protocol-specified time window” (2.2% and 5.5% of RIV4 and IIV4 participants, respectively) and “IMP administered but not within the protocol-specified time window” (3.3% in each group). A

total of 2 participants, both (1.1%) in the IIV4 group, had at least 1 critical protocol deviation: "Study Informed consent/Assent form obtained with a misconduct in consent process or documentation". Review of the listings (Appendix 16.2, Listing 2.1) described both deviations as follows:

- ID(b) (6) and ID(b) (6) : ICF signed for incorrect study. Site personnel reviewed the VAP00026 ICF with the participant but then accidentally "grabbed" a VAP00027 ICF for the participant to sign and did not realize it until after the visit was over.

Reviewer Comment: *Evaluation of the electronic datasets was consistent with the Applicant's report of the disposition of participants and protocol deviations. Individual categories of deviations were relatively low in frequency and generally balanced between treatment groups. The percentage of participants whose serology samples were collected out of the pre-specified time window, RIV4 2.2% and IIV4 5.5%, were also relatively low and unlikely to have had a large impact on the primary immunogenicity analyses.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary objective of the study was to demonstrate the NI immune response of RIV4 as compared to IIV4 for all 4 vaccine strains, as measured by the HI assay using egg-derived antigen, in all participants 3 to 8 years of age.

As described in Section 6.2.9 of this review, due to enrollment challenges, the protocol was amended to conduct an IA of immunogenicity and the PPoS for each of the 8 NI statistical tests included in the primary objective and for the overall study. Independent unblinded statisticians calculated that the PPoS for meeting the primary objective was <1% and the study was terminated for futility. The final NI analysis was conducted on participants enrolled before study termination, 26% of planned enrollment, and, therefore, had very low statistical power. Please see the statistical review for additional information.

Tables 25 and 26 present results of NI analyses of GMT ratios and SCR differences between RIV4 and IIV4 at 28 days after the last vaccination for all participants 3 through 8 years of age in the PPAS.

Table 25. Noninferiority Analysis of GMTs for RIV4 versus IIV4 at 28 Days Postvaccination, Per Protocol Analysis Set, Study VAP00026*

Antigen Strain	RIV4 GMT N=160	RIV4 95% CI N=160	IIV4 GMT N=158	IIV4 N=158 95% CI	RIV4/IIV4 GMT Ratio	RIV4/IIV4 GMT Ratio 95% CI	NI
A/H1N1	998	(779, 1279)	640	(493, 831)	1.28	(0.948, 1.73)	Y
A/H3N2	2398	(1914, 3004)	889	(772, 1095)	2.53	(1.93, 3.30)	Y
B/Victoria	337	(263,432)	605	(480, 762)	0.515	(0.397, 0.668)	N
B/Yamagata	789	(634, 983)	708	(590, 850)	1.02	(0.799, 1.30)	Y

Source: Modified from STN 125285/613, Module 5, FSR VAP00026, Tables 9, 8.118
Abbreviations: GMT=geometric mean titer; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; CI=confidence interval; LL=lower limit of the 2-sided 95% CI; NI=noninferiority; Y=yes, met NI endpoint; N=No, did not meet NI endpoint; 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
Number of participants with available data for the endpoint for RIV4=159 and for IIV4=158.
Success criteria for noninferiority of GMTs: For each vaccine strain, the LL of the 95% CI for the GMT ratio (RIV4 / GMT IIV4) must be >0.667.
Denominators for RIV4: n=159 for all 4 strains. Denominators for IIV4: n=158 for all 4 strains.
*ClinicalTrials.gov identifier: NCT05513391

Table 26. Noninferiority Analysis of SCRs for RIV4 versus IIV4 at 28 Days Postvaccination, Per Protocol Analysis Set, Study VAP00026*

Antigen Strain	RIV4 SCR (%) N=160	RIV4 95% CI N=160	IIV4 SCR (%) N=158	IIV4 95% CI N=158	SCR Difference (RIV4 – IIV4) (%)	SCR Difference 95% CI	NI
A/H1N1	84.8	(78.2, 90.0)	77.7	(70.4, 84.0)	7.10	(-1.55, 15.7)	Y
A/H3N2	82.3	(75.4, 87.9)	66.9	(58.9, 74.2)	15.4	(5.80, 24.7)	Y
B/Victoria	85.4	(79.0. 90.5)	92.4	(87.0, 96.0)	-6.91	(-14.02, 0.10)	N
B/Yamagata	88.6	(82.6, 93.1)	82.8	(76.0,88.4)	5.81	(-1.99, 13.6)	Y

Source: Modified from STN 125285/613, Module 5, FSR VAP00026, Tables 10, 8.120
Abbreviations: SCR=seroconversion rate; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; CI=confidence interval; LL=lower limit of the 2-sided 95% CI; NI=noninferiority; Y=yes, met NI endpoint; N=No, did not meet NI endpoint; 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
Number of participants with available data for the endpoint for RIV4=130-140 and for IIV4=105-145.
Success criteria for noninferiority of GMTs: For each vaccine strain, the LL of the 95% CI for the SCR Difference (SCR RIV4 – SCR IIV4) must be >-10%.
Denominators for RIV4: n=158 for all 4 strains. Denominators for IIV4: n=157 for all 4 strains.
*ClinicalTrials.gov identifier: NCT05513391

Study VAP00026 did not meet the primary endpoint of NI GMTs and SCRs for RIV4 as compared with IIV4 for all 4 vaccine antigens. For the B/Victoria strain, the LL of the 95% CI for the GMT ratio was 0.397 (less than the pre-specified success criterion of >0.667) and the LL of the 95% CI for the difference in SCRs was -14.02% (less than the pre-specified criterion of >-10%). Additionally, the PPoS calculation was <1%, indicating that the probability of meeting the primary objective by the end of the study (with the targeted enrollment) was very low.

Individually, NI analyses for the A/H1N1, A/H3N2 and B/Yamagata strains met success criteria for both GMT ratios and SCR differences. The Applicant conducted NI analyses and calculated the PPoS using the FAS (VAP00026 FSR Tables 8.119 and 8.121) and obtained similar results as reported for the PPAS.

The FDA statistical reviewer also calculated the PPoS and obtained results similar to that of the Applicant with an overall PPoS of <1% for the study.

> ***Reviewer Comments:*** *Although the PPoS indicated that the two influenza A strains and the B/Yamagata strain (now extinct and no longer included in the Flublok trivalent formulation) were likely to have rejected the null hypothesis and meet success criteria if the planned enrollment had been achieved, the B/Victoria strain and the overall study were very likely to have failed to meet the primary immunogenicity endpoint. Minutes of the FIC meeting held on September 22, 2023 were included in the FSR Appendix 10 (SAP) and stated that the FIC reviewed unblinded IA key results and, based on the pre-defined futility criteria in the FIC charter, recommended stopping further enrollment in the study. Therefore, the Applicant terminated the study for futility.*
>
> *On December 21, 2023, under IND 15784 Amendment 117, the Applicant had responded to FDA's request for a repeat futility analysis restricted to the subgroup of participants 6 through 8 years of age in whom the IA of study VAP00026 had shown higher immune responses as compared with children 3 through 5 years of age. In the 6 through 8 years age group, the GMT ratio and SCR difference for the B/Victoria strain were 0.758 (95% CI: 0.489, 1.18) and -0.98 (95% CI: -10.59, 9.06), respectively. The PPoS for the GMT ratio and SCR difference for the B/Victoria strain were 29.5% and 83.8%, respectively. The PPoS for*

the GMT ratio and SCR difference for each of the A/H1N1, A/H3N2 and B/Yamagata strains ranged from 94.3% to 100%. The PPoS for the GMT ratio and SCR for all four strains collectively were 29.3% and 79.0%. The PPoS for the overall study (eight co-primary endpoints) was 23.2%. During review of the current license application (STN 125285/613.7), the Applicant referred to their previous response to our request for a futility analysis restricted to participants 6 through 8 years of age and stated that the PPoS of 23.2% predicted a very low probability of demonstrating noninferiority in the older age subgroup. The Applicant also emphasized that the futility analysis had been planned for a larger sample size and had not pre-specified a statistical hypothesis for the 6 through 8 years age subgroup and that the exploratory analyses must be interpreted with caution.

Although the study was extremely underenrolled and underpowered, individual analyses for the RIV4 A/H1N1, A/H3N2 and B/Yamagata strains met success criteria for NI GMT ratios and SCR differences. This may be because those vaccine antigens were more immunogenic than assumed in pre-specified power calculations. However, due to the low immunogenicity of the B/Victoria antigen, the unplanned small sample size did not provide adequate statistical power for inferential hypothesis testing of all 4 vaccine strains. Additionally, due to the low immunogenicity of the B/Victoria strain, the PPoS suggests that the study would have failed to meet the primary endpoint even if it had an adequate sample size and statistical power. Reasons for the relatively lower immunogenicity of the B/Victoria strain could be due to differences in prior exposure (wildtype or vaccinations), lack of priming in younger children, antigen epitopes, HI assay sensitivity, and/or other factors. Please see a summary of the Applicant's thoughts on potential causes in Section 6.1.11.3 of this review. Statistical power issues aside, even if we were to consider approval of RIV4 in children 3 through 8 years of age, because the B/Yamagata strain is no longer recommended for inclusion in seasonal influenza vaccine formulations, the RIV3 vaccine may only be effective against influenza A strains and not protect young children against influenza type B which is known to be a more serious disease in children than in adults. Therefore, this reviewer agrees with the Applicant's futility conclusion.

6.2.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objective was to summarize the HI immune response induced by RIV4 and IIV4 for the 4 strains based on egg-derived antigen in participants 3 through 8 years of age in terms of HI titers, GMTs, SCRs, and percentages of participants with HI titers ≥1:40 prior to vaccination on Day 1 and at 28 days after the last vaccination (Day 29 or Day 57).

HI Antibody Titers

Evaluation of HI GMTs at baseline (Day 1) and at 28 days after the last vaccination (Day 29 or Day 57) was conducted on the PPAS by treatment group in all participants and by priming status. At baseline, GMTs for RIV4 were higher as compared with IIV4, respectively, with overlapping 95% CIs:

- A/H1N1 strain: 70.5 (95% CI: 52.2, 95.2) vs 46.5 (95% CI: 33.9, 63.7)
- A/H3N2 strain: 141 (95% CI: 103, 193) vs 112 (95% CI: 81.1, 156)
- B/Victoria strain: 20.9 (95% CI: 16.9, 25.8) vs 18.4 (14.9, 22.7)
- B/Yamagata strain: 65.2 (95% CI: 50.9, 83.5) vs 54.7 (95% CI: 42.8, 70.1)

At D29 or D57 (28 days after the last vaccination), GMTs increased for each antigen, highest for A/H3N2 and lowest for B/Victoria. Postvaccination GMTs for RIV4 as compared with IIV4, respectively, were:

- A/H1N1: 998 (95% CI: 779, 1279) vs 640 (95% CI: 493, 831)
- A/H3N2: 2398 (95% CI: 1914, 3004) vs 889 (95% CI: 722, 1095)
- B/Victoria: 337 (95% CI: 263, 432) vs 605 (95% CI: 480, 762)
- B/Yamagata: 789 (95% CI: 634, 983) vs 708 (95% CI: 590, 850)

The fold-rise in GMTs between baseline and 28 days postvaccination were similar between RIV4 and IIV4, respectively, for A/H1N1 (14.2 and 13.8) and B/Yamagata (12.2 and 13.1), were higher for RIV4 for A/H3N2 (17.1 and 7.86) and lower for B/Victoria (16.0 and 32.7). The same patterns in postvaccination fold-rise in GMTs were observed for the previously vaccinated (primed) and previously unvaccinated (unprimed) single and two-dose groups, respectively (data not shown).

Post-vaccination HI titers ≥1:40 at 28 Days Postvaccination

The number and percentage of participants in the PPAS who were seropositive (detectable HI titer ≥1:10) and with HI titers ≥1:40 (%HI ≥1:40) at Day 1 and Day 29 are presented in Table 11 of the FSR. At baseline, the percentages of participants with HI titer ≥1:10 for each strain were similar between RIV4 (69.8%-87.4%) and IIV4 (63.1%-87.3%) groups, lowest for B/Victoria. At baseline, the %HI ≥1:40 for each strain were similar between treatment groups, ranging from 35.8% to 76.1% for RIV4 and from 33.8% to 70.1% for IIV4, % HI ≥1:40 were lowest for B/Victoria in both groups.

Table 27 below shows the percentages of participants with postvaccination HI titers ≥1:40 at Day 29 or Day 57 by treatment group and vaccine strain.

Table 27. Percentages of Participants with HI titers ≥1:40 at 28 Days Postvaccination by Treatment Group and Vaccine Antigen Strain, Per Protocol Analysis Set, Study VAP00026*

Antigen Strain	RIV4 % HI ≥1:40 (95% CI) N=160	IIV4 % HI ≥1:40 (95% CI) N=158
A/H1N1	97.5 (93.7, 99.3)	96.2 (91.9, 98.6)
A/H3N2	98.1 (94.6, 99.6)	98.1 (94.6, 99.6)
B/Victoria	92.5 (87.2, 96.0)	96.8 (92.8, 99.0)
B/Yamagata	99.4 (96.5, 100)	99.4 (96.5, 100)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Tables 11 and 8.122
Abbreviations: HI=hemagglutination inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for RIV4: 159 for all 4 strains. Denominators for IIV4: 158 for all 4 strains.
*ClinicalTrials.gov identifier: NCT05513391

Reviewer Comment: *The lower limits of the 95% CI for the percentages of participants 3 through 8 years of age with postvaccination HI titers ≥1:40 were >70% in both treatment groups but were lower for the B/Victoria strain in the RIV4 group as compared with the IIV4 group, 87.2% and 92.8%, respectively.*

Seroconversion Rates

The percentages of participants with seroconversion to each vaccine strain, are presented in Table 28. At 28 days after the last vaccination, as compared with IIV4, SCRs were higher in the RIV4 group for the A/H1N1 and A/H3N2 strains, lower in the RIV4 group for the B/Victoria strain, and were similar for the B/Yamagata strain.

Table 28. HI Seroconversion Rates at 28 Days Post-Vaccination by Treatment Group and Vaccine Antigen Strain, Per Protocol Analysis Set, Study VAP00026*

Antigen Strain	RIV4 SCR (%) (95% CI) N=160	IIV4 SCR (%) (95% CI) N=158
A/H1N1	84.8 (78.2, 90.0)	77.7 (70.4, 84.0)
A/H3N2	82.3 (75.4, 87.9)	66.9 (58.9, 74.2)
B/Victoria	85.4 (79.0, 90.5)	92.4 (87.0, 96.0)
B/Yamagata	88.6 (82.6, 93.1)	82.8 (76.0, 88.4)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Tables 11 and 8.122
Abbreviations: HI=hemagglutination inhibition; SCR=seroconversion rate; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for RIV4: 158 for all 4 strains. Denominators for IIV4: 157 for all 4 strains.
*ClinicalTrials.gov identifier: NCT05513391

> ***Reviewer Comment:*** *The lower limits of the 95% CI for SCRs in participants 3 through 8 years of age were >40% in both treatment groups but were lower for the B/Victoria strain in the RIV4 group as compared with the IIV4 group, 79.0% and 87.0%, respectively.*

6.2.11.3 Subpopulation Analyses

Subgroup analyses of HI GMTs, % HI ≥1:40, and SCRs according to age, sex, race, ethnicity, priming status, and baseline seropositivity were conducted on the PPAS and described in detail in Section 5.1.2 (Table 11) and Appendix 15 (Tables 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22) of the FSR.

Priming Status

HI Antibody Titers

In previously unvaccinated (unprimed) participants, at 28 days after the second vaccination (Day 57), GMTs increased in both RIV4 and IIV4 treatment groups, respectively, as follows:

- A/H1N1: 1704 (95% CI: 1246; 2330) vs 979 (95% CI: 685; 1399)
- A/H3N2: 2986 (95% CI: 2068; 4313) vs 895 (95% CI: 663; 1208)
- B/Victoria: 567 (95% CI: 394; 816) vs 1514 (95% CI: 1196; 1916)
- B/Yamagata: 606 (95% CI: 424; 865) vs 700 (95% CI: 535; 916)

As compared with IIV4, postvaccination HI GMTs in RIV4 recipients were higher for the A/H3N2 strain and lower for the B/Victoria strain. Postvaccination GMTs against A/H1N1 and B/Yamagata were similar.

In previously vaccinated (primed) participants, at 28 days after a single vaccination, HI GMTs increased in both RIV4 and IIV4 groups, respectively, as follows:

- A/H1N1: 703 (95% CI: 500; 989) vs 486 (95% CI: 340; 695)

- A/H3N2: 2076 (95% CI: 1560; 2764) vs 886 (95% CI: 665; 1179);
- B/Victoria: 240 (95% CI: 174; 330) vs 334 (95% CI: 249; 449);
- B/Yamagata: 938 (95% CI: 711; 1239) vs 713 (95% CI: 556; 915)

As compared with IIV4, postvaccination HI GMTs were higher for the A/H3N2 strain while no meaningful differences were observed between treatment groups for the other 3 strains.

Comparison of postvaccination HI GMTs between previously unvaccinated and previously vaccinated participants in the RIV4 group, showed that previously unvaccinated participants had higher postvaccination GMTs against the A/H1N1 and B/Victoria strains as compared with previously vaccinated RIV4 recipients. Although postvaccination GMTs in unprimed RIV4 recipients as compared with previously vaccinated participants were similar for the A/H3N2 and B/Yamagata strains.

Table 29 presents postvaccination GMTs and GMT ratios for RIV4 relative to IIV4 according to priming status and vaccine strain.

Table 29. Postvaccination HI GMTs and GMT Ratios by Priming Status*, Treatment Group, and Vaccine Strain, Per Protocol Analysis Set, Study VAP00026**

Priming Status	Antigen/ Strain	RIV4 GMT N=160	RIV4 95%CI N=160	IIV4 GMT N=158	IIV4 95% CI N=158	GMT Ratio	GMT Ratio 95% CI
Previously unvaccinated	A/H1N1	1704	(1246,2330)	979	(685,1399)	1.74	(1.09, 2.78)
Previously vaccinated	A/H1N1	703	(500,989)	486	(340,695)	1.45	0.884, 2.36)
Previously unvaccinated	A/H3N2	2986	(2068, 4313)	895	(663,1208)	3.34	(2.08, 5.34)
Previously vaccinated	A/H3N2	2076	(1560,2764)	886	(665,1179)	2.34	(1.57, 3.50)
Previously unvaccinated	B/Victoria	567	(394,816)	1514	(1196,1916)	0.375	(0.244, 0.576)
Previously vaccinated	B/Victoria	240	(174,330)	334	(249,449)	0.717	(0.466, 1.11)
Previously unvaccinated	B/Yamagata	606	(424,865)	700	(535,916)	0.865	(0.555, 1.35)
Previously vaccinated	B/Yamagata	938	(711,1239)	713	(556,915)	1.32	(0.908, 1.91)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Appendix 15, Table 16.
Abbreviations: GMT=geometric mean titer; HI=hemagglutination inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for Previously Unvaccinated: RIV4 n=63; IIV4 n=62.
Denominators for Previously Vaccinated: RIV4 n=96; IIV4 n=96.
*Previously unvaccinated defined as participants who did not receive an influenza vaccination in the previous influenza season (two-dose group; postvaccination HI titer collected at Day 57). Previously vaccinated defined as participants who received an influenza vaccination in the previous season (single dose group; postvaccination HI titer collected at Day 29).
**ClinicalTrials.gov identifier: NCT05513391

Reviewer Comment: *Within the RIV4 group, a trend was observed toward higher postvaccination GMTs in previously unvaccinated participants as compared with previously vaccinated participants (other than for the B/Yamagata strain). Although the study was not powered to evaluate NI GMT ratios by priming status, previously unvaccinated (unprimed) RIV4 participants did not meet success criteria for the B/Victoria or B/Yamagata strains (LLs of the 95% CI for the GMT ratios: 0.244 and 0.555, respectively) and previously vaccinated*

(primed) RIV4 recipients did not meet success criteria for the B/Victoria strain (LL of the 95% CI: 0.466). For all 4 vaccine strains, differences in GMT ratios according to priming status were not meaningfully different (95% CIs overlapped for all strains). However, the relative effect of priming status on postvaccination GMTs was more apparent in responses to the B/Victoria strain where the GMT ratio of 0.375 in the previously unvaccinated group was nearly half the GMT ratio of 0.717 estimated in the previously vaccinated group. Relative differences in GMT ratios between these subgroups were less pronounced for the other three vaccine strains.

Percentages with HI titer ≥1:40

In previously unvaccinated participants, at 28 days after the second vaccination (Day 57) with RIV4 or IIV4, the percentages of participants with HI titers ≥1:40 were high for all 4 strains and similar between both vaccination groups, ranging from 98.4% to 100% in both groups.

In previously vaccinated participants, at 28 days after a single vaccination (Day 29) with RIV4 or IIV4, the percentages of participants with HI titers ≥1:40 were high and similar between the respective treatment groups except for the B/Victoria strain where the %HI ≥1:40 was lower in RIV4 recipients as compared with IIV4: A/H1N1 (95.8% vs 94.8%); A/H3N2 (97.9% vs 97.9%); B/Victoria (88.5% vs 94.8%); and B/Yamagata (100% vs 99.0%).

Seroconversion Rates

SCRs for previously vaccinated and previously unvaccinated participants followed patterns observed for the entire population in general, showing higher SCRs for A/H3N2 and lower SCRs for B/Victoria following RIV4 as compared with IIV4. SCRs and SCR differences by priming status are presented in Table 30.

Table 30. Postvaccination Seroconversion Rates and Seroconversion Rate Differences by Priming Status*, Treatment Group and Vaccine Strain, Per Protocol Analysis Set, Study VAP00026**

Priming Status	Antigen Strain	RIV4 SCR (%) N=160	RIV4 95%CI N=160	IIV4 SCR (%) N=158	IIV4 95% CI N=158	SCR Difference (RIV4-IIV4) (%)	SCR Difference 95% CI
Previously unvaccinated	A/H1N1	93.5	(84.3,98.2)	88.5	(77.8, 95.3)	5.02	(-5.68, 16.1)
Previously vaccinated	A/H1N1	79.2	(69.7, 86.8)	70.8	(60.7, 79.7)	8.33	(-3.93, 20.3)
Previously unvaccinated	A/H3N2	85.5	(74.2, 93.1)	68.9	(55.7, 80.1)	16.6	(1.75, 30.8)
Previously vaccinated	A/H3N2	80.2	(70.8, 87.6)	65.6	(55.2, 75.0)	14.6	(2.00, 26.6)
Previously unvaccinated	B/Victoria	96.8	(88.8, 99.6)	100	(94.1, 100)	-3.23	(-11.02, 3.14)
Previously vaccinated	B/Victoria	78.1	(68.5, 85.9)	87.5	(79.2, 93.4)	-9.38	(-20.00, 1.39)
Previously unvaccinated	B/Yamagata	91.9	(82.2, 97.3)	95.1	(86.3, 99.0)	-3.15	(-13.15, 6.57)
Previously vaccinated	B/Yamagata	86.5	(78.0, 92.6)	75.0	(65.1, 83.3)	11.5	(0.24, 22.4)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Appendix 15, Table 18.
Abbreviations: SCR=seroconversion rate, defined as pre-vaccination HI titer <1:10 and a postvaccination titer ≥1:40 or pre-vaccination titer ≥1:10 and a ≥4-fold increase in postvaccination titer; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for Previously Unvaccinated: RIV4 n=62; IIV4 n=61.
Denominators for Previously Vaccinated: RIV4 n=96; IIV4 n=96.

*Previously unvaccinated defined as participants who did not receive an influenza vaccination in the previous influenza season (two-dose group; postvaccination HI titer collected at Day 57). Previously vaccinated defined as participants who received an influenza vaccination in the previous season (single dose group; postvaccination HI titer collected at Day 29).
**ClinicalTrials.gov identifier: NCT05513391

In the RIV4 group, SCRs were higher in previously unvaccinated participants than in previously vaccinated participants for the B/Victoria strain [96.8% (95% CI: 88.8, 99.6) vs 78.1% (95% CI: 68.5, 85.9)], showed a trend to be higher in previously unvaccinated participants for the A/H1N1 strain, and were comparable between subgroups for the A/H3N2 and B/Yamagata strains.

In the IIV4 group, SCR were higher in previously unvaccinated participants than in previously vaccinated participants for B/Victoria lineage strain [100% (95% CI: 94.1; 100) vs 87.5% (95% CI: 79.2; 93.4)] and B/Yamagata strain [95.1% (95% CI: 86.3; 99.0) vs 75.0% (95% CI: 65.1; 83.3)], showed a trend to be higher for A/H1N1, and were comparable between subgroups for the A/H3N2 strain.

Noninferiority comparisons between treatment groups showed that previously unvaccinated participants had LLs of the 95% CI for SCR differences (RIV4 minus IIV4) less than -10% for the B/Victoria and B/Yamagata strains, -11.02 and -13.15, respectively, and previously vaccinated participants had LLs of the 95% CI for the SCR difference less than -10% for the B/Victoria strain (-20.00). SCR differences between the previously unvaccinated and previously vaccinated subgroups were not meaningfully different for any of the vaccine strains.

> ***Reviewer Comment:*** *Although we might postulate that previously vaccinated participants had higher baseline HI GMTs and, therefore, more difficulty achieving a 4-fold rise in HI titer to at least 1:40 (i.e., seroconversion), low immune responses to the B/Victoria strain were also observed in previously unvaccinated RIV4 participants relative to IIV4, and consistently in various other subgroup analyses. This observation is not readily explained by priming status, could be affected by other factors such as prior wildtype exposure, inherent differences in antigenicity among vaccine strains, and/or vaccine platforms, but is essentially unknown. Our ability to draw definitive conclusions is also limited by the small sample sizes for both primary and secondary immunogenicity analyses and insufficient statistical power to test hypotheses.*

Baseline Serostatus

HI Antibody Titers

Analyses by baseline seropositivity showed that at 28 days post-vaccination, HI GMTs for each strain were higher in baseline seropositive participants than in baseline seronegative participants in both the RIV4 and IIV4 groups:

- RIV4 baseline seropositive (n=110 to 138): A/H1N1 1480; A/H3N2 3161; B/Victoria 450; B/Yamagata 1000.
- RIV4 baseline seronegative (n=20 to 48): A/H1N1 231; A/H3N2 355; B/Victoria 172; B/Yamagata 210.
- IIV4 baseline seropositive (n=99-137): A/H1N1 1042; A/H3N2 1206; B/Victoria 658; B/Yamagata 772.
- IIV4 baseline seronegative (n=20 to 58): A/H1N1 201; A/H3N2 224; B/Victoria 516; B/Yamagata 422.

The study was not powered to assess noninferiority in subgroup analyses. However, the relative effect of baseline serostatus was more pronounced in the RIV4 group as compared with IIV4 and for the B/Victoria strain. The LL of the 95% CIs for GMT ratios (RIV4 / IIV4) were ≤0.667

(i.e., not NI) for all strains in the baseline seronegative group and for B/Victoria in the baseline seropositive group as shown in Table 31 below.

Table 31. Postvaccination GMT Ratios (RIV4/IIV4) by Baseline Serostatus* and Vaccine Strain, Per Protocol Analysis Set, Study VAP00026**

Baseline serostatus*	A/H1N1 RIV4/IIV4 GMT ratio (95% CI)	A/H3N2 RIV4/IIV4 GMT ratio (95% CI)	B/Victoria RIV4/IIV4 GMT ratio (95% CI)	B/Yamagata RIV4/IIV4 GMT ratio (95% CI)
Baseline seropositive	1.42 (0.992, 2.04)	2.62 (2.00, 3.43)	0.683 (0.472, 0.990)	1.30 (0.966, 1.74)
Baseline seronegative	1.15 (0.566, 2.34)	1.59 (0.619, 4.07)	0.333 (0.169, 0.656)	0.497 (0.245, 1.01)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Appendix 15, Table 20.
Abbreviations: GMT=geometric mean titer; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for Per Protocol Analysis Set: RIV4=160; IIV4=158
Denominators for Baseline Seropositive: RIV4 n=110-138; IIV4 n=99-137
Denominators for Baseline Seronegative: RIV4 n=20-48; IIV4 n=20-58
Postvaccination HI titers collected at Day 29 or Day 57 (single or 2-dose group, respectively)
*Baseline seropositive defined as baseline (prevaccination Day 0) HI antibody titer ≥1:10; Baseline seronegative defined as baseline (prevaccination Day 0) antibody titer <1:10.
**ClinicalTrials.gov identifier: NCT05513391

Seroconversion Rates

In baseline seropositive participants, SCRs were higher for A/H3N2, A/H1N1 and B/Yamagata, and lower for B/Victoria in the RIV4 group (n=110 to 138) as compared with IIV4 (n=99 to 137). In baseline seronegative participants, SCRs were similar between treatment groups, except for the B/Victoria strain for which the SCR was lower in the RIV4 group. Within the RIV4 and IIV4 groups, SCRs were not notably different by baseline serostatus except for SCRs for the A/H3N2 strain in the IIV4 group which were higher in baseline seronegative participants. SCRs and 95% CIs for the RIV4 group by baseline serostatus were as follows:

- RIV4 baseline seropositive (n=110 to 138): A/H1N1 83.1% (75.3, 89.2); A/H3N2 80.4% (72.8, 86.7); B/Victoria 86.4% (78.5, 92.2); B/Yamagata 86.7% (79.7, 91.9).
- RIV4 baseline seronegative (n=20 to 48): A/H1N1 91.2% (76.3, 98.1); A/H3N2 95.0% (75.1, 99.9); B/Victoria 83.3% (69.8, 92.5); B/Yamagata 100% (85.2, 100).

The study was not powered to assess noninferiority in these subgroup analyses. However, the LL of the 95% CIs for SCR differences (RIV4 minus IIV4) were ≤-10% (not NI) for all strains in the baseline seronegative group and for B/Victoria in the baseline seropositive group (data are located in VAP00026 FSR Appendix 15, Table 22).

> ***Reviewer Comments:*** *Subgroup analyses by baseline serostatus suggest a trend towards NI SCRs for RIV4 as compared with IIV4 in baseline seropositive participants but not in baseline seronegative participants for the A/H1N1, A/H3N2, and B/Yamagata strains. SCRs for B/Victoria were not NI to IIV4 in both subgroups. The subgroup analyses were not powered for hypothesis testing and the clinical significance of the results are inconclusive.*
>
> *Please see Section 6.1.11.3 of this review for the Applicant's thoughts on the low immunogenicity of the B/Victoria strain in general and regarding Study VAP00027. Regarding Study VAP00026, the Applicant also noted that postvaccination GMTs to B/Victoria in the RIV4 group were lower in the younger age group (3 through 5 years) as compared with older children (6 through 8 years) while GMTs were more comparable*

between age groups following IIV4, suggesting that age may have a greater influence in the immune response to B/Victoria in RIV4 recipients as compared with IIV4. In both RIV4 and IIV4 groups, postvaccination GMTs to B Victoria were lower in previously unvaccinated children than in previously vaccinated children but the size of the effect was stronger in RIV4 group. Similarly, for both RIV4 and IIV4, postvaccination GMTs against B Victoria tended to be lower in children seronegative at baseline, with relatively lower responses following RIV4 as compared with IIV4. The Applicant noted that, as compared with IIV4, RIV4 consistently showed lower GMTs to the B/Victoria strain across various subgroups, indicating a generally lower immune response. This was particularly true for younger children (3 through 5 years of age), suggesting limited effectiveness in this age group. The Applicant concluded that the very low Ab responses observed in immunologically naive individuals suggest that RIV4 may be less appropriate as a vaccine for primary immunization, particularly in younger children and those without prior exposure to influenza antigens.

Age Subgroups

HI Antibody Titers

Postvaccination (Day 29 or Day 57) HI GMTs (95% CIs) for RIV4 versus IIV4 participants 3 through 5 years of age were as follows:

- A/H1N1: 856 (95% CI: 559, 1311) vs 511 (95% CI: 349, 747)
- A/H3N2: 2052 (95% CI: 1374, 3066) vs 897 (95% CI: 643, 1253)
- B/Victoria: 264 (95% CI: 173, 404) vs 680 (95% CI: 491, 942)
- B/Yamagata: 464 (95% CI: 324, 666) vs 686 (95% CI: 517, 911)

Postvaccination (Day 29 or Day 57) HI GMTs (95% CI) for RIV4 versus IIV4 participants 6 through 8 years of age were as follows:

- A/H1N1: 1123 (95% CI: 835, 1511) vs 806 (95% CI: 563, 1155)
- A/H3N2: 2702 (95% CI: 2090, 3493) vs 881 (95% CI: 684, 1135)
- B/Victoria: 406 (95% CI: 303, 545) vs 536 (95% CI: 383, 749)
- B/Yamagata: 1185 (95% CI: 927, 1515) vs 731 (95% CI: 578, 925)

In both age subgroups, GMTs were highest against the A/H3N2 strain and were higher in the RIV4 age subgroups as compared to IIV4. In both age subgroups, GMTs against the A/H1N1 strain were robust and similar (overlapping 95% CIs) between treatment groups.

In both age subgroups, GMTs were lowest against the B/Victoria strain and tended to be lower in the RIV4 subgroups as compared with IIV4, particularly in participants 3 through 5 years of age. GMTs against the B/Yamagata strain were robust in the 6 through 8 years of age subgroup and notably lower for RIV4 in the 3 through 5 years of age subgroup.

Within the RIV4 group, GMTs against all 4 strains were tended to be higher in the 6 through 8 years of age subgroup as compared with 3 through 5 years of age and with the largest difference (and non-overlapping 95% CIs) observed for the B/Yamagata strain.

Seroconversion Rates

SCRs and SCR differences between RIV4 and IIV4 by age subgroups are presented in Table 32.

Table 32. HI Seroconversion Rates at 28 Days Postvaccination by Age Subgroup, Treatment Group and Vaccine Antigen Strain, Per Protocol Analysis Set, Study VAP00026*

Age Subgroup	Antigen Strain	RIV4 SCR (%) 95% CI N=160	IIV4 SCR (%) 95% CI N=158	SCR Difference (%) RIV4-IIV4 (95% CI)
3-5 years	A/H1N1	91.3 (82.0, 96.7)	81.0 (70.6, 89.0)	10.3 (-1.19, 21.3)
3-5 years	A/H3N2	89.9 (80.2, 95.8)	77.2 (66.4, 85.9)	12.6 (0.43, 24.2)
3-5 years	B/Victoria	81.2 (69.9, 89.6)	94.9 (87.5, 98.6)	-13.78 (-24.98, -3.36)
3-5 years	B/Yamagata	88.4 (78.4, 94.9)	89.9 (81.0, 95.5)	-1.47 (-12.29, 8.80)
6-8 years	A/H1N1	79.8 (69.9, 87.6)	74.4 (63.2, 83.6)	5.42 (-7.25, 18.2)
6-8 years	A/H3N2	76.4 (66.2, 84.8)	56.4 (44.7, 67.6)	20.0 (5.67, 33.4)
6-8 years	B/Victoria	88.8 (80.3, 94.5)	89.7 (80.8, 95.5)	-0.98 (-10.59, 9.06)
6-8 years	B/Yamagata	88.8 (80.3, 94.5)	75.6 (64.6, 84.7)	13.1 (1.53, 24.8)

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Appendix 15, Table 6.
Abbreviations: HI=hemagglutination inhibition; SCR=seroconversion rate; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; 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; CI=confidence interval
Denominators for RIV4: 3-5 yrs, n=69; 6 through 8 yrs, n=89. Denominators for IIV4: 3 through 5 yrs, n=79; 6 through 8 yrs, n=78.
*ClinicalTrials.gov identifier: NCT05513391

In the 3 through 5 years age subgroup, as compared with IIV4, SCRs in RIV4 recipients were higher against A/H1N1 and A/H3N2, lower against B/Victoria, and similar for B/Yamagata strains, all with overlapping 95% CIs. The LLs of the 95% CI for SCR differences between RIV4 and IIV4 were less than -10% for B/Victoria (-24.98%) and B/Yamagata (-12.29%).

In the 6 through 8 years age subgroup, as compared with IIV4, SCRs in RIV4 recipients were higher against A/H1N1, A/H3N2 and B/Yamagata (most notably for A/H3N2 but with overlapping 95% CIs) and were similar for the B/Victoria strain. The LLs of the 95%CIs for SCR differences between RIV4 and IIV4 were less than -10% for the B/Victoria strain (-10.59%).

In both treatment groups, SCRs in participants 3 through 5 years of age tended to be higher as compared with participants 6 through 8 years of age but 95% CIs were overlapping. The LLs of the 95% CIs for SCR differences (RIV4 minus IIV4) in participants 3 through 5 years of age were less than -10% for B/Victoria (-24.98%) and B/Yamagata (-12.29%) whereas in participants 6 through 8 years the LL of the 95% CI for the SCR difference was only slightly less than -10% for the B/Victoria strain (-10.59%).

> ***Reviewer Comment:*** *If we were to apply success criteria for NI SCR differences to the age subgroup analyses (i.e., the LL of the 95% CI for SCR RIV4 minus SCR IIV4 must be >-10%), RIV4 recipients 6 through 8 years of age would have met success criteria for 3 of 4 strains and missed criteria for the B/Victoria only marginally. However, the sample sizes were small, CIs wide and the study was not adequately powered for inferential hypothesis testing of primary or secondary endpoints in subgroups. Please also see comments regarding the futility analysis and PPoS earlier in this review.*

6.2.11.4 Dropouts and/or Discontinuations

Dropouts were not replaced. Missing data were not imputed. The study was terminated after enrolling only 26% of the targeted study population. Immunogenicity results must be interpreted with caution.

6.2.11.5 Exploratory and Post Hoc Analyses

Results of SN Ab responses are presented in Section 5.1.3 of the FSR and will not be discussed in detail in this review. The Applicant concluded that SN Ab responses were generally similar to the HI Ab results.

6.2.12 Safety Analyses

6.2.12.1 Methods

The SafAS, defined as all participants who received one dose of vaccine, was used to summarize all safety data. The SafAS was comprised of 362 participants, including 181 participants in each treatment group. Denominators for the SafAS were used to calculate percentages of unsolicited AEs, SAEs, AESIs and MAAEs. Within the SafAS, denominators used to calculate percentages of solicited AEs were the number of participants with non-missing data for the relevant endpoint. Overall, 359 (98.1%) of 366 randomized participants (179 [97.8%] and 180 [98.4%] randomized to the RIV4 and IIV4 groups, respectively) provided any solicited AE data within the solicited AE period. Please see Section 6.2.7 of this review for additional information regarding methods used to collect and assess safety data for Study VAP00026.

Unsolicited AEs occurring within 28 days after vaccination were pre-specified in the Section 4.2.1.2 of the SAP as AEs that occurred with a time of onset between Day 1 and Day 29 and/or missing onset. An AE with missing time of onset was also considered to have occurred just after vaccination. An AEs with a verbatim term but Grade 0 intensity were not included in the analysis but were listed separately. SAEs, AESIs and MAAEs were analyzed as occurring within 28 days after vaccination, from Day 29 to 180 days after vaccination (Day 181), and within 180 days after vaccination (Day 181).

6.2.12.2 Overview of Adverse Events

Table 33 presents an overview of AEs reported in Study VAP00026 according to treatment group and overall.

Table 33. Solicited and Unsolicited Adverse Events Reported through Day 29 and Long-Term Safety through Day 181, SafAS, Study VAP00026*

Adverse Event	RIV4 % N=181	IIV4 % N=181	All % N=362
Immediate unsolicited AE within 30 minutes after vaccination	0	0	0
Immediate unsolicited adverse reaction	0	0	0
Any solicited reaction**	45.8	51.7	48.7
Grade 3 solicited reaction**	7.8	8.9	8.35
Any solicited injection site reaction**	39.1	42.2	40.7
Grade 3 solicited injection site reaction**	4.5	4.4	4.45
Any solicited systemic reaction**	27.9	36.7	32.3
Grade 3 solicited systemic reaction**	3.9	5.0	4.45

Adverse Event	RIV4 % N=181	IIV4 % N=181	All % N=362
Within 28 days after vaccination	--	--	--
Unsolicited AE	24.3	26.0	25.1
Unsolicited AR	2.2	1.1	1.6
AE leading to discontinuation	0	0	0
SAE	0	0.6	0.3
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	9.9	6.6	8.3
During 6-month follow-up period	--	--	--
SAE	0	0	0
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	1.1	1.1	1.1
AE leading to discontinuation	0	0	0
During the study***	--	--	--
SAE	0	0.6	0.3
Death (also an SAE)	0	0	0
AESI	0	0	0
MAAE	10.5	7.7	9.1
AE leading to discontinuation	0	0	0

Source: Modified from STN 125285/613, Module 5, VAP00026 FSR, Tables 13, 14, 8.24, 8.27, and evaluation of the electronic datasets.
Abbreviations: SafAS=safety analysis set; RIV4=Flublok Quadrivalent; IIV4=Fluzone Quadrivalent; AE=adverse event; AR=adverse reaction; SAE=serious adverse event; AESI=adverse event of special interest; MAAE=medically attended adverse event.
*ClinicalTrials.gov identifier: NCT05513391
**Solicited injection site and systemic adverse reactions were all considered related to study vaccine and were collected during the 7 days following vaccination (Day 1 through Day 8). Denominators for Solicited Adverse Reactions safety subsets were used to calculate the percentages of solicited ARs and represented the number of participants who had non-missing data for the relevant endpoint. Non-missing data for solicited reactions included any of the following reactions: None/No presence; Grade 1; Grade 2; and Grade 3. Denominators for both analysis sets for Any Solicited Adverse Reaction, Any Solicited Injection Site Reaction, and Any Solicited Systemic Reaction were: Overall n=359; RIV4 n=179; and IIV4 n=180.
***For long-term safety (SAEs, AESIs, and MAAEs), numbers and percentages of participants with events collected during the 6-month follow-up period represents the interval from Day 29 through the end of the study (Day 181). The period labeled “during the study” represent the number and percentages of participants with events collected within 28 days following vaccination and during the 6-month follow-up period (Day 1 through Day 181).

Overall, no participants in either treatment group experienced an immediate unsolicited AE or AR within 30 minutes postvaccination. Fewer participants in the RIV4 group experienced solicited local or systemic reactions after any vaccination (39.1% and 27.9%, respectively) as compared to participants in the IIV4 group (42.2% and 36.7%, respectively). Within 28 days after vaccination, unsolicited AEs were also reported by slightly fewer RIV4 recipients as compared to IIV4 (24.3% vs 26.0%). Within 180 days after vaccination, percentages of SAEs were low (0 and 0.6%, respectively) in both RIV4 and IIV4 groups. Within 180 days of vaccination, RIV4 recipients had more MAAEs as compared to IIV4 recipients (10.5% and 7.7%, respectively). No deaths, AESIs, or AEs leading to discontinuation were reported during the study.

> ***Reviewer Comment:*** *Evaluation of the electronic datasets yielded numbers and percentages of solicited and unsolicited AEs, and percentages of severity of AEs, consistent with the Applicant’s report.*

Solicited Local Injection Site Reactions

The percentages of solicited local injection site reactions reported in the seven days following vaccination were reviewed, overall, by severity, dose, age, and treatment group. For more detailed information please refer to the VAP00026 FSR, Tables 14, 8.27, 8.28, 8.29, 8.36, 8.37 and 8.38, and the electronic datasets.

A total of 179 and 180 participants in the RIV4 and IIV4 treatment groups, respectively, (79 and 100 RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 91 and 89 IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively) provided data for solicited injection site reactions. Overall, 39.1% and 42.2% of RIV4 and IIV4 participants, respectively, reported any solicited injection site reaction, including 32.9% and 44.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 40.7% and 43.8% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. Overall, Grade 3 solicited injection site reactions occurred in 4.5% and 4.4% of RIV4 and IIV4 recipients, respectively, including 2.5% and 6.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 2.2% and 6.7% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively.

The most commonly reported (≥10%) solicited injection site reactions in the RIV4 or IIV4 groups, respectively, were pain (34.1% and 36.7%), erythema (13.5% and 16.8%), swelling (10.7% and 9.6%), and induration (9.6% and 10.7%). Percentages of injection site reactions in both treatment groups were generally higher in children 6 through 8 years of age as compared with children 3 through 5 years of age, respectively, with the largest imbalance observed for injection site pain: RIV4 40.0% versus 26.6% and IIV4 39.3% versus 34.1%.

> ***Reviewer Comment:*** *Overall, percentages of solicited injection site reactions and Grade 3 reactions were generally similar between treatment groups.*

Most injection site reactions were Grade 1 (mild) or Grade 2 (moderate) in intensity, began between Day 1 and Day 4 after vaccination, and resolved spontaneously after 1-3 days (or 4-7 days for bruising).

Among participants who received two doses of study vaccine (i.e., previously unvaccinated participants), percentages of solicited injection site pain and most other reactions were generally lower following the second vaccination as compared to the first.

Solicited Systemic Reactions

The percentages of solicited systemic reactions reported in the seven days following vaccination were reviewed, overall, by severity, dose, age, and treatment group. For more detailed information please refer to the VAP00026 FSR, Tables 15, 8.27, 8.28, 8.29, 8.54, 8.55, and 8.56, and the electronic datasets.

A total of 179 and 180 participants in the RIV4 and IIV4 treatment groups, respectively, (79 and 100 RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 91 and 89 IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively) provided data for solicited systemic reactions. Overall, 27.9% and 36.7% of RIV4 and IIV4 participants 3 through 8 years of age, respectively, reported any solicited systemic reaction, including 30.4% and 26.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 31.9% and 41.6% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively. Overall, Grade 3 solicited systemic reactions occurred in 3.9% and 5.0% of RIV4

and IIV4 recipients, respectively, including 2.5% and 5.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 2.2% and 7.9% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively.

Overall, the most commonly reported (≥10%) solicited systemic reactions following any vaccination in the RIV4 or IIV4 groups, respectively, were malaise (19.6% and 20.6%), myalgia (16.2% and 23.9%), and headache (12.8% and 16.7%). Percentages of solicited systemic reactions were generally higher in children 6 through 8 years of age as compared to children 3 through 5 years of age, respectively, particularly following IIV4, with the largest imbalances observed for myalgia [RIV4 18.0% vs 13.9% and IIV4 30.3% vs 17.6%] and headache [RIV4 13.0% vs 12.7% and IIV4 20.2% vs 13.2%]. Fever was reported in 4.5% and 7.2% of all RIV4 and IIV4 recipients, respectively, including in 5.1% and 4.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and in 6.6% and 7.9% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively.

> ***Reviewer Comment:*** *Overall, as compared with RIV4, solicited systemic reactions occurred in higher percentages of children in the IIV4 group, driven by the subgroup of children 6 through 8 years of age.*

Most solicited systemic reactions were Grade 1 (mild) or Grade 2 (moderate) in intensity, began between Day 1 and Day 4 after vaccination, and resolved spontaneously, or with medication for fever, after 1-3 days. Grade 3 fever occurred in 1 (0.6%) and 5 (2.8%) children 3 through 8 years of age who received RIV4 or IIV4, respectively.

Among participants who received two doses of study vaccine (i.e., previously unvaccinated participants), percentages of solicited systemic reactions were generally lower following the second vaccination as compared to the first. The percentages and severity of reactions between study groups and age subgroups showed similar patterns as were observed following any vaccination in the overall study population. In previously unvaccinated children, solicited systemic reactions following the first vaccination occurred in a total of 18.2% of RIV4 recipients 3 through 8 years of age (17.9% in 3 through 5 years and 18.4% in 6 through 8 years) and 24.4% of IIV4 recipients 3 through 8 years of age (15.9% in 3 through 5 years and 35.3% of 6 through 8 years). In previously unvaccinated children, solicited systemic reactions following the second vaccination occurred in a total of 16.4% of RIV4 recipients 3 through 8 years of age (16.7% in 3 through 5 years and 16.2% in 6 through 8 years) and 11.3% of IIV4 recipients 3 through 8 years of age (4.8% in 3 through 5 years and 20.7% of 6 through 8 years). The overall percentages of Grade 3 reactions were generally similar between RIV4 and IIV4 groups in children 3 through 5 years of age (2.6% and 2.8%, respectively, after the first vaccination and 2.8% and 0 after the second vaccination). The imbalance in Grade 3 solicited systemic reactions observed between RIV4 and IIV4 in children 6 through 8 years of age following any vaccination was also observed in children previously unvaccinated, with 2.6% and 8.8%, respectively, reporting Grade 3 reactions after the first vaccination and 2.7% and 6.9%, respectively, after the second vaccination.

> ***Reviewer Comment:*** *In previously unvaccinated children, solicited systemic reactions were generally lower following the second vaccination. As compared with RIV4, children in the IIV4 group, in particular those 6 through 8 years of age reported higher percentages of solicited systemic reactions. A higher percentage of participants in the IIV4 group reported use of antipyretic and analgesic agents in the 7 days postvaccination as compared with RIV4 (13.3% vs 7.2%).*

Unsolicited Adverse Events within 28 Days after Any Vaccination

Unsolicited AEs that began following exposure to study treatment were included in the analyses of unsolicited AEs. AEs were coded according to MedDRA PT and SOC, version 26.1. Please see Table 33 at the beginning of Section 6.2.12.2 for an overview of unsolicited AEs.

Immediate Unsolicited Adverse Events

No participants experienced an immediate unsolicited AE within 30 minutes following vaccination.

Unsolicited Adverse Events with 28 Days

Unsolicited AEs experienced by participants within 28 days following any study injection were reviewed. Please see the FSR and Tables 16, 8.69, 8.72 and 8.75 for detailed information.

Overall, a total of 44 (24.3%) and 47 (26.0%) of participants in the RIV4 and IIV4 groups, respectively, reported unsolicited AEs within 28 days of any vaccination, including 28.4% and 21.0% of RIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively, and 29.7% and 22.2% of IIV4 recipients 3 through 5 years and 6 through 8 years of age, respectively.

The most frequently (≥5%) reported events in either the RIV4 or IIV4 groups, respectively, as categorized by MedDRA SOC were: infections and infestations (14.4% and 12.7%); respiratory, thoracic and mediastinal disorders (6.1% and 8.8%); and gastrointestinal disorders (5.5% and 5.0%).

The most frequently (≥2%) reported AEs in the RIV4 and IIV4 groups, respectively, as categorized by PT were: upper respiratory tract infection (4.4% in each group), pharyngitis streptococcal (3.9% and 1.7%); diarrhea (2.8% and 0.6%); influenza (2.8% and 0); rhinorrhea (2.8% and 3.3%); cough (2.2% and 3.9%); vomiting (0% and 2.8%); and headache (0% and 2.2%). Among children 3 through 5 years of age, diarrhea occurred in 6.2% of RIV4 vs no IIV4 recipients while cough occurred in no RIV4 recipients and 5.5% of IIV4 recipients. Percentages of individual events were otherwise generally balanced between treatment groups.

In both treatment groups, most unsolicited AEs were mild to moderate in intensity (Grade 1 or 2). In the RIV4 group, 11.6%, 7.2% and 3.3% of participants 3 through 8 years of age experienced an unsolicited AE of maximum intensity assessed as mild, moderate, or severe, respectively. In the IIV4 group, 11.0%, 9.9% and 3.9% of participants 3 through 8 years of age experienced an unsolicited AE of maximum intensity assessed as mild, moderate, or severe, respectively. The onset of unsolicited AEs was similar between treatment groups and the duration of most AEs were between 1 to 3 days or 4 to 7 days.

In both treatment groups, most unsolicited AEs were assessed by the investigator as being unrelated to study vaccine. The percentages of participants 3 through 8 years of age in the RIV4 and IIV4 groups who were assessed as experiencing related unsolicited AEs were 2.2% (n=4) and 1.1% (n=2), respectively. AEs assessed as related in the RIV4 group included injection site erythema and induration, nausea, fatigue, pallor, and oropharyngeal pain. AEs assessed as related in the IIV4 group included: digestive system symptoms and ear pain.

Severe (Grade 3) Unsolicited Adverse Events

A total of 6 (3.3%) participants in the RIV4 group, including 3 participants in each age subgroup, and 7 (3.9%) participants in the IIV4 group, including 3 participants 3 through 5 years and 4

participants 6 through 8 years of age, experienced a total of 15 severe (Grade 3) unsolicited AEs.

Among RIV4 recipients 3 through 5 years of age, Grade 3 AEs included injection site erythema (n=1), injection site induration (n=1), gastroenteritis (n=1) pharyngitis streptococcal (n=1), and psychomotor hyperactivity (n=1). Grade 3 AEs reported in RIV4 recipients 6 through 8 years of age were pyrexia (n=1), influenza (n=1) and pharyngitis streptococcal (n=1).

Among IIV4 recipients 3 through 5 years of age, Grade 3 AEs included pyrexia (n=1) and gastroenteritis (n=2). Grade 3 AEs reported in IIV4 recipients 6 through 8 years of age were pyrexia (n=1), bacterial infection (n=1), gastritis viral (n=1), and gastroenteritis (n=1). The AE of bacterial infection (ID (b) (6)) was also assessed as serious is described in Section 6.2.12.4 of this review.

A total of 2 Grade 3 AEs were assessed as related to study vaccine, injection site erythema and injection site induration, both occurring in a 5-year-old participant (ID (b) (6) in the RIV4 group. Onset of both events was on the day following a single dose vaccination (Day 2). Both events resolved spontaneously after 6 and 2 days, respectively.

> ***Reviewer Comments:*** *The Applicant did not include a table of all unsolicited AEs that occurred within 28 days of any vaccination by maximum severity, MedDRA SOC and PT, but did provide a tabular summary of all Grade 1, 2 and 3 AEs according to treatment group (FSR Table 8.75) and narrative text summarizing Grade 3 AEs. Evaluation of the datasets confirmed the Applicant's report of overall numbers of AEs by treatment group and maximum severity, including all Grade 3 events.*
>
> *Overall, evaluation of the electronic datasets showed that the types, percentages, intensities, and assessment of relatedness of unsolicited AEs, including Grade 3 AEs, were consistent with the Applicant's report.*

Subgroup Analyses

The Applicant provided subgroup analyses of the overview of safety in Section 5.2.1 of the FSR, Appendix 15, Tables 1-3, and STN 125285/613 Amendment 5. Subgroup analyses by sex, race, ethnicity, and previous vaccination status were reviewed and showed no notable differences. Analyses were limited by small numbers of participants and wide, overlapping CIs, did not allow meaningful conclusions, and will not be discussed further in this review.

6.2.12.3 Deaths

No deaths occurred during the study.

6.2.12.4 Nonfatal Serious Adverse Events

One SAE, "bacterial infection, unspecified", was reported during the study and occurred three days after vaccination with IIV4 in a 6-year-old male participant (ID (b) (6)) at a study site in Poland. The case narrative was reviewed and indicated that the participant had a history of tonsillitis treated with amoxicillin. Prior vaccinations were not reported. Three days postvaccination, he developed fever and was hospitalized the following day with a temperature of 102.2º F, vomiting and coughing. Examination revealed an inflamed throat. Leukocytes were normal (4.34 x 10^3/mcL). C reactive protein (CRP) and procalcitonin levels were elevated. EBV, COVID-19, RSV and mycoplasma were excluded. Cultures were not reported. He was treated with intravenous (IV) cefuroxime. On the fourth day of symptoms, an otolaryngology consult

revealed enlarged tonsils without acute inflammation. He was discharged 9 days postvaccination in “good health” and recovered. His parents withdrew him from the study prior to the second planned vaccination. The investigator and Applicant assessed the SAE as unrelated to study vaccine. This SAE was also reported as MAAE.

> ***Reviewer Comment:*** *Although no specific infectious etiology for the patient’s symptoms was identified in the report, the participant’s constellation of symptoms, elevated CRP and procalcitonin, and treatment with empiric IV antibiotics suggest that an infectious etiology is a more plausible explanation for the SAE than the study vaccine. This reviewer agrees with the investigator assessment.*

6.2.12.5 Adverse Events of Special Interest (AESIs)

No AESIs were reported during the study.

Medically Attended Adverse Events

Overall, MAAEs were reported in a higher percentage of participants in the RIV4 group than the IIV4 group during the entire study (10.5% versus 7.7%, respectively), including within the 28 days following any vaccination (9.9% versus 6.6%, respectively). The majority of MAAEs in both groups (8.3% and 4.4%, respectively) were categorized in the MedDRA SOC of Infections and Infestations. No MAAEs were assessed as related to study vaccine and none were Grade 3 in severity. The SAE of bacterial infection, unspecified (IIV4 participant (b) (6)) was also reported as an MAAE.

6.2.12.6 Clinical Test Results

Clinical safety laboratories were not collected in this study.

6.2.12.7 Dropouts and/or Discontinuations

No AEs leading to discontinuation were reported during the study.

6.2.13 Study Summary and Conclusions

Due to challenges in enrollment, the Applicant conducted an IA for futility after only 366 participants (26% of the planned enrollment) had been enrolled and vaccinated.

Immunogenicity Conclusions

The primary objective of the study was to demonstrate the NI immune response of RIV4 as compared with IIV4 for all 4 vaccine strains, as measured by the HI assay using egg-derived antigen, in all participants 3 through 8 years of age. Although the statistical tests for non-inferiority lacked adequate power for inferential hypothesis testing because the study only achieved 26% of planned enrollment, interim analyses of the primary endpoint were performed. Individually, NI analyses for the A/H1N1, A/H3N2 and B/Yamagata strains met success criteria for both GMT ratios and SCR differences. However, for the B/Victoria strain, the LL of the 95% CI for the GMT ratio was 0.397 (less than the pre-specified success criterion of >0.667) and the LL of the 95% CI for the difference in SCRs was -14.02% (less than the pre-specified criterion of >-10%). Therefore, Study VAP00026 did not meet the primary endpoints of NI GMTs and SCRs for RIV4 as compared with IIV4 for all 4 vaccine antigens. The Applicant also calculated that the PPoS was <1%, indicating that the probability of meeting the primary objective by the end of the study (i.e., if the planned enrollment had been achieved) was very low. Therefore, the Applicant terminated the study for futility as recommended by the independent FIC.

Subgroup analyses showed that immune responses were higher in the age subgroup of children 6 through 8 years and met success criteria for NI for 7 of 8 GMT and SCR endpoints for A/H1N1, A/H3N2, and B/Yamagata, and for the GMT ratio for B/Victoria. Immune responses to the B/Victoria strain missed the SCR success criterion by only a small margin, SCR of -0.98% (95% CI: -10.59, 9.06). The review team considered the feasibility of recommending that the Applicant continue or repeat a study to support an indication in the subgroup of children 6 through 8 years of age. At our request, the Applicant calculated the overall PPoS for meeting the primary endpoint in the subgroup of children 6 through 8 years of age and found that the PPoS was only 23.2%. Because the prespecified interim futility analysis was not adequately powered for inferential hypothesis testing on the subgroup of children 6 through 8 years of age, the post hoc PPoS calculations were limited and interpreted with caution.

Safety Conclusions

Safety data in Study VAP00026 were limited to 366 participants 3 through 8 years of age, 181 participants in both the RIV4 and IIV4 treatment groups, including 81 children 3 through 5 years and 100 children 6 through 8 years of age in the RIV4 group. Overall, safety data following administration of RIV4 to healthy children 3 through 8 years of age were comparable to U.S.-licensed IIV4 and identified no safety concerns.

The most common solicited local and systemic reactions (≥10%) following any vaccination with RIV4 in children 3 through 5 years of age were injection site pain (26.6%), injection site erythema (10.3%), malaise (22.8%), myalgia (13.9%), and headache (12.7%). The most common solicited reactions following administration of RIV4 in children 6 through 8 years of age were injection site pain (40.0%), injection site erythema (16.0%), injection site swelling and induration (each 12.1%), myalgia (18.0%), malaise (17.0%), and headache (13.0%). Most solicited reactions were Grade 1 (mild) or Grade 2 (moderate) in intensity, occurred within 3 days following vaccination, and resolved spontaneously within 3 days. Following RIV4 vaccination, Grade 3 solicited injection site and systemic reactions were reported by 4.5% and 3.9% of participants 3 through 8 years of age, respectively, and were comparable in frequency to Grade 3 reactions following IIV4, 4.4% and 5.0%, respectively.

In general, solicited injection site and systemic reactions were reported less frequently after the second vaccination as compared to the first.

Unsolicited AEs occurred with low percentages in both groups, were mostly mild to moderate in severity, and showed no unusual patterns or imbalances.

No deaths, AESIs or AEs leading to discontinuation were reported during the study. One SAE, an unspecified bacterial infection in the IIV4 group, occurred and was assessed as unrelated to study vaccine.

7. Integrated Overview of Efficacy

7.1 Indication #1

Not applicable.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

Not applicable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

This sBLA contained no new data pertaining to human reproduction and pregnancy.

9.1.2 Use During Lactation

Please see Section 9.1.1.

9.1.3 Pediatric Use and PREA Considerations

Please see Section 2.5 of this review for a detailed regulatory history of the pediatric PMRs initially associated with Flublok then replaced with Flublok Quadrivalent. A Phase 3 pediatric PMR to evaluate the safety, immunogenicity and efficacy in children 3 through 17 years of age was associated with the approval of Flublok Quadrivalent on October 7, 2016. The FSR was due by June 30, 2020. On April 18, 2022, because of challenges related to a business acquisition and the COVID-19 pandemic, FDA agreed to release the Applicant from the PMR and to replace the efficacy study with two safety and immunogenicity studies, VAP00026 (in children 3 through 8 years) and VAP00027 (in children and adolescents 9 through 17 years). The FSRs were due on December 31, 2023. On September 29, 2023, due to challenges in enrollment, the Applicant submitted a DER for PMRs VAP00026 and VAP00027. The Applicant also informed FDA that, following an IA of immunogenicity data, they had terminated Study VAP00026 for futility. FDA granted the Applicant a Deferral Extension on November 13, 2023. The new milestone dates for submission of the PMRs were extended to May 31, 2024 for VAP00027 and June 30, 2024 for VAP00026.

Submission of STN 125285/613 required a PeRC review because the supplement contained data from the two PREA PMR assessments. On January 21, 2025, the PeRC concurred with the review team's assessment that data from Study VAP00027 support licensure of Flublok and Flublok Quadrivalent in children and adolescents 9 through 17 years of age. The PeRC also agreed that data from Study VAP00026 do not support approval in children 3 through 8 years of age. The PeRC agreed that with submission of the FSRs and approval of the current efficacy supplement STN 125285/613, Sanofi will have fulfilled the two PREA PMRs.

9.1.4 Immunocompromised Patients

Immunocompromised children were excluded from studies VAP00027 and VAP00026. Data regarding the safety and effectiveness of Flublok and Flublok Quadrivalent in immunocompromised individuals are insufficient to support recommendations in this population.

9.1.5 Geriatric Use

Flublok and Flublok Quadrivalent, respectively, were granted accelerated approval for use in adults ≥50 years of age on October 29, 2014 and traditional approval on October 7, 2016. This application did not provide additional data in the geriatric population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Immunogenicity and safety data from Study VAP00027 submitted to this efficacy supplement support traditional approval of Flublok and Flublok Quadrivalent for use in children and adolescents 9 through 17 years of age. Data from Study VAP00026, terminated early due to enrollment challenges and an IA suggesting lack of effectiveness, are not sufficient to support approval for use in children 3 through 8 years of age. Review of limited data from VAP00026 did not identify safety concerns.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 34 presents Risk-Benefit Considerations relating to approval of Flublok and Flublok Quadrivalent in children and adolescents 9 through 17 years of age.

Table 34. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza causes annual epidemics affecting ~5-20% of the population each year. Due to frequent mutations in viral envelope glycoproteins (primarily HA), the extent and severity of seasonal epidemics are variable and unpredictable. • From 2010 to 2023, the CDC estimated that influenza caused 9.3 to 41 million illnesses, 100,000-710,000 hospitalizations and 4,900-51,000 deaths. Complications, hospitalizations, and deaths from seasonal influenza disproportionately affect persons ≥65 years, children <5 years, especially those <2 years, and persons of any age with underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. • Pediatric mortality due to influenza is <1 per 100,000 person years. During the 10 most recent influenza seasons up to February 2023, the absolute number of pediatric deaths ranged from 1 (during the 2020-2021 COVID-19 pandemic) to 205 (2023-2024), lower than the 358 pediatric deaths during the 2009 H1N1 pandemic. During the last 4 influenza seasons, 2021-2022 through 2024-2025, 18.4% to 29.9% of all pediatric deaths (<18 years of age) occurred in adolescents 11 through 17 years of age. Pediatric deaths may be underestimated due to undiagnosed cases. The importance of vaccination is reflected in data showing that ~50% of reported deaths have occurred in otherwise healthy children and ~80% have occurred in children who were not fully vaccinated. • The influenza B strain may cause serious disease in children. Although influenza B causes ~25% of all clinical disease, 34% to 38% of the pediatric deaths reported between 2004 and 2011 season were due to influenza B.	• Influenza is a serious, sometimes life-threatening disease. Persons of all ages are at risk for significant morbidity and mortality. • The primary mode of controlling influenza disease is by immunoprophylaxis. During the 2022-2023 influenza season, the CDC estimated that influenza vaccination prevented 6.0 million influenza-related illnesses, 2.9 million healthcare visits, 65,000 hospitalizations, and 3,700 deaths.
Unmet Medical Need	• Because the B/Yamagata strain is no longer circulating, beginning in the 2024-2025 season, only trivalent influenza vaccines will be distributed in the U.S.. In the pediatric population, five IIV3 vaccines are available for use in persons 6 months and older [Afluria, Fluarix, Flucelvax, FluLaval, and Fluzone]. Of these, Flucelvax (ccIIV3) is manufactured in cell culture and the other four are manufactured in eggs. LAIV3 (FluMist) is approved in persons 2 years through 49 years of age. • The CDC estimates that ~143 million doses of influenza vaccine will be available for distribution in the U.S. in the 2024-2025 season. Influenza vaccine coverage rates are relatively stagnant and remain below the DHHS Healthy People 2030 target of 70% in persons 6 months and older. Coverage rates in the pediatric population 6 months through 17 years of age have declined from 56% in 2019-2020 to 47% in 2023-2024 (41% in children 12-17 years). Although this does not appear to be due to a shortage of vaccine, the doses of vaccine distributed for the 2024-2025 influenza season are less than the population for whom the vaccine is indicated. • Flublok is manufactured without the use of eggs, an attribute which has been cited by the Applicant as a potential advantage in egg-allergic persons. However, the risk of anaphylaxis following egg-based IIVs is rare and reviews of studies of administration of egg-based IIVs to persons with egg allergy, including a history of serious allergic reactions, have showed no cases of serious hypersensitivity reactions. Conversely, severe and serious allergic reactions have been reported following administration of RIV to egg-allergic persons.	• RIV3 is an alternative to egg-based IIVs and could meet an unmet medical need in the event that a shortage of eggs negatively impacts the manufacture of IIVs. • Absence of egg protein in Flublok does not represent a major safety benefit over egg-based IIVs.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• In a trial (PSC04) conducted in the U.S. during the 2007-2008 influenza season, 4648 healthy adults 18 through 49 years of age were randomized 1:1 to receive RIV3 or placebo. RIV3 demonstrated VE against culture-confirmed influenza-like illness (cc-ILI) of 44.8% (95% CI 24.4, 60.0). Almost all influenza isolates were antigenically mismatched relative to the vaccine strains (primarily A/H3N2 and B/lineage). Sub-analyses of VE against cc-ILI due to the B strain (23 isolates) was 37.2% (95% CI -8.9, 64.5). In a second trial (PSC12) conducted in the U.S. during the 2014-2015 influenza season, 8963 adults ≥50 years were randomized 1:1 to receive RIV4 or IIV4. The relative vaccine efficacy (rVE) of RIV4 against polymerase chain reaction (PCR)-confirmed ILI was 30% (95% CI 10, 47). Sub-analyses of protection against influenza B showed an rVE of 4% (95% CI -72, 46). • Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. In Study VAP00027, vaccination of children 9 through 17 years of age with RIV4 elicited HI Ab responses to the influenza A/H1N1, A/H3N2 and B lineage vaccine virus strains that were noninferior (NI) to adults 18 through 49 years of age thereby inferring clinical benefit in the age group 9 through 17 years. Antibody responses to the B/Victoria strain were lower relative to the other vaccine strains in both age groups 9-17 years and 18-49 years for reasons that are unclear but likely multifactorial including due to prior exposures by vaccination and natural infection. • Study VAP00026 was terminated early due to inability to enroll an adequate sample size and an interim analysis (IA) that met criteria for futility. The IA, conducted after enrolling 26% of the target population, showed that vaccination of children 3 through 8 years of age with RIV4 failed to demonstrate NI immunogenicity as compared with IIV4. A PPoS analysis indicated a <1% probability of meeting the primary endpoint even if the target enrollment was achieved. Results were driven by low HI Ab responses to the B/Victoria strain.	• RIV3 and RIV4 have demonstrated clinical efficacy in adults 18 years and older. • The clinical benefit of RIV4 and RIV3 in children and adolescents 9 through 17 years of age can be inferred by clinical efficacy in adults and NI immunogenicity demonstrated in VAP00027. • Results of immunogenicity and futility analyses for Study VAP00026 suggest that RIV4 and RIV3 would not be effective, primarily against the B/Victoria strain, and do not support approval in children 3 through 8 years of age. • Subpopulation analyses of immunogenicity do not allow definitive conclusions regarding effectiveness in children 6 through 8 years of age.
Risk	• The most common adverse reactions following vaccination with RIV4 and RIV3 are mild to moderate injection site reactions, primarily pain, and systemic symptoms, primarily fatigue, headache and myalgias. No unusual patterns or large imbalances in non-serious unsolicited AEs or MAAEs were observed in studies VAP00027 or VAP00026. No related SAEs, AESIs or deaths were reported. • Uncommon or rare AEs associated with influenza vaccines include neurologic events, such as encephalitis, myelitis, and Guillain-Barre syndrome (GBS), and allergic or immediate hypersensitivity reactions, including anaphylaxis. No severe or serious neurologic or allergic reactions were observed in VAP00027 or VAP00026.	• Studies VAP00027 and VAP00026 showed an acceptable reactogenicity and safety profile and raised no new concerns. • Subpopulation analyses in persons 9 through 17 years and 3 through 8 years of age showed trends toward higher percentages of reactogenicity and unsolicited AEs in females as compared with males and in White as compared with Black or African American participants. No statistically significant differences were observed between Hispanic/Latino and non-Hispanic/non-Latino participants in either study. Subpopulation analyses were limited by small sample sizes and the descriptive nature of the analyses and do not allow definitive conclusions.
Risk Management	• Any potential for increased local and systemic reactogenicity or hypersensitivity associated with RIV3 and RIV4 can be further described in postmarketing surveillance. • The clinical review team and OBPV determined that a safety PMR, Risk Evaluation and Mitigation Strategy (REMS) or a Black Box warning were not required for RIV3 and RIV4.	• The known safety profile of RIV3 and RIV4 will be described in the package insert (PI) without the need for a PMR, REMS, or Black Box warning. • Please see the OBPV review for details

11.2 Risk-Benefit Summary and Assessment

Influenza is a serious and potentially life-threatening disease for which immunoprophylaxis is the primary means of preventing infection and serious complications. Flublok (RIV3) and Flublok Quadrivalent (RIV4) have demonstrated clinical efficacy in adults ≥18 years of age. In Study VAP00027, RIV4 demonstrated NI immunogenicity in children and adolescents 9 through 17 years of age as compared with adults 18 through 49 years of age, suggesting that RIV4 and RIV3 are likely to confer protection against influenza in this pediatric age population. Study VAP00026 was underpowered due to under-enrollment, failed to demonstrate NI immunogenicity of RIV4 as compared with U.S.-licensed IIV4 in an IA, and was terminated early for futility. VAP00026 showed that RIV4 failed to elicit an adequate immune response against the B/Victoria strain and statistical analyses predicted that the study would have failed even if it had been fully enrolled due to low effectiveness against B/Victoria. Influenza B has been associated with serious illness and higher mortality in children as compared with adults. Therefore, evidence is insufficient to support a potential benefit of RIV4 or RIV3 in children 3 through 8 years of age.

Safety data submitted to support licensure in children and adolescents 9 through 17 years of age were acceptable and did not identify new concerns. Available safety data for RIV4 in children 3 through 8 years of age were comparable to IIV4 and raised no concerns. However, the size of the safety database in this age population was less than planned and what we would usually require for licensure.

In children and adolescents 9 through 17 years, it is reasonable to conclude that the potential benefits of RIV4 and RIV3 outweigh potential risks. In children 3 through 8 years of age, available immunogenicity and safety data are limited and inadequate to support a conclusion that potential benefits outweigh potential risks in this age population.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support extension of traditional approval of Flublok and Flublok Quadrivalent in individuals 9 years and older for the active immunization against disease caused by the influenza virus subtypes A and types B contained in the vaccine.

11.4 Recommendations on Regulatory Actions

From the clinical reviewer perspective, data from VAP00027 support traditional approval of Flublok and Flublok Quadrivalent in children and adolescents 9 through 17 years of age. Data do not support approval of RIV3 or RIV4 in children 3 through 8 years of age. The Applicant has submitted pediatric assessments in children 3 through 17 years of age as required under PREA regulations. Therefore, the review team recommends that PMR #1 and PMR #2 be considered fulfilled following review of this supplement.

In accordance with scientific expert recommendations, because the B/Yamagata strain has not circulated since 2020, RIV4 will no longer be marketed in the U.S. OVRR advised the review team that, although we may extend the indication for the quadrivalent formulation, we are unable to approve an updated PI for the RIV4 formulation because

CMC data for a B/Yamagata strain are not available to support an updated Section 11, Description, of the PI.

11.5 Labeling Review and Recommendations

The Applicant submitted draft RIV3 and RIV4 PIs updated with revisions approved under STN 125285/580 (transition to trivalent formulations), 125285/610 (data from a pregnancy registry), and data from the pediatric PMRs. The RIV4 PI was not reviewed for this supplement for reasons explained in Section 11.4 of this review.

Labeling negotiations were ongoing at the time the clinical review was finalized. Major changes to the Applicant's draft Flublok PI and areas of negotiation were as follows:

- Highlights were revised with the new Indications and Usage in persons 9 years of age and older and Adverse Reactions in persons 9 through 17 years of age.
- Section 6, Adverse Reactions, was revised to include data from Study VAP00027 in persons 9 through 17 years of age. The PI indicates that data from studies conducted with RIV4 are relevant to RIV3 because the two vaccines are manufactured by the same processes and have overlapping compositions.
- Section 8.4, Pediatric Use, was updated to indicate that the safety and effectiveness of RIV4 have been evaluated in children 3 through 8 years of age and that 1 or 2 doses of Flublok Quadrivalent did not induce an acceptable level of immunogenicity as compared with IIV4, strongly suggesting that RIV4 or RIV3 would not be effective in this population.
- Section 14, Clinical Studies, was revised to include immunogenicity data from VAP00027 in persons 9 through 17 years of age.

11.6 Recommendations on Postmarketing Actions

Pediatric PMRs are fulfilled with this supplement. No new or potential risks were identified that would necessitate a PMC or PMR. The clinical review team recommends routine pharmacovigilance as outlined by OBPV.