QU-FOR-0055625

Sponsor: Sanofi Pasteur **Drug substance(s):** Quadrivalent Recombinant Influenza Vaccine	**Study Identifiers:** BB-IND:015784; EU trial number: 2022-000576-19; NCT05513391; WHO:U1111-1256-8841 **Study code:** VAP00026

Title of the study:

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 center(s):

This study was conducted at 31 centers that randomized participants in the United States (US) and Europe.

Study period:

Study initiation date: 10 November 2022 (first participant first visit)

Final data report date: 22 May 2023 (last participant last visit)

Study Status: Terminated. Sponsor decision to prematurely stop the study. This decision was made without any safety concerns.

Phase of development: III

Objectives:

Primary:

- To demonstrate the non-inferior HAI immune response of RIV4 vs licensed IIV4 for the 4 strains based on the egg-derived antigen in all participants aged 3 to 8 years

Key Secondary

Immunogenicity

- To summarize the HAI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg derived antigen in participants aged 3 to 8 years

Safety

- To assess the safety profile of each vaccine in all participants and by age group

Methodology:

VAP00026 study was a Phase III, randomized, modified double-blind, active-controlled (standard-dose quadrivalent influenza vaccine, IIV4), multi-center study to demonstrate the non-inferior HAI immune response of RIV4 vs licensed IIV4 for the 4 strains based on the egg-derived antigen in all participants aged 3 to 8 years and to describe the immunogenicity and safety profile of RIV4 compared to IIV4 in participants aged 3 to 8 years.

This study included an early safety data review performed by the Safety Management Team.

Participants were enrolled on the day of their first vaccination to receive 1 or 2 doses 28 days apart of either RIV4 or IIV4; depending on if they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively; and were followed for 6 months after the last vaccination.

In order to maintain consistent vaccination schedule rules across all countries and sites for the classification of children considered previously influenza vaccinated and previously influenza unvaccinated, all study sites followed the US Advisory Committee on Immunization Practices recommendations for influenza vaccine.

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

Number of study participants:

The planned sample size and the actual number of participants in each analysis set are presented in Table S1.

Approximately 1412 participants 3 to 8 years of age (approximately 50% participants in the age group 3-5 years and 50% participants in the age group 6-8 years) were expected to be randomized. Approximately 50% of participants randomized were planned to be previously unvaccinated against influenza and 50% of participants were planned to be previously vaccinated against influenza.

Table S1 – VAP00026 study sample size

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

Diagnosis and criteria for inclusion:

The study was conducted in healthy participants aged 3 to 8 years on the day of inclusion.

Study products

The main characteristics of the study interventions administered to participants are described in Table S2:

Table S2 – Study interventions, dose, mode of administration, and batch numbers

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

Abbreviations: HA: hemagglutinin; IM: intramuscular

Duration of study intervention:

The participation duration was approximately 6 months for participants previously vaccinated against influenza and approximately 7 months for participants previously unvaccinated against influenza.

Criteria for evaluation:

Primary

- Individual HAI titer 28 days after last vaccination (Day [D]29 or D57)
- Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29 or D57, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D29 or D57)

Key Secondary

Immunogenicity

- Individual HAI titer on D01 and 28 days after the last vaccination (D29 or D57)
- Detectable HAI titer, ie, with a titer ≥ 10 (1/dil) at D01 and 28 days after the last vaccination (D29 or D57)
- Individual HAI titer ratio: 28 days after the last vaccination (D29 or D57) / D01
- Seroconversion (titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29 or D57, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold-rise in titer [1/dil] at D29 or D57)
- Participants with titers ≥ 40 (1/dil) on D01 and 28 days after the last vaccination (D29 or D57)

Safety

- Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination
- Occurrence of solicited (pre-listed in the participant's diary card [DC]/electronic DC [eDC] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 8 days after each vaccination
- Occurrence of unsolicited AEs up to 28 days after each vaccination
- Occurrence of medically attended adverse event (MAAEs) up to 28 days after each vaccination
- Occurrence of serious adverse events (SAEs) (including adverse events of special interest [AESIs]) throughout the study
- Occurrence of AESIs throughout the study

Statistical methods:

The number of participants enrolled and their age at enrollment, sex, race, and ethnic origin were summarized for each vaccine group, as well as the number and description of protocol deviations. In general, categorical variables were summarized and presented by frequency counts, percentages, and confidence intervals (CIs). The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates were calculated using normal approximation of log-transformed titers.

Primary endpoints

The primary objective included 8 endpoints (GMTs and SC rates for each of the 4 strains).

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

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

Since all 8 NI hypotheses had to be rejected at 0.025 significance level, no formal adjustment for multiplicity was necessary.

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

As per protocol amendment, an interim analysis was conducted to assess the likelihood of the study success by the end of enrollment (eg, 1412 participants) based on the immunogenicity data accumulated after randomizing and vaccinating approximatively 366 children (approximately 25% of participants) and to review safety.

Secondary endpoints (immunogenicity)

Immunogenicity parameters by HAI measurement method were summarized by study group with 95%CI.

Reverse cumulative distribution curves (RCDCs) of pre-vaccination titer at D01 and post-vaccination titer 28 days after the last vaccination (D29 or D57) were generated for each study group.

Secondary endpoints (safety)

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

Analysis was conducted for each study group, by strata of age and according to the number of doses received.

Summary Results:

Demographic and other baseline characteristics:

A total of 366 participants were enrolled in the study and randomized to receive RIV4 or IIV4 (183 participants were randomized in each vaccination group).

Among them, 178 (48.6%) were male and 188 (51.4%) were female. The male/female sex ratio was 0.95. The distribution was balanced in each vaccination group.

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

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

Of the 366 participants randomized in the study, 210 participants were previously vaccinated and 156 were previously unvaccinated against influenza. In each priming status group, participants aged 3 to 8 years were randomized according to a 1:1 ratio between the RIV4 and IIV4 groups.

Exposure:

Visit 1 (D01) – All participants

Overall, almost all randomized participants received the study intervention at V01:

・98.9% (181 of 183) of participants in the RIV4 group (104 and 77 previously vaccinated and unvaccinated participants, respectively)

・98.9% (181 of 183) of participants in the IIV4 group (103 and 78 previously vaccinated and unvaccinated participants, respectively)

Visit 2 (D29) – Previously unvaccinated participants

Only previously unvaccinated participants received a second vaccination at V02. A total of 151 participants (96.8%) received the study intervention:

・75 participants (96.2%) in the RIV4 group

・76 participants (97.4%) of participants in the IIV4 group

Immunogenicity results:

Primary Objective – Non-Inferiority

The study was stopped for futility when approximately 25% of the planned number of participants were vaccinated.

At the time of the final analysis, the statistical test for NI was only conducted on the participants enrolled before stopping the study for futility. Thus, the NI analysis was conducted on a small sample size, which was lower than the one initially planned and with a low overall study power.

Overall, the primary objective of this study was not met since the non-inferior HAI immune response of RIV4 versus licensed IIV4 was not demonstrated for all 4 strains on the participants recruited during the 2022-2023 season.

The NI of HAI immune response of RIV4 versus licensed IIV4 was demonstrated separately in 3 of the 4 strains based on the GMTs in the per-protocol analysis set (PPAS), regardless of the previous vaccination status. The lower limit of the 2-sided 95% CI of the geometric mean titers ratio (GMTR) (GMT RIV4 / GMT IIV4) was higher than 0.667 for A/H1N1 strain, A/H3N2 strain, and B/Yamagata lineage strain, but not for B/Victoria lineage strain, with a GMTR of 0.515 (95% CI: 0.397; 0.668). The lower limit of the 2 sided 95% CI of the difference in SC rates (RIV4 - IIV4) was higher than -10% for A/H1N1 strain, A/H3N2 strain, and B/Yamagata lineage strain, but not for B/Victoria lineage strain with a difference in SC rates of -6.91 (95% CI: -14.02; 0.10).

Secondary Objective – HAI Immune Response

Individual HAI Antibody Titers

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

At D29 or D57 (28 days after the last vaccination), the GMTs highly increased for each antigen, with the highest values observed for the A/H3N2 strain and the lowest for the B/Victoria lineage strain. The post-vaccination GMTs against each strain in the RIV4 group and in the IIV4 group, respectively, were:

・998 (95% CI: 779; 1279) and 640 (95% CI: 493; 831) for the A/H1N1 strain

・2398 (95% CI: 1914; 3004) and 889 (95% CI: 722; 1095) for the A/H3N2 strain

・337 (95% CI: 263; 432) and 605 (95% CI: 480; 762) for the B/Victoria lineage strain

・789 (95% CI: 634; 983) and 708 (95% CI: 590; 850) for the B/Yamagata lineage strain

The GMTRs (D29 or D57/D01) were similar between the RIV4 group and the IIV4 group for the A/H1N1 strain and the B/Yamagata lineage strain, higher in the RIV4 for the A/H3N2 strain, and higher in the IIV4 group for the B/Victoria lineage strain:

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

An immune response was observed after 1 or 2 vaccinations with RIV4 or IIV4 based on HAI antibody GMTs.

HAI Antibody Titers >= 40 and Detectable HAI Titers

At D01 (baseline for all participants), the percentage of participants with HAI titers ≥ 40 (1/dil) was similar between both vaccination groups, ranging from 54.8% (95% CI: 46.6; 62.7) to 65.4% (95% CI: 57.5; 72.8) for A/H1N1 strain, 70.1% (95% CI: 62.2; 77.1) to 76.1% (95% CI: 68.7; 82.5) for A/H3N2 strain, 33.8% (95% CI: 26.4; 41.7) to 35.8% (95% CI: 28.4; 43.8) for B/Victoria lineage strain, and 66.2% (95% CI: 58.3; 73.6) to 69.8% (95% CI: 62.0; 76.8) for B/Yamagata lineage strain.

At D29 or D57 (28 days after the last vaccination), the percentage of participants with HAI titers ≥ 10 (1/dil) was high in both vaccination groups for all 4 strains and was similar for the corresponding strain between RIV4 and IIV4 groups, ranging from 98.1% to 100%.

At D29 or D57 (28 days after the last vaccination), the percentage of participants with HAI titers ≥ 40 (1/dil) was high in both vaccination groups for all 4 strains. For the A/H1N1 strain, A/H3N2 strain, and B/Yamagata lineage strain, the percentage was similar for the corresponding strain between RIV4 and IIV4 groups, ranging from 96.2% to 99.4%. For the B/Victoria lineage strain, the percentage of participants with HAI titers ≥ 40 (1/dil) tended to be lower in the RIV4 group (92.5% [95% CI: 87.2; 96.0]) than in the IIV4 group (96.8% [95% CI: 92.8; 99.0]).

High seropositivity and seroprotection rates were observed after 1 or 2 vaccinations with RIV4 or IIV4.

Seroconversion Rates

At D29 or D57 (28 days after the last vaccination), the SC rates tended to be higher in the RIV4 group for A/H1N1 strain, were higher in the RIV4 group for A/H3N2 strain, tended to be lower in the RIV4 group than in the IIV4 group for B/Victoria lineage strain, and were similar between the RIV4 and IIV4 groups for B/Yamagata lineage strain:

- 84.8% (95% CI: 78.2; 90.0) and 77.7% (95% CI: 70.4; 84.0) for the A/H1N1 strain
- 82.3% (95% CI: 75.4; 87.9) and 66.9% (95% CI: 58.9; 74.2) for the A/H3N2 strain
- 85.4% (95% CI: 79.0; 90.5) and 92.4% (95% CI: 87.0; 96.0) for the B/Victoria lineage strain
- 88.6% (95% CI: 82.6; 93.1) and 82.8% (95% CI: 76.0; 88.4) for the B/Yamagata lineage strain

An immune response was observed after 1 or 2 vaccinations with RIV4 or IIV4 based on SC rates.

Safety results:

Immediate Unsolicited AEs and ARs

Overall, none of the participants experienced any immediate unsolicited adverse event (AE) or adverse reaction (AR) within 30 minutes after any vaccination with RIV4 or IIV4.

Solicited Reactions

The percentage of participants who experienced at least 1 solicited reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (45.8% [82/179] and 51.7% [93/180], respectively).

The percentage of participants who experienced at least 1 Grade 3 solicited reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (7.8% [14/179] and 8.9% [16/180], respectively).

The percentage of participants who experienced at least 1 solicited injection site reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (39.1% [70/179] and 42.2% [76/180], respectively).

Pain was the most frequently reported solicited injection site reaction within 7 days after any vaccination, with 34.1% (61/179) of participants in the RIV4 group and 36.7% (66/180) of participants in the IIV4 group.

The percentage of participants who experienced at least 1 Grade 3 solicited injection site reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (4.5% [8/179] and 4.4% [8/180], respectively).

The percentage of participants who experienced at least 1 solicited systemic reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (27.9% [50/179] and 36.7% [66/180], respectively).

In the RIV4 and IIV4 groups, respectively, the most frequently reported solicited systemic reactions within 7 days after any vaccination consisted of:

・Malaise in 19.6% (35/179) and 20.6% (37/180) of participants

・Myalgia in 16.2% (29/179) and 23.9% (43/180) of participants

・Headache in 12.8% (23/179) and 16.7% (30/180) of participants

The percentage of participants who experienced at least 1 Grade 3 solicited systemic reaction within 7 days after any vaccination was similar between RIV4 and IIV4 groups (3.9% [7/179] and 5.0% [9/180], respectively).

In both vaccination groups, most solicited reactions were of Grade 1 or 2 intensity, started between D01 and D04, and resolved spontaneously after 1 to 3 days. Overall, the number of solicited reactions decreased after the 2nd vaccination.

Unsolicited AEs

The percentage of participants who experienced at least 1 unsolicited AE within 28 days after any vaccination was similar between RIV4 and IIV4 groups (24.3% [44/181] and 26.0% [47/181], respectively).

The percentage of participants who experienced at least 1 Grade 3 unsolicited AE within 28 days after any vaccination was similar between RIV4 and IIV4 groups (3.3% [6/181] and 3.9% [7/181], respectively).

In the RIV4 and IIV4 groups, respectively, unsolicited AEs occurring within 28 days after any vaccination were mainly reported in the following System Organ Classes (SOCs):

・“Infections and infestations” in 14.4% (26/181) and 12.7% (23/181) of participants

・“Respiratory, thoracic, and mediastinal disorders” in 6.1% (11/181) and 8.8% (16/181)

・“Gastrointestinal disorders” in 5.5% (10/181) and 5.0% (9/181) of participants

Unsolicited ARs

The percentage of participants who experienced at least 1 unsolicited AR within 28 days after any vaccination was similar between RIV4 and IIV4 groups (2.2% [4/181] and 1.1% [2/181], respectively).

A total of 2 Grade 3 unsolicited ARs were reported by 1 previously vaccinated participant 5 years of age who experienced injection site induration and injection site erythema 1 day after the vaccination with RIV4. Both events resolved spontaneously.

MAAEs

The percentage of participants who experienced at least 1 MAAE within 28 days after any vaccination was similar between RIV4 and IIV4 groups (9.9% [18/181] and 6.6% [12/181], respectively).

MAAEs occurring within 28 days after any vaccination were mainly reported in the SOC “Infections and infestations” and consisted of 8.3% (15/181) of the participants in the RIV4 group and 4.4% [8/181] of the participants in the IIV4 group.

Deaths, AESIs, Discontinuations due to AEs, and SAEs

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

One SAE was reported during the study: 1 previously unvaccinated participant aged 6 years experienced a Grade 3 bacterial infection (infectious agent unspecified). The event occurred 2 days after the 1st vaccination with IIV4 and lasted 7 days. The event was assessed as not related to the study vaccine and was considered as a MAAE.

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