27 February 2025
EMA/CHMP/556176/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of variations including an extension of indication

Invented name: Supemtek Tetra

Common name: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture)

Procedure No. EMEA/H/C/005159/II/0021/G

Marketing authorisation holder (MAH): Sanofi Winthrop Industrie

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AR	adverse reaction
CBER	Center for Biologics Evaluation and Research/ US Food and Drug Administration
CI	confidence interval
CRF	case report form
D	day
DS	Drug substance
FDA	Food and Drug Administration
FVFS	first visit of the first subject
GMT	geometric means of titres
GPV	Global Pharmacovigilance
HAI	Haemagglutination Inhibition
IIV4	quadrivalent inactivated influenza vaccine (Fluarix Tetra)
IM	intramuscular
IRB	Institutional Review Board
LB	lower bound
LCLS	last contact last subject
LVLS/LCLS	last visit of the last subjects/last contact of the last subject
MAAE	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
NT	neutralization test
PT	preferred term
rHA	recombinant haemagglutinin
RIV4	quadrivalent recombinant influenza vaccine, Supemtek Tetra
SAE	serious adverse event
SOC	System Organ Class
SN	seroneutralisation
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur submitted to the European Medicines Agency on 18 July 2024 an application for a group of variations.

The Marketing Authorisation was transferred to Sanofi Winthrop Industrie on 28 November 2024.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Grouped application comprising two type II variations as follows:

C.I.6.a – Extension of indication to include the treatment of children 9 years of age and older for Supemtek, based on final results from study VAP00027; this is a Phase III, non-randomised, open-label, uncontrolled study to demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

C.I.4 - Update of sections 4.8 and 5.1 of the SmPC in order to update paediatric information based on final results from study VAP00026; this is a Phase III, randomised, modified double-blind, active-controlled 2-arm 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. Version 2.0 of the RMP has also been submitted.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	18 July 2024
Start of procedure:	17 August 2024
CHMP Rapporteur Assessment Report	17 October 2024
PRAC Rapporteur Assessment Report	18 October 2024
PRAC Outcome	31 October 2024
CHMP members comments	4 November 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 November 2024
Request for supplementary information (RSI)	14 November 2024
CHMP Rapporteur Assessment Report	03 February 2025
PRAC Rapporteur Assessment Report	03 February 2025
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	13 February 2025
CHMP members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. It is typically characterised by the rapid onset of fever, myalgia, sore throat, and non-productive cough. Influenza can cause severe malaise, which lasts for several days. While influenza affects all age groups, the very young, older adults, and persons with underlying health problems are at increased risk for complications. Complications in the paediatric population include secondary bacterial pneumonia, acute otitis media, bronchitis, febrile seizures, Reye's syndrome, myositis, neurologic conditions, and exacerbations of underlying conditions. Vaccination remains the most effective means of preventing influenza infection and complications associated with the disease.

Supemtek Tetra (RIV4) was approved in the U.S. since October 2016 (Trade name Flublok Quadrivalent). In the EU, RIV4 is indicated for active immunisation in persons 18 years of age and

older for the prevention of influenza disease caused by influenza A subtype viruses and type B virus lineages contained in the vaccine. As of today, RIV4 is registered in 37 countries worldwide (of which 30 are in Europe).

In context of further development of the RIV4 in the paediatric population, 2 Phase III studies (VAP00027 and VAP00026) were conducted in children/adolescents 9 to 17 years of age and in children 3 to 8 years of age, respectively.

2.2. Clinical aspects

2.2.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Summary of Phase III studies supporting the efficacy of RIV4

Study Identifiers	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects (Actual Sample Size)	Countries; Trial Period (FVFS – LVLS/LCLS*)	Healthy Subjects or Diagnosis of Patients
VAP00027 NCT05513053	Primary Objective: To demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years. Secondary Objectives: To summarize the HAI immune response induced by RIV4 in all participants. To describe the safety profile of RIV4 vaccine in all participants and by age group. Exploratory Objective: To describe the neutralizing antibody immune response in a subset of participants.	Phase III, non-randomised, open-label, uncontrolled	One injection of RIV4 containing 45 µg of HA per strain (2022-2023 influenza season) Intramuscular (IM) route	N = 1308	US, Czech Republic, Poland, and Spain From Oct 2022 to Oct 2023	Healthy participants aged 9 to 49 years
VAP00026 NCT05513391	Primary Objective: To demonstrate the non-inferior HAI immune response of RIV4 vs authorised IIV4 for the 4 strains based on the egg-derived antigen in all participants.	Phase III, randomised, modified double-blind, active-controlled 2-arm	One or 2 injections 28 days apart of RIV4 containing 45 µg of HA per strain (2022-2023	N = 183 (RIV4) N = 183 (IIV4)	US, Poland, and Spain FVFS – LCLS: Nov 2022 to Oct 2023	Healthy children aged 3 to 8 years

Study Identifiers	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects (Actual Sample Size)	Countries; Trial Period (FVFS – LVLS/LCLS*)	Healthy Subjects or Diagnosis of Patients
	Secondary Objectives: To summarize the HAI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg-derived antigen in participants. To assess the safety profile of each vaccine in all participants and by age group.		influenza season) One or 2 injections 28 days apart of IIV4 containing 15 µg of HA per strain (2022-2023 influenza season) IM route		Early termination date: 07 Dec 2023	

* FVFS - LVLS/LCLS: First visit of the first subject - last visit of the last subject/last contact of the last subject

These studies were part of PIP EMEA-002418-PIP01-18.

2.2.2. Pharmacodynamics

Mechanism of action

Supemtek Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. It induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

The pharmacodynamic profile of vaccines is defined by their immunogenicity profile, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

Primary and secondary pharmacology

The haemagglutination inhibition (HAI) assay is one of the main tests that detects Ab directed against the HA antigen and is commonly used to assess the immunogenicity of influenza vaccines. It measures the ability of antibodies to inhibit the agglutination of red blood cells induced by the binding of influenza virus. This method was used to assess the immunogenicity objectives in studies VAP00027 and VAP00026. The HAI titres have been shown to be a reliable predictor of protective efficacy and the magnitude of HAI response expected to provide acceptable immunogenicity has been standardized in Center for Biologics Evaluation and Research (CBER) Guidance for Clinical Data Required to Support the Licensure of Seasonal Inactivated Influenza Vaccines. HAI titres were performed using validated assays that employed egg- derived antigens matching the 4 strains selected by the World Health Organization (WHO) for the 2022-2023 season by Q2 Solutions, Duhram, North Carolina (previously Focus Laboratory, Cypress, CA, US).

The immune response was also measured by influenza virus neutralisation test, hereafter named seroneutralisation (SN) assay. The SN assay was used in a randomised subset of participants in Studies VAP00027 and VAP00026. The SN assay quantifies functional antibodies directed against the viral neutralisation epitopes of the influenza virus, which could be different from the haemagglutination epitopes. The SN assay was validated and performed by GCI in Swiftwater, PA, US.

2.2.3. Discussion on clinical pharmacology

Immunogenicity of the vaccine was assessed using a haemagglutination inhibition test (HAI). HAI titres are not a true correlate of protection in the sense that there is not a globally accepted cut-off titre that defines clinical protection. Nonetheless, it has been widely shown that higher HAI titres tend to correlate with better protection so HAI assay can be used as immunological marker for comparative assessment. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype.

The use of validated HAI and SN assays is acknowledged. The validation data demonstrate that the HAI and SN methods perform reliably and are suitable for monitoring of immunogenicity in clinical studies.

2.2.4. Conclusions on clinical pharmacology

The CHMP considers that all aspects dealing with clinical pharmacology have been well addressed by the MAH.

2.3. Clinical efficacy

Clinical efficacy data were not obtained in studies VAP00027 and VAP00026. The clinical efficacy is to be inferred by clinical immunogenicity data.

2.3.1. Main studies

VAP00027: 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

Methods

Study participants

Main inclusion criteria are:

- Aged 9 to 49 years on the day of inclusion
- A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies: is of non-childbearing potential or is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first study intervention administration until at least 4 weeks after the last study intervention administration

Main exclusion criteria are:

- Known or suspected congenital or acquired immunodeficiency (e.g., HIV); or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within

the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

- Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances
- Thrombocytopenia, or known thrombocytopenia, as reported by the participant or by the parent(s)/legally acceptable representative, contraindicating intramuscular vaccination based on the investigator's judgment
- Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination based on the investigator's judgment
- Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion
- Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥38.0° C [≥100.4° F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided
- Personal or family history of Guillain-Barré Syndrome (GBS)
- Any condition that in the opinion of the investigator would pose a health risk to the participant if enrolled or could interfere with the evaluation of the study intervention
- Personal history of clinically significant development delay (at the discretion of the investigator), neurologic disorder, or seizure disorder
- 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 be 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 past 3 months

Treatments

The vaccine strain composition of RIV4 used and their commercial batch numbers are presented in the table below.

Table 2: Vaccine strain composition used in Studies VAP00026 and VAP00027

Study	Influenza Season	A/H1N1	A/H3N2	B (Victoria Lineage)	B (Yamagata Lineage)	Batch Number
VAP00027	NH 2022-2023	A/Wisconsin/588/2019	A/Darwin/6/2021	B/Austria/1359417/2021	B/Phuket/3073/2013	VA030496
VAP00026	NH 2022-2023	A/Wisconsin/588/2019	A/Darwin/6/2021	B/Austria/1359417/2021	B/Phuket/3073/2013	VA030631

The IIV4 control vaccine used in Study VAP00026 contained the Victoria/2570/2019 (H1N1)pdm09-like virus, A/Darwin/9/2021 (H3N2)-like virus, B/Austria/1359417/2021 (B/Victoria lineage)-like virus, and B/Phuket/3073/2013 (B/Yamagata lineage)-like virus, as recommended by WHO and the European Union for quadrivalent vaccines for the Northern Hemisphere season 2022-2023.

Objectives, outcomes/endpoints

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

Primary endpoints:

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

Secondary immunogenicity objective: To summarise the HAI immune response induced by RIV4 in all participants.

Secondary immunogenicity endpoints:

- Individual-HAI titre on D01 and 28 days after vaccination (D29)
- Detectable HAI titre, i.e., with a titre ≥10 (1/dil) at D01 and 28 days after vaccination (D29)
- Individual titre ratio: 28 days after vaccination (D29) /D01
- Participants with titre ≥40 (1/dil) on D01 and 28 days after vaccination (D29)
- Seroconversion (titre < 10 [1/dil] at D01 and post-injection titre ≥ 40 (1/dil) at D29 or titre ≥10 (1/dil) at D01 and a ≥4-fold rise in titre (1/dil) at D29)

Exploratory immunogenicity objective: To describe the neutralizing antibody immune response in a subset of participants.

- Individual seroneutralisation (SN) antibody (Ab) titre on D01 and 28 days after vaccination (D29)
- Individual SN Ab titre ratio (fold increase in post-vaccination titre relative to D01) at 28 days after vaccination (D29)
- Participants with SN Ab titres ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at 28 days after vaccination (D29)
- Fold-increase in SN Ab titre (post/pre) ≥ 2 and ≥ 4 at 28 days after vaccination (D29)
- Detectable SN Ab titre (SN Ab titre ≥ 10 [1/dil]) at D01 and 28 days after vaccination (D29)

Sample size

A total of approximately 1200 evaluable participants 9 to 49 years of age (600 children and adolescents 9 to 17 years of age [approximately 30% children 9 to 11 years of age] and 600 adults 18 to 49 years of age) was planned for the study.

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

Assuming in each vaccine group the same expected SC rates (0.7, 0.5, 0.6, 0.5) for each of the 4 strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria), based on conservative estimates from historical data, and a NI margin of 10%, the NI for SC rate can be demonstrated with a study power of approximately 80.10% (96.66%, 93.70%, 94.38% and 93.70% for each strain, respectively).

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

Randomisation and blinding (masking)

This study was open label and not randomised.

Statistical methods

The analyses of non-inferiority (primary objective) and descriptive (secondary, exploratory objectives) analyses were based on results obtained with the HAI assay. The descriptive analyses also included results obtained with the SN assay. The following analysis sets are defined in the following table.

Table 3: Analysis sets

Participant Analysis Set	Description
Enrolled	All participants with data in the CRF. Note: the study groups are not randomized. The study groups are determined based on age. However, a subset of participants from each age group will be randomly selected in order for their blood to be tested using the SN method.
Safety Analysis Set (SafAS)	Participants who have received one dose of the study vaccine. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of participants who received one dose of the study vaccine and had a post-vaccination blood sample. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from FAS who were randomized in the exploratory subset (FAS-SN).
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following criteria will be excluded from the PPAS: · Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria · Participant did not receive vaccine in the proper time window · Preparation and / or administration of vaccine was not done as per-protocol · Participant did not provide the post-dose serology sample at V02 in the proper time window or a post-dose serology sample was not drawn · Participant received a protocol-prohibited medications impacting or that may have an impact on the immune response as described in Section 6.8. The above criteria leading to exclusion from PPAS may be detailed and completed if necessary in the SAP, following the review of protocol deviations during the study conduct. PPAS(s) definition(s) will be finalized before the first database lock. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from PPAS who were randomized in the exploratory subset (PPAS-SN).

The PPAS was the main analysis set for the non-inferiority analysis. The non-inferiority analysis was also planned to be performed on the FAS for confirmation, if the difference in size between the 2 analysis sets was greater than 10%.

Of note, excluding participants from analysis as Per Protocol Analysis Set definition does not fully align with principal stratification as outlined in the Addendum. The subset of subjects who experience an intercurrent event on the test treatment will often be a different subset from those who experience the same intercurrent event on control. Treatment effects defined by comparing outcomes in these subsets confound the effects of the different treatments with the differences in outcomes possibly due to the differing characteristics of the subjects.

The descriptive analyses of results with the SN assay were performed on the participants from PPAS who were randomised in the exploratory subset (PPAS-SN).

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

The primary analysis was conducted in 2 steps starting with testing for non-inferiority of GMTs between the 9 to 17 years age group and the 18 to 49 years age group. If non-inferiority of GMTs of the 4 strains was demonstrated, then non-inferiority of the seroconversion rates was tested.

The immunogenicity parameters will be calculated in each study group with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio. In addition, subgroup analyses were performed; in particular, immunogenicity was described according to age subgroups, sex, race, season, previous influenza vaccination status (seropositive and seronegative are defined as baseline Ab titre $\geq$ 1:10 or < 1:10), and baseline seropositivity status, as appropriate according to number of participants in the respective subgroups.

Step 1: Geometric Mean Titres

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

The statistical methodology was based on a 2-sided 95% CI of the ratio of the GMTs (RIV4 [9-17 years] divided by RIV4 [18-49 years]) at 28 days after vaccination. Non-inferiority for GMTs was demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio was > 0.667 for each of the 4 virus strains. The 95% CI was calculated using normal approximation of log-transformed titres.

Step 2: Seroconversion Rates

The statistical methodology was based on a 2-sided 95% CI of the difference in seroconversion rates (RIV4 [9-17 years] minus RIV4 [18-49 years]) at 28 days after vaccination. Non-inferiority for seroconversion rates was demonstrated if the lower limit of the 2-sided 95% CI was >-10% for the 4 strains. The 95% CI of the rate difference was computed using the Wilson Score method without continuity correction.

The 95% CI of the difference in proportions PRIV4(9-17y) - PRIV4(18-49y) was computed using the Wilson Score method without continuity correction.

All 4 strains had to demonstrate non-inferiority of the seroconversion rate in order for study seroconversion rates to demonstrate non-inferiority success.

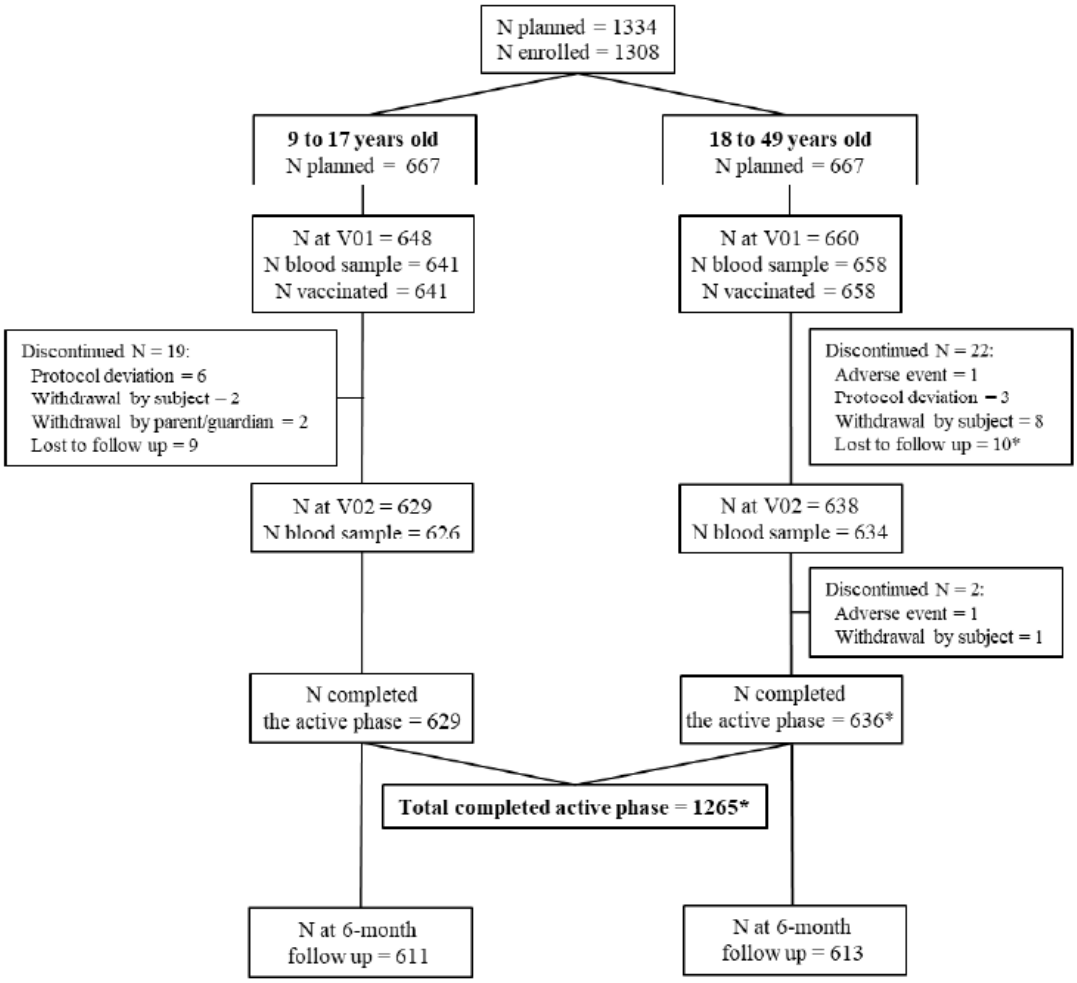
No imputation was conducted for missing values in any of the main analyses. No interim analysis was planned.

Results

Participant flow

A total of 1308 participants (648 aged 9 to 17 years and 660 aged 18 to 49 years) were enrolled. Of the total number enrolled, 1264 participants (96.6%) completed the active phase of the study: 629 participants (97.1%) in the 9 to 17 years group and 635 participants (96.2%) in the 18 to 49 years group.

Figure 1: Participant disposition flow chart



* One participant was mistakenly counted as lost to follow up during the active phase despite completion of V02 assessments and active phase. Actually, this participant was lost to follow up at the time of the 6-month follow-up.

Source: Section 8, Tables 8.2 and 8.9, and Appendix 16.1, Listing 1.1, Appendix 16.2, Listing 2.1, and Appendix 16.4, Listing 4.7.

Recruitment

Study started on 27 October 2022 with the first participant first visit, and it was completed on 02 June 2023 with the last participant last visit. Last participant last contact: 27 October 2023. The study was conducted in 36 sites in Europe and the US. Database lock date of 21 December 2023.

Conduct of the study

Non-substantial changes to the protocol were introduced.

Baseline data

Table 4: Baseline demographic by age group - Per Protocol Analysis Set

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

n: number of study participants fulfilling the item listed
Q1 ; Q3: first quartile ; third quartile
Study: VAP00027 Program: T08014_TO_T08019.sas Dataset=ADSL Output: PRODOPS/SP0234/VAP00027/CSR_01/REPORT/OUTPUT/T08016_i.rtf (29JAN2024 9:18)

Source: Section 8, Table 8.16

There were more males in the 9 to 17 years group (51.9%) who received RIV4 and more females in the 18 to 49 years group (59.4%) who received RIV4. In the 9 to 17 years age group, the mean age was 13.0 years; and there were fewer participants in the 9 to 11 years age subgroup (30.5%) than in the 12 to 17 years age subgroup (69.5%). In the 18 to 49 years age group, the mean age was 34.1 years; and the proportions of participants in the 18 to 34 years and 35 to 49 years age subgroups were the same (50%). Overall, the majority of participants were White (77.4%), and 18.9% were African American/Black.

Numbers analysed

The number and percentages of those included in the PPAS (primary and secondary immunogenicity objective) and FAS (secondary immunogenicity objective) are presented below . It is to be noted that the attrition rate from FAS to PPAS was lower than 10%; therefore, the statistical outputs in the FAS were not produced.

The immunogenicity population (N=1215) included 609 participants in the 9 to 17 years group and 606 participants in the 18 to 49 years group. The immunogenicity population included all participants enrolled and vaccinated. Furthermore, participants in the immunogenicity population had to have serum samples obtained pre- and post-vaccination on D01 and D29, respectively, and did not present major protocol deviations that could adversely impact immunogenicity.

Table 5:Study VAP00027 - Participant disposition

	9 to 17 years (N=648) n (%)	18 to 49 years (N=660) n (%)	All (N=1308) n (%)
Full Analysis Set (FAS)	626 (96.6)	634 (96.1)	1260 (96.3)
Not injected	7 (1.1)	2 (0.3)	9 (0.7)
Did not provide a post-dose serology sample	22 (3.4)	26 (3.9)	48 (3.7)
Per-protocol analysis set (PPAS)	609 (94.0)	606 (91.8)	1215 (92.9)
Per-protocol analysis set (PPAS-SN)	185 (28.5)	178 (27.0)	363 (27.8)

n: number of study participants fulfilling the item listed

Note: a study participant may be associated with more than one criterion

Source: Modified from 5.3.5.1, VAP00027 CSR, Section 8, Table 8.10 and Table 8.11

Outcomes and estimation

Primary Objective – Non-inferiority

The non-inferiority data based on GMTs and seroconversion rates at D29 after vaccination for the PPAS are presented in the below tables.

The primary objective of non-inferiority of HAI immune response induced by RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by GMTs and seroconversion rates at D29 was met. Non-inferiority was demonstrated for all 8 variables included in the non-inferiority assessment (4 ratios of GMTs and 4 differences in seroconversion) as the lower limit of the 95% CIs was higher than 0.667 for the ratios of GMTs and higher than -10% for the differences of seroconversion rates (RIV4 [9 to 17 years] minus RIV4 [18 to 49 years]) for all 4 strains.

Table 6: Study VAP00027 – Non-inferiority of immune response in terms of GMTs at D29 after vaccination of 9 to 17 years vs 18 to 49 years – PPAS

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

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013

M: number of participants with available data for the considered endpoint

§ Non-inferiority is concluded if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (9 to 17 years/18 to 49 years) is > 0.667 for each strain

Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.54

Table 7: Study VAP00027 – Non-inferiority of immune response in terms of seroconversion rates after vaccination of 9 to 17 years vs 18 to 49 years – PPAS

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

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013

M: number of participants with available data for the considered endpoint

§ Non-inferiority for SC rates is demonstrated if the lower limit of the 2-sided 95% CI is >-10% for the 4 strains

Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.56

Secondary Objective – HAI Immune Response

Pre- and post-vaccination (D29) HAI titres from all participants (N= 609 and 606 in the 9 to 17 years and 18 to 49 years age groups, respectively) were analysed. A summary of HAI Ab response are presented below.

Table 8:Study VAP00027 – Summary of HAI antibody response for each antigen – PPAS

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

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

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
n: number of participants experiencing the endpoint listed in the first 3 columns
M: number of participants with available data for the considered endpoint.
Seroconversion is defined as either a pre-dose titer < 1:10 at D01 and a post-dose titer >= 1:40 at D29 or a pre-dose titer >= 1:10 at D01 and a >= 4-fold increase in post-vaccination titer.
GMTR: Ratio of the individual titers post-dose over pre-dose
The 2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method. The 2-sided 95% CI for a GM is based on the Student t-distribution
Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.62

At baseline, the HAI Ab GMTs participants 9 to 17 years of age ranged from 48.1 for the B/Victoria lineage to 272 or the B/Yamagata lineage strain and were higher than the 18 to 49 years age group for all strains, except for B/Yamagata lineage strain where GMTs were similar. The percentages of participants 9 to 17 years of age with HAI Ab titre ≥ 40 (1/dil) and detectable titres (≥ 10 [1/dil]) ranged from 61.4% (B/Victoria lineage) to 93.1% (B/Yamagata lineage strain) and from 89.2% (A/H3N2) and 97.9% (B/Yamagata lineage strain), respectively. For both HAI Ab titres ≥ 40 (1/dil) and ≥ 10 (1/dil), the percentages of participants were higher in participants 9 to 17 years of age than in participants 18 to 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 lineage strains.

At D29, the HAI Ab GMTs increased for the 9 to 17 years age group (ranged from 405 for the B/Victoria lineage strain to 1975 for the A/H3N2 strain) and were higher than those in participants in the 18 to 49 years age group for each virus strain. GMTRs in the 9 to 17 years age group ranged from 7.13 for the B/Yamagata lineage strain to 17.9 for the A/H3N2 strain and were similar to those in the 18 to 49 years age group for all strains except for B/Yamagata lineage strain where GMTRs were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age.

At D29, the percentages of participants 9 to 17 years of age with HAI Ab titre ≥ 40 (1/dil) and ≥ 10 (1/dil) increased and were high for all 4 virus strains (≥ 95.6% and ≥ 99.5% of participants, respectively); similarly high percentages were also seen in the 18 to 49 years age group. The seroconversion rates for participants 9 to 17 years of age ranged from 77.2% for B/Yamagata lineage strain to 86.5% for A/H3N2 strain; these rates were similar to the 18 to 49 years age group for all strains except for the B/Yamagata lineage strain where seroconversion was higher in participants 9 to 17 years than in participants 18 to 49 years.

Exploratory Objective – SN Immune Response

A summary of SN Ab GMTs (1/dil) at D01 (baseline) and D29 (28 days post vaccination) are presented in the PPAS-SN in Table 9, and data for the 9 to 17 years age group are as described below.

Table 9: Study VAP00027 – Summary of Neutralizing Ab titres (SN assay) at D01 and D29 after vaccine injection – PPAS-SN Subset

		9 to 17 years (N=185)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	184	184	184	184
	Geometric Mean	614	200	65.8	466
	(95% CI)	(496 ; 760)	(172 ; 233)	(52.5 ; 82.6)	(378 ; 573)
	Participants with titers >= 10	184 (100)	184 (100)	166 (90.2)	183 (99.5)
	(95% CI)	(98.0 ; 100)	(98.0 ; 100)	(85.0 ; 94.1)	(97.0 ; 100)
Post-dose (D29)	M	184	184	184	184
	Geometric Mean	7529	1406	545	3733
	(95% CI)	(6378 ; 8887)	(1211 ; 1634)	(443 ; 669)	(3136 ; 4444)
	Participants with titers >= 10	184 (100)	184 (100)	183 (99.5)	184 (100)
	(95% CI)	(98.0 ; 100)	(98.0 ; 100)	(97.0 ; 100)	(98.0 ; 100)
	Participants with titers >= 20	184 (100)	184 (100)	180 (97.8)	184 (100)
	(95% CI)	(98.0 ; 100)	(98.0 ; 100)	(94.5 ; 99.4)	(98.0 ; 100)
	Participants with titers >= 40	184 (100)	184 (100)	173 (94.0)	183 (99.5)
	(95% CI)	(98.0 ; 100)	(98.0 ; 100)	(89.6 ; 97.0)	(97.0 ; 100)
	Participants with titers >= 80	184 (100)	183 (99.5)	166 (90.2)	181 (98.4)
	(95% CI)	(98.0 ; 100)	(97.0 ; 100)	(85.0 ; 94.1)	(95.3 ; 99.7)
Post-dose response based on pre-dose (D29/D01)	M	183	183	183	183
	GMTR	12.2	6.97	8.31	8.01
	(95% CI)	(9.38 ; 15.8)	(5.88 ; 8.26)	(6.73 ; 10.3)	(6.53 ; 9.82)
	>=2 fold rise				
	n (%)	150 (82.0)	156 (85.2)	155 (84.7)	161 (88.0)
	(95% CI)	(75.6 ; 87.2)	(79.3 ; 90.0)	(78.7 ; 89.6)	(82.4 ; 92.3)
	>=4 fold rise				
	n (%)	128 (69.9)	128 (69.9)	124 (67.8)	126 (68.9)
	(95% CI)	(62.7 ; 76.5)	(62.7 ; 76.5)	(60.5 ; 74.5)	(61.6 ; 75.5)

		18 to 49 years (N=178)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	177	177	177	177
	Geometric Mean	258	117	34.2	320
	(95% CI)	(202 ; 328)	(104 ; 131)	(28.5 ; 41.0)	(258 ; 398)
	Participants with titers >= 10	171 (96.6)	177 (100)	154 (87.0)	174 (98.3)
	(95% CI)	(92.8 ; 98.7)	(97.9 ; 100)	(81.1 ; 91.6)	(95.1 ; 99.6)
Post-dose (D29)	M	177	177	177	177
	Geometric Mean	4048	564	240	2212
	(95% CI)	(3388 ; 4837)	(471 ; 676)	(193 ; 298)	(1869 ; 2617)
	Participants with titers >= 10	177 (100)	177 (100)	176 (99.4)	177 (100)
	(95% CI)	(97.9 ; 100)	(97.9 ; 100)	(96.9 ; 100)	(97.9 ; 100)
	Participants with titers >= 20	177 (100)	177 (100)	164 (92.7)	177 (100)
	(95% CI)	(97.9 ; 100)	(97.9 ; 100)	(87.8 ; 96.0)	(97.9 ; 100)
	Participants with titers >= 40	176 (99.4)	177 (100)	158 (89.3)	177 (100)
	(95% CI)	(96.9 ; 100)	(97.9 ; 100)	(83.7 ; 93.4)	(97.9 ; 100)
	Participants with titers >= 80	176 (99.4)	167 (94.4)	134 (75.7)	175 (98.9)
	(95% CI)	(96.9 ; 100)	(89.9 ; 97.3)	(68.7 ; 81.8)	(96.0 ; 99.9)
Post-dose response based on pre-dose (D29/D01)	M	176	176	176	176
	GMTR	15.5	4.80	7.05	6.82
	(95% CI)	(11.8 ; 20.3)	(4.10 ; 5.61)	(5.81 ; 8.55)	(5.49 ; 8.46)
	>=2 fold rise				
	n (%)	149 (84.7)	134 (76.1)	146 (83.0)	140 (79.5)
	(95% CI)	(78.5 ; 89.6)	(69.1 ; 82.2)	(76.6 ; 88.2)	(72.8 ; 85.2)
	>=4 fold rise				
	n (%)	124 (70.5)	85 (48.3)	110 (62.5)	110 (62.5)
	(95% CI)	(63.1 ; 77.1)	(40.7 ; 55.9)	(54.9 ; 69.7)	(54.9 ; 69.7)

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
M: number of participants with available data for the considered endpoint
GMTR: Geometric means of individual titer ratios (post-dose over pre-dose).
X-Fold rise is defined as the computed value (=post-vaccination computed value / baseline computed value) > X.
The 2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method. The 2-sided 95% CI for the GM is based on the Student t-distribution.
Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.74

At baseline, the SN Ab GMTs for participants in the 9 to 17 years age group ranged from 65.8 for the B/Victoria lineage strain to 614 for the A/H1N1 strain and were higher than the 18 to 49 years age group for all 4 virus strains. The percentages of participants 9 to 17 years of age with SN Ab titre ≥ 10 (1/dil) at baseline were ≥ 90.2% and were similar, or tended to be higher, in participants 9 to 17 years of age than in participants 18 to 49 years of age for each virus strain.

At D29, the SN Ab GMTs increased for the 9 to 17 years age group (ranged from 545 for B/Victoria lineage strain to 7529 for A/H1N1 strain) and were higher than in participants 18 to 49 years of age for each virus strain. Post-vaccination SN Ab GMTRs in the 9 to 17 years age group ranged from 6.97 for A/H3N2 strain to 12.2 for A/H1N1 strain and were similar to those in the 18 to 49 years age group for all strains except for the A/H3N2 strain where GMTRs were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age.

At D29, the percentages of participants 9 to 17 years of age in the PPAS-SN with SN Ab titre ≥ 20, ≥ 40 or ≥ 80 (1/dil) were high for A/H1N1, A/H3N2, and B/Yamagata lineage strains (100%, ≥ 99.5%, and ≥ 98.4%, respectively) and reached lower levels for B/Victoria lineage strain (97.8%, 94.0%, and 90.2% of participants had SN Ab titre ≥ 20, ≥ 40 and ≥ 80 [1/dil] for B/Victoria lineage strain, respectively); these percentages were similar in both age groups for the A/H1N1, A/H3N2, and B/Yamagata lineage strains and tended to be higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for the B/Victoria lineage strain.

The percentage of participants 9 to 17 years of age with ≥ 2-fold rise and ≥ 4-fold rise post-/ pre-vaccination was similar for each strain (ranges: from 82.0% for A/H1N1 to 88.0% for B/Yamagata lineage strains and from 67.8% for B/Victoria lineage to 69.9% for A/H1N1 and A/H3N2 strains, respectively) and were similar or slightly higher than in participants 18 to 49 years of age.

At D29, the percentages of participants 9 to 17 years of age with SN Ab titre ≥ 10 (1/dil) were ≥ 99.5% of participants for each virus strain and were similar to those of participants 18 to 49 years of age.

Ancillary analyses

Impact of Age Group

Immunogenicity data by age group for children/adolescents (9 to 17 years) and adults (18 to 49 years) who received RIV4 are described above. Additional analyses according to age subgroups (9-11 years old, 12-17 years old, 18-34 years old, and 35-49 years old) are summarised below.

Subgroup analyses to describe HAI Ab GMTs according to age subgroups showed that post-vaccination HAI Ab GMTs were the highest in participants 9 to 11 years of age for A/H1N1 and A/H3N2 strains (2101 [95% CI: 1786; 2472] and 2550 [95% CI: 2129; 3055], respectively) and in participants 12 to 17 years of age for B/Victoria and B/Yamagata lineage strains (456 [95% CI: 402; 517] and 2286 [95% CI: 2094; 2496], respectively). The age subgroup analysis showed that seroconversion rates were similar in the 4 age subgroups for A/H1N1, A/H3N2, B/Victoria lineage strains and the highest in participants 9 to 11 years of age for B/Yamagata lineage strain (81.7% [95% CI: 75.4; 87.0]).

The SN immune responses for children/adolescents assessed by age subgroup showed that GMTs for A/H1N1 were similar between participants 9 to 11 years and 12 to 17 years of age; however, GMTs for participants 9 to 11 years of age were higher than participants 12 to 17 years of age for A/H3N2 and were lower than participants 12 to 17 years of age for B/Victoria and B/Yamagata lineage strains. For adults, SN data were similar between the 18 to 34 and 35 to 49 age subgroups for B/Victoria lineage strain but were higher for participants 18 to 34 years of age than participants 35 to 49 years of age for the other 3 strains.

Impact of Previous Influenza Vaccination

The analysis by priming status showed that post-vaccination HAI Ab GMTs were higher in participants unvaccinated than in participants vaccinated in the previous season for A/H1N1 (1630 [95% CI: 1496; 1776] and 960 [95% CI: 855; 1077], respectively) and B/Yamagata lineage (1889 [95% CI: 1757; 2030] and 1502 [95% CI: 1366; 1651], respectively) strains. There was no difference according to priming status of participants in post vaccination HAI Ab GMTs for A/H3N2 and B/Victoria lineage strains.

The analysis by priming status showed that SC rates were higher in participants unvaccinated than in participants vaccinated in the previous season for A/H1N1 (85.7% [95% CI: 83.2; 88.0] and 59.5% [95% CI: 54.3; 64.5], respectively), B/Victoria lineage (81.6% [95% CI: 78.8; 84.2] and 61.1% [95% CI: 56.0; 66.1], respectively), and B/Yamagata lineage strains (78.9% [95% CI: 76.0; 81.6] and

50.4% [95% CI: 45.2; 55.6], respectively). There was no difference according to priming status of participants in seroconversion rates for A/H3N2 strain.

There were no meaningful differences in the SN immune response assessed by previous influenza vaccination status.

Impact of Serological Status at Baseline

Analysis by baseline seropositivity serostatus showed that post-vaccination HAI Ab GMTs were higher in baseline seropositive participants than in baseline seronegative participants for each strain whatever the age group, although the number of participants seronegative at baseline was low for A/H1N1 and B/Yamagata strains.

- A/H1N1 strain: 1550 (95% CI: 1453; 1652) and 276 (95% CI: 181; 421), respectively
- A/H3N2 strain: 1573 (95% CI: 1448; 1709) and 175 (95% CI: 140; 218), respectively
- B/Victoria lineage strain: 364 (95% CI: 338; 392) and 83.5 (95% CI: 63.1; 110), respectively
- B/Yamagata lineage strain: 1819 (95% CI: 1721; 1922) and 141 (95% CI: 58.5; 337), respectively

The analysis by baseline seropositivity serostatus did not show any consistent differences between subgroups in seroconversion of HAI Ab titre. In the SN subset the number of participants seronegative at baseline was too low to draw any conclusion.

Impact of Race and Sex

The analysis by race and by sex did not show any meaningful differences between subgroups in post-vaccination HAI Ab GMTs or seroconversion of HAI Ab titre, whatever the age group. Overall, there were no meaningful differences in the SN immune response assessed by race and sex.

Summary of main study

The following tables summarise the immunogenicity results from the main studies supporting the extension of indication included in the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10: Summary of Efficacy for trial VAP00027

Title: Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years		
Study identifier	VAP00027	
Design	Phase III, non-randomised, open-label, uncontrolled, multi-centre study in participants 9 to 49 years of age in Europe and the US	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	29 Days not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	9 – 17 yoa	Treatment: RIV4, 648 randomised
	18 – 49 yoa	Treatment: RIV4, 660 randomised

Endpoints and definitions	Primary endpoint	To demonstrate the non-inferior haemagglutination inhibition (HAI) immune response of quadrivalent recombinant influenza vaccine (RIV4) for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years	• Individual HAI titre 28 days after vaccination (D29) • Seroconversion (titre < 10 [1/dil] at D01 and post-injection titre ≥ 40 [1/dil] at D29, or titre ≥ 10 [1/dil] at D01 and a ≥ 4-fold rise in titre [1/dil] at D29)
	Secondary endpoint	To summarise the HAI immune response induced by RIV4 in all participants.	• Individual-HAI titre on D01 and 28 days after vaccination (D29) • Detectable HAI titre, i.e., with a titre ≥ 10 (1/dil) at D01 and 28 days after vaccination (D29) • Individual titre ratio: 28 days after vaccination (D29) /D01 • Participants with titre ≥ 40 (1/dil) on D01 and 28 days after vaccination (D29) • Seroconversion (titre < 10 [1/dil] at D01 and post-injection titre ≥ 40 (1/dil) at D29 or titre ≥ 10 (1/dil) at D01 and a ≥ 4-fold rise in titre (1/dil) at D29)
Database lock	21 December 2023		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol Analysis Set			
Descriptive statistics and estimate variability	Treatment group	9 – 17 yoa	18 – 49 yoa	Effect comparison:
	Number of subject	609	606	
	Endpoint: HAI GMT	A/H1N1: 1946 A/H3N2: 1975 B/Victoria: 405 B/Yamagata: 1941	A/H1N1: 982 A/H3N2: 604 B/Victoria: 258 B/Yamagata: 1593	GMT Ratio: 1.98 3.27 1.57 1.22
	variability statistic: 95% CI	1795; 2109 1771; 2202 362; 452 1779; 2118	881; 1094 531; 687 233; 285 1477; 1717	1.73; 2.27 2.76; 3.87 1.35; 1.82 1.09; 1.37
	Endpoint: Seroconversion %	A/H1N1: 78.3 A/H3N2: 86.5 B/Victoria: 76.8 B/Yamagata: 77.2	76.4 87.1 73.6 62.9	Difference: 1.92 -0.59 3.29 14.3
	variability statistic: Difference 95% CI	74.8 ; 81.5 83.6 ; 89.1 73.3 ; 80.1 73.6 ; 80.5	72.8 ; 79.7 84.2 ; 89.7 69.8 ; 77.0 58.9 ; 66.7)	-2.78; 6.62 -4.41; 3.23 -1.57; 8.14 9.17; 19.3

Notes	Non-inferiority of a single dose of RIV4 (Supemtek Tetra) in 9-17 year old adolescents as compared to 18-49 year old adults was demonstrated.

VAP00026: 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

Methods

Study participants

Main inclusion criteria are:

- Aged 3 to 8 years on the day of inclusion

Main exclusion criteria are:

Main exclusion criteria are:

- Known or suspected congenital or acquired immunodeficiency (e.g., HIV); or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
- Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances
- Thrombocytopenia, or known thrombocytopenia, as reported by the participant or by the parent(s)/legally acceptable representative, contraindicating intramuscular vaccination based on the investigator's judgment
- Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination based on the investigator's judgment
- Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion
- Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥38.0° C [≥100.4° F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided
- Personal or family history of Guillain-Barré Syndrome (GBS)
- Any condition that in the opinion of the investigator would pose a health risk to the participant if enrolled or could interfere with the evaluation of the study intervention
- Personal history of clinically significant development delay (at the discretion of the investigator), neurologic disorder, or seizure disorder
- 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 be 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 past 3 months

Treatments

The vaccine strain composition used in study VAP00026 is presented in the table below.

Table 11: Vaccine compositions

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

Objectives, outcomes/endpoints

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

Primary endpoints:

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

Secondary immunogenicity objective: 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.

Secondary endpoints:

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

Exploratory objective: To describe the neutralising antibody immune response based on the egg-derived antigen in a randomised subset of participants.

Exploratory endpoints:

- Individual seroneutralisation (SN) antibody (Ab) titre on D01 and 28 days after the last vaccination (D29 or D57)
- Individual SN Ab titre ratio (fold increase in post-vaccination titre relative to D01) at 28 days after the last vaccination (D29 or D57)

Sample size

In this study, approximately 1200 participants aged 3 to 8 years will be assessed, with equal distribution between the 3-5 and 6-8 age groups, and further divided into primed and unprimed groups. The study aims to demonstrate non-inferiority (NI) for geometric mean titres (GMTs) with a power of 99.6% and for seroconversion (SC) rates with a power of 82.0% across four influenza strains. To maintain a study power above 80%, the sample size was increased to account for an estimated 15% attrition rate, resulting in a total enrolment of approximately 1412 participants.

Randomisation

Participants will be randomised in a 1:1 ratio, stratified by season, site, age subgroup and by vaccination status for influenza, such as each study randomised vaccine group will have approximately 50% of participants aged 3 to 5 years and 50% of participants aged 6 to 8 years, to receive either RIV4 or IIV4.

Blinding (masking)

This is a double blind study. Participant, participant's parent(s)/legally acceptable representative, Investigators, and study staff who conduct the safety assessment and immunogenicity assays will not know which study vaccine is administered.

Statistical methods

The analyses of non-inferiority (primary objective) and descriptive (secondary, exploratory objectives) analyses were based on results obtained with the HAI assay. The descriptive analyses also included results obtained with the SN assay. The following analysis sets are defined in the following table.

Table 12: Analysis sets

Participant Analysis Set	Description
Randomized	All participants randomized by study IRT to one of the study groups.
Safety Analysis Set (SafAS)	Participants who have received at least one dose of the study vaccine. All participants will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine and had a post-vaccination blood sample. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from FAS who were randomized in the exploratory subset (FAS-SN). Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following criteria will be excluded from the PPAS: Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria Participant did not complete the vaccination schedule Participant received a vaccine other than the one that he / she was randomized to receive Preparation and / or administration of vaccine was not done as per-protocol Participant did not receive vaccine in the proper time window Participant did not provide the post-dose serology sample at visit 2 or at visit 3 in the proper time window ([D26, D39] or VAC2+[D26, D39] respectively) or a post-dose serology sample was not drawn at visit 2 or visit 3 Participant received protocol-prohibited medications impacting or that may have an impact on the immune response as described in Section 6.8 The above criteria leading to exclusion from PPAS may be detailed and completed if necessary in the SAP, following the review of protocol deviations during the study conduct. PPAS(s) definition(s) will be finalized before the first database lock. For the assessment of the immune response by SN assay, the analysis will be performed on the participants from PPAS who were randomized in the exploratory subset (PPAS-SN). In the event of a local or national immunization program with any other vaccine as needed, participants who receive 1 or more doses of the vaccine listed above at any time during the study will not be withdrawn from the study.

The Per-Protocol Analysis Set (PPAS) was used as the primary analysis set for the interim futility and final analyses for Study VAP00026, and the full analysis set (FAS) was also used for confirmation.

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

For each strain, the non-inferiority methodology was applied to compare the post-vaccination GMTs and the seroconversion 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 into 2 steps starting with testing for non-inferiority of GMTs between RIV4 and IIV4. If non-inferiority of GMTs based on the 4 strains was demonstrated, then non-inferiority for seroconversion was also tested.

Step1: Geometric Mean Titres

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

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

Step 2: Seroconversion Rates

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

Interim analysis

Following the planned recruitment period of 2022-2023 season, only approximately 25% out of the 1412 targeted participants aged 3 to 8 years had been enrolled and vaccinated in the study. An interim analysis to review safety and assess the likelihood of the study success by the end of enrolment of approximately 1412 participants based on the immunogenicity data accumulated in approximately 25% of participants.

The pre-defined futility criteria were set as follows:

- The overall Predictive Power of Success (PPoS) of the 4 GMTs and 4 seroconversion non-inferiority statistical tests, based on a guidance PPoS of less or equal 20%, also considering the consistency across different endpoints:
    - The overall PPoS of the 4 GMTs non-inferiority statistical tests
    - The overall PPoS of the 4 seroconversion non-inferiority statistical tests
    - The individual PPoS to meet non-inferiority for each vaccine strain and each parameter (GMTs and seroconversion rates)
- Additionally, the following was taken into consideration:
    - RIV4 immunogenicity results with regards to comparator in each age, priming status and baseline serological status subgroups to inform the decision, and
    - Safety results

The overall PPoS of the 4 GMTs and 4 seroconversion non-inferiority statistical tests when comparing RIV4 to IIV4 was less than 1%. The extremely low overall PPoS was due to poorer GMT response to RIV4 as compared with IIV4 for the B/Victoria strain. Consistent results were obtained for PPoS estimates when using the FAS. The study was stopped for futility.

Therefore, the non-inferiority analysis was not performed according to the planned sample size (approximately 1412 participants) and study power. Thus, descriptive data are provided as additional supportive information only.

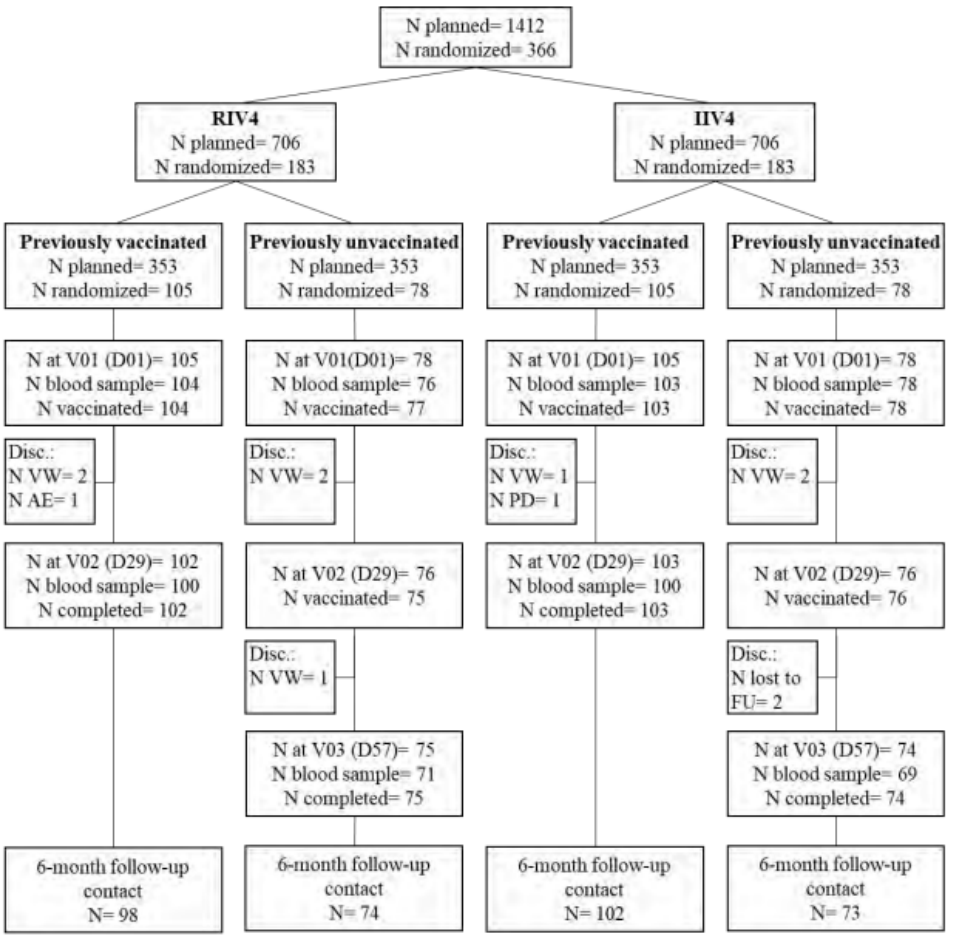
In addition, subgroup analyses were performed; in particular, immunogenicity was described according to age subgroups, sex, race, season, previous influenza vaccination status (seropositive and seronegative are defined as baseline Ab titre ≥ 1:10 or < 1:10), and baseline seropositivity status, as appropriate according to number of participants in the respective subgroups.

Results

Participant flow

As a result, a total of 366 participants were enrolled in the study and randomised to receive RIV4 or IIV4 (183 participants were randomised in each vaccination group).

Figure 2: Participant disposition flow chart



Abbreviations: AE, adverse event; D, day; Disc.: discontinued; FU, follow-up; PD, protocol deviation; VW, voluntar withdrawal

- A total of 210 previously vaccinated participants were enrolled and randomised: 92 were aged 3 to 5 years (43 were to receive RIV4 and 49 were to receive IIV4) and 118 were aged 6 to 8 years (62 were to receive RIV4 and 56 were to receive IIV4). Out of the 105 previously vaccinated participants each in the RIV4 and IIV4 groups, a total of 102 (97.1%) and 103 (98.1%) participants, respectively, completed the study up to V02.
- A total of 156 previously unvaccinated participants were enrolled and randomised: 83 were aged 3 to 5 years (39 were to receive RIV4 and 44 were to receive IIV4) and 73 were aged

6 to 8 years (39 were to receive RIV4 and 34 were to receive IIV4) Out of the 78 previously unvaccinated participants who were randomised in the RIV4 group and the 78 participants in the IIV4 group, a total of 75 (96.2%) and 74 (94.9%) participants, respectively, completed the study up to V03.

Recruitment

Study started on 10 November 2022 with the first participant first visit, and it was completed on 22 May 2023 with the last participant last visit. Last participant last contact: 07 December 2023. The study was conducted in 31 sites in Europe and the US. Database lock date of 21 December 2023.

Conduct of the study

A substantial amendment in the protocol was included in amendment 2 (dated 22 September 2022) to introduce an interim analysis for futility at the end of the 2022-2023 influenza season.

Baseline data

Table 13: Baseline demographic by randomised group - Per Protocol Analysis Set

Age group		RIV4 (N=160)	IIV4 (N=158)	All (N=318)
All	Sex: n/M (%)			
	Male	74/160 (46.3)	76/158 (48.1)	150/318 (47.2)
	Female	86/160 (53.8)	82/158 (51.9)	168/318 (52.8)
	Missing	0	0	0
	Sex ratio: Male/Female	0.86	0.93	0.89
	Age (Year)			
	M	160	158	318
	Mean (SD)	5.80 (1.73)	5.51 (1.63)	5.66 (1.68)
	Min ; Max	3.00 ; 8.00	3.00 ; 8.00	3.00 ; 8.00
	Median	6.00	5.00	6.00
	Q1 ; Q3	4.50 ; 7.00	4.00 ; 7.00	4.00 ; 7.00
	Racial origin: n/M (%)			
	White	128/160 (80.0)	118/158 (74.7)	246/318 (77.4)
	Asian	0/160	0/158	0/318
	Black	27/160 (16.9)	29/158 (18.4)	56/318 (17.6)
	American Indian or Alaska Native	2/160 (1.3)	0/158	2/318 (0.6)
	Native Hawaiian or Other Pacific Islander	0/160	1/158 (0.6)	1/318 (0.3)
	Mixed origin	2/160 (1.3)	10/158 (6.3)	12/318 (3.8)
	Unknown	1/160 (0.6)	0/158	1/318 (0.3)
	Not reported	0/160	0/158	0/318
	Missing	0	0	0
	Ethnicity: n/M (%)			
	Hispanic or Latino	15/160 (9.4)	25/158 (15.8)	40/318 (12.6)
	Not-Hispanic or Latino	144/160 (90.0)	133/158 (84.2)	277/318 (87.1)
	Unknown	1/160 (0.6)	0/158	1/318 (0.3)
3 to 5 years	Sex: n/M (%)			
	Male	32/69 (46.4)	41/80 (51.3)	73/149 (49.0)
	Female	37/69 (53.6)	39/80 (48.8)	76/149 (51.0)
	Missing	0	0	0
	Sex ratio: Male/Female	0.86	1.05	0.96
	Age (Year)			
	M	69	80	149
	Mean (SD)	4.07 (0.880)	4.11 (0.779)	4.09 (0.825)
	Min ; Max	3.00 ; 5.00	3.00 ; 5.00	3.00 ; 5.00
	Median	4.00	4.00	4.00
	Q1 ; Q3	3.00 ; 5.00	3.50 ; 5.00	3.00 ; 5.00
	Racial origin: n/M (%)			
	White	61/69 (88.4)	58/80 (72.5)	119/149 (79.9)
	Asian	0/69	0/80	0/149
	Black	6/69 (8.7)	16/80 (20.0)	22/149 (14.8)
	American Indian or Alaska Native	1/69 (1.4)	0/80	1/149 (0.7)
	Native Hawaiian or Other Pacific Islander	0/69	0/80	0/149
	Mixed origin	1/69 (1.4)	6/80 (7.5)	7/149 (4.7)
	Unknown	0/69	0/80	0/149
	Not reported	0/69	0/80	0/149
	Missing	0	0	0
	Ethnicity: n/M (%)			
	Hispanic or Latino	7/69 (10.1)	13/80 (16.3)	20/149 (13.4)
	Not-Hispanic or Latino	62/69 (89.9)	67/80 (83.8)	129/149 (86.6)
6 to 8 years	Sex: n/M (%)			
	Male	42/91 (46.2)	35/78 (44.9)	77/169 (45.6)
	Female	49/91 (53.8)	43/78 (55.1)	92/169 (54.4)
	Missing	0	0	0
	Sex ratio: Male/Female	0.86	0.81	0.84
	Age (Year)			
	M	91	78	169
	Mean (SD)	7.11 (0.823)	6.95 (0.804)	7.04 (0.816)
	Min ; Max	6.00 ; 8.00	6.00 ; 8.00	6.00 ; 8.00
	Median	7.00	7.00	7.00
	Q1 ; Q3	6.00 ; 8.00	6.00 ; 8.00	6.00 ; 8.00
	Racial origin: n/M (%)			
	White	67/91 (73.6)	60/78 (76.9)	127/169 (75.1)
	Asian	0/91	0/78	0/169
	Black	21/91 (23.1)	13/78 (16.7)	34/169 (20.1)
	American Indian or Alaska Native	1/91 (1.1)	0/78	1/169 (0.6)
	Native Hawaiian or Other Pacific Islander	0/91	1/78 (1.3)	1/169 (0.6)
	Mixed origin	1/91 (1.1)	4/78 (5.1)	5/169 (3.0)
	Unknown	1/91 (1.1)	0/78	1/169 (0.6)
	Not reported	0/91	0/78	0/169
	Missing	0	0	0
	Ethnicity: n/M (%)			
	Hispanic or Latino	8/91 (8.8)	12/78 (15.4)	20/169 (11.8)
	Not-Hispanic or Latino	82/91 (90.1)	66/78 (84.6)	148/169 (87.6)
	Unknown	1/91 (1.1)	0/78	1/169 (0.6)

n: number of study participants fulfilling the item listed
Q1 ; Q3: first quartile ; third quartile
Study: VAP00026 Program: T08017.sas Dataset=ADSL Output: PRODOPS/SP0234/VAP00026/CSR_01/REPORT/OUTPUT/T08017_x.pdf (02FEB2024 9:22)

Numbers analysed

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

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

Among the 366 randomised participants, 183 (50.0%) were included in the exploratory subsets for SN assay (FAS-SN and PPPAS-SN).

- 170 (46.4%) were included in the FAS-SN, with 92 participants in the RIV4 group and 78 participants in the IIV4 group
- 157 (42.9%) were included in the PPAS-SN, with 84 participants in the RIV4 group and 73 participants in the IIV4 group

Table 14: Study VAP00026 – Participant disposition – Randomised study participants

Group		RIV4 (N=183) n/M (%)	IIV4 (N=183) n/M (%)	All (N=366) n/M (%)
All	Full Analysis Set (FAS)	171/183 (93.4)	169/183 (92.3)	340/366 (92.9)
	Per-protocol analysis set (PPAS)	160/183 (87.4)	158/183 (86.3)	318/366 (86.9)

n: number of study participants fulfilling the item listed
M: number of participants with available data for the corresponding group
Note: a study participant may be associated with more than one criterion
Source: Modified from 5.3.5.1, VAP00026 CSR, Section 8, Table 8.11

Outcomes and estimation

Primary Objective – Non-inferiority

At the time of the final analysis, the statistical test for non-inferiority was conducted on the participants enrolled before stopping the study for futility due to very low probability of demonstrating that the non- inferior immune response induced by the RIV4 vaccine to the one induced by the IIV4 vaccine. Thus, the non-inferiority data are described below are for supportive information only.

The non-inferiority data based on the GMTs and seroconversion rates 28 days after the last vaccination (D29 or D57) for the PPAS are presented in Table 15 and Table 16, respectively.

Overall, the primary objective of this study was not met since the non-inferior HAI immune response of RIV4 versus an authorised IIV4 was not demonstrated for all 4 strains. The non-inferior HAI immune response of RIV4 versus an authorised IIV4 was demonstrated in the PPAS for 3 of the 4 strains based on the GMTs. As shown in Table 15, 28 days after the last vaccination, the lower limit of the 2-sided 95% confidence interval (CI) of the GMT ratio 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 non-inferior HAI immune response of RIV4 versus an authorised IIV4 was also demonstrated in the PPAS for 3 of the 4 strains based on the seroconversion rates. As shown in Table 16, 28 days after the last vaccination, the lower limit of the 2-sided 95% CI of the difference in seroconversion rates

(RIV - 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).

Similar results were observed in the FAS.

Table 15: Study VAP00026 – Immunogenicity primary objective: Non-inferiority of immune response in terms of GMTs at D29 after last vaccine injection of RIV4 vs IIV4 – PPAS

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

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
M: number of participants with available data for the considered endpoint
§ The study was stopped for futility - when approximately 25% of the planned number of subjects were vaccinated, because of the very low PPoS (predictive power of success).
The statistical test for non-inferiority (NI) was conducted on the subjects enrolled before stopping the study for futility.
The results of this analysis (NI) are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).
Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.118

Table 16: Study VAP00026 – Immunogenicity primary objective: Non-inferiority of immune response in terms of seroconversion rates after vaccination RIV4 vs IIV4 - PPAS

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

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
M: number of participants with available data for the considered endpoint

	RIV4 (N=160)			IIV4 (N=158)			RIV4 minus IIV4		
Antigen/strain	n/M	%	(95% CI)	n/M	%	(95% CI)	Difference (%)	(95% CI)	Non-inferiority

§ The study was stopped for futility - when approximately 25% of the planned number of subjects were vaccinated, because of the very low PPoS (predictive power of success).
The statistical test for non-inferiority (NI) was conducted on the subjects enrolled before stopping the study for futility.
The results of this analysis (NI) are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).
Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.120

Secondary Objective – HAI Immune Response

A summary of HAI Ab response at D01 and 28 days after the last vaccination (D29 or D57) is presented in Table 17, and descriptions for the RIV4 vaccine are provided below.

Table 17: Study VAP00026 – Summary of HAI antibody response for each antigen – PPAS

		RIV4 (N=160)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	159	159	159	159
	Geometric Mean	70.5	141	20.9	65.2
	(95% CI)	(52.2 ; 95.2)	(103 ; 193)	(16.9 ; 25.8)	(50.9 ; 83.5)
	Participants with titers < 10 (1/dil):	34 (21.4)	20 (12.6)	48 (30.2)	23 (14.5)
	(95% CI)	(15.3 ; 28.6)	(7.9 ; 18.8)	(23.2 ; 38.0)	(9.4 ; 20.9)
	Participants with titers >= 10 (1/dil):	125 (78.6)	139 (87.4)	111 (69.8)	136 (85.5)
	(95% CI)	(71.4 ; 84.7)	(81.2 ; 92.1)	(62.0 ; 76.8)	(79.1 ; 90.6)
	Participants with titers >= 40 (1/dil):	104 (65.4)	121 (76.1)	57 (35.8)	111 (69.8)
	(95% CI)	(57.5 ; 72.8)	(68.7 ; 82.5)	(28.4 ; 43.8)	(62.0 ; 76.8)
Post-dose (D29 or D57)	M	159	159	159	159
	Geometric Mean	998	2398	337	789
	(95% CI)	(779 ; 1279)	(1914 ; 3004)	(263 ; 432)	(634 ; 983)
	Participants with titers < 10 (1/dil):	2 (1.3)	0	1 (0.6)	0
	(95% CI)	(0.2 ; 4.5)	(0 ; 2.3)	(0 ; 3.5)	(0 ; 2.3)
	Participants with titers >= 10 (1/dil):	157 (98.7)	159 (100)	158 (99.4)	159 (100)
	(95% CI)	(95.5 ; 99.8)	(97.7 ; 100)	(96.5 ; 100)	(97.7 ; 100)
	Participants with titers >= 40 (1/dil):	155 (97.5)	156 (98.1)	147 (92.5)	158 (99.4)
	(95% CI)	(93.7 ; 99.3)	(94.6 ; 99.6)	(87.2 ; 96.0)	(96.5 ; 100)

		RIV4 (N=160)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D29 or D57/D01)	M	158	158	158	158
	Seroconversion				
	n (%)	134 (84.8)	130 (82.3)	135 (85.4)	140 (88.6)
	(95% CI)	(78.2 ; 90.0)	(75.4 ; 87.9)	(79.0 ; 90.5)	(82.6 ; 93.1)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	14.2	17.1	16.0	12.2
	(95% CI)	(10.7 ; 18.6)	(12.9 ; 22.6)	(12.8 ; 20.1)	(9.96 ; 14.9)
	Median	16.0	16.0	16.0	16.0
	Q1 ; Q3	4.00 ; 64.0	4.00 ; 64.0	8.00 ; 32.0	8.00 ; 32.0
	Min ; Max	0.002 ; 512	0.004 ; 1024	1.00 ; 512	0.125 ; 512
	Log10: Mean (SD)	1.15 (0.761)	1.23 (0.778)	1.20 (0.625)	1.09 (0.559)
Post-dose (D29)	M	96	96	96	96
	Geometric Mean	703	2076	240	938
	(95% CI)	(500 ; 989)	(1560 ; 2764)	(174 ; 330)	(711 ; 1239)
	Participants with titers < 10 (1/dil):	2 (2.1)	0	1 (1.0)	0
	(95% CI)	(0.3 ; 7.3)	(0 ; 3.8)	(0 ; 5.7)	(0 ; 3.8)
	Participants with titers >= 10 (1/dil):	94 (97.9)	96 (100)	95 (99.0)	96 (100)
	(95% CI)	(92.7 ; 99.7)	(96.2 ; 100)	(94.3 ; 100)	(96.2 ; 100)
	Participants with titers >= 40 (1/dil):	92 (95.8)	94 (97.9)	85 (88.5)	96 (100)
	(95% CI)	(89.7 ; 98.9)	(92.7 ; 99.7)	(80.4 ; 94.1)	(96.2 ; 100)

		RIV4 (N=160)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D29/D01)	M	96	96	96	96
	Seroconversion				
	n (%)	76 (79.2)	77 (80.2)	75 (78.1)	83 (86.5)
	(95% CI)	(69.7 ; 86.8)	(70.8 ; 87.6)	(68.5 ; 85.9)	(78.0 ; 92.6)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	8.72	14.6	8.48	8.23
	(95% CI)	(6.26 ; 12.2)	(10.1 ; 21.1)	(6.73 ; 10.7)	(6.60 ; 10.3)
	Median	8.00	16.0	8.00	8.00
	Q1 ; Q3	4.00 ; 32.0	4.00 ; 64.0	4.00 ; 16.0	4.00 ; 16.0
	Min ; Max	0.002 ; 512	0.004 ; 512	1.00 ; 256	0.125 ; 512
	Log10: Mean (SD)	0.941 (0.710)	1.16 (0.793)	0.928 (0.495)	0.916 (0.474)
Post-dose (D57)	M	63	63	63	63
	Geometric Mean	1704	2986	567	606
	(95% CI)	(1246 ; 2330)	(2068 ; 4313)	(394 ; 816)	(424 ; 865)
	Participants with titers < 10 (1/dil):	0	0	0	0
	(95% CI)	(0 ; 5.7)	(0 ; 5.7)	(0 ; 5.7)	(0 ; 5.7)
	Participants with titers >= 10 (1/dil):	63 (100)	63 (100)	63 (100)	63 (100)
	(95% CI)	(94.3 ; 100)	(94.3 ; 100)	(94.3 ; 100)	(94.3 ; 100)
	Participants with titers >= 40 (1/dil):	63 (100)	62 (98.4)	62 (98.4)	62 (98.4)
	(95% CI)	(94.3 ; 100)	(91.5 ; 100)	(91.5 ; 100)	(91.5 ; 100)

		RIV4 (N=160)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D57/D01)	M	62	62	62	62
	Seroconversion				
	n (%)	58 (93.5)	53 (85.5)	60 (96.8)	57 (91.9)
	(95% CI)	(84.3 ; 98.2)	(74.2 ; 93.1)	(88.8 ; 99.6)	(82.2 ; 97.3)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	29.9	21.9	42.8	22.4
	(95% CI)	(19.6 ; 45.8)	(14.1 ; 33.9)	(30.8 ; 59.5)	(15.9 ; 31.4)
	Median	32.0	22.6	32.0	16.0
	Q1 ; Q3	8.00 ; 128	8.00 ; 64.0	16.0 ; 128	8.00 ; 64.0
	Min ; Max	0.500 ; 512	1.00 ; 1024	2.00 ; 512	1.00 ; 256
	Log10: Mean (SD)	1.48 (0.727)	1.34 (0.747)	1.63 (0.563)	1.35 (0.581)

		IIV4 (N=158)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	157	157	157	157
	Geometric Mean	46.5	112	18.4	54.7
	(95% CI)	(33.9 ; 63.7)	(81.1 ; 156)	(14.9 ; 22.7)	(42.8 ; 70.1)
	Participants with titers < 10 (1/dil):	46 (29.3)	29 (18.5)	58 (36.9)	20 (12.7)
	(95% CI)	(22.3 ; 37.1)	(12.7 ; 25.4)	(29.4 ; 45.0)	(8.0 ; 19.0)
	Participants with titers >= 10 (1/dil):	111 (70.7)	128 (81.5)	99 (63.1)	137 (87.3)
	(95% CI)	(62.9 ; 77.7)	(74.6 ; 87.3)	(55.0 ; 70.6)	(81.0 ; 92.0)
	Participants with titers >= 40 (1/dil):	86 (54.8)	110 (70.1)	53 (33.8)	104 (66.2)
	(95% CI)	(46.6 ; 62.7)	(62.2 ; 77.1)	(26.4 ; 41.7)	(58.3 ; 73.6)
Post-dose (D29 or D57)	M	158	158	158	158
	Geometric Mean	640	889	605	708
	(95% CI)	(493 ; 831)	(722 ; 1095)	(480 ; 762)	(590 ; 850)
	Participants with titers < 10 (1/dil):	3 (1.9)	1 (0.6)	0	0
	(95% CI)	(0.4 ; 5.4)	(0 ; 3.5)	(0 ; 2.3)	(0 ; 2.3)
	Participants with titers >= 10 (1/dil):	155 (98.1)	157 (99.4)	158 (100)	158 (100)
	(95% CI)	(94.6 ; 99.6)	(96.5 ; 100)	(97.7 ; 100)	(97.7 ; 100)
	Participants with titers >= 40 (1/dil):	152 (96.2)	155 (98.1)	153 (96.8)	157 (99.4)
	(95% CI)	(91.9 ; 98.6)	(94.6 ; 99.6)	(92.8 ; 99.0)	(96.5 ; 100)

		IIV4 (N=158)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D29 or D57/D01)	M	157	157	157	157
	Seroconversion				
	n (%)	122 (77.7)	105 (66.9)	145 (92.4)	130 (82.8)
	(95% CI)	(70.4 ; 84.0)	(58.9 ; 74.2)	(87.0 ; 96.0)	(76.0 ; 88.4)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	13.8	7.86	32.7	13.1
	(95% CI)	(10.2 ; 18.8)	(5.89 ; 10.5)	(24.8 ; 43.1)	(10.2 ; 16.8)
	Median	16.0	8.00	32.0	16.0
	Q1 ; Q3	4.00 ; 64.0	2.00 ; 32.0	8.00 ; 128	4.00 ; 32.0
	Min ; Max	0.001 ; 512	0.002 ; 1024	0.250 ; 2048	0.031 ; 512
	Log10: Mean (SD)	1.14 (0.843)	0.895 (0.793)	1.51 (0.760)	1.12 (0.690)
Post-dose (D29)	M	96	96	96	96
	Geometric Mean	486	886	334	713
	(95% CI)	(340 ; 695)	(665 ; 1179)	(249 ; 449)	(556 ; 915)
	Participants with titers < 10 (1/dil):	3 (3.1)	1 (1.0)	0	0
	(95% CI)	(0.6 ; 8.9)	(0 ; 5.7)	(0 ; 3.8)	(0 ; 3.8)
	Participants with titers >= 10 (1/dil):	93 (96.9)	95 (99.0)	96 (100)	96 (100)
	(95% CI)	(91.1 ; 99.4)	(94.3 ; 100)	(96.2 ; 100)	(96.2 ; 100)
	Participants with titers >= 40 (1/dil):	91 (94.8)	94 (97.9)	91 (94.8)	95 (99.0)
	(95% CI)	(88.3 ; 98.3)	(92.7 ; 99.7)	(88.3 ; 98.3)	(94.3 ; 100)

		IIV4 (N=158)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D29/D01)	M	96	96	96	96
	Seroconversion				
	n (%)	68 (70.8)	63 (65.6)	84 (87.5)	72 (75.0)
	(95% CI)	(60.7 ; 79.7)	(55.2 ; 75.0)	(79.2 ; 93.4)	(65.1 ; 83.3)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	8.54	6.17	12.8	7.66
	(95% CI)	(5.88 ; 12.4)	(4.29 ; 8.86)	(10.0 ; 16.4)	(5.73 ; 10.2)
	Median	8.00	4.00	16.0	8.00
	Q1 ; Q3	2.00 ; 32.0	2.00 ; 22.6	8.00 ; 32.0	2.83 ; 16.0
	Min ; Max	0.001 ; 512	0.002 ; 1024	0.250 ; 256	0.031 ; 256
	Log10: Mean (SD)	0.931 (0.798)	0.790 (0.777)	1.11 (0.527)	0.884 (0.624)
Post-dose (D57)	M	62	62	62	62
	Geometric Mean	979	895	1514	700
	(95% CI)	(685 ; 1399)	(663 ; 1208)	(1196 ; 1916)	(535 ; 916)
	Participants with titers < 10 (1/dil):	0	0	0	0
	(95% CI)	(0 ; 5.8)	(0 ; 5.8)	(0 ; 5.8)	(0 ; 5.8)
	Participants with titers >= 10 (1/dil):	62 (100)	62 (100)	62 (100)	62 (100)
	(95% CI)	(94.2 ; 100)	(94.2 ; 100)	(94.2 ; 100)	(94.2 ; 100)
	Participants with titers >= 40 (1/dil):	61 (98.4)	61 (98.4)	62 (100)	62 (100)
	(95% CI)	(91.3 ; 100)	(91.3 ; 100)	(94.2 ; 100)	(94.2 ; 100)

		IIV4 (N=158)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Post-dose response based on pre-dose (D57/D01)	M	61	61	61	61
	Seroconversion				
	n (%)	54 (88.5)	42 (68.9)	61 (100)	58 (95.1)
	(95% CI)	(77.8 ; 95.3)	(55.7 ; 80.1)	(94.1 ; 100)	(86.3 ; 99.0)
	Ratio of titers (GMTR)				
	Geometric Mean (GM)	29.6	11.5	143	30.2
	(95% CI)	(18.3 ; 47.6)	(7.20 ; 18.4)	(99.8 ; 206)	(20.8 ; 43.9)
	Median	32.0	8.00	128	32.0
	Q1 ; Q3	8.00 ; 128	2.00 ; 64.0	64.0 ; 512	16.0 ; 64.0
	Min ; Max	0.250 ; 512	0.500 ; 1024	8.00 ; 2048	2.00 ; 512
	Log10: Mean (SD)	1.47 (0.810)	1.06 (0.796)	2.16 (0.615)	1.48 (0.632)

Antigen/strain assessment for RIV4 and IIV4: A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
n: number of participants experiencing the endpoint listed in the first 3 columns
M: number of participants with available data for the considered endpoint
Seroconversion is defined as either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and a >= four-fold increase in post-vaccination titer
GMTR: Ratio of the individual titers post-dose over pre-dose.
The 2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method. The 2-sided 95% CI for a GM is based on the Student t-distribution.
Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.122

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. The percentage of participants in the RIV4 group with HAI titres ≥ 40 (1/dil) ranged from 35.8% for B/Victoria lineage strain to 76.1% for A/H3N2 strain, and these percentages were similar to those in the IIV4 vaccination group.

Previously vaccinated participants (1 dose received in VAP00026 study)

At D29 (28 days after a single vaccination with RIV4), the GMTs highly increased for each antigen with post-vaccination GMTs ranging from 240 for B/Victoria lineage strain to 2076 for A/H3N2 strain. The GMTRs (D01/D29) in the RIV4 group ranged from 8.23 for B/Yamagata lineage strain to 14.6 for A/H3N2 strain.

At D29, the percentage of participants in the RIV4 group with detectable HAI titres (≥ 10 [1/dil]) increased for all 4 strains (ranging from 98.7% for A/H1N1 strain to 100% for A/H3N2 strain and B/Yamagata lineage strain) and was similar for the corresponding strain between RIV4 and IIV4 groups. The percentage of participants in the RIV4 group with HAI titres ≥ 40 (1/dil) was high (ranging from 92.5% for B/Victoria lineage strain to 99.4% for B/Yamagata lineage strain) and tended to be slightly higher in the RIV4 group than in the IIV4 group.

At D29, the seroconversion rates in the RIV4 group ranged from 78.1% for B/Victoria lineage strain to 86.5% for B/Yamagata lineage strain. These percentages in the RIV4 group tended to be higher than the IIV4 group for the A/H3N2 strain and B/Yamagata lineage strain, and they tended to be lower than in the IIV4 group for the B/Victoria lineage strain:

Previously unvaccinated participants (2 doses received in VAP00026 study)

At D57 (28 days after the last vaccination with RIV4), the GMTs highly increased for each antigen with post-vaccination GMTs ranging from 567 for B/Victoria lineage strain to 2986 for A/H3N2 strain. The GMTR (D01/D57) in the RIV4 group ranged from 21.9 for A/H3N2 strain to 42.8 for B/Victoria lineage strain.

At D57, all the participants in the RIV group achieved detectable HAI titres at ≥ 10 (1/dil) for all 4 strains and were the same results as for the IIV4 group. The percentages of participants in the RIV4 group with HAI titres ≥ 40 (1/dil) were high for all 4 strains (ranging from 98.4% to 100%) and were similar percentages in the IIV4 group.

At D57, the seroconversion rates induced by the RIV4 ranged from 85.5% for A/H3N2 strain to 96.8% for B/Victoria lineage strain. The seroconversion rates induced by the RIV4 were similar to those induced by the IIV4 for the corresponding strain, with the exception of rates for A/H3N2 strain, which were numerically higher than the IIV4 vaccine.

Exploratory Objective – SN Immune Response

A summary of neutralizing Ab responses measured by SN assay to each strain at D01 and 28 days after the last vaccination (D29 or D57) is presented for the PPAS-SN subset in Table 18, and descriptions for the RIV4 vaccine are provided below.

Table 18: Study VAP00026 – Summary of Neutralizing Ab *titre*s (SN assay) at D01 and D29 after last vaccine injection – PPAS-SN Subset

		RIV4 (N=84)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	81	81	81	81
	Geometric Mean	302	208	23.7	93.8
	(95% CI)	(183 ; 498)	(165 ; 262)	(17.2 ; 32.8)	(64.7 ; 136)
	Participants with titers >= 10	73 (90.1)	80 (98.8)	53 (65.4)	74 (91.4)
	(95% CI)	(81.5 ; 95.6)	(93.3 ; 100)	(54.0 ; 75.7)	(83.0 ; 96.5)
Post-dose (D29 or D57)	M	84	84	84	84
	Geometric Mean	5785	1655	468	1381
	(95% CI)	(4185 ; 7997)	(1305 ; 2099)	(336 ; 653)	(976 ; 1954)
	Participants with titers >= 10	84 (100)	84 (100)	84 (100)	84 (100)
	(95% CI)	(95.7 ; 100)	(95.7 ; 100)	(95.7 ; 100)	(95.7 ; 100)
	Participants with titers >= 20	84 (100)	84 (100)	82 (97.6)	84 (100)
	(95% CI)	(95.7 ; 100)	(95.7 ; 100)	(91.7 ; 99.7)	(95.7 ; 100)
	Participants with titers >= 40	84 (100)	84 (100)	78 (92.9)	83 (98.8)
	(95% CI)	(95.7 ; 100)	(95.7 ; 100)	(85.1 ; 97.3)	(93.5 ; 100)
	Participants with titers >= 80	83 (98.8)	83 (98.8)	72 (85.7)	81 (96.4)
	(95% CI)	(93.5 ; 100)	(93.5 ; 100)	(76.4 ; 92.4)	(89.9 ; 99.3)
Post-dose response based on pre-dose (D29 or D57/D01)	M	81	81	81	81
	GMTR	18.9	7.85	19.3	14.6
	(95% CI)	(12.2 ; 29.2)	(6.18 ; 9.98)	(13.8 ; 27.0)	(11.9 ; 17.8)
	>=2 fold rise				
	n (%)	75 (92.6)	72 (88.9)	79 (97.5)	80 (98.8)
	(95% CI)	(84.6 ; 97.2)	(80.0 ; 94.8)	(91.4 ; 99.7)	(93.3 ; 100)
	>=4 fold rise				
	n (%)	61 (75.3)	59 (72.8)	73 (90.1)	77 (95.1)
	(95% CI)	(64.5 ; 84.2)	(61.8 ; 82.1)	(81.5 ; 95.6)	(87.8 ; 98.6)

		IIV4 (N=73)			
		A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Pre-dose (D01)	M	71	71	71	71
	Geometric Mean	134	217	17.4	57.5
	(95% CI)	(82.9 ; 218)	(175 ; 268)	(12.6 ; 24.1)	(41.4 ; 79.8)
	Participants with titers >= 10	64 (90.1)	71 (100)	40 (56.3)	65 (91.5)
	(95% CI)	(80.7 ; 95.9)	(94.9 ; 100)	(44.0 ; 68.1)	(82.5 ; 96.8)
Post-dose (D29 or D57)	M	72	72	72	72
	Geometric Mean	3289	627	556	1078
	(95% CI)	(2349 ; 4605)	(508 ; 773)	(400 ; 774)	(820 ; 1417)
	Participants with titers >= 10	72 (100)	72 (100)	72 (100)	72 (100)
	(95% CI)	(95.0 ; 100)	(95.0 ; 100)	(95.0 ; 100)	(95.0 ; 100)
	Participants with titers >= 20	72 (100)	72 (100)	71 (98.6)	72 (100)
	(95% CI)	(95.0 ; 100)	(95.0 ; 100)	(92.5 ; 100)	(95.0 ; 100)
	Participants with titers >= 40	72 (100)	72 (100)	68 (94.4)	72 (100)
	(95% CI)	(95.0 ; 100)	(95.0 ; 100)	(86.4 ; 98.5)	(95.0 ; 100)
	Participants with titers >= 80	71 (98.6)	72 (100)	64 (88.9)	69 (95.8)
	(95% CI)	(92.5 ; 100)	(95.0 ; 100)	(79.3 ; 95.1)	(88.3 ; 99.1)
Post-dose response based on pre-dose (D29 or D57/D01)	M	70	70	70	70
	GMTR	24.3	2.89	30.9	18.9
	(95% CI)	(16.0 ; 36.9)	(2.37 ; 3.53)	(20.3 ; 46.8)	(13.8 ; 25.9)
	>=2 fold rise				
	n (%)	65 (92.9)	42 (60.0)	67 (95.7)	67 (95.7)
	(95% CI)	(84.1 ; 97.6)	(47.6 ; 71.5)	(88.0 ; 99.1)	(88.0 ; 99.1)
	>=4 fold rise				
	n (%)	59 (84.3)	23 (32.9)	62 (88.6)	61 (87.1)
	(95% CI)	(73.6 ; 91.9)	(22.1 ; 45.1)	(78.7 ; 94.9)	(77.0 ; 93.9)

A/H1N1 = A/Victoria/2570/2019 (H1N1) IVR-215; A/H3N2 = A/Darwin/9/2021 (H3N2); B/Victoria= B/Michigan/01/2021; B/Yamagata= B/Phuket/3073/2013
M: number of participants with available data for the considered endpoint
GMTR: Geometric means of individual titer ratios (post-dose over pre-dose).
X-Fold rise is defined as the computed value (=post-vaccination computed value / baseline computed value) > X.
The 2-sided exact 95% CI for the single proportion is based on the Clopper-Pearson method. The 2-sided 95% CI for the GM is based on the Student t-distribution.
Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.134

At D01 (baseline for all participants), the GMTs against all influenza strains ranged from 23.7 (95% CI: 17.2; 32.8) for B/Victoria lineage strain to 302 (95% CI: 183; 498) for A/H1N1 strain in the RIV4 group and from 17.4 (95% CI: 12.6; 24.1) for B/Victoria lineage strain to 217 (95% CI: 175; 268) for A/H3N2 strain in the IIV4 group. The percentages of participants in the RIV4 group with SN detectable titres ≥ 10 (1/dil) were high for 3 of the 4 vaccine strains (ranged from 90.1% for the A/H1N1 strain to 100% for A/H3N2 strain), but had a lower value for the B/Victoria lineage strain (56.3%); and percentages were similar to those in the IIV4 group.

At D29 or D57 (28 days the last vaccination with RIV4), the GMTs highly increased for each antigen with post-vaccination GMTs ranging from 1381 (95% CI: 976; 1954) for the B/Yamagata lineage strain to 5785 (95% CI: 4185; 7997) for the A/H1N1 strain. The GMTRs for participants in the RIV4 group ranged from 7.85 for A/H3N2 strain to 19.3 for B/Victoria lineage strain; these GMTRs were similar to the IIV4 group for A/H1N1 strain and B/Yamagata lineage strain, higher than in the IIV4 group for A/H3N2 strain, and tended to be lower than in the IIV4 group for B/Victoria lineage strain.

At D29 or D57, the percentages of participants in the RIV4 group with ≥ 2-fold rise and ≥ 4-fold rise post/pre-vaccination ranged from 88.9% for A/H3N2 strain to 98.38% for B/Yamagata lineage strain and from 72.8% for A/H3N2 strain to 95.1% for B/Yamagata lineage strain, respectively. These percentages were similar to those in the IIV4 group for the corresponding strain, with the exception of the A/H3N2 strain, for which percentages were higher in the RIV4 group than in the IIV4 group.

At D29 or D57, the percentage of participants in the RIV4 group with SN titres ≥ 10 (1/dil) reached 100% for all 4 strains; and the same results were seen for the IIV4 group. The percentages of participants in the RIV4 group with SN titres ≥ 20, ≥ 40, or ≥ 80 (1/dil) were high with ranges from 92.9% to 100% across all strains and a slightly lower outlier for B/Victoria at ≥ 80 (1/dil) (85.7%); these percentages were similar to those in the IIV4 group.

Ancillary analyses

Impact of Age Group

HAI Ab data for 3 to 8 years old who received either RIV4 or IIV4 are described above. Additional analyses according to age subgroups (3 to 5 years and 6 to 8 years) are summarised below.

Subgroup analyses to describe HAI Ab GMTs according to age subgroups showed that post-vaccination HAI GMTs in the RIV4 group tended to be higher in participants aged 6 to 8 years than in participants aged 3 to 5 years. The difference between both age groups was most marked for B/Yamagata lineage strain, with 464 (95% CI: 324; 666) and 1185 (95% CI: 927; 1515) in participants aged 3 to 5 years and 6 to 8 years, respectively. In the IIV4 group, post-vaccination HAI GMTs were comparable for all strains between both age groups, except for A/H1N1 strain for which GMTs tended to be higher in participants aged 6 to 8 years.

In the RIV4 group, the analysis by age group showed that seroconversion rates tended to be higher in participants aged 3 to 5 years than in participants aged 6 to 8 years for A/H1N1 (91.3% and 79.8%, respectively) and A/H3N2 strains (89.9% and 76.4%, respectively), and were comparable between both age groups for B/Victoria and B/Yamagata lineage strains. In the IIV4 group, seroconversion rates were comparable between both age groups for A/H1N1 strain, B/Victoria lineage strain, and B/Yamagata lineage strain, and tended to be higher in participants aged 3 to 5 years than in participants aged 6 to 8 years for A/H3N2 strain.

Impact of Previous Influenza Vaccination

Post-vaccination HAI GMTs in the RIV4 group were higher in previously unvaccinated participants than in previously vaccinated participants for A/H1N1 strain (1704 [95% CI: 1246; 2330] and 606 [95% CI: 424; 865]) and B/Victoria lineage strain (567 [95% CI: 394; 816] and 240 [95% CI: 174; 330]). For A/H3N2 strain, GMTs tended to be higher in previously unvaccinated participants. Conversely, for B/Yamagata lineage strain, GMTs tended to be higher in previously vaccinated participants. In the IIV4 group, post-vaccination HAI GMTs were overall similar between both subgroups, except for B/Victoria lineage strain for which GMTs were higher in previously unvaccinated participants (1514 [95% CI: 1196; 1916]) than in previously vaccinated participants (334 [95% CI: 249; 449]).

In the RIV4 group, seroconversion rates were higher in previously unvaccinated participants than in previously vaccinated participants for B/Victoria lineage strain (96.8% [95% CI: 88.8; 99.6] and 78.1% [95% CI: 68.5; 85.9]), tended to be higher in previously unvaccinated participants than in previously vaccinated participants for A/H1N1 strain, and were comparable between subgroups for A/H3N2 strain and B/Yamagata lineage strain. In the IIV4 group, seroconversion rates were higher in previously unvaccinated participants than in previously vaccinated participants for B/Victoria lineage strain (100% [95% CI: 94.1; 100] and 87.5% [95% CI: 79.2; 93.4]) and B/Yamagata lineage strain (95.1% [95% CI: 86.3; 99.0] and 75.0% [95% CI: 65.1; 83.3]), and were comparable between subgroups for A/H3N2 strain.

Impact of Serological Status at Baseline

The analysis by baseline seropositivity showed that post-vaccination HAI GMTs for each strain were higher or tended to be higher in baseline seropositive participants than in baseline seronegative participants in the RIV4 group and IIV4 group, respectively, with values ranging from:

- 450 for B/Victoria lineage strain to 3161 for A/H3N2 strain in baseline seropositive RIV4 participants and from 172 for B/Victoria lineage strain to 355 for A/H3N2 strain in baseline seronegative RIV4 participants
- 658 for B/Victoria lineage strain to 1206 for A/H3N2 strain in baseline seropositive IIV4 participants and from 201 for A/H1N1 strain to 516 for B/Victoria lineage strain in baseline seronegative IIV4 participants

The analysis by baseline seropositivity showed that seroconversion rates for each strain in the RIV4 group were comparable between seropositive participants and seronegative participants. In the IIV4 group, seroconversion rates were comparable between subgroups for B/Victoria lineage strain and was higher or tended to be higher in seronegative participants than in seropositive participants for the other strains.

Impact of Race and Sex

The analysis by race and by sex did not show any meaningful differences between subgroups in post-vaccination HAI Ab GMTs or seroconversion of HAI Ab titre, except for A/H3N2 strain, for which GMTs were higher in Black participants (4137 [95% CI: 2963; 5775]) than in White participants (2061 [95% CI: 1581; 2689]). Due to the smaller number of Black than White participants, the data analysis by race should be taken with caution.

2.3.2. Discussion on clinical efficacy

Upon completion of the two paediatric studies VAP00026 and VAP00027, conducted with RIV4 (Supemtek Tetra) and being part of the PIP EMEA-002418-PIP01-18, the MAH submitted a type II grouped submission for:

- the extension of indication from 9 years of age (based on results from the study VAP00027), and
- an update of the SmPC to add information on paediatric population between 3 to 8 years of age based on results from study VAP00026, which do not support a paediatric indication.

Studies VAP00027 and VAP00026 were performed in 2022-2023 in the US and Europe using batches made from a RIV4 commercial batch.

The primary objective of study VAP00027 was to demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in participants aged 9 to 17 years versus participants aged 18 to 49 years. The secondary objective was to describe the HAI immune response induced by RIV4 in all participants. The exploratory objective was to describe the neutralising Ab immune response in a subset of participants.

For study VAP00027, non-inferiority of RIV4 in the 9 to 17 years age group as compared to the 18 to 49 years age group after vaccination of both age groups with RIV4, was conducted for GMTs and seroconversion rates. This is in line with the Guideline on Influenza Vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014), where it is indicated that demonstration of vaccine efficacy for the age group between approximately 9 years to < 18 years, is not required. Authorisation may be based on a direct comparison of immune response to the candidate vaccine between subjects aged 9-<18 years of age and young adults. The primary analysis was conducted in 2 steps starting with testing for non-inferiority of GMTs between the 9 to 17 years age group and the 18 to 49 years age group. If non-inferiority of GMTs of the 4 strains was demonstrated, then non-inferiority of the seroconversion rates was tested. Non-inferiority for GMTs was demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio was > 0.667 for each of the 4 virus strains and non-inferiority for seroconversion rates was demonstrated if the lower limit of the 2-sided 95% CI was >-10% for the 4 strains. The 2-step statistical analysis is reasonable and criteria for demonstrating non-inferiority are considered acceptable.

Use of validated HAI and SN assays is acknowledged. As the HAI assay is commonly used for the evaluation of immunogenicity against influenza viruses, it is acknowledged that these titres lay the basis for the primary non-inferiority analysis.

While the demographics in study VAP00027 are not fully balanced, this is deemed acceptable for the purpose of this study.

The primary objective of non-inferiority of HAI immune response induced by RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by GMTs and seroconversion rates at D29 was met for all four strains.

The analysis of neutralising Abs (SN assays) against the 4 influenza virus strains generally followed the analysis of HAI titres. In the SN analyses, the pronounced differences were observed in the numerical GMT values against the different influenza virus strains, potentially indicating differences in protection or its duration against the different strains.

Sub-group analyses were provided and did not identify substantial differences in the analysed sub-groups.

The second part of this grouped application related to an update of the SmPC with paediatric information on population between 3 and 8 years of age, based on VAP00026 study results which did not support a paediatric indication. The updates in sections 4.2 and 5.1 of the SmPC were acceptable. The study was stopped for futility. Overall, the primary objective of this study was not met, since the non-inferior HAI immune response of RIV4 versus an authorised IIV4 was not demonstrated for all 4 strains.

The non-inferior HAI immune response of RIV4 versus an authorised IIV4 was demonstrated in the PPAS for 3 of the 4 strains based on the GMTs. 28 days after the last vaccination, the lower limit of the 2-sided 95% confidence interval (CI) of the GMT ratio 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 non-inferior HAI immune response of RIV4 versus an authorised IIV4 was also demonstrated in the PPAS for 3 of the 4 strains based on the seroconversion rates. 28 days after the last vaccination, the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (RIV - 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).

The finding that a previous (season) influenza vaccination did not result in higher GMT titres as compared to participants not vaccinated in the previous season is unexpected. This is also in contrast to the finding that HAI GMTs tended to be higher in baseline seropositive participants. The reason for this is unclear. The composition of the previously versus currently used vaccine or earlier contact with different virus strains could potentially bias the results.

2.3.3. Conclusions on the clinical efficacy

For study VAP00027 the primary objective of non-inferiority of HAI immune response induced by Supemtek Tetra in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by GMTs and seroconversion rates at D29 was met. Consequently, the extension of indication from 9 years of age to 17 years of age is acceptable from an efficacy point of view.

The update of the SmPC regarding paediatric data derived from study VAP00026, not as part of the indication, is also acceptable.

2.4. Clinical safety

Introduction

The duration of AE collection, requirements for AE reporting, and methods used for safety evaluation were consistent across both studies. However, there was an additional monitoring period following the second vaccination in study VAP00026 (*Table 19*). All participants were observed for at least 30 minutes after administration of IMP for any immediate unsolicited systemic AEs. Information pertaining to the intensity of the injection site and systemic reactions was recorded in a diary card on the day of vaccination and for the subsequent 7 days in the case of solicited reactions and within 28 days after vaccination in the case of unsolicited AEs. The safety analysis of unsolicited AEs was performed on the safety analysis set (SafAS), defined as all randomised participants who received at least 1 dose of study vaccine and for whom some safety data were available after administration of the study vaccines.

Table 19: Safety assessment in Studies VAP00027 and VAP00026

Safety Data Collected	Adverse Events or Reactions Collected	Time Window for Capture
Solicited Injection Site Reactions	Injection site pain, erythema, swelling, induration, and bruising	D01-D09 (both) and D29-D37 (VAP00026)
Solicited Systemic Reactions	Fever, headache, malaise, myalgia and chills	D01-D09 (both) and D29-D37 (VAP00026)
Unsolicited AEs	Any other AE that occurred between D01 and D09 (VAP00027 and VAP00026) and/or D29-D37 (VAP00026) and that did not correspond to one of the reactions pre-listed or any AE that occurred between D10 and D29 (VAP00027 and VAP00026) and/or D30 and D57 (VAP00026)	D01-D29 (both) and D29-D57 (VAP00026)
MAAEs	Any AE that prompted a participant to seek medical attention	From D01 up to D29 (both) and D29 to D57 (VAP00026)
SAEs	Any AE that resulted in any of the following outcomes: death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in congenital anomaly/birth defect, resulted in persistent or significant disability or incapacity	From D01 up to 6 months after vaccination

Patient exposure

Table 20: Number of participants included in the safety population

Study	Age Population	RIV4	IIV4
VAP00027	9 to 49 years 9 to 17 years 18 to 49 years	1 299 641 658	N/A N/A N/A
VAP00026	3 to 8 years 3-5 years 6-8 years:	181 81 100	181 91 90

Source: 5.3.5.1 VAP00027 CSR, Section 8, Table 8.13; 5.3.5.1 VAP00026 CSR, Section 8, Table 8.14

Due to early termination, only a total of 366 participants were enrolled in study VAP00026.

Adverse events

Solicited Adverse reactions

Study VAP00027

The incidence of solicited reactions tended to be numerically slightly lower in children/adolescents 9 to 17 years of age (44.3%) compared with adults 18 to 49 years of age (52.9%). This trend was observed for solicited local and for solicited systemic ARs.

The majority of solicited local and systemic adverse reactions was of mild to moderate intensity in both age groups. The proportion of severe solicited reactions was correspondingly low, but tended to be except for injection site induration, injection site bruising and chills numerically higher in the younger age group compared with the older age group.

Solicited injection site reactions

At least one solicited injection site reaction was reported by 35.6% of participants in the younger age group and by 40.8% of participants in the older age group. At least one systemic solicited adverse reaction was reported by 29.6% and 36.2% participants, respectively. The most frequently reported solicited injection site reaction in both age groups was injection site pain reported by 34.4% and 40.2% of participants in the younger and the older age group, respectively. Other injection site reactions with a lower incidence were bruising, induration, swelling, and erythema (2.4% to 4.5% of participants) in the 9 to 17 years age group; and induration, erythema, swelling, and bruising (1.1% to 3.3% of participants) in the 18 to 49 years age group (listed in order of decreasing frequency).

Most solicited injection site reactions started within Day 1 to Day 4 and resolved spontaneously after 1-3 days.

The majority of injections site reactions in both groups was mild to moderate in intensity. The incidence of severe solicited injection site reactions was low in both groups but tended to be numerically slightly higher in the younger age group. Severe solicited injection site reactions were reported by 3.1% of participants 9 to 17 years of age and by 1.4% of participants 18-49 years of age. The most frequent severe solicited injection site reaction in the younger age group was injection site swelling (1.5%), followed by injection site erythema (1.1%), injection site pain and induration (0.8% each), and by injection site bruising (0.5%). The most frequent solicited local reaction in the adult group was injection site induration (0.8%), followed by injection site bruising, swelling, and erythema (0.5% each), and injection site pain (0.3%).

Solicited injection site reactions in the younger and older age group by maximum intensity are shown in the table below.

Table 21: Study VAP00027 – Solicited injection site reactions after vaccine injection, by maximum intensity during the solicited period – SafAS (source: Table 11 summary of clinical safety)

		9 to 17 years (N=641)			18 to 49 years (N=658)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Injection site pain	**Any**	212/617	34.4	(30.6 ; 38.3)	255/635	40.2	(36.3 ; 44.1)
	Grade 1	137/617	22.2	(19.0 ; 25.7)	198/635	31.2	(27.6 ; 34.9)
	Grade 2	70/617	11.3	(9.0 ; 14.1)	55/635	8.7	(6.6 ; 11.1)
	Grade 3	5/617	0.8	(0.3 ; 1.9)	2/635	0.3	(0 ; 1.1)
Injection site erythema	**Any**	28/618	4.5	(3.0 ; 6.5)	17/635	2.7	(1.6 ; 4.3)
	Grade 1	17/618	2.8	(1.6 ; 4.4)	8/635	1.3	(0.5 ; 2.5)
	Grade 2	4/618	0.6	(0.2 ; 1.6)	6/635	0.9	(0.3 ; 2.0)
	Grade 3	7/618	1.1	(0.5 ; 2.3)	3/635	0.5	(0.1 ; 1.4)
Injection site swelling	**Any**	23/618	3.7	(2.4 ; 5.5)	17/635	2.7	(1.6 ; 4.3)
	Grade 1	8/618	1.3	(0.6 ; 2.5)	5/635	0.8	(0.3 ; 1.8)
	Grade 2	6/618	1.0	(0.4 ; 2.1)	9/635	1.4	(0.7 ; 2.7)
	Grade 3	9/618	1.5	(0.7 ; 2.7)	3/635	0.5	(0.1 ; 1.4)
Injection site induration	**Any**	19/618	3.1	(1.9 ; 4.8)	21/635	3.3	(2.1 ; 5.0)
	Grade 1	11/618	1.8	(0.9 ; 3.2)	12/635	1.9	(1.0 ; 3.3)
	Grade 2	3/618	0.5	(0.1 ; 1.4)	4/635	0.6	(0.2 ; 1.6)
	Grade 3	5/618	0.8	(0.3 ; 1.9)	5/635	0.8	(0.3 ; 1.8)
Injection site bruising	**Any**	15/618	2.4	(1.4 ; 4.0)	7/635	1.1	(0.4 ; 2.3)
	Grade 1	9/618	1.5	(0.7 ; 2.7)	3/635	0.5	(0.1 ; 1.4)
	Grade 2	3/618	0.5	(0.1 ; 1.4)	1/635	0.2	(0 ; 0.9)
	Grade 3	3/618	0.5	(0.1 ; 1.4)	3/635	0.5	(0.1 ; 1.4)

n: number of participants experiencing the endpoint listed in the first two columns
M: number of participants with available data for the relevant endpoint
Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.27

Solicited systemic adverse reactions

Any solicited systemic adverse reaction was reported by 29.6% of participants in the 9-17 years of age group and by 36.2% in the 18-49 years of age group. Myalgia was the solicited systemic reaction with the highest frequency in the younger age group (19.3% of participants), followed (in order of decreasing frequency) by headache, malaise, chills, and fever (18.5% to 2.8% of participants). The most frequent solicited systemic adverse reaction in the adult age group was headache (22.8%) followed by myalgia, malaise, chills, and fever (20.3% to 1.7% to of participants). Most solicited systemic reactions started within Day 1 to Day 4 and resolved spontaneously after 1-3 days. Most solicited systemic reactions were of mild to moderate intensity. The frequency of severe systemic solicited adverse reactions was low in both age groups but tended to be higher for all solicited systemic adverse reactions except for chills. Severe solicited systemic adverse reactions were reported by 4.6% of participants in the 9 to 17 years age group and by 3.1% in the 18-49 years of age group. The most frequently reported severe reactions in the younger group were headache and malaise (2.6% each), followed by myalgia (1.5%), fever (1.0%), and chills (0.7%). In the older age group, the most frequently reported severe systemic solicited adverse reaction was malaise (1.6%), followed by headache (1.3%), Myalgia (0.9%), chills (0.6%), and fever (0.5%).

An overview of solicited systemic adverse reactions in the two age groups by maximum intensity is given below.

Table 22: Study VAP00027 – Solicited systemic reactions after vaccine injection, by, maximum intensity during the solicited period – SafAS (source: table 13, clinical overview)

		9 to 17 years (N=641)			18 to 49 years (N=658)		
Participants experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	17/608	2.8	(1.6 ; 4.4)	11/633	1.7	(0.9 ; 3.1)
	Grade 1	5/608	0.8	(0.3 ; 1.9)	7/633	1.1	(0.4 ; 2.3)
	Grade 2	6/608	1.0	(0.4 ; 2.1)	1/633	0.2	(0 ; 0.9)
	Grade 3	6/608	1.0	(0.4 ; 2.1)	3/633	0.5	(0.1 ; 1.4)
Headache	Any	114/615	18.5	(15.5 ; 21.8)	145/635	22.8	(19.6 ; 26.3)
	Grade 1	52/615	8.5	(6.4 ; 10.9)	60/635	9.4	(7.3 ; 12.0)
	Grade 2	46/615	7.5	(5.5 ; 9.9)	77/635	12.1	(9.7 ; 14.9)
	Grade 3	16/615	2.6	(1.5 ; 4.2)	8/635	1.3	(0.5 ; 2.5)
Malaise	Any	99/615	16.1	(13.3 ; 19.2)	105/635	16.5	(13.7 ; 19.7)
	Grade 1	35/615	5.7	(4.0 ; 7.8)	33/635	5.2	(3.6 ; 7.2)
	Grade 2	48/615	7.8	(5.8 ; 10.2)	62/635	9.8	(7.6 ; 12.3)
	Grade 3	16/615	2.6	(1.5 ; 4.2)	10/635	1.6	(0.8 ; 2.9)
Myalgia	Any	119/615	19.3	(16.3 ; 22.7)	129/635	20.3	(17.3 ; 23.7)
	Grade 1	56/615	9.1	(7.0 ; 11.7)	60/635	9.4	(7.3 ; 12.0)
	Grade 2	54/615	8.8	(6.7 ; 11.3)	63/635	9.9	(7.7 ; 12.5)
	Grade 3	9/615	1.5	(0.7 ; 2.8)	6/635	0.9	(0.3 ; 2.0)
Chills	Any	45/615	7.3	(5.4 ; 9.7)	40/635	6.3	(4.5 ; 8.5)
	Grade 1	20/615	3.3	(2.0 ; 5.0)	20/635	3.1	(1.9 ; 4.8)
	Grade 2	21/615	3.4	(2.1 ; 5.2)	16/635	2.5	(1.4 ; 4.1)
	Grade 3	4/615	0.7	(0.2 ; 1.7)	4/635	0.6	(0.2 ; 1.6)

n: number of participants experiencing the endpoint listed in the first two columns
M: number of participants with available data for the relevant endpoint
Source: 5.3.5.1, VAP00027 CSR, Section 8, Table 8.33

Study VAP00026

The safety objective of study VAP00026 was to assess the safety profile of RIV4 with an authorised standard dose IIV4 comparator in children aged 3 to 8 years. Participants were stratified according to their previous influenza vaccination status and their age. The two age strata included participants 3-5 years of age and 6 to 8 years of age.

The percentage of participants who experienced at least 1 solicited adverse reaction was 45.8% in the RIV4 vaccine group, including 43.0% of participants aged 3 to 5 years and 48.0% of participants 6 to 8 years, respectively. In the IIV vaccine group 51.7% of participants reported at least one solicited adverse reaction, including 50.5% and 52.8% of participants aged 3 to 5 years and 6 to 8 years, respectively.

The majority of solicited adverse reactions was mild to moderate. The percentage of participants who experienced at least 1 Grade 3 solicited reaction was 7.8% of participants in the RIV4 vaccine group, including 5.1% and 10.0% of participants aged 3 to 5 years and 6 to 8 years, respectively.

In the IIV4 vaccine group 8.9% of subjects 3 to 8 years of age reported at least one solicited Grade 3 adverse reaction, including 4.4% and 13.5% of participants aged 3 to 5 and 6 to 8 years, respectively.

Solicited injection site reactions after any injection

The percentage of participants who experienced at least 1 solicited injection site reaction was 39.1% in the RIV4 vaccine group, including 32.9% and 44.0% of participants aged 3 to 5 years and 6 to 8 years, respectively. In the IIV4 vaccine group the incidence of solicited injection site reactions was 42.2%, including 40.7% and 43.8% of participants aged 3 to 5 years and 6 to 8 years, respectively.

The majority of injections site reactions was mild to moderate in both vaccine groups and both age groups. The percentage of participants who experienced at least 1 Grade 3 solicited injection site reaction was 4.5% in the RIV4 vaccine group, including 2.5% and 6.0% of participants aged 3 to 5 years and 6 to 8 years, respectively. In the IIV vaccine group the incidence of Grade 3 solicited injection site reactions was 4.4%, including 2.2% and 6.7% of participants aged 3 to 5 years and 6 to 8 years, respectively.

Pain was the most frequently reported solicited injection site reaction in both vaccine and both age subgroups. Injection site pain was reported by 34.1% of participants in the RIV 4 vaccine group, including 26.6% and 40.0% of participants aged 3 to 5 years and 6 to 8 years, respectively. In the IIV4 vaccine group the incidence of injections site pain was 36.7% including 39.3% and 34.1% of participants aged 3 to 5 years and 6 to 8 years, respectively.

In both vaccine groups and both age subgroups, most solicited injection site reactions started between Day 1 and Day 4 and resolved spontaneously after 1 to 3 days, and respectively 4 to 7 days for bruising. Solicited injection site reactions after any injection are shown in *Table 23*.

Table 23: Study VAP00026 – Solicited injection site reactions within 7 days after any vaccine injection, by maximum intensity during the solicited period – SafAS (source: Table 12, summary of clinical safety)

		RIV4								
		3 to 5 years (N=81)			6 to 8 years (N=100)			3 to 8 years (N=181)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Injection site pain	Any	21/79	26.6	(17.3 ; 37.7)	40/100	40.0	(30.3 ; 50.3)	61/179	34.1	(27.2 ; 41.5)
	Grade 1	15/79	19.0	(11.0 ; 29.4)	26/100	26.0	(17.7 ; 35.7)	41/179	22.9	(17.0 ; 29.8)
	Grade 2	6/79	7.6	(2.8 ; 15.8)	12/100	12.0	(6.4 ; 20.0)	18/179	10.1	(6.1 ; 15.4)
	Grade 3	0/79	0	(0 ; 4.6)	2/100	2.0	(0.2 ; 7.0)	2/179	1.1	(0.1 ; 4.0)
Injection site erythema	Any	8/78	10.3	(4.5 ; 19.2)	16/100	16.0	(9.4 ; 24.7)	24/178	13.5	(8.8 ; 19.4)
	Grade 1	6/78	7.7	(2.9 ; 16.0)	11/100	11.0	(5.6 ; 18.8)	17/178	9.6	(5.7 ; 14.9)
	Grade 2	0/78	0	(0 ; 4.6)	1/100	1.0	(0 ; 5.4)	1/178	0.6	(0 ; 3.1)
	Grade 3	2/78	2.6	(0.3 ; 9.0)	4/100	4.0	(1.1 ; 9.9)	6/178	3.4	(1.2 ; 7.2)
Injection site swelling	Any	7/78	9.0	(3.7 ; 17.6)	12/99	12.1	(6.4 ; 20.2)	19/177	10.7	(6.6 ; 16.3)
	Grade 1	6/78	7.7	(2.9 ; 16.0)	7/99	7.1	(2.9 ; 14.0)	13/177	7.3	(4.0 ; 12.2)
	Grade 2	0/78	0	(0 ; 4.6)	1/99	1.0	(0 ; 5.5)	1/177	0.6	(0 ; 3.1)
	Grade 3	1/78	1.3	(0 ; 6.9)	4/99	4.0	(1.1 ; 10.0)	5/177	2.8	(0.9 ; 6.5)
Injection site induration	Any	5/78	6.4	(2.1 ; 14.3)	12/99	12.1	(6.4 ; 20.2)	17/177	9.6	(5.7 ; 14.9)
	Grade 1	4/78	5.1	(1.4 ; 12.6)	10/99	10.1	(5.0 ; 17.8)	14/177	7.9	(4.4 ; 12.9)
	Grade 2	0/78	0	(0 ; 4.6)	1/99	1.0	(0 ; 5.5)	1/177	0.6	(0 ; 3.1)
	Grade 3	1/78	1.3	(0 ; 6.9)	1/99	1.0	(0 ; 5.5)	2/177	1.1	(0.1 ; 4.0)
Injection site bruising	Any	4/78	5.1	(1.4 ; 12.6)	3/99	3.0	(0.6 ; 8.6)	7/177	4.0	(1.6 ; 8.0)
	Grade 1	4/78	5.1	(1.4 ; 12.6)	3/99	3.0	(0.6 ; 8.6)	7/177	4.0	(1.6 ; 8.0)
	Grade 2	0/78	0	(0 ; 4.6)	0/99	0	(0 ; 3.7)	0/177	0	(0 ; 2.1)
	Grade 3	0/78	0	(0 ; 4.6)	0/99	0	(0 ; 3.7)	0/177	0	(0 ; 2.1)
		IIV4								
		3 to 5 years (N=91)			6 to 8 years (N=90)			3 to 8 years (N=181)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Injection site pain	Any	31/91	34.1	(24.5 ; 44.7)	35/89	39.3	(29.1 ; 50.3)	66/180	36.7	(29.6 ; 44.2)
	Grade 1	19/91	20.9	(13.1 ; 30.7)	17/89	19.1	(11.5 ; 28.8)	36/180	20.0	(14.4 ; 26.6)
	Grade 2	12/91	13.2	(7.0 ; 21.9)	16/89	18.0	(10.6 ; 27.5)	28/180	15.6	(10.6 ; 21.7)
	Grade 3	0/91	0	(0 ; 4.0)	2/89	2.2	(0.3 ; 7.9)	2/180	1.1	(0.1 ; 4.0)
Injection site erythema	Any	14/91	15.4	(8.7 ; 24.5)	16/88	18.2	(10.8 ; 27.8)	30/179	16.8	(11.6 ; 23.1)
	Grade 1	12/91	13.2	(7.0 ; 21.9)	6/88	6.8	(2.5 ; 14.3)	18/179	10.1	(6.1 ; 15.4)
	Grade 2	0/91	0	(0 ; 4.0)	7/88	8.0	(3.3 ; 15.7)	7/179	3.9	(1.6 ; 7.9)
	Grade 3	2/91	2.2	(0.3 ; 7.7)	3/88	3.4	(0.7 ; 9.6)	5/179	2.8	(0.9 ; 6.4)
Injection site swelling	Any	6/90	6.7	(2.5 ; 13.9)	11/88	12.5	(6.4 ; 21.3)	17/178	9.6	(5.7 ; 14.9)
	Grade 1	4/90	4.4	(1.2 ; 11.0)	5/88	5.7	(1.9 ; 12.8)	9/178	5.1	(2.3 ; 9.4)
	Grade 2	1/90	1.1	(0 ; 6.0)	3/88	3.4	(0.7 ; 9.6)	4/178	2.2	(0.6 ; 5.7)
	Grade 3	1/90	1.1	(0 ; 6.0)	3/88	3.4	(0.7 ; 9.6)	4/178	2.2	(0.6 ; 5.7)
Injection site induration	Any	7/90	7.8	(3.2 ; 15.4)	12/88	13.6	(7.2 ; 22.6)	19/178	10.7	(6.6 ; 16.2)
	Grade 1	6/90	6.7	(2.5 ; 13.9)	6/88	6.8	(2.5 ; 14.3)	12/178	6.7	(3.5 ; 11.5)
	Grade 2	1/90	1.1	(0 ; 6.0)	4/88	4.5	(1.3 ; 11.2)	5/178	2.8	(0.9 ; 6.4)
	Grade 3	0/90	0	(0 ; 4.0)	2/88	2.3	(0.3 ; 8.0)	2/178	1.1	(0.1 ; 4.0)
Injection site bruising	Any	6/90	6.7	(2.5 ; 13.9)	6/88	6.8	(2.5 ; 14.3)	12/178	6.7	(3.5 ; 11.5)
	Grade 1	6/90	6.7	(2.5 ; 13.9)	4/88	4.5	(1.3 ; 11.2)	10/178	5.6	(2.7 ; 10.1)
	Grade 2	0/90	0	(0 ; 4.0)	1/88	1.1	(0 ; 6.2)	1/178	0.6	(0 ; 3.1)
	Grade 3	0/90	0	(0 ; 4.0)	1/88	1.1	(0 ; 6.2)	1/178	0.6	(0 ; 3.1)

n: number of participants experiencing the endpoint listed in the first two columns

M: number of participants with available data for the relevant endpoint

Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.36

Solicited Systemic Reactions after any injection

The percentage of participants who experienced at least 1 solicited systemic reaction was 27.9% in the RIV4 vaccine group, including 30.4% and 26.0% of participants aged 3 to 5 years and 6 to 8 years, respectively. In the IIV4 vaccine group the incidence was 36.7%, including 31.9% and 41.6% of participants aged 3 to 5 years and 6 to 8 years, respectively.

In the RIV4 and IIV4 groups, respectively, the most frequently reported solicited systemic reaction was Malaise reported for 11.8% and 17.9% of participants in the RIV4 and the IIV4 vaccine group, including 13.2% and 15.9% of participants aged 3 to 5 years, and 10.5% and 20.6% of participants aged 6 to 8 years, respectively.

The majority of solicited systemic reactions was mild to moderate in both vaccine groups and both age strata. The percentage of participants who experienced at least 1 Grade 3 solicited systemic reaction in the IIV4 vaccine group was 3.9%, including 2.5% and 5.0% of participants aged 3 to 5 and 6 to 8 years, respectively.

Most solicited systemic reactions started between Day 0 and Day 4 in both vaccination groups and between Day and Day 8 for fever. The solicited systemic adverse reactions resolved after 1 to 3 days. Solicited systemic adverse reactions after any injection are provided in *Table 24*.

Table 24: Study VAP00026 – Solicited systemic reactions within 7 days after any vaccine injection, by maximum intensity during the solicited period – SafAS (source: table 14 summary of clinical safety)

		RIV4								
		3 to 5 years (N=81)			6 to 8 years (N=100)			3 to 8 years (N=181)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	4/79	5.1	(1.4 ; 12.5)	4/100	4.0	(1.1 ; 9.9)	8/179	4.5	(1.9 ; 8.6)
	Grade 1	3/79	3.8	(0.8 ; 10.7)	2/100	2.0	(0.2 ; 7.0)	5/179	2.8	(0.9 ; 6.4)
	Grade 2	1/79	1.3	(0 ; 6.9)	1/100	1.0	(0 ; 5.4)	2/179	1.1	(0.1 ; 4.0)
	Grade 3	0/79	0	(0 ; 4.6)	1/100	1.0	(0 ; 5.4)	1/179	0.6	(0 ; 3.1)
Headache	Any	10/79	12.7	(6.2 ; 22.0)	13/100	13.0	(7.1 ; 21.2)	23/179	12.8	(8.3 ; 18.7)
	Grade 1	5/79	6.3	(2.1 ; 14.2)	4/100	4.0	(1.1 ; 9.9)	9/179	5.0	(2.3 ; 9.3)
	Grade 2	4/79	5.1	(1.4 ; 12.5)	7/100	7.0	(2.9 ; 13.9)	11/179	6.1	(3.1 ; 10.7)
	Grade 3	1/79	1.3	(0 ; 6.9)	2/100	2.0	(0.2 ; 7.0)	3/179	1.7	(0.3 ; 4.8)
Malaise	Any	18/79	22.8	(14.1 ; 33.6)	17/100	17.0	(10.2 ; 25.8)	35/179	19.6	(14.0 ; 26.1)
	Grade 1	6/79	7.6	(2.8 ; 15.8)	5/100	5.0	(1.6 ; 11.3)	11/179	6.1	(3.1 ; 10.7)
	Grade 2	10/79	12.7	(6.2 ; 22.0)	7/100	7.0	(2.9 ; 13.9)	17/179	9.5	(5.6 ; 14.8)
	Grade 3	2/79	2.5	(0.3 ; 8.8)	5/100	5.0	(1.6 ; 11.3)	7/179	3.9	(1.6 ; 7.9)
Myalgia	Any	11/79	13.9	(7.2 ; 23.5)	18/100	18.0	(11.0 ; 26.9)	29/179	16.2	(11.1 ; 22.4)
	Grade 1	7/79	8.9	(3.6 ; 17.4)	11/100	11.0	(5.6 ; 18.8)	18/179	10.1	(6.1 ; 15.4)
	Grade 2	3/79	3.8	(0.8 ; 10.7)	7/100	7.0	(2.9 ; 13.9)	10/179	5.6	(2.7 ; 10.0)
	Grade 3	1/79	1.3	(0 ; 6.9)	0/100	0	(0 ; 3.6)	1/179	0.6	(0 ; 3.1)
Chills	Any	4/79	5.1	(1.4 ; 12.5)	7/100	7.0	(2.9 ; 13.9)	11/179	6.1	(3.1 ; 10.7)
	Grade 1	3/79	3.8	(0.8 ; 10.7)	4/100	4.0	(1.1 ; 9.9)	7/179	3.9	(1.6 ; 7.9)
	Grade 2	1/79	1.3	(0 ; 6.9)	3/100	3.0	(0.6 ; 8.5)	4/179	2.2	(0.6 ; 5.6)
	Grade 3	0/79	0	(0 ; 4.6)	0/100	0	(0 ; 3.6)	0/179	0	(0 ; 2.0)
		IIV4								
		3 to 5 years (N=91)			6 to 8 years (N=90)			3 to 8 years (N=181)		
Participants experiencing at least one:	**Maximum intensity:**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever	Any	6/91	6.6	(2.5 ; 13.8)	7/89	7.9	(3.2 ; 15.5)	13/180	7.2	(3.9 ; 12.0)
	Grade 1	3/91	3.3	(0.7 ; 9.3)	1/89	1.1	(0 ; 6.1)	4/180	2.2	(0.6 ; 5.6)
	Grade 2	1/91	1.1	(0 ; 6.0)	3/89	3.4	(0.7 ; 9.5)	4/180	2.2	(0.6 ; 5.6)
	Grade 3	2/91	2.2	(0.3 ; 7.7)	3/89	3.4	(0.7 ; 9.5)	5/180	2.8	(0.9 ; 6.4)
Headache	Any	12/91	13.2	(7.0 ; 21.9)	18/89	20.2	(12.4 ; 30.1)	30/180	16.7	(11.5 ; 22.9)
	Grade 1	7/91	7.7	(3.1 ; 15.2)	10/89	11.2	(5.5 ; 19.7)	17/180	9.4	(5.6 ; 14.7)
	Grade 2	5/91	5.5	(1.8 ; 12.4)	3/89	3.4	(0.7 ; 9.5)	8/180	4.4	(1.9 ; 8.6)
	Grade 3	0/91	0	(0 ; 4.0)	5/89	5.6	(1.8 ; 12.6)	5/180	2.8	(0.9 ; 6.4)
Malaise	Any	17/91	18.7	(11.3 ; 28.2)	20/89	22.5	(14.3 ; 32.6)	37/180	20.6	(14.9 ; 27.2)
	Grade 1	6/91	6.6	(2.5 ; 13.8)	6/89	6.7	(2.5 ; 14.1)	12/180	6.7	(3.5 ; 11.4)
	Grade 2	11/91	12.1	(6.2 ; 20.6)	7/89	7.9	(3.2 ; 15.5)	18/180	10.0	(6.0 ; 15.3)
	Grade 3	0/91	0	(0 ; 4.0)	7/89	7.9	(3.2 ; 15.5)	7/180	3.9	(1.6 ; 7.8)
Myalgia	Any	16/91	17.6	(10.4 ; 27.0)	27/89	30.3	(21.0 ; 41.0)	43/180	23.9	(17.9 ; 30.8)
	Grade 1	9/91	9.9	(4.6 ; 17.9)	12/89	13.5	(7.2 ; 22.4)	21/180	11.7	(7.4 ; 17.3)
	Grade 2	7/91	7.7	(3.1 ; 15.2)	12/89	13.5	(7.2 ; 22.4)	19/180	10.6	(6.5 ; 16.0)
	Grade 3	0/91	0	(0 ; 4.0)	3/89	3.4	(0.7 ; 9.5)	3/180	1.7	(0.3 ; 4.8)
Chills	Any	3/91	3.3	(0.7 ; 9.3)	9/89	10.1	(4.7 ; 18.3)	12/180	6.7	(3.5 ; 11.4)
	Grade 1	1/91	1.1	(0 ; 6.0)	2/89	2.2	(0.3 ; 7.9)	3/180	1.7	(0.3 ; 4.8)
	Grade 2	2/91	2.2	(0.3 ; 7.7)	5/89	5.6	(1.8 ; 12.6)	7/180	3.9	(1.6 ; 7.8)
	Grade 3	0/91	0	(0 ; 4.0)	2/89	2.2	(0.3 ; 7.9)	2/180	1.1	(0.1 ; 4.0)

n: number of participants experiencing the endpoint listed in the first two columns

M: number of participants with available data for the relevant endpoint

Source: 5.3.5.1, VAP00026 CSR, Section 8, Table 8.51

Unsolicited Adverse Events

VAP00027

In study VAP00027, RIV4 was generally well tolerated in participants aged 9 to 49 years. Unsolicited AEs were reported by 14.5% of participants in the 9–17 years age group and by 18.1% the 18–49 years age group, with most AEs being mild to moderate in intensity. Grade 3 AEs were infrequent, occurring in 1.6% of participants aged 9–17 and 2.1% of those aged 18–49 (Table 25).

In the 9-17 years old age group, the most frequently reported System Organ Class (SOCs) were "Infections and infestations" (4.8% of participants), "Respiratory, thoracic and mediastinal disorders" (4.1% of participants), and "Gastrointestinal disorders" (2.5% of participants).

In the 18-49 years age group, "Infections and infestations" (7.4% of participants), "Respiratory, thoracic and mediastinal disorders" (4.4% of participants), and "Nervous system disorders" (2.3% of participants) were the most frequently reported SOCs.

The most frequently reported AEs by preferred term (PT) were upper respiratory tract infections (1.1% in the 9–17 age group vs. 3.3% in the 18–49 year age group), oropharyngeal pain (1.6% vs. 1.7%) and cough (1.7% vs. 1.2%). The onset of AEs was most frequently within the first four days following vaccination in both age groups (5.9% in younger vs. 5.6% in older participants), and the majority of AEs lasting 1 to 3 days (5.6% vs. 5.8%) (Table 26).

Table 25: Summary of Unsolicited AEs within 28 days after vaccine injection

	9 to 17 years (N=641)				18 to 49 years (N=658)				All (N=1299)			
Participants experiencing at least one:	n	%	(95% CI)	n AEs	n	%	(95% CI)	n AEs	n	%	(95% CI)	n AEs
Immediate unsolicited AE	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Grade 3 immediate unsolicited AE	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.3)	0
Immediate unsolicited AR	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.3)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.3)	0
Unsolicited AE	93	14.5	(11.9 ; 17.5)	146	119	18.1	(15.2 ; 21.2)	178	212	16.3	(14.4 ; 18.4)	324
Grade 3 unsolicited AE	10	1.6	(0.8 ; 2.9)	14	14	2.1	(1.2 ; 3.5)	21	24	1.8	(1.2 ; 2.7)	35
Unsolicited AR	30	4.7	(3.2 ; 6.6)	43	26	4.0	(2.6 ; 5.7)	35	56	4.3	(3.3 ; 5.6)	78
Grade 3 unsolicited AR	7	1.1	(0.4 ; 2.2)	10	6	0.9	(0.3 ; 2.0)	11	13	1.0	(0.5 ; 1.7)	21
Unsolicited injection site AR	9	1.4	(0.6 ; 2.6)	12	8	1.2	(0.5 ; 2.4)	13	17	1.3	(0.8 ; 2.1)	25
Grade 3 unsolicited injection site AR	6	0.9	(0.3 ; 2.0)	9	6	0.9	(0.3 ; 2.0)	11	12	0.9	(0.5 ; 1.6)	20
Unsolicited systemic AE	86	13.4	(10.9 ; 16.3)	134	113	17.2	(14.4 ; 20.3)	165	199	15.3	(13.4 ; 17.4)	299
Grade 3 unsolicited systemic AE	4	0.6	(0.2 ; 1.6)	5	8	1.2	(0.5 ; 2.4)	10	12	0.9	(0.5 ; 1.6)	15
Unsolicited systemic AR	21	3.3	(2.0 ; 5.0)	31	19	2.9	(1.7 ; 4.5)	22	40	3.1	(2.2 ; 4.2)	53
Grade 3 unsolicited systemic AR	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
SAE	1	0.2	(0 ; 0.9)	2	5	0.8	(0.2 ; 1.8)	7	6	0.5	(0.2 ; 1.0)	9
Grade 3 SAE	1	0.2	(0 ; 0.9)	2	4	0.6	(0.2 ; 1.5)	6	5	0.4	(0.1 ; 0.9)	8

n: number of participants experiencing the endpoint listed in the first column
n AEs: number of AEs
AR: reactions related the study vaccine
Study: VAP00027 Program: T08038.sas Datasets=ADSL ADAE Output: PRODOPS/SP0234/VAP00027/CSR_01/REPORT/OUTPUT/T08038_x.pdf (29JAN2024 9:21)

Table 26: Unsolicited AEs within 28 days after vaccine injection, by maximum intensity, onset and duration

Period/ Participants experiencing at least one:	9 to 17 years (N=641) n	%	(95% CI)	n AEs	18 to 49 years (N=658) n	%	(95% CI)	n AEs	All (N=1299) n	%	(95% CI)	n AEs
Unsolicited AE	93	14.5	(11.9 ; 17.5)	146	119	18.1	(15.2 ; 21.2)	178	212	16.3	(14.4 ; 18.4)	324
Maximum intensity												
Missing	3	0.5	(0.1 ; 1.4)	3	5	0.8	(0.2 ; 1.8)	7	8	0.6	(0.3 ; 1.2)	10
Grade 1	41	6.4	(4.6 ; 8.6)	74	66	10.0	(7.8 ; 12.6)	98	107	8.2	(6.8 ; 9.9)	172
Grade 2	39	6.1	(4.4 ; 8.2)	55	34	5.2	(3.6 ; 7.1)	52	73	5.6	(4.4 ; 7.0)	107
Grade 3	10	1.6	(0.8 ; 2.9)	14	14	2.1	(1.2 ; 3.5)	21	24	1.8	(1.2 ; 2.7)	35
Time of onset												
Missing	0	0	(0 ; 0.6)	0	2	0.3	(0 ; 1.1)	2	2	0.2	(0 ; 0.6)	2
D01-D04	38	5.9	(4.2 ; 8.0)	49	37	5.6	(4.0 ; 7.7)	46	75	5.8	(4.6 ; 7.2)	95
D05-D08	19	3.0	(1.8 ; 4.6)	27	30	4.6	(3.1 ; 6.4)	45	49	3.8	(2.8 ; 5.0)	72
D09-D15	10	1.6	(0.8 ; 2.9)	20	17	2.6	(1.5 ; 4.1)	23	27	2.1	(1.4 ; 3.0)	43
D16 or later	26	4.1	(2.7 ; 5.9)	50	33	5.0	(3.5 ; 7.0)	62	59	4.5	(3.5 ; 5.8)	112
Duration												
Missing	5	0.8	(0.3 ; 1.8)	11	8	1.2	(0.5 ; 2.4)	14	13	1.0	(0.5 ; 1.7)	25
1-3 days	36	5.6	(4.0 ; 7.7)	60	38	5.8	(4.1 ; 7.8)	66	74	5.7	(4.5 ; 7.1)	126
4-7 days	25	3.9	(2.5 ; 5.7)	39	25	3.8	(2.5 ; 5.6)	38	50	3.8	(2.9 ; 5.0)	77
8 days or more	27	4.2	(2.8 ; 6.1)	36	48	7.3	(5.4 ; 9.6)	60	75	5.8	(4.6 ; 7.2)	96

n: number of participants experiencing the endpoint listed in the first column
n AEs: number of AEs
Study: VAP00027 Program: T08040.sas Datasets=ADSL ADAE Output: PRODOPS/SP0234/VAP00027/CSR_01/REPORT/OUTPUT/T08040_x.pdf (29JAN2024 9:21)

VAP00026

In study VAP00026, both RIV4 and IIV4 were generally well tolerated in participants aged 3-8 years. Overall, the frequency of participants with at least one unsolicited AE was similar between the RIV4 (24.3%) and IIV4 (26.0%) groups. Unsolicited AEs were reported by 28.4% of participants in the 3–5 years subgroup and 21.0% of those aged 6–8 years in the RIV4 group and by 29.7% and 22.2% in the respective age subgroups of the IIV4 group. Most AEs were mild to moderate in intensity, with Grade 3 AEs being infrequent (3.3% in RIV4 vs. 3.9% in IIV4 participants) (Table 27).

Unsolicited AEs were mainly reported in the SOCs of "Infections and infestations" (14.4% in RIV4 vs. 12.7% in IIV4), "Respiratory, thoracic, and mediastinal disorders" (6.1% vs. 8.8%), and "Gastrointestinal disorders" (5.5% vs. 5.0%). The most frequently reported AEs by PT were upper respiratory tract infection (4.4% in both groups), pharyngitis streptococcal (3.9% in RIV4 vs. 1.7% in IIV4), rhinorrhoea (2.8% vs. 3.3%) and cough (2.2% vs. 3.9%).

Following the first vaccination, unsolicited AEs occurred in 16.9% of those receiving RIV4 and 15.4% of those receiving IIV4, with similar frequencies observed following the second vaccination (10.7% vs. 15.8%).

The onset of unsolicited AEs after any vaccination occurred most frequently between days 5 to 8 in the RIV4 group (7.7%) and within the first four days and 16 days or later in the IIV4 group (both 8.3%). The majority of AEs lasted 4 to 7 days in the IIV4 group (10.2 %), whereas in the RIV4 group AEs lasted mostly 8 days or more (12.7%) (

Table *28*). Only minor differences were seen between Visit 1 and Visit 2. The RIV4 group tended to have unsolicited AEs with a later onset and longer duration after the first dose, which became shorter after the second dose. In the IIV4 group, AEs tended to occur earlier and resolve more quickly after both doses.

The safety profile of RIV4 was comparable between previously vaccinated and unvaccinated participants.

Table 27: Summary of Unsolicited AEs within 28 days after any vaccine injection

	RIV4											
	3 to 5 years (N=81)				6 to 8 years (N=100)				3 to 8 years (N=181)			
Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**	**n**	**%**	**(95% CI)**	**n AEs**
Immediate unsolicited AE	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Immediate unsolicited AR	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Unsolicited AE	23	28.4	(18.9 ; 39.5)	34	21	21.0	(13.5 ; 30.3)	39	44	24.3	(18.3 ; 31.2)	73
Grade 3 unsolicited AE	3	3.7	(0.8 ; 10.4)	5	3	3.0	(0.6 ; 8.5)	3	6	3.3	(1.2 ; 7.1)	8
Unsolicited AR	2	2.5	(0.3 ; 8.6)	3	2	2.0	(0.2 ; 7.0)	3	4	2.2	(0.6 ; 5.6)	6
Grade 3 unsolicited AR	1	1.2	(0 ; 6.7)	2	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	2
Unsolicited injection site AR	1	1.2	(0 ; 6.7)	2	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	2
Grade 3 unsolicited injection site AR	1	1.2	(0 ; 6.7)	2	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	2
Unsolicited systemic AE	23	28.4	(18.9 ; 39.5)	32	21	21.0	(13.5 ; 30.3)	39	44	24.3	(18.3 ; 31.2)	71
Grade 3 unsolicited systemic AE	2	2.5	(0.3 ; 8.6)	3	3	3.0	(0.6 ; 8.5)	3	5	2.8	(0.9 ; 6.3)	6
Unsolicited systemic AR	1	1.2	(0 ; 6.7)	1	2	2.0	(0.2 ; 7.0)	3	3	1.7	(0.3 ; 4.8)	4
Grade 3 unsolicited systemic AR	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
SAE	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Grade 3 SAE	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Immediate unsolicited AE	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Grade 3 immediate unsolicited AE	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Immediate unsolicited AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Grade 3 immediate unsolicited AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Unsolicited AE	27	29.7	(20.5 ; 40.2)	47	20	22.2	(14.1 ; 32.2)	30	47	26.0	(19.7 ; 33.0)	77
Grade 3 unsolicited AE	3	3.3	(0.7 ; 9.3)	3	4	4.4	(1.2 ; 11.0)	4	7	3.9	(1.6 ; 7.8)	7
Unsolicited AR	1	1.1	(0 ; 6.0)	1	1	1.1	(0 ; 6.0)	1	2	1.1	(0.1 ; 3.9)	2
Grade 3 unsolicited AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Unsolicited injection site AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Grade 3 unsolicited injection site AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Unsolicited systemic AE	27	29.7	(20.5 ; 40.2)	47	20	22.2	(14.1 ; 32.2)	30	47	26.0	(19.7 ; 33.0)	77
Grade 3 unsolicited systemic AE	3	3.3	(0.7 ; 9.3)	3	4	4.4	(1.2 ; 11.0)	4	7	3.9	(1.6 ; 7.8)	7
Unsolicited systemic AR	1	1.1	(0 ; 6.0)	1	1	1.1	(0 ; 6.0)	1	2	1.1	(0.1 ; 3.9)	2
Grade 3 unsolicited systemic AR	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
SAE	0	0	(0 ; 4.0)	0	1	1.1	(0 ; 6.0)	1	1	0.6	(0 ; 3.0)	1
Grade 3 SAE	0	0	(0 ; 4.0)	0	1	1.1	(0 ; 6.0)	1	1	0.6	(0 ; 3.0)	1

Table 28: Unsolicited AEs within 28 days after any vaccine injection, by maximum intensity, onset and duration

Period/ Participants experiencing at least one:	RIV4 3 to 5 years (N=81) n	%	(95% CI)	n AEs	6 to 8 years (N=100) n	%	(95% CI)	n AEs	3 to 8 years (N=181) n	%	(95% CI)	n AEs
Unsolicited AE	23	28.4	(18.9 ; 39.5)	34	21	21.0	(13.5 ; 30.3)	39	44	24.3	(18.3 ; 31.2)	73
Maximum intensity												
Missing	2	2.5	(0.3 ; 8.6)	3	2	2.0	(0.2 ; 7.0)	5	4	2.2	(0.6 ; 5.6)	8
Grade 1	11	13.6	(7.0 ; 23.0)	15	10	10.0	(4.9 ; 17.6)	22	21	11.6	(7.3 ; 17.2)	37
Grade 2	7	8.6	(3.5 ; 17.0)	11	6	6.0	(2.2 ; 12.6)	9	13	7.2	(3.9 ; 12.0)	20
Grade 3	3	3.7	(0.8 ; 10.4)	5	3	3.0	(0.6 ; 8.5)	3	6	3.3	(1.2 ; 7.1)	8
Time of onset												
Missing	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
D01-D04	5	6.2	(2.0 ; 13.8)	7	4	4.0	(1.1 ; 9.9)	5	9	5.0	(2.3 ; 9.2)	12
D05-D08	8	9.9	(4.4 ; 18.5)	11	6	6.0	(2.2 ; 12.6)	6	14	7.7	(4.3 ; 12.6)	17
D09-D15	5	6.2	(2.0 ; 13.8)	6	4	4.0	(1.1 ; 9.9)	7	9	5.0	(2.3 ; 9.2)	13
D16 or later	5	6.2	(2.0 ; 13.8)	10	7	7.0	(2.9 ; 13.9)	21	12	6.6	(3.5 ; 11.3)	31
Duration												
Missing	0	0	(0 ; 4.5)	1	0	0	(0 ; 3.6)	2	0	0	(0 ; 2.0)	3
1-3 days	5	6.2	(2.0 ; 13.8)	9	3	3.0	(0.6 ; 8.5)	12	8	4.4	(1.9 ; 8.5)	21
4-7 days	6	7.4	(2.8 ; 15.4)	12	7	7.0	(2.9 ; 13.9)	10	13	7.2	(3.9 ; 12.0)	22
8 days or more	12	14.8	(7.9 ; 24.4)	12	11	11.0	(5.6 ; 18.8)	15	23	12.7	(8.2 ; 18.5)	27
Unsolicited AE	27	29.7	(20.5 ; 40.2)	47	20	22.2	(14.1 ; 32.2)	30	47	26.0	(19.7 ; 33.0)	77
Maximum intensity												
Missing	0	0	(0 ; 4.0)	0	2	2.2	(0.3 ; 7.8)	3	2	1.1	(0.1 ; 3.9)	3
Grade 1	14	15.4	(8.7 ; 24.5)	22	6	6.7	(2.5 ; 13.9)	14	20	11.0	(6.9 ; 16.5)	36
Grade 2	10	11.0	(5.4 ; 19.3)	22	8	8.9	(3.9 ; 16.8)	9	18	9.9	(6.0 ; 15.3)	31
Grade 3	3	3.3	(0.7 ; 9.3)	3	4	4.4	(1.2 ; 11.0)	4	7	3.9	(1.6 ; 7.8)	7
Time of onset												
Missing	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
D01-D04	7	7.7	(3.1 ; 15.2)	9	8	8.9	(3.9 ; 16.8)	8	15	8.3	(4.7 ; 13.3)	17
D05-D08	4	4.4	(1.2 ; 10.9)	5	4	4.4	(1.2 ; 11.0)	7	8	4.4	(1.9 ; 8.5)	12
D09-D15	5	5.5	(1.8 ; 12.4)	9	4	4.4	(1.2 ; 11.0)	7	9	5.0	(2.3 ; 9.2)	16
D16 or later	11	12.1	(6.2 ; 20.6)	24	4	4.4	(1.2 ; 11.0)	8	15	8.3	(4.7 ; 13.3)	32
Duration												
Missing	0	0	(0 ; 4.0)	0	1	1.1	(0 ; 6.0)	2	1	0.6	(0 ; 3.0)	2
1-3 days	7	7.7	(3.1 ; 15.2)	21	6	6.7	(2.5 ; 13.9)	12	13	7.2	(3.9 ; 12.0)	33
4-7 days	11	12.1	(6.2 ; 20.6)	17	8	8.9	(3.9 ; 16.8)	11	19	10.5	(6.4 ; 15.9)	28
8 days or more	9	9.9	(4.6 ; 17.9)	9	5	5.6	(1.8 ; 12.5)	5	14	7.7	(4.3 ; 12.6)	14

Unsolicited Adverse Reactions

VAP00027

In study VAP00027, unsolicited ARs were reported by 4.7% of participants aged 9 to 17 years and 4.0% of those aged 18 to 49 years. Most ARs were mild to moderate in intensity. Grade 3 ARs were reported in 1.1% of participants aged 9–17 and 0.9% of those aged 18–49. For both age groups, Grade 3 unsolicited injection site ARs were reported for 0.9% of participants. Overall, one participant (0.2%) in the 9 to 17 years age group experienced at least 1 unsolicited systemic AR rated as Grade 3 within 28 days of vaccination (1 report of Grade 3 nausea). No participants in the 9 to 17 years age group reported any Grade 3 unsolicited systemic ARs within 28 days of vaccination (*Table 29* and

Table 30).

The most frequently reported ARs by PT were rhinorrhoea (0.8% in the 9–17 age group vs. 0.3% in the 18–49 age group), oropharyngeal pain (0.3% vs. 0.6%), and cough (0.6% vs. 0.2%). The onset of ARs was most frequently within the D01-D04 time period and the majority of ARs lasted 1 to 3 days. In the age group 9-17 years, one participant with a medical history of asthma reported an asthma exacerbation on Day 2. This AE was judged to be related by the investigator.

Table 29: Unsolicited ARs within 28 days after vaccine injection, by SOC and PT

	9 to 17 years (N=641)				18 to 49 years (N=658)				All (N=1299)			
Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	30	4.7	(3.2 ; 6.6)	43	26	4.0	(2.6 ; 5.7)	35	56	4.3	(3.3 ; 5.6)	78
Gastrointestinal disorders	7	1.1	(0.4 ; 2.2)	9	6	0.9	(0.3 ; 2.0)	7	13	1.0	(0.5 ; 1.7)	16
Abdominal discomfort	1	0.2	(0 ; 0.9)	1	1	0.2	(0 ; 0.8)	1	2	0.2	(0 ; 0.6)	2
Diarrhoea	1	0.2	(0 ; 0.9)	2	4	0.6	(0.2 ; 1.5)	4	5	0.4	(0.1 ; 0.9)	6
Nausea	5	0.8	(0.3 ; 1.8)	5	2	0.3	(0 ; 1.1)	2	7	0.5	(0.2 ; 1.1)	7
Vomiting	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
General disorders and administration site conditions	11	1.7	(0.9 ; 3.0)	14	8	1.2	(0.5 ; 2.4)	13	19	1.5	(0.9 ; 2.3)	27
Fatigue	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Injection site bruising	3	0.5	(0.1 ; 1.4)	3	3	0.5	(0.1 ; 1.3)	3	6	0.5	(0.2 ; 1.0)	6
Injection site erythema	1	0.2	(0 ; 0.9)	1	2	0.3	(0 ; 1.1)	2	3	0.2	(0 ; 0.7)	3
Injection site induration	2	0.3	(0 ; 1.1)	2	3	0.5	(0.1 ; 1.3)	3	5	0.4	(0.1 ; 0.9)	5
Injection site pain	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	1	<0.1	(0 ; 0.4)	1
Injection site pruritus	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1	3	0.2	(0 ; 0.7)	3
Injection site swelling	2	0.3	(0 ; 1.1)	2	3	0.5	(0.1 ; 1.3)	3	5	0.4	(0.1 ; 0.9)	5
Swelling	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Vaccination site induration	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Vaccination site rash	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Infections and infestations	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1	3	0.2	(0 ; 0.7)	3
Rhinitis	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Upper respiratory tract infection	1	0.2	(0 ; 0.9)	1	1	0.2	(0 ; 0.8)	1	2	0.2	(0 ; 0.6)	2
Metabolism and nutrition disorders	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Decreased appetite	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Nervous system disorders	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1	3	0.2	(0 ; 0.7)	3
Dizziness	2	0.3	(0 ; 1.1)	2	0	0	(0 ; 0.6)	0	2	0.2	(0 ; 0.6)	2
Dysgeusia	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	1	<0.1	(0 ; 0.4)	1
Respiratory, thoracic and mediastinal disorders	11	1.7	(0.9 ; 3.0)	15	10	1.5	(0.7 ; 2.8)	11	21	1.6	(1.0 ; 2.5)	26
Asthma	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Cough	4	0.6	(0.2 ; 1.6)	4	1	0.2	(0 ; 0.8)	1	5	0.4	(0.1 ; 0.9)	5
Nasal congestion	2	0.3	(0 ; 1.1)	2	4	0.6	(0.2 ; 1.5)	4	6	0.5	(0.2 ; 1.0)	6
Oropharyngeal pain	2	0.3	(0 ; 1.1)	2	4	0.6	(0.2 ; 1.5)	4	6	0.5	(0.2 ; 1.0)	6
Productive cough	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	1
Rhinorrhoea	5	0.8	(0.3 ; 1.8)	5	2	0.3	(0 ; 1.1)	2	7	0.5	(0.2 ; 1.1)	7
Skin and subcutaneous tissue disorders	0	0	(0 ; 0.6)	0	2	0.3	(0 ; 1.1)	2	2	0.2	(0 ; 0.6)	2
Rash	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	1	<0.1	(0 ; 0.4)	1
Urticaria	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	1	<0.1	(0 ; 0.4)	1

n: number of participants experiencing the endpoint listed in the first column
n ARs: number of ARs
Percentages are based on N
MedDRA Version: 26.1.
Related: relationship reported by investigator to the study vaccine as related. If relationship is missing, the AE will be considered as related to the study vaccine.
Study: VAP00027 Program: T08041.sas Datasets=ADSL ADAE Output: PRODOPS/SP0234/VAP00027/CSR_01/REPORT/OUTPUT/T08041_x.pdf (29JAN2024 9:21)

Table 30: Unsolicited ARs within 28 days after vaccine injection, by maximum intensity, onset and duration

	9 to 17 years (N=641)				18 to 49 years (N=658)				All (N=1299)			
Period/ Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	30	4.7	(3.2 ; 6.6)	43	26	4.0	(2.6 ; 5.7)	35	56	4.3	(3.3 ; 5.6)	78
Maximum intensity												
Missing	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1	3	0.2	(0 ; 0.7)	3
Grade 1	12	1.9	(1.0 ; 3.2)	19	14	2.1	(1.2 ; 3.5)	17	26	2.0	(1.3 ; 2.9)	36
Grade 2	9	1.4	(0.6 ; 2.6)	12	5	0.8	(0.2 ; 1.8)	6	14	1.1	(0.6 ; 1.8)	18
Grade 3	7	1.1	(0.4 ; 2.2)	10	6	0.9	(0.3 ; 2.0)	11	13	1.0	(0.5 ; 1.7)	21
Time of onset												
Missing	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.3)	0
D01-D04	25	3.9	(2.5 ; 5.7)	35	22	3.3	(2.1 ; 5.0)	29	47	3.6	(2.7 ; 4.8)	64
D05-D08	4	0.6	(0.2 ; 1.6)	6	4	0.6	(0.2 ; 1.5)	6	8	0.6	(0.3 ; 1.2)	12
D09-D15	1	0.2	(0 ; 0.9)	2	0	0	(0 ; 0.6)	0	1	<0.1	(0 ; 0.4)	2
D16 or later	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.3)	0
Duration												
Missing	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	5	1	<0.1	(0 ; 0.4)	5
1-3 days	21	3.3	(2.0 ; 5.0)	28	15	2.3	(1.3 ; 3.7)	18	36	2.8	(1.9 ; 3.8)	46
4-7 days	4	0.6	(0.2 ; 1.6)	8	7	1.1	(0.4 ; 2.2)	8	11	0.8	(0.4 ; 1.5)	16
8 days or more	5	0.8	(0.3 ; 1.8)	7	3	0.5	(0.1 ; 1.3)	4	8	0.6	(0.3 ; 1.2)	11

n: number of participants experiencing the endpoint listed in the first column
n ARs: number of ARs
Study: VAP00027 Program: T08042.sas Datasets=ADSL ADAE Output: PRODOPS/SP0234/VAP00027/CSR_01/REPORT/OUTPUT/T08042_x.pdf (29JAN2024 9:21)

VAP00026

2.2% of participants in the RIV4 group and 1.1% in the IIV4 group experienced an AR. Most ARs were mild in intensity, occurred within the first four days after vaccination and resolved within 1 to 3 days. No unsolicited ARs were reported after the second vaccination. Two cases of Grade 3 unsolicited ARs (injection site induration and injection site erythema) were reported by a 5 year old participant one day after receiving the RIV4 vaccination (Table 31:).

Table 31: Unsolicited ARs within 28 days after any vaccine injection, by SOC and PT

RIV4

	3 to 5 years (N=81)				6 to 8 years (N=100)				3 to 8 years (N=181)			
Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	2	2.5	(0.3 ; 8.6)	3	2	2.0	(0.2 ; 7.0)	3	4	2.2	(0.6 ; 5.6)	6
Ear and labyrinth disorders	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Ear pain	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Gastrointestinal disorders	1	1.2	(0 ; 6.7)	1	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	1
Gastrointestinal disorder	0	0	(0 ; 4.5)	0	0	0	(0 ; 3.6)	0	0	0	(0 ; 2.0)	0
Nausea	1	1.2	(0 ; 6.7)	1	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	1
General disorders and administration site conditions	1	1.2	(0 ; 6.7)	2	1	1.0	(0 ; 5.4)	1	2	1.1	(0.1 ; 3.9)	3
Fatigue	0	0	(0 ; 4.5)	0	1	1.0	(0 ; 5.4)	1	1	0.6	(0 ; 3.0)	1
Injection site erythema	1	1.2	(0 ; 6.7)	1	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	1
Injection site induration	1	1.2	(0 ; 6.7)	1	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	1
Respiratory, thoracic and mediastinal disorders	0	0	(0 ; 4.5)	0	1	1.0	(0 ; 5.4)	1	1	0.6	(0 ; 3.0)	1
Oropharyngeal pain	0	0	(0 ; 4.5)	0	1	1.0	(0 ; 5.4)	1	1	0.6	(0 ; 3.0)	1
Vascular disorders	0	0	(0 ; 4.5)	0	1	1.0	(0 ; 5.4)	1	1	0.6	(0 ; 3.0)	1
Pallor	0	0	(0 ; 4.5)	0	1	1.0	(0 ; 5.4)	1	1	0.6	(0 ; 3.0)	1

IIV4

	3 to 5 years (N=91)				6 to 8 years (N=90)				3 to 8 years (N=181)			
Participants experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited AR	1	1.1	(0 ; 6.0)	1	1	1.1	(0 ; 6.0)	1	2	1.1	(0.1 ; 3.9)	2
Ear and labyrinth disorders	0	0	(0 ; 4.0)	0	1	1.1	(0 ; 6.0)	1	1	0.6	(0 ; 3.0)	1
Ear pain	0	0	(0 ; 4.0)	0	1	1.1	(0 ; 6.0)	1	1	0.6	(0 ; 3.0)	1
Gastrointestinal disorders	1	1.1	(0 ; 6.0)	1	0	0	(0 ; 4.0)	0	1	0.6	(0 ; 3.0)	1
Gastrointestinal disorder	1	1.1	(0 ; 6.0)	1	0	0	(0 ; 4.0)	0	1	0.6	(0 ; 3.0)	1
Nausea	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
General disorders and administration site conditions	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Fatigue	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Injection site erythema	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Injection site induration	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Respiratory, thoracic and mediastinal disorders	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Oropharyngeal pain	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Vascular disorders	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0
Pallor	0	0	(0 ; 4.0)	0	0	0	(0 ; 4.0)	0	0	0	(0 ; 2.0)	0

n: number of participants experiencing the endpoint listed in the first column
n ARs: number of ARs
Percentages are based on N
MedDRA Version: 26.1.
Related: relationship reported by investigator to the study vaccine as related. If relationship is missing, the AE will be considered as related to the the study vaccine.
Study: VAP00026 Program: T08078.sas Datasets=ADSL ADAE Output: PRODOPS/SP0234/VAP00026/CSR_01/REPORT/OUTPUT/T08078_x.pdf (02FEB2024 9:29)

Serious adverse event/deaths/other significant events

SAEs

VAP00027

In the study, SAEs within 28 days after vaccination were reported in 0.2% of participants aged 9-17 years (1 participant) and 0.8% in the 18-49 years age group (5 participants), with none of the SAEs

judged to be related to the IMP. Overall, 0.5% of participants (6 participants) experienced SAEs within this period.

During the entire study period, SAEs were reported in 0.5% of participants aged 9 - 17 years (3 participants) and 1.1% in the 18 - 49 years age group (7 participants). None of these SAEs were judged to be related to the vaccine (Table 32).

Table 32: All and related SAEs within 28 days after vaccine injection, by SOC and PT

	9 to 17 years (N=641)								18 to 49 years (N=658)							
	All SAEs				Related SAEs				All SAEs				Related SAEs			
Participants experiencing at least one:	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs
SAE	1	0.2	(0 ; 0.9)	2	0	0	(0 ; 0.6)	0	5	0.8	(0.2 ; 1.8)	7	0	0	(0 ; 0.6)	0
Injury, poisoning and procedural complications	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	2	0.3	(0 ; 1.1)	2	0	0	(0 ; 0.6)	0
Intentional overdose	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Overdose	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Gastric cancer recurrent	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Nervous system disorders	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Seizure	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Psychiatric disorders	1	0.2	(0 ; 0.9)	2	0	0	(0 ; 0.6)	0	2	0.3	(0 ; 1.1)	2	0	0	(0 ; 0.6)	0
Major depression	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Suicidal ideation	1	0.2	(0 ; 0.9)	2	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Respiratory, thoracic and mediastinal disorders	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0
Acute respiratory failure	0	0	(0 ; 0.6)	0	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1	0	0	(0 ; 0.6)	0

	All (N=1299)							
	All SAEs				Related SAEs			
Participants experiencing at least one:	n	%	(95% CI)	n SAEs	n	%	(95% CI)	n SAEs
SAE	6	0.5	(0.2 ; 1.0)	9	0	0	(0 ; 0.3)	0
Injury, poisoning and procedural complications	2	0.2	(0 ; 0.6)	2	0	0	(0 ; 0.3)	0
Intentional overdose	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Overdose	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Gastric cancer recurrent	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Nervous system disorders	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Seizure	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Psychiatric disorders	3	0.2	(0 ; 0.7)	4	0	0	(0 ; 0.3)	0
Major depression	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Suicidal ideation	2	0.2	(0 ; 0.6)	3	0	0	(0 ; 0.3)	0
Respiratory, thoracic and mediastinal disorders	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0
Acute respiratory failure	1	<0.1	(0 ; 0.4)	1	0	0	(0 ; 0.3)	0

VAP00026

One SAE was reported during the study for a participant in the IIV group (not considered related to the vaccine). No SAEs were observed in the RIV4 group.

Deaths

No Deaths were reported during the studies.

AESIs

No AESIs were reported during the studies.

MAAEs

VAP00027

MAAEs within 28 days after vaccination were reported in 4.2% in the 9 - 17 years age group and 5.3% in the 18- 49 years age group. Overall, 4.8% of participants experienced at least one MAAE during this period. None of these MAAEs were considered related to the vaccine by the investigators.

VAP00026

MAAEs within 28 days after vaccination were more frequent in the RIV4 group (9.9%) compared to the IIV4 group (6.6%) among children aged 3 - 8 years. The most common MAAEs were infections and infestations, notably streptococcal pharyngitis, which occurred more often in the RIV4 group. None of these events were considered related to the vaccine in either group.

Discontinuation due to adverse events

VAP00027

Two participants in the 18-49 years age group and none in the 9 - 17 years age group experienced an AE leading to study discontinuation. One participant experienced an intentional overdose on D07, judged to be not related to the IMP. The other participant experienced urticaria on day 1 after injection, followed by chills, fever, headache, malaise, myalgia, injection site swelling, bruising, erythema, pain, and induration on D02. These events were considered to be related to the IMP by the Investigator.

VAP00026

There were no AEs leading to study discontinuation in this study.

2.4.1. Discussion on clinical safety

The safety population in study VAP00027 included a total of 1299 participants aged 9 to 49 years, with 641 participants aged 9 to 17 years receiving RIV4. In study VAP00026, due to early termination, a total of 362 participants aged 3 to 8 years were enrolled, with 181 participants receiving RIV4 and 181 receiving the comparator IIV4. The size of the safety database, in the 9 to 17 years age group, is considered sufficient for the assessment of RIV4's safety profile in this procedure. However, it remains unclear how meaningful the safety data in participants aged 3 to 8 years from the VAP00026 study are due to its early termination.

Both studies used appropriate and consistent methods for assessing reactogenicity and safety. Participants were monitored for immediate AEs for at least 30 minutes post-vaccination. Solicited injection site and systemic reactions were recorded from Day 1 to Day 9 after vaccination and in the case of study VAP00026 from Day 29 to Day 37 following the second vaccination. Unsolicited AEs were captured from Day 1 to Day 29, with SAEs and MAAEs monitored throughout the study duration and up to six months post-vaccination.

In study VAP00027, the incidence of solicited ARs tended to be lower in participants aged 9 -17 years (44.3%) compared to adults aged 18 - 49 years (52.9%). The most common solicited injection site reaction was pain, reported by 34.4% of participants in the younger age group. Other injection site reactions such as bruising, induration, swelling, and erythema were reported less frequently (2.4% to 4.5%). The most frequent solicited systemic reactions in the younger group were myalgia (19.3%) and headache (18.5%), followed by malaise, chills, and fever. Most reactions were mild to moderate in intensity and resolved spontaneously within 1 to 3 days. Severe reactions were infrequent, but tended to be higher in the younger age group (4.6%) compared to adults (3.1%). In study VAP00026, the incidence of solicited ARs after any injection was comparable between the RIV4 group (45.8%) and the

IIV4 group (51.7%) among children aged 3 to 8 years. Injection site pain was the most commonly reported reaction in both vaccine groups and age subgroups. The majority of solicited reactions were mild to moderate in intensity. Severe reactions were reported by 7.8% of participants in the RIV4 group and 8.9% in the IIV4 group.

Unsolicited AEs were reported by 14.5% of participants aged 9 to 17 years and 18.1% of adults in study VAP00027. The most frequently reported SOCs were "Infections and infestations," "Respiratory, thoracic and mediastinal disorders," and "Gastrointestinal disorders." Most unsolicited AEs were mild to moderate, with severe AEs occurring in 1.6% of participants aged 9 to 17 years. In study VAP00026, unsolicited AEs were reported by 24.3% of participants in the RIV4 group and 26.0% in the IIV4 group. The most common AEs were infections and infestations, respiratory disorders, and gastrointestinal symptoms. Severe unsolicited AEs were infrequent in both vaccine groups. The safety profile of RIV4 was comparable between previously vaccinated and unvaccinated participants.

In study VAP00027, SAEs within 28 days after vaccination were reported in 0.2% of participants aged 9 to 17 years and 0.8% of adults aged 18 to 49 years. None of these SAEs were deemed vaccine related. During the entire study period, SAEs were reported in 0.5% of participants aged 9 to 17 years and 1.1% of adults, with no SAEs considered related to the vaccine. In study VAP00026, only one SAE was reported in the IIV4 group, with none observed in the RIV4 group. MAAEs within 28 days after vaccination were reported in 4.2% of participants aged 9 to 17 years and 5.3% of adults in study VAP00027. None of these MAAEs were considered to be related to the vaccine. In study VAP00026, MAAEs were more frequent in the RIV4 group (9.9%) compared to the IIV4 group (6.6%) among children aged 3 to 8 years. None of these events were considered related to the vaccine in either group.

Overall, no major imbalances in the duration of AEs were observed in either of the studies.

2.4.2. Conclusions on clinical safety

The safety profile of RIV4 appears to be comparable. The vaccine is generally well tolerated in the studied population, with the majority of ARs being mild or moderate in intensity and resolving within one to three days. The most frequently reported ARs were injection site pain, myalgia and headache. Severe reactions were rare and not considered to be vaccine related. Overall, the proportions of participants experiencing SAEs were low and comparable across age groups and vaccine types, and none of these were considered related to RIV. No new safety concerns were identified. In conclusion, the safety profile of RIV4 in the paediatric population is consistent with that expected for influenza vaccines.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

Safety concerns

None

Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Development of Robust Innovative Vaccine Effectiveness (DRIVE) (Cat. 3)				
Development of Robust Innovative Vaccine Effectiveness Assessment of the feasibility of building a sustainable platform in Europe able to generate brand specific IVE data in Europe. Is deferred and awaiting EMA update on guideline.	To measure seasonal IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type, then by overall IV.	This is epidemiological study for assesing effectiveness of routine IV. No data on adverse events will be collected. The measurement of IVE support Safety Benefit Risk analyses for Influenza The product specific vaccine effectivness data supports benefits of IV versus risks related for AEs	Annual reports at the end of influenza season.	Annual at the end of influenza season.

AE: Adverse Event; DRIVE: Development of Robust Innovative Vaccine Effectiveness; EMA: European Medicines Agency; IV: Influenza Vaccination; IVE: Influenza Vaccine Effectiveness.

Risk minimisation measures

None.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to include editorial changes in the SmPC and Annex II.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

The following section relates to the extension of indication to include the active immunisation of children and adolescents from 9 years of age.

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. It is typically characterised by the rapid onset of fever, myalgia, sore throat, and non-productive cough. Influenza can cause severe malaise, which lasts for several days. While influenza affects all age groups, the very young, older adults, and persons with underlying health problems are at increased risk for complications. Complications in the paediatric population include secondary bacterial pneumonia, acute otitis media, bronchitis, febrile seizures, Reye's syndrome, myositis, neurologic conditions, and exacerbations of underlying conditions.

3.1.2. Available therapies

There are antiviral medicines approved in the European Union to treat influenza. For the best clinical benefit, treatment with antivirals should be given early in the infection, within 48 hours (the earlier the better), to reduce the fever and flu-like symptoms. The use of antivirals can induce drug-resistant mutants. The level of antiviral resistance is closely followed by public health authorities.

Vaccination is the most effective form of influenza prevention. In Europe, different type of influenza vaccines (Split virion, inactivated; surface antigen, inactivated; live-attenuated) are authorised (via centralised or mutual-recognition procedures) for active immunisation for the prevention of influenza disease in children and adolescents.

3.1.3. Main clinical studies

The main evidence of immunogenicity and safety submitted is the pivotal Phase III, non-randomised, open-label, uncontrolled study to demonstrate the non-inferior haemagglutination inhibition immune response of Supemtek Tetra in participants aged 9 to 17 years compared to participants aged 18 to 49 years (VAP00027). The study was conducted in the European Union and United States. The study objective is in line with the Guideline on Influenza Vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014).

3.2. Favourable effects

The primary objective of non-inferiority of haemagglutination inhibition immune response induced by Supemtek Tetra in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by geometric mean titres and seroconversion rates at day 29 was met. Non-inferiority was demonstrated for all 8 variables included in the non-inferiority assessment (4 ratios of geometric mean titres and 4 differences in seroconversion) as the lower limit of the 95% confidence interval was higher than 0.667 for the ratios of geometric mean titres and higher than -10% for the differences of seroconversion rates (Supemtek Tetra [9 to 17 years] minus Supemtek Tetra [18 to 49 years]) for all 4 strains.

3.3. Uncertainties and limitations about favourable effects

Geometric mean titres values against the different influenza strains are variable, with geometric mean tires values against strain B/Victoria being the lowest in both groups. While the CHMP considered that

this could translate into some differences in terms of protection or its duration against the different strains, the overall demonstration of non-inferiority for all 4 strains (as discussed above) was reassuring.

Antibody titres are only surrogates for clinical efficacy and the clinical relevance of this difference is unknown. The marketing authorisation holder plans to generate vaccine effectiveness data as indicated in the risk management plan, i.e. by means of a study measuring seasonal influenza vaccine effectiveness against medically attended laboratory confirmed influenza.

3.4. Unfavourable effects

The safety profile of Supemtek Tetra in participants aged 9 to 17 years was generally favourable and comparable to that observed in adults. Less than half of the participants aged 9 to 17 years experienced one or more adverse events, with the most commonly reported being solicited adverse events. In participants aged 9 to 17 years, 44.3% experienced at least one solicited adverse reaction within 7 days after vaccination. The most commonly reported solicited adverse reaction were injection-site pain (34.4%), myalgia (19.3%), headache (18.5%), and malaise (16.1%). Most reactions were mild to moderate in intensity and resolved within a few days.

Overall the proportions of participants with serious adverse events were low and comparable across intervention groups. 0.5% of participants aged 9 to 17 years and 1.1% of participants aged 18 to 49 years reported at least one serious adverse events; none were considered related to the vaccine. No deaths or adverse events of special interests were reported in any age group during the study.

Two participants in the 18 to 49 years age group discontinued due to an adverse event, while no participants in the 9 to 17 years age group discontinued for this reason.

No new safety signals were identified. Overall, Supemtek Tetra was safe and well tolerated.

3.5. Uncertainties and limitations about unfavourable effects

The size of the safety database (641 participants) limits the ability to detect rare adverse events.

The CHMP considered that this uncertainty can be adequately managed with routine pharmacovigilance.

3.6. Effects Table

Table 33: Effects Table for Supemtek Tetra in persons 9 years of age and older

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
GMTR	Age group 9-17 yoa / age group 18-49 yoa		RIV4 (GMT in 9-17 yoa)	RIV4 GMT in 18-49 yoa)	GMTR (95% CI)	Study VAP00027
	A/H1N1		1946	982	1.98 (1.73; 2.27)	
	A/H3N2		1975	604	3.27 (2.76; 3.87)	
	B/Victoria		405	258	1.57 (1.35; 1.82)	
	B/Yamagata		1941	1593	1.22 (1.09; 1.37)	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Seroconversion Difference	Age group 9-17 yoa minus age group 18-49 yoa	%	RIV4 (GMT in 9-17 yoa)	RIV4 GMT in 18-49 yoa)	95% CI	
	A/H1N1		78.3	76.4	1.92 (-2.78; 6.62)	
	A/H3N2		86.5	87.1	-0.59 (-4.41; 3.23)	
	B/Victoria		76.8	73.6	3.29 (-1.57; 8.14)	
	B/Yamagata		77.2	62.9	14.3 (9.17; 19.3)	
Unfavourable Effects						
Solicited ARs		%	44.3	52.9		Study VAP00027
Solicited local ARs		%	35.6	40.8		
	Injection site pain	%	34.4	40.2		
	Injection Site Erythema	%	4.5	2.7		
	Injection Site Swelling	%	3.7	2.7		
	Injection site induration	%	3.1	3.3		
Solicited systemic ARs		%	29.6	36.2		
	Myalgia	%	19.3	20.3		
	Headache	%	18.5	22.8		
	Malaise	%	16.1	16.5		
	Chills	%	7.3	6.3		
Local ARs Grade 3		%	3.1	1.4		
Systemic ARs Grade 3		%	4.6	3.1		

GMTR: geometric mean titres ratio, RIV4: Supemtek Tetra, GMT: geometric mean titres, CI: confidence intervals, yoa: years of age, ARs: adverse reactions

3.7. Benefit-risk assessment and discussion

The primary objective of non-inferiority of haemagglutinin inhibition immune response induced by Supemtek Tetra in participants 9 to 17 years of age versus participants 18 to 49 years of age as assessed by geometric mean titres and seroconversion rates at day 29 was met. Non-inferiority was demonstrated for all 8 variables included in the non-inferiority assessment (4 ratios of geometric mean tires and 4 differences in seroconversion) as the lower limit of the 95% confidence interval was higher than 0.667 for the ratios of geometric mean titres and higher than -10% for the differences of seroconversion rates (Supemtek Tetra [9 to 17 years] minus Supemtek Tetra [18 to 49 years]) for all 4 strains.

The vaccine is generally well tolerated in this population, with the majority of adverse reactions being mild or moderate in intensity and resolving within one to three days. The most frequently reported adverse reactions were injection site pain, myalgia and headache. Severe reactions were rare and not considered to be vaccine related. Overall, the proportions of participants experiencing serious adverse events were comparable across age groups and vaccine types. No new safety concerns were identified.

In conclusion, the safety profile of Supemtek Tetra in the paediatric population is consistent with that expected for influenza vaccines.

3.7.1. Importance of favourable and unfavourable effects

Immunogenicity data submitted as part of study VAP00027 demonstrate non-inferior immune response in the age group 9-17 years of age compared to 18-49 years of age after vaccination with Supemtek Tetra. The majority of adverse reactions were mild to moderate in intensity and resolved within a few days. No new safety concerns were identified. Serious adverse events were rare and not considered to be related to the vaccine.

3.7.2. Balance of benefits and risks

Non-inferiority after vaccination with Supemtek Tetra in adolescents 9-17 years of age as compared to 18-49 years of age could be demonstrated. Supemtek Tetra is overall well tolerated with the safety and reactogenicity profile comparable to adults.

3.8. Conclusions

The overall B/R of Supemtek Tetra in children and adolescents from 9 years of age is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends, the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Grouped application comprising two type II variations as follows:

C.I.6.a – Extension of indication to include the active immunisation of children 9 years of age and older for Supemtek Tetra, based on final results from study VAP00027; this is a Phase III, non-randomised, open-label, uncontrolled study to demonstrate the non-inferior HAI immune response of Supemtek Tetra in participants aged 9 to 17 years compared to participants aged 18 to 49 years; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been approved.

C.I.4 - Update of sections 4.2 and 5.1 of the SmPC in order to update paediatric information of children between 3 to 8 years of age based on final results from study VAP00026; this is a Phase III, randomised, modified double-blind, active-controlled 2-arm to demonstrate the non-inferior HAI

immune response of Supemtek Tetra compared to an authorised inactivated tetravalent influenza vaccine.

The MAH also took the opportunity to include editorial updates in the SmPC and Annex II.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.