29 January 2026
– Corr. 1 [1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Supemtek

Common name: Trivalent influenza vaccine (recombinant, prepared in cell culture)

Procedure No. EMEA/H/C/006674/0000

Note

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

[1] Corrected date 20 February 2026 to correct the active substance strains and to remove the paediatric statement in the final CHMP outcome.

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List of abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADR	adverse drug reaction
AcNPV	Autographa californica Nuclear Polyhedrosis Virus
AE	adverse event
AS	Active substance
ATC	Anatomical Therapeutic Chemical
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CTD	Common Technical Document
DART	Developmental and Reproductive Toxicology
DNA	Deoxyribonucleic acid
DSP	downstream manufacturing process
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERL	WHO essential regulatory laboratory
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FOB	Functional Observational Battery
FP	finished product
GCP	good clinical practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GMR	geometric mean titre ratios
GMT	geometric mean titre
HA	haemagglutinin
HAI	haemagglutination inhibition
ICH	International Council for Harmonisation
IIV4	quadrivalent inactivated influenza vaccine / Fluarix Quadrivalent / Fluarix Tetra
ILI	influenza like illness
IM	intramuscular
INN	international nonproprietary name
IP	intraperitoneally
MAA	Marketing Authorisation Application
MAAE	medically-attended adverse event
MCB	Master cell bank
MDCK	Madin-Darby canine kidney
MVB	master virus bank
N/A	not applicable
NA	neuraminidase
nAb	neutralisation antibody
NCT	National Clinical Trial
NH	northern hemisphere
NIBSC	National Institute for Biological Standards and Control (UK)
NT	influenza virus neutralisation testing
Ph.Eur.	European Pharmacopoeia
PBS	phosphate buffered saline
PD	pharmacodynamics
Penh	enhanced pause
PK	pharmacokinetics
PP	per-protocol
PPAS	per-protocol analysis set
PPI	per-protocol immunogenicity
PQ	process qualification
PSC	Protein Sciences Corporation
PSFM	Protein sciences formulary medium

PV	process validation
QIV	quadrivalent influenza vaccine
QP	qualified person
rHA	recombinant haemagglutinin
RIV3	trivalent recombinant influenza vaccine / Supemtek (EU) / Flublok (US)
RIV4	quadrivalent recombinant influenza vaccine / Supemtek Tetra (EU) / Flublok Quadrivalent (US)
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
rVE	relative vaccine efficacy
SAE	serious adverse event
SC	subcutaneous
SCR	seroconversion rate
SOC	System Organ Class
SRID	single radial immunodiffusion
TIV	trivalent influenza vaccine
TSE	transmissible spongiform encephalopathies
UK	United Kingdom
ULOQ	upper limit of quantification
US	United States
USA	United States of America
USP	upstream manufacturing process
VE	vaccine efficacy
YoA	Years of age
WCB	working cell bank
WHO	World Health Organization
WVB	working virus bank
WVS	working virus seed

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Supemtek
Active substance	A/California/07/2009 (H1N1)pdm09-like strain (A/California/07/2009) A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012) B/Brisbane/60/2008-like strain (B/Brisbane/60/2008)
INN or common name	Trivalent influenza vaccine (recombinant, prepared in cell culture)
Applicant	Sanofi Winthrop Industrie 82 Avenue Raspail 94250 Gentilly FRANCE
EMA product number	EMEA/H/C/006674
ATC code and pharmacotherapeutic group	J07BB02; Vaccines, influenza vaccine
Pharmaceutical form(s) and strength (s)	Solution for injection 45 micrograms per HA
Packaging	pre-filled syringe (glass)
Package size(s)	1 pre-filled syringe, 1 pre-filled syringe + 1 needle, 5 pre-filled syringes, 5 pre-filled syringes + 5 needles, 10 pre-filled syringes, 10 pre-filled syringes + 10 needles,
Route of administration	Intramuscular use
Device or diagnostic	pre-filled syringe (glass)
Orphan designation	No
Orphan indication status confirmed	No
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Supemtek is indicated for active immunisation for the prevention of influenza disease in adults and children from 9 years of age and older. Supemtek should be used in accordance with official recommendations.
New active substance status	Not applied for

1.2. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.3. Eligibility to the centralised procedure

The applicant Sanofi Winthrop Industrie submitted on 6 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Supemtek (trivalent Influenza Vaccine (recombinant, prepared in cell culture)), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

"Supemtek is indicated for active immunization for the prevention of influenza disease in adults and children from 9 years of age and older.

Supemtek should be used in accordance with official recommendations."

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0220/2024 the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0220/2024 had been completed.

The PDCO issued an opinion on compliance for the PIP P/0220/2024.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

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

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Jan Mueller-Berghaus
Co-rapporteur:	Daniela Philadelphy

The application was received by the EMA on	6 March 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	17 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	20 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	2 July 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	5 September 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	20 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	13 November 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	18 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	14 January 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Supemtek on	29 January 2026

1.8. Final CHMP outcome

1.8.1. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.8.2. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Supemtek is favourable in the following indication(s):

"*Supemtek is indicated for active immunisation for the prevention of influenza disease in adults and children from 9 years of age and older.*

Supemtek should be used in accordance with official recommendations."

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.8.3. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.8.4. Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory, or a laboratory designated for that purpose.

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. Periodic safety update reports

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.

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.8.8. Proposed list of recommendations

Table 1. Proposed list of recommendations

Description of recommendation(s)
Establishment of a Working Cell Bank (WCB) manufacturer.
Submission of the validation report including results of the PBS preparation scale-up according to the qualification and validation strategy described in the "Risk Assessment of Validation Matrix Strategy for Manufacture of Supemtek TIV" (VV-QUAL-0834405, Ver 2.0), i.e., single-use components qualification and storage time validation results for the new PBS preparation process (before the first annual strain update).

Description of recommendation(s)
Submission of the following RIV product specific validation reports: Endotoxin, SRID - including the validation reports for each antigen as recommended, and Sterility as well as the reagent validation reports, in the first annual strain update.
eCTD Section 3.2.P.5.3 Validation of Analytical Procedures core document should contain a summary of the validation of a trivalent vaccine (in the next Annual Strain Variation filed with EMA).
Submission of analytical data confirming successful transfer of the SRID method to Sanofi Val de Reuil in the next annual strain variation submitted in the EU.
Submission of batch analysis data for the formulated bulks and the finished drug products from the first three batches for both manufacturing sites in eCTD Section 3.2.P.5.4 Batch Analyses (in the next Annual Strain Variation filed with EMA).

2. Introduction

2.1. Therapeutic context

Seasonal influenza is a highly contagious viral respiratory infection with significant global public health implications. The disease is caused by influenza A and B viruses, both of which belong to the Orthomyxoviridae family. These viruses are characterised by their ability to undergo frequent antigenic changes, either through antigenic drift, caused by point mutations in the haemagglutinin (HA) or neuraminidase (NA) genes, or through antigenic shift, which results in the emergence of novel subtypes and may lead to pandemics. The HA and neuraminidase proteins are key antigens in eliciting a protective immune response and form the basis for influenza vaccine composition.

Influenza epidemics occur annually, predominantly during the winter months in the Northern and Southern hemispheres. Influenza A subtypes H1N1 and H3N2 have consistently accounted for the majority of seasonal influenza cases in recent years. However, influenza B viruses also circulate widely and contribute to the overall burden of disease, typically appearing later in the season. Since 2001, the two influenza B lineages, B/Victoria and B/Yamagata, have co-circulated with variable predominance. Notably, no confirmed circulation of B/Yamagata lineage viruses has been reported globally since March 2020. As a result, leading public health authorities including WHO, EMA, FDA, and national immunisation committees have recommended the exclusion of the B/Yamagata antigen from seasonal influenza vaccines starting with the 2024 to 2025 season. EMA has formally advised completion of the transition to trivalent vaccine formulations for the 2025 to 2026 Northern Hemisphere season.

Clinically, influenza typically presents with the sudden onset of high fever, myalgia, headache, malaise, dry cough, sore throat, and nasal congestion. Although the disease is self-limiting in most cases, it poses a substantial risk of complications and mortality in specific high-risk groups, including older adults, young children, pregnant women, and individuals with chronic comorbidities or immunosuppression. In the European Union and European Economic Area, seasonal influenza is estimated to cause between 4 and 50 million symptomatic cases annually and results in approximately 15,000 to 70,000 deaths. On a global level, seasonal influenza is estimated to affect up to one billion individuals annually, including 3 to 5 million cases of severe illness and up to 650,000 respiratory deaths. In addition to the direct health burden, seasonal influenza places a considerable strain on healthcare systems and leads to substantial economic loss due to absenteeism and reduced productivity.

Preventive strategies in the EU focus primarily on vaccination. A wide array of inactivated influenza vaccines is available, including split-virion and subunit vaccines produced using either egg-based or cell-based manufacturing processes. These are available in both trivalent and quadrivalent formulations, with each dose typically containing 15 micrograms of HA per strain. In addition, high-dose and adjuvanted trivalent vaccines are available for use in older adults, though these are not indicated for use in younger adult populations.

Recombinant influenza vaccines produced using baculovirus expression vector systems represent an alternative to conventional production methods. These vaccines do not require live virus propagation or egg-based substrates, which may allow for faster production and increased antigenic fidelity. RIV3, a trivalent recombinant HA vaccine (Flublok), was first approved in the United States in 2013 for adults aged 18 years and older. Its quadrivalent version, RIV4, was subsequently authorised in the US in 2016 and in the EU and UK in 2020. Following the global absence of B/Yamagata virus circulation, the RIV3 license was reactivated in the US in March 2024. The present application seeks to obtain EU authorisation for RIV3 to support influenza immunisation efforts with a trivalent recombinant formulation.

2.2. Aspects of development

The clinical development programme for RIV3 was originally initiated in the United States and laid the foundation for the subsequent development of RIV4. The recombinant vaccine is produced using baculovirus expression technology and contains HA proteins without viral components or adjuvants. The active substance and excipients in RIV4 are identical to those in RIV3, except for the addition of a second B lineage antigen. Therefore, the safety and immunogenicity profiles of the two formulations were expected to be similar.

The clinical development programme supporting the current application for RIV3 in individuals aged 9 years and above builds primarily on three pivotal studies. These were conducted with RIV4 (PSC12, PSC16, and VAP00027), and one forth study supportive for efficacy was conducted with RIV3 (PSC04):

- **PSC12:** the study confirmed efficacy in the vulnerable older population (adults 50 years of age and older)
- **PSC16:** the immunogenicity of RIV4 is similar to that observed in older adults in study PSC12, and supports the inference that efficacy in younger adults is at least as robust as that observed in older adults
- **VAP00027:** the immunogenicity of RIV4 in 9 to 17 years old age group is similar to that observed in 18 to 49 years old age group, so efficacy data in adults can be inferred to this age group
- **PSC04:** study conducted with the trivalent recombinant vaccine (RIV3) provides data that support the efficacy of a recombinant influenza vaccine in younger healthy adults from 18 to 49 years of age and evaluated the absolute efficacy of RIV3 versus placebo in adults aged from 18 to 49 years

VAP00026 and **VAP00007** are both supportive studies that provide additional data on respectively, 3 to 8 years age group and pregnant women in order to inform specific sections of the product information.

2.3. Description of the product

Supemtek is a recombinant trivalent influenza vaccine containing purified haemagglutinin (HA) proteins produced using baculovirus expression vector technology in insect cells. The trivalent formulation (RIV3) under assessment consists of HA proteins derived from two influenza A virus strains (H1N1 and H3N2) and one influenza B strain (B/Victoria lineage).

The mechanism of action is based on the induction of strain-specific humoral immune responses directed against the HA surface glycoprotein, which is the primary target for virus neutralisation. Protective efficacy is mediated by the generation of haemagglutination-inhibiting antibodies.

RIV3 is currently approved in the United States for active immunisation against influenza in adults aged 18 years and older. The present application seeks approval in the European Union for active immunisation against influenza in individuals from 9 years of age and older, in accordance with national immunisation recommendations.

The proposed posology is one 0.5 mL dose administered intramuscularly, preferably in the deltoid muscle. The vaccine must not be administered intravenously and must not be mixed with other medicinal products in the same syringe.

In September 2023, the World Health Organization (WHO) issued a recommendation stating that "inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible".

In March 2024, the Emergency Task Force (ETF) issued a statement stating that "antigens of the B/Yamagata lineage should be removed from the live attenuated influenza vaccines ideally for the 2024/2025 influenza season".

In order to follow the above WHO recommendation and ETF statement a new marketing authorisation is applied for Supemtek (trivalent).

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product is presented as solution for injection in pre-filled syringe containing 45 microgram/dose each, of recombinant haemagglutinin from Influenza A virus subtype H1N1, Influenza A virus subtype H3N2 and Influenza B virus Victoria lineage, as active substance). The HA is cloned from the strains recommended by the WHO and endorsed by CHMP/EMA for the manufacture of influenza vaccine for the current season.

Other ingredients are: sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, polysorbate 20 (E 432) and water for injections to 0.5 mL.

The product is available in pre-filled syringe (Type I borosilicate glass) with plunger stopper (grey butyl rubber), with separate needle or without needle.

The Applicant has submitted a Trivalent (TIV) market authorisation dossier based on the licensed Quadrivalent (QIV) dossier (Supemtek Tetra EMEA/H/C/005159). The active substance process of TIV remains essentially the same as the licensed QIV product and was updated with minimal changes to present the most relevant quality data of the TIV vaccine.

3.2. Active substance

3.2.1. General information

The active substances included in the final finished product (Purified Recombinant Influenza Hemagglutinin (derived from H1, H3, B viral strains)) consist of three separately manufactured recombinant hemagglutinin (rHA) proteins:

rHA protein, derived from Influenza A virus subtype H1N1, and named rHA H1.

rHA protein, derived from Influenza A virus subtype H3N2, and named rHA H3.

rHA protein, derived from Influenza B virus Victoria lineage, and named rHA B.

Each of the three hemagglutinin genes are cloned from the WHO recommended influenza viruses on an annual basis. Because adjustments (updates) are made annually, based on the influenza virus strain changes proposed by WHO, additional DNA and amino acid sequence information will be submitted annually as appropriate. Recombinant haemagglutinins are expressed in proprietary expresSF+ insect cells (derived from *Spodoptera frugiperda* cells) using baculovirus (Autographa californica Nuclear Polyhedrosis Virus (AcNPV)) as the vector for protein expression.

The recombinant HA antigens (rHA) are full length, uncleaved glycoproteins with molecular weights of approximately 65,000 Daltons and are widely considered to be the most essential antigenic component of influenza virus vaccines.

The rHA molecules are glycoproteins, and glycosidase analyses have been used to characterise the oligosaccharide side chains of the molecules. The pattern of glycosidase sensitivity observed in these studies is consistent with what has been seen previously with other glycoproteins produced in the baculovirus insect cell expression system. Although the glycosylation pattern in insects differs somewhat from mammals, these differences do not abrogate the functional activity and immunogenic properties of rHA produced in insect cells.

The biological activity of rHA, i.e., hemagglutination, also supports the observation that rHA forms multimers. Hemagglutination occurs when HA on the surface of influenza viruses interacts with sialic acid on the surface of the red blood cells forming a network of cells linked by HA. Like the influenza virus, purified rHA can agglutinate red blood cells, which reflects the antigen's ability to recognise the cellular sialic acid receptors. Hemagglutination also requires a higher order association of HA, e.g. rosettes, in order to link the red blood cells together, supporting the oligomeric nature of the recombinant protein. Thus, hemagglutination demonstrates both biological activity and the proper formation of higher order structures of the rHA.

3.2.2. Manufacture, process controls and process development

Description of manufacturing process and process controls

Name and address of the manufacturer of the Active Substance:
Unigen Inc.
11 Miyaji, Ikeda-cho, Ibi-gun Gifu,
503-2406
Japan

The applicant provided information about AS manufacturers, their responsibilities and the corresponding QP declaration. Appropriate GMP certification is in place for all sites. Manufacture of Master and Working Cell Banks and Master and Working Virus Banks and relevant production sites are described. Sanofi Pasteur Inc. will continue to manufacture the Working Virus bank. The applicant has committed to establish a new Working Cell Bank (WCB) manufacturer (**Recommendation 1**).

The manufacturing process for recombinant hemagglutinin (rHA) active substance consists of two major process blocks: the upstream manufacture of the active substance, includes culturing of expresSF+ cells, baculovirus infection and expansion and protein production. Recombinant baculoviruses are expanded in parallel in expresSF+ cells from the working virus bank (WVB) through to the working virus stock (WVS). WVS is used for inoculation of the working volume culture. The upstream manufacturing process is considered appropriately described and is adequately controlled. The downstream processing includes centrifugation, extraction of recombinant HA from the cell pellet, followed by clarification of the crude extract column chromatography, DNA removal, ultrafiltration and final AS formulation and bulk filtration. The USP steps are identical for rHA antigens derived from all influenza strains. The DSP has been adapted so that the basic steps in the extraction and purification are the same for all antigens (i.e., the universal process). Minor differences in the buffers, detergent concentrations, and conditions used in the downstream processes are necessary to accommodate the differences in the physico-chemical properties of the rHAs derived from different influenza strains. No reprocessing is claimed and hence not allowed.

The description of manufacturing process and process controls is described in sufficient detail. Process parameters and in-process tests are listed. The description of manufacturing process and process controls is based on QIV influenza virus strain recommendation for 2018/2019, which is considered acceptable. Process readjustments are made annually within the process design space registered in the dossier. In case a process change out of the registered design space is needed, this would be submitted as a dossier variation.

Control of materials

The host cell line used for recombinant protein manufacturing is a serum-free Lepidopteran insect cell line designated expresSF+ (SF+). Generation of this MCB has been described in detail by the applicant. Test results demonstrated no evidence for the presence of adventitious agents and the cell line was

found to be non-tumorigenic. The generation of these WCB has been described in detail by the applicant. Qualification tests of WCBs include testing for identity, microbial contaminants and adventitious agents.

Autographa californica nuclear polyhedrosis virus (AcNPV) was originally isolated from a single field collected alfalfa looper larva. AcNPV is the prototype virus of the family Baculoviridae. The master virus bank (MVB) was generated from the parent viral vector.

The working virus bank was generated by cloning of the relevant HA gene into the master virus bank (MVB) to create the working virus bank (WVB). The WVBs described in the dossier were used for the production of recombinant influenza virus (RIV)4 for the 2018/2019 Northern Hemisphere vaccine season. The qualification of these WVBs is representative of the qualification of all WVBs. This section is updated on an annual basis following the recommendation by WHO of influenza strains to be included in the vaccine. Isolates of the viral strains to be used in recombinant hemagglutinin (rHA) vaccine production are obtained from the U.S. Centers for Disease Control and Prevention (CDC), Atlanta, GA and may be modified by site directed mutagenesis to match the amino acid sequence of the relevant reference HA. The virus certificates (from CDC) and the certificates of analysis (from Protein Sciences Corporation) for the four virus strains have been provided by the applicant. The nucleotide and amino acid sequences of the cloned HAs are provided in the dossier.

Generation of recombinant baculoviruses (Working Virus Banks, WVBs): The sequences containing the rHA gene from the transfer plasmid are incorporated into the baculovirus genome in the culture of SF+ cells. Virus clones are isolated and amplified, when they are frozen as WVB stocks. Stability of each new WVB is demonstrated through viral passage as part of the clone selection process. Working Virus Bank (WVB) is tested and released and the corresponding qualification tests and acceptance criteria are described in the eCTD.

The applicant purchases raw materials from audited and approved vendors. Non-compendial raw materials are tested according to the manufacturer's Certificate of Analysis. The growth medium used for culturing of the SF+ cells is the only raw material of biological origin used in the manufacturing process. Cod liver oil is the animal derived ingredient in the medium. There are no ruminant-derived materials used in the manufacturing process of this growth medium (see adventitious agents section). A CoA for PSFM has been provided, which is considered acceptable. Overall, the information provided on S.2.3 Control of Materials is considered acceptable.

Control of critical steps and intermediates

Process intermediates are listed and described in sufficient detail. Process intermediates for the upstream process are defined. In the downstream process, there are no holding times.

The hold time for P5 WVSs was established based on the hold times used for PQ and PV batches.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

Prior to Process Validation (PV), Performance Qualification (PQ) studies were executed according to a Validation Master Plan. The objective of the PQ phase was to provide documented verification that the facilities and equipment can perform reproducibly to produce a product meeting its predetermined specifications and quality attributes. Commercial scale batches of rHA A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010 were manufactured, sampled, and tested during PQ.

Process validation included a suitable number of process validation runs at commercial scale on each of 4 rHA antigens (H1 A/California, H3 A/Texas, B/Massachusetts, and B/Brisbane) at the commercial site. Validation of cell culture passage and preparation of virus suspension was also conducted and are acceptable. All PV reports are submitted in the dossier. In addition, in 2016, Unigen produced one batch of each rHA antigen from the 2016/2017 trivalent vaccine formulation for use in comparability studies. Shipping of bulk active substance was validated and is described. Resin reuse is described. Shipping of bulk active substance was validated and is described.

Manufacturing process development

Development of the upstream process largely took place under a series of Investigational New Drug Applications (INDs) and included several Phase 1/2 safety, immunogenicity, and dose-ranging studies. In this time, cell culture and infection process were developed. The transition from serum-requiring Sf9 cells to PSC's SF+ cells, which are grown without added serum was the most important development.

The commercial process at an earlier manufacturing site process is supported by Quadrivalent Recombinant Influenza Vaccine (RIV4) studies PSC08, PSC12, and PSC16. Protein Science established Unigen Inc. and built a manufacturing plant in Gifu, Japan designed for the manufacture of recombinant hemagglutinin using the Protein Sciences RIV manufacturing process. A number of changes have been introduced in order to increase the production scale. These changes have been analysed for their impact on size or quality of the rHA. The commercial scale facility was inspected and approved by the US FDA for manufacture of commercial RIV active substance. Approval was based on comprehensive bioanalytical comparability studies. The aim of these studies was to demonstrate biocomparability of rHA active substance produced by the commercial site, Unigen in Gifu, Japan, and the manufacturing site of the active substance used in clinical trials and further demonstrate lot-to-lot consistency of rHA active substance produced at Unigen. Comparability studies, bridging the Gifu-produced active substance to the active substance site (where Phase 3 clinical and commercial product is produced) and therefore no new clinical data were generated.

The manufacturing process for RIV rHA active substance is designed to be a universal process so that the basic steps in the extraction and purification are identical for all antigens. Minor differences in the downstream processes are necessary to accommodate the differences in the physico-chemical properties of the rHAs derived from different influenza strains.

The process readjustments made annually are within the process design space registered in the dossier. Minor differences used in the downstream processes (DSP) might be necessary to accommodate the differences in the physico-chemical properties of the rHAs derived from different influenza strains. Specifically, DSP process steps are evaluated since these steps have strain specific process parameters and conditions.

In case a process change out of the registered design space is needed, this would be submitted as a dossier variation.

The manufacturing process implemented in Gifu, Japan for commercial AS production has been linked to the pivotal phase III clinical study material by a comparability study addressing exclusively quality-related parameters. The main comparability study has been performed with rHA antigen of each viral strain (H1 A/California /07/2009 rHA, H3 A/Hong Kong/4801/2014 rHA, and B/Brisbane/60/2008 rHA). Additionally, a comparability assessment has been performed by the applicant and the corresponding report is provided in the eCTD.

The provided comparability dataset is identical to the to the licensed QIV (Supemtek Tetra) and is considered acceptable.

3.2.3. Characterisation and impurities

The amino acid composition of rHA samples was determined and compared to that predicted by the amino acid sequence deduced from the rHA genes. The amino acid compositions were in good agreement with those predicted from the cloned HA genes.

A battery of methods was used to characterise the active substances.

The glycosylation pattern and the conformation of the rHA proteins was analysed. Results confirmed that the purified rHA proteins were in a native, properly folded conformation.

Further information on the conformation of rHA proteins demonstrated that rHA assembles into complexes of HA trimers.

The potency of each rHA is measured with the single radial immunodiffusion assay (SRID). Immunogenicity studies in various animals demonstrated a robust serological response as measured by enzyme-linked immunosorbent assay (ELISA), hemagglutination inhibition (HAI) or neutralisation assays.

The rHA proteins are sufficiently characterised to control for identity, glycosylation and higher order conformation. Functionality is tested by adequate methods which demonstrate the appropriate antigenic activity of the rHA proteins.

Since there are no product-related impurities, only process-related impurities are discussed in the dossier. DNA derived from both host cells and baculovirus may be present. Total DNA content is a release test for AS. The host cell protein content of the active substance batches has been investigated.

The major protein impurities in a batch of rHA were analysed in more detail. For other process-derived impurities, the maximum amount that may carry over into the purified active substance has been assessed. Testing for residual infectious baculovirus is performed for release of rHA active substance. Other potential residuals are expected to be reduced by the manufacturing process to negligible concentrations in the final AS bulk.

Cell substrate-derived impurities, cell culture-derived impurities and downstream impurities have therefore been identified and are generally considered adequately examined by the applicant.

3.2.4. Control of active substance

Specifications

The active substance specifications 8 include appropriate tests for appearance, identity, purity, host cell protein, endotoxin, sterility, potency, total protein content, infectious baculovirus content, SRID/protein ratio, pH, total DNA and rHA size.

Compendial tests are performed) on manufactured AS. All other AS release tests are performed at the registered control testing site. Specifications are identical to the licensed Supemtek Tetra and are considered acceptable.

Analytical procedures and reference standards

Appearance, Endotoxin, Sterility and pH are compendial methods (JP, USP and EP. Appearance and pH only "based on" Ph.Eur.). The applicant states that their suitability has been confirmed, but no formal method validation has been performed. This is accepted.

For the other methods, validation reports are included in the dossier.

The potency of rHA bulk active substance and finished product is determined using the single radial immunodiffusion (SRID) assay. The SRID assay is an immunodiffusion test method in which an antibody/antigen complex forms a precipitin ring when the test antigen diffuses into an agarose matrix containing antiserum against the target antigen. The ring sizes are plotted versus the dilution level of the solutions, and the sample concentration is determined by parallel line analysis of the sample series curve against the reference series curve. The influenza reference antigen material is obtained from World Health Organization Essential Regulatory Laboratories (ERLs) for each of the three seasonal hemagglutinin strains. The reference antigen is strain specific and has been standardised by the ERL. This material is provided in vialed portions that are reconstituted to a known concentration prior to use. Other reference material is described in the eCTD.

Other reference standards and materials used have been sufficiently described.

Batch analysis

AS batch analysis is based on QIV data, which is considered acceptable and includes a suitable number of commercial scale batches of each strain. The recombinant hemagglutinins used to validate the active substance production process at Unigen were derived from influenza strains A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Brisbane/60/2008, and B/Massachusetts/2/2012.

All batches met all specifications.

Container closure

The container used for the storage and transport of the monovalent bulk active substance concentrate is a single use bag. This system is designed for the storage and shipping of large volumes of sterile liquid for the pharmaceutical industry and was chosen for its suitability for the storage and shipping of rHA monovalent bulk active substance. The bags received have been sterilised.

A representative Certificate of Release for the bags used for storage and shipment of rHA active substance is included in the eCTD. The container closure system is identical to the licensed QIV (Supemtek Tetra).

3.2.5. Stability

The primary stability indicating parameters for rHA active substance are defined. Stability studies were conducted in line with ICH guidelines. This is accepted.

The shelf life was confirmed with stability data from AS batches manufactured at Unigen.

The applicant provided the following commitment: For each Northern Hemisphere vaccine campaign, a minimum of 3 batches of each rHA antigen are included in the annual stability study.

The data confirmed the proposed shelf life and storage conditions for AS produced at Unigen.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

Trivalent Recombinant Influenza Vaccine (RIV3) consists of three full-length recombinant hemagglutinins (rHAs) derived from the influenza strains selected by WHO and endorsed by CHMP for

each year's seasonal vaccine. These proteins are produced in PSC's expresSF+ (Lepidopteran) insect cells, using a baculovirus expression vector.

Supemtek is a sterile liquid without preservatives, antibiotics, or adjuvants for intramuscular injection and supplied in a single dose syringe (Type I glass barrel with latex free elastomer stopper) containing 0.5 mL.

The nominal potency of the final container finished product is 90 µg/mL (45 µg/0.5 mL dose) per strain.

All excipients are of compendial quality. Novel excipients or excipients of animal/human origin are not used for manufacture of RIV.

The composition is shown in Table 2.

Table 2. Composition of Finished product – one dose

Ingredient	Reference	Nominal amount per 0.5 mL	Function
rHA Influenza A/H1N1 A/California/07/2009 (H1N1)pdm09-like strain (A/California/07/2009)	Internal	45 µg §	Active substance
rHA Influenza A/H3N2 A/Texas/50/2012 (H3N2)-like strain (A/Texas/50/2012)	Internal	45 µg §	Active substance
rHA Influenza B/Victoria lineage B/Brisbane/60/2008-like strain (B/Brisbane/60/2008)	Internal	45 µg §	Active substance
Sodium phosphate monobasic§	USP, BP		Buffer component
Sodium phosphate dibasic§	USP, EP, JP*		Buffer component
Sodium chloride	USP, EP*		Maintenance of osmolality
Polysorbate 20 (Tween20)	USP, EP, JP, BP*		Stabiliser
Water for injections (WFI)	EP*		Solvent

§ Calculated from the anhydrous form
* USP- United States Pharmacopeia; EP -European Pharmacopoeia; BP – British Pharmacopoeia; JP – Japanese Pharmacopoeia

Pharmaceutical development

Formulation development was based mainly on RIV and quadrivalent RIV (RIV4) clinical studies. The RIV4 pivotal clinical studies were performed with the intended commercial formulation of RIV4. The appropriateness of the commercial formulation is sufficiently confirmed by these studies and by the stability data provided.

The data set provided in this section for RIV focuses on RIV4, due to the initial authorisation of RIV4 in the EU. However, this is considered acceptable.

The formulation and manufacturing process for the Trivalent RIV finished product is based on the current licensed Quadrivalent RIV finished product manufacturing process.

At manufacturing sites, container closure validation was conducted to evaluate the container closure system to ensure that the integrity of the finished product is preserved.

This finished product is not reconstituted or mixed with other diluents or drug formulations.

3.3.2. Manufacture of the product and process controls

Name and Address of the manufacturer responsible for batch release:
Sanofi Winthrop Industrie
Voie de l'Institut - Parc Industriel
D'Incarville
P.O. Box 101
27100 Val de Reuil
France

The stated commercial batch sizes are supported by RIV4 process validation data, which are considered applicable for trivalent RIV.

The manufacturing process of the FP follows a standard process namely mixing of AS with PBS and polysorbate, final filtration and filling.

The manufacturing process described in the dossier for manufacturing sites is a straightforward standard process for this type of product. Critical quality attributes have been adequately identified. The control strategy is considered acceptable. There are no intermediates defined for the process. Re-processing is not claimed.

Site 1:

The vaccine components (rHA H1, H3 and B active substances) are shipped at 2-8°C.

The product is formulated with buffer. The aseptic filling of syringes and plunger insertion, labelling, and packaging are performed. Following stoppering, syringes are inspected in accordance with procedure.

The manufacturing process presented in the dossier corresponds to the RIV4 process with the exception of some changes to the PBS preparation process and the removal of the B/Yam antigen and the consequent adjustment.

CPPs, IPCs and hold times are validated for RIV4 and they are presented in the dossier.

Site 2:

A technical assessment has been performed that provides evidence that the formulation, filling and manufacturing processes for RIV can be implemented. No changes will be made to process equipment, parameters, or controls except for the removal of the B/Yam antigen and the consequent adjustment.

Production of the Trivalent RIV Final Bulk Product involves combining three rHA active substance antigens (one rHA H1, one rHA H3, and one rHA B-Victoria lineage antigens) in the formulation tank, addition of formulation buffer if needed, mixing, and sterile filtration.

Formulated bulk may be held for a specified time prior to filling. The manufacturing process presented in the dossier corresponds to the RIV4 process, including the validated RIV4 formulation.

CPPs and IPCs are validated for RIV4 and they are presented in the dossier.

Process controls

The identified process-related variables that must be tightly controlled because they have the potential to cause an adverse effect on the identity, strength, quality, purity, potency, safety, or yield of the product were defined.

The strategy of the Applicant is to utilise the previously validated processes for the manufacture of finished products and all applicable existing studies and documentation from the RIV4 MAA will be utilised for both sites. The general approach is agreed as trivalent RIV specific data will be provided with the next annual strain update before marketing in the EU (**Recommendation 6**).

Process validation / verification

Trivalent finished product process validation at both manufacturing sites is based on data on quadrivalent RIV4 processes. A suitable number of consecutive successful process validation (PV) formulation and fills at scale of Quadrivalent RIV in syringes were executed. Consecutive lots of Quadrivalent RIV Final Bulk were manufactured. A risk assessment / technical assessment has been provided. It is agreed that, due to the removal of the RIV4 strain, the process validation data are applicable to RIV, since the RIV4 process can be considered the worst case for validation due to its higher antigen content. Validation reports provided for both sites comply with the current dossier content for the authorised RIV4 product. As committed, batch release and stability data of the first three RIV batches manufactured at each site will be included in the core dossier.

The Company commits to submit the validation report including results of the PBS preparation scale-up at specified site 1 for the new PBS preparation process before the first annual strain update (**Recommendation 2**).

3.3.3. Control of Finished Product

Specifications

The Trivalent influenza vaccine finished product specifications are described in the dossier. The test methods include appropriate physico-chemical methods and methods for identity, purity and potency.

The specification parameters comply with the requirements of general monographs Ph. Eur. 0784 and 0153 as well as guideline ICH Q6B. The proposed acceptance criteria for RIV at finished product release and end of shelf-life are based on the batches from RIV4 clinical trials and process validation studies.

To be in line with EMA Q&A´s for biological medicinal products, unequivocal identifiers for in-house analytical methods are included in the specification table for finished product, the method descriptions, and the method validation summaries, as requested.

Nitrosamine risk assessment was performed in 2020 for RIV4 AS and FP. It is agreed that the risk assessment done on RIV4 is a worst case as compared to RIV and can be extrapolated to RIV. The risk for elemental impurities is evaluated as low.

Analytical procedures and reference standards. The analytical methods for release testing have been adequately described and correspond to the approved methods applied for RIV4 testing.

In accordance with the trivalent composition of the vaccine, the SRID potency method has been adapted with regard to the single B-strain.

The Applicant concludes that the FP analytical method validations already approved for RIV4 are applicable to RIV. This approach can be largely agreed upon, due to the vaccine matrix. However, a commitment has been made to provide the validation reports with the next annual strain update (**Recommendation 3**). Additionally, eCTD Section 3.2.P.5.3 Validation of Analytical Procedures core document should contain a summary of the validation of a trivalent vaccine (in the next Annual Strain Variation filed with EMA).

The reference standards used for non-compendial methods are listed and otherwise described in sufficient detail. New SRID reagents are qualified and the qualification information is part of the strain change supplement.

Batch analysis

The batch results for all RIV4 process validation batches manufactured at the approved finished product formulation and manufacturing sites have been provided, and they comply with the acceptance criteria.

It is agreed that manufacturing of the finished product for trivalent RIV is based on authorised RIV4, and that existing process validation studies can be used for the RIV process, as outlined in the risk/technical assessment.

A commitment to submit batch analysis data for the formulated bulks and the finished products from the first three batches for both manufacturing sites in eCTD Section 3.2.P.5.4 *Batch Analyses* on the next Annual Strain Variation filed with EMA has been made (**Recommendation 5**).

3.3.4. Stability of the product

The proposed shelf-life of the trivalent RIV FP is 12 months at 2 – 8°C.

Container closure system

At site 1, the packaging configuration and size for RIV is a 0.5 mL fill in a 1 mL glass syringe. The barrel and plunger stopper are the only components of the container system with product contact. The glass barrel, the elastomeric tip cap and the plunger stopper conform to relevant quality standards.

The syringe barrels and the plunger stoppers are sterilised and the sterilisation sites are described.

A risk assessment was performed to evaluate risk of the extractable components in the pre-filled syringes. Function and performance as well as container closure integrity have been sufficiently demonstrated. Furthermore, the shipping process has been validated.

The applicant justified that there are no changes in terms of design, safety and performance characteristics, intended use, usability, and instructions for use regarding the medical device used in currently authorized quadrivalent vaccine manufactured at a specified site, and in agreement with the European Commission, a Notified Body Opinion waiver requested by the applicant was accepted in this exceptional case.

The needle packaged with RIV from both sites is CE-marked, when included.

At the other specified site, the packaging configuration and size for RIV is a dose of NLT 0.5 mL fill in a 1.5 mL glass syringe with a tip cap and a stopper. The syringe barrel, plunger stopper, tip cap and the lubricant comply with relevant quality standards.

The syringe barrels and the plunger stoppers are sterilised. The sterilisation sites for syringe barrels and plunger stoppers are described.

Elemental extractables and leachables risk has also been assessed. The shipping process for the 1.5 mL PFS has been validated.

A Notified Body Opinion has been provided for the 1.5 mL syringe used at Swiftwater, PA site for RIV4 and is considered applicable for RIV.

The same container closure systems as for the authorised RIV4 are used for the trivalent rHA vaccine. Based on the experience gained for RIV4 the container closure systems are deemed suitable for the trivalent vaccine.

Considering the timing for annual strain updates and that the same device components as for Supemtek Tetra are used and the intended purpose of the device parts remains the same, the Art 117 waiver for a Notified Body opinion is acceptable.

Stability data

The formulation and manufacturing process for the trivalent RIV finished product is based on the licensed quadrivalent RIV4 finished product.

Expiry of RIV finished product is calculated from the Date of Manufacture (DOM).

Extensive real time stability data for a number of commercial RIV and RIV4 lots comprising trivalent and quadrivalent lots (including RIV4 process validation lots) manufactured at the proposed commercial sites for RIV are presented by the Applicant.

The shelf-life claim proposed for the initial RIV4 marketing authorisation has been largely justified with stability data obtained for trivalent RIV finished product lots.

Stability data for historical trivalent lots, confirm that the lower protein concentration does not impact stability. Considering this and the extensive historical data set, the proposed shelf-life could be agreeable.

Of note, Supemtek Tetra is approved in the EU since 2020 with a shelf-life of 12 months at 2 – 8°C. However, despite different amendments to Module 3 during life cycle, the product has never undergone a seasonal strain change in the EU and not EU marketed at all. Therefore, the applicant has been requested to provide, at the latest as part of the annual update, accelerated stability data for batches manufactured using the current processes at both sites. In response, updated real time and accelerated stability data for RIV trivalent FP manufactured in 2024 at both sites for the NH 2024-2025 have been provided. The provided stability data are acknowledged and considered acceptable.

The photostability studies presented show that RIV4 in the primary packaging is sensitive to light but sufficiently protected by the secondary packaging.

The Applicant provided a stability commitment for annual stability studies and the respective stability protocol. For each vaccine campaign, a specified number of lots of RIV from each manufacturing site are included in the annual stability study. This is considered acceptable. The analytical program includes relevant stability indicating methods and safety related tests.

Information on quality of the vaccine after temporary exposure to temperature conditions outside the recommended storage conditions has been submitted; the presented data support the storage information added to Section 6.4 of the SmPC i.e. stability data indicate that the vaccine components are stable for up to 72 hours when stored at temperatures up to 28°C. After this period, Supemtek should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only

A shelf-life of the trivalent RIV FP of 12 months at 2 – 8°C is agreed.

3.3.5. Post approval change management protocol(s)

Not applicable.

3.3.6. Adventitious agents

The active substance manufacturing process of TIV remains essentially the same as the licensed QIV product. Therefore, the applicant's statement that the adventitious agents' safety evaluation performed for QIV is applicable for TIV is considered acceptable.

Non-viral adventitious agents, including bacteria, fungi and mycoplasma/spiroplasma, are controlled throughout the production of RIV.

The applicant provided a viral safety risk assessment.

The applicant confirms that no bovine-derived ingredients have been nor are currently used in the establishment of the master cell banks, working cell banks, master virus banks, working virus banks, nor the production process of rHA active substance bulk. Cod liver oil is a component of the cell culture medium. Cod is not considered to be a TSE-relevant animal species as outlined in the European guideline "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01Rev 3)."

The insect cell line expresSf9+ is used for production of the rHA from the baculovirus expression system. The MCB was tested in vivo and in vitro for adventitious agents, in line with Ph. Eur. requirements. Qualification tests of WCBs include testing for adventitious agents.

The MVS is tested for adventitious agents (in vitro and in vivo). The WVB has been tested for adventitious agent by in vitro test. Source materials have been assessed for their contaminating risk.

Adventitious agents tests are performed as release tests during production. The absence of infectious baculovirus is a release test for the active substance.

The applicant has conducted a series of viral clearance studies to examine and demonstrate the capacity of the active substance manufacturing process to inactivate and remove infectious baculoviruses and inactivate and remove potential viral contaminations.

These studies as such were adequately designed and conducted for the intended purpose in accordance with the concepts and requirements as laid down in ICH guideline 5A: "Viral safety evaluation of biotechnology products derived from cell lines of human and animal origin".

3.3.7. GMO

The finished product is not a GMO.

3.4. Discussion and conclusions on quality aspects

Active substance

The active substances of Supemtek consist of three separately manufactured recombinant hemagglutinin (rHA) proteins. The active substance process of TIV remains essentially the same as the licensed QIV product and was updated with minimal changes to present the most relevant quality data of the TIV vaccine. A new WCB manufacturing site will be added post-approval (**Recommendation 1**). The manufacturing process and the process validation are described appropriately. Characterisation data have been previously assessed for the quadrivalent vaccine and are sufficient. No changes to the

specifications including acceptance criteria or analytical methods used are proposed for the trivalent vaccine compared to the approved tetravalent vaccine. Since Supemtek has never been marketed in the EU, no new batch data are available. Information on reference materials, container closure system and stability data are identical to those previously submitted and approved for the quadrivalent vaccine. Hence, no re-assessment of these data has been made.

Finished product

For manufacturing of trivalent RIV finished product, A/H1N1 rHA, A/H3N2 rHA and B/Victoria rHA active substances are formulated in phosphate buffered saline. Sodium chloride is added to maintain osmolality. The rHA proteins are stabilised by the addition of Tween 20. Except for the removed B/Yamagata lineage component and the resulting lower total protein content, the formulation of the trivalent vaccine is identical to the authorised Supemtek Tetra. All excipients are of compendial quality (EP or BP/USP). No animal/human-derived excipients are used. Trivalent RIV is provided in single doses in 1mL or 1.5mL USP/EP/JP Type I Glass syringes with a latex free elastomer stopper.

The formulation and manufacturing process for the RIV finished product are based on the authorised quadrivalent recombinant influenza vaccine, Supemtek Tetra. The finished product processes at manufacturing sites have been validated based solely on data from RIV4 manufacture. Valid GMP certificates are available for all manufacturers. Trivalent RIV establishes a scale up of the phosphate buffered saline preparation process. The applicant commits to submit the validation report including results of the PBS preparation scale-up for the new PBS preparation process before the first annual strain update (**Recommendation 2**).

A risk assessment / technical assessment has been conducted, and it is agreed that the process validation results are applicable to RIV due to the removal of the B/Yam strain, since the RIV4 process can be considered the worst case for validation due to its higher antigen content.

Apart from the removal of the Yamagata lineage component and associated reduction of the total protein content, the manufacturing process and control strategy remains the same for the trivalent vaccine. The specifications for the trivalent vaccine have been adapted to reflect the removal of the B/Yamagata component. Considering this, the Applicant´s approach to largely leverage knowledge and experience from Supemtek Tetra manufacture is acceptable.

Development of Supemtek and Supemtek Tetra was largely based on a trivalent formulation of the vaccine, which is licensed in the USA since 2013. Overall, the development information provided in the dossier is acceptable. Comparability of product produced at the intended commercial manufacturing sites has been previously demonstrated for Supemtek Tetra. Except for the minor change at the buffer preparation step introduced for manufacture of the trivalent vaccine, the same manufacturing equipment as for manufacture of Supemtek Tetra will be used for the trivalent vaccine. Considering the above, it is acceptable that no new comparability studies have been provided.

Batch analyses are presented for the Supemtek Tetra PPQ batches manufactured. The same batch data were filed for the MAA of the quadrivalent vaccine and for the subsequent introduction of/changes at the second site. The Applicant´s position that no new PPQ data are warranted is acceptable. However, release data for bulk and finished product should be provided for both manufacturing sites with the next annual strain update (**Recommendation 6**).

The same container closure systems as for Supemtek Tetra is used for the trivalent rHA vaccine. Based on the experience gained for Supemtek Tetra the container closure systems are deemed suitable for the trivalent vaccine. Considering the timing for annual strain updates and that the same device components as for Supemtek Tetra are used and the intended purpose of the device parts remains the same, the Art 117 waiver for a Notified Body opinion is acceptable. The optionally co-packed syringe needle is CE marked.

The release parameters and analytical methods for formulated bulk are essentially identical for the trivalent vaccine and Supemtek Tetra which is endorsed. Except for identity, potency and total protein content, which were adapted to the reflect the removal of the B/Yamagata component, the release acceptance criteria for the trivalent vaccine and Supemtek Tetra are identical and mainly justified based on data for quadrivalent clinical and PPQ lots. Considering the similarity of the tri- and quadrivalent vaccine this is acceptable.

The available description & validation of the analytical methods are generally acceptable though points for clarification still remain for the SRID method and its transfer to the release testing site. RIV product specific validation reports and method transfer results should be provided with the next Annual Strain Variation in the EU (**Recommendations 3, 4 and 5**). Reference materials are sufficiently described.

Supemtek Tetra was approved in the EU in 2020. Since then, various CMC variations, including the implementation of a second FP manufacturing site, have been submitted. The vaccine has never undergone a seasonal annual strain update in the EU, nor has it ever been on the EU market. Therefore, a set of trivalent RIV (accelerated) NH 2024/2025 stability data on vaccine batches manufactured by the current processes has been provided and is considered acceptable. The shelf life of the vaccine is 1 year stored in a refrigerator (2 °C – 8 °C).

A new active substance claim is not made.

3.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Establishment of a Working Cell Bank (WCB) manufacturer.
2. Submission of the validation report including results of the PBS preparation scale-up at Site 1 according to the qualification and validation strategy described in the "Risk Assessment of Validation Matrix Strategy for Manufacture of Supemtek TIV" (VV-QUAL-0834405, Ver 2.0), i.e., single-use components qualification and storage time validation results for the new PBS preparation process (before the first annual strain update).
3. Submission of the following RIV product specific validation reports: Endotoxin, SRID - including the validation reports for each antigen as recommended, and Sterility as well as the reagent validation reports, in the first annual strain update.
4. eCTD Section 3.2.P.5.3 Validation of Analytical Procedures core document should contain a summary of the validation of a trivalent vaccine (in the next Annual Strain Variation filed with EMA).
5. Submission of analytical data confirming successful transfer of the SRID method to Sanofi Val de Reuil in the next annual strain variation submitted in the EU.
6. Submission of batch analysis data for the formulated bulks and the finished drug products from the first three batches for both manufacturing sites in eCTD Section 3.2.P.5.4 Batch Analyses(in the next Annual Strain Variation filed with EMA).

4. Non-clinical aspects

4.1. Introduction

The nonclinical development for RIV3 to support the authorisation of RIV3 in the EU contains nonclinical studies with RIV3 which were already assessed in Supemtek Tetra MAA (EMEA/H/C/005159). The applicant submitted nonclinical study data with a former version of RIV3, conducted between 2006 and 2009. Immunogenicity, safety pharmacology, single-dose toxicity, repeat-dose toxicity, local tolerance and development and reproductive toxicity of RIV3 were investigated in animal models. All safety and toxicity studies were GLP-compliant.

4.2. Analytical methods

Immunogenicity of RIV and rH3 was analysed by ELISA, HAI assay and/or standard plaque-reduction assay on MDCK cell monolayers (for neutralising antibody titre).

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Two nonclinical immunogenicity studies were conducted with monovalent recombinant H3 strain (M0117 and M0139) and one study was conducted with trivalent recombinant influenza vaccine (M0163) in CD-1 mice.

In study M0117, high levels of anti-HA and HAI antibodies were produced in the rHA A/Beijing/32/92 (H3) (without aluminium) immunised mice after a single dose via intraperitoneal (IP) route. The tested dose levels were 5 µg, 15 µg and 50 µg rH3. Levels of anti-HA IgG (ELISA), haemagglutination inhibition (HAI), and neutralising antibodies were analysed in the mice. The immune responses were dose-dependent such that a 10-fold increase in antigen resulted in approximately a three-fold increase in antibody and HAI titres. Furthermore, aluminium was tested as adjuvant in the vaccine formulation. Mice immunised with 15 µg rHA A/Beijing/32/92 (H3) adsorbed to aluminium produced high levels of anti-HA antibodies. All concentrations of aluminium tested significantly increased the immunogenicity of rH3 in mice compared to rHA vaccine given in PBS. Four of ten mice that received 15 µg of rH3 in PBS produced HAI antibodies with a mean titre of 200 in the positive animals, whereas 29/30 mice immunised with 15 µg of rH3 in the three concentrations of aluminium (0.25 mg, 0.125 mg or 0.05 mg) produced specific HAI antibodies with mean titres of 889, 1,888, and 1,024, respectively. This is approximately 10-times the HAI levels observed with rH3 in PBS and is higher than that produced in the mice immunised with 50 µg rHA in PBS.

In study M0139, CD-1 mice were immunised once via intramuscular (IM) route with 15 µg of purified rHA A/Beijing/32/92 (H3) made in Sf9 cells grown in media containing 10% foetal bovine serum or with 15 µg of rHA from the same strain made in insect cells adapted to a serum-free medium. Two weeks post-injection the mice were bled and serum samples prepared. Each mouse serum was analysed for anti-HA IgG by ELISA and for HAI antibodies. Both rHA produced in Sf9 cells and rHA antigen produced in SF+ cells under serum-free conditions elicited similar titres of anti-HA (ELISA) and HAI antibodies. Due to the added safety and reproducibility of manufacturing with serum-free

fermentation, cultured insect cells adapted to serum-free media were subsequently used for production of recombinant influenza HA antigens.

Study M0163 evaluated the immunogenicity of RIV3 that contained 15 µg per 0.5 mL dose of rHA of each of the following strains: A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2) and B/Panama/45/90. The rHA antigens were formulated in phosphate buffered saline without added adjuvant. CD-1 mice were immunised with 0.5 mL RIV3 and bled at 0 and 3 weeks. Serum samples were analysed for anti-HA IgG antibodies by ELISA against the three strains of influenza rHA proteins, for HAI antibodies against egg-grown influenza virus, and for neutralising antibodies against egg-grown influenza viruses. Vaccination with trivalent rHA induced high levels of anti-HA serum IgG ELISA antibodies against the three strains of influenza present in the vaccine. HAI and nAb against the specific influenza A and B strain viruses were also produced.

4.3.1.2. Secondary pharmacodynamics

No studies on the secondary pharmacodynamics have been performed, which is in accordance with applicable guidelines.

4.3.1.3. Safety pharmacology

Three GLP-compliant safety pharmacology studies were performed to evaluate the effects of RIV3 (135 µg x 3 HA strain) following a single subcutaneous injection of one human dose. No significant differences in the blood pressure, heart rate and ECG parameters were observed in dogs compared to control animals (Study P081016). No significant differences in the respiratory rate, tidal volume, minute volume and Penh were observed in rats compared to control animals (Study P081015). No abnormal findings or no significant differences in all the parameters of the FOB tests, locomotor activity and body temperature were observed in rats (Study P081014).

4.3.2. Pharmacokinetics

In accordance with the WHO guidelines on nonclinical evaluation of vaccines, no pharmacokinetics evaluation was conducted as this is not required for vaccines.

4.4. Toxicology

4.4.1. Single-dose toxicity

The objective of study B-6407 was to evaluate the toxicity of RIV3 following a single subcutaneous (SC) injection to rats (135 µg x 3 HA strains). Two groups of 5 male and 5 female Sprague Dawley rats received one SC injection (Day 0) of either PBS-T or one dose of RIV3 in a dose volume of 0.5 mL. All animals were kept for 14 days of observation and then were necropsied. There were no premature deaths, no clinical signs, no effects on body weights and no macroscopic findings. In conclusion, the single SC injection of RIV3 in rats did not induce toxicity effects under the study conditions.

The objective of the study B-6494 was to evaluate the toxicity of RIV3 following a single SC injection to dogs (135 µg x 3 HA strains). Two groups of 2 male Beagle dogs received one SC injection (Day 0) of PBS-T or one dose of RIV3 in a dose volume of 0.5 mL. All animals were kept for 14 days of observation and then were necropsied. There were no premature deaths, no vaccine-related clinical signs, no local reaction, no effects on body weights or food consumption and no macroscopic findings.

In conclusion, the single SC injection of RIV3 in dogs did not induce toxicity effects under the study conditions.

4.4.2. Repeat-dose toxicity

The objectives of the repeat-dose toxicity study B-6408 were to determine the systemic toxicity and local tolerance of RIV3 in rats, following five consecutive SC injections seven days apart, and to evaluate the reversibility or delayed occurrence of any local and systemic reaction over a subsequent 4-week observation period. Two groups of 16 male and 16 female Sprague Dawley rats received five SC injections (135 µg x 3 HA strains per dose) at 7-day intervals (Days 1, 8, 15, 22 and 29) of either an aqueous solution of PBS-T or one dose of RIV3 in a dose volume of 0.5 mL. Ten animals/sex/group were necropsied one day after the last injection (Day 30) and the other 6 animals/sex/group were necropsied 4 weeks after the last injection (Day 59). There were no premature deaths, no clinical signs, no local reactions and no ophthalmological changes related to the vaccine injection. Body weight and food consumption were unaffected in all animals. There were no vaccine-related effects on clinical pathology parameters, organ weights and macroscopic findings. At histopathological examination, vaccine-related findings were limited to an increased cellular infiltration at the last injection site when compared to the control group, accompanied with oedema in some animals, corresponding to an acute inflammation in the last injected area. At the end of the recovery period, the inflammatory changes showed a total recovery. In conclusion, five SC injections of RIV3 given at 7-day intervals to SD rats were locally and systemically well tolerated. The only change was limited to a transient acute inflammation at the injected area, which was considered typical of that observed following injection of an influenza vaccine.

4.4.3. Genotoxicity

No genotoxicity studies were performed with RIV3, which is in accordance with applicable regulatory guidelines.

4.4.4. Carcinogenicity

No carcinogenicity studies were performed with RIV3, which is in accordance with applicable regulatory guidelines.

4.4.5. Developmental and reproductive toxicity

The objective of the study 2146-001 was to evaluate the effects of RIV3 on female rats and on pre- and post-natal offspring development following intramuscular injections to female rats twice prior to mating and once during gestation. This study was conducted under GLP conditions in rats, with a 2006-2007 RIV3 formulation. This batch was manufactured with a process comparable to that intended for commercial use. Two groups of 50 female Sprague Dawley rats received three intramuscular injections (31 and 12 days before the start of mating and on Gestation Day 6, respectively) of PBS or one dose of RIV3 (45 µg x 3 strains) in 0.5 mL. Twenty-five female rats per group underwent a caesarean section at the end of gestation (i.e. Day 20 post-coitum) and were submitted to routine embryotoxicity evaluations (caesarean sub-group). The remaining twenty-five rats were allowed to deliver their litter and the offspring development was observed up to weaning (littering sub-group). RIV3 at the human dose induced an active immune response to the three strains in all rat dams from the vaccine group. The exposure of foetuses and pups to vaccine-specific maternal antibodies was also demonstrated. There were no treatment-related premature deaths, no vaccine-related clinical signs

and no local reaction before mating, during the gestation and/or lactation periods. There were no vaccine-effects on body weight, body weight gain or food consumption of the dams during the premating, gestation and/or lactation periods. There was no influence of the vaccine on mating performance or fertility of the females. In the caesarean sub-group, there was also no effect of the vaccine on the pre- and post-implantation data, gravid uterus weight, litter size, foetal weight or sex ratio. In the littering sub-group, the mean duration of gestation, mean numbers of implantation sites and delivered pups were comparable in both groups. There was no vaccine-related effect on post-natal survival, foetal malformation, sex ratio, growth, physical or functional development and macroscopic observations of the offspring.

4.4.6. Local tolerance

Two local tolerance studies were conducted.

The objectives of the study I-3235 were to determine the local tolerance of RIV3 following a single IM injection to the SPF Japanese White male rabbit and to evaluate the possible regression of any local reaction during a 7-day observation period. Six rabbits received one dose of RIV3 at one dose (135 µg x 3 HA strains) or PBS-T (0.5 mL/injection), or one dose of 0.425% or 1.7% of acetic acid (positive control groups) or one dose of physiological saline solution (negative group control). All animals were necropsied 2 or 7 days after injection to evaluate the possible reversibility or delayed occurrence of any local reaction. There were no premature deaths, no clinical signs and no local reactions related to vaccine injection. Body weights were unaffected by the vaccine in all animals. Two or seven days after injection, there were no significant effects on the muscle weight in any group. There were no macroscopic findings at the injected muscles from animals given either the test item, control item or negative control or at untreated sites. Macroscopic haemorrhages and white- or brown-coloured changes of injection sites were observed in animals given the positive controls. At histopathological examination, two days after injection, the injected muscles showed necrosis of muscle fibres, infiltration of neutrophils and histiocytes or mineralisation of muscle fibres. Seven days after injection, the muscle fibres necrosis was no longer observed, and a regeneration and fibrosis of muscle fibres as well as lymphocyte infiltration were noted, indicating a partial recovery at the injected muscles. The local reactions observed after RIV3 administration were stronger than those observed with physiological saline but were equal to or less than 0.425% acetic acid. The irritation caused by PBS-T was similar to that caused by physiological saline.

The objectives of the study I-3234 were to determine the local tolerance of RIV3 following a single SC injection to SPF Japanese White male rabbits and to evaluate the possible regression of any local reaction over a 7-day observation period. Six male rabbits were given on Day 0 concomitant SC injections of one human dose of RIV3 (135 µg x 3 HA strains), PBS-T (control item), and physiological saline (negative control). The three injections were performed in an area of the abdomen. All animals were necropsied 2 or 7 days after dosing to evaluate the possible reversibility or delayed occurrence of any local reaction. There were no premature deaths, no clinical signs, no vaccine-related local reactions and no vaccine-related macroscopic findings. Body weights were unaffected by the vaccine. Two or seven days after injection, a minimal cell infiltration was observed in the injected areas, in or around the subcutaneous blood vessels and in dermis and this with all tested compounds. Consequently, these findings were considered not related to the vaccine or its vehicle PBS-T.

4.4.7. Other toxicity studies

Not applicable

4.4.8. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

The nonclinical study program for Supemtek (RIV3) is primarily based on immunogenicity and non-clinical safety data obtained with trivalent recombinant influenza vaccine (RIV3, Flublok). Nonclinical in vivo studies were performed during the period from 2006 to 2009. The same nonclinical data package has been submitted previously for Supemtek Tetra MAA in EU (EMEA/H/C/005159). This submission strategy was accepted by EMA in pre-submission discussions.

The manufacturing process of Supemtek (RIV3) is based on the manufacturing process used for Supemtek Tetra (RIV4) and former trivalent RIV versions. Supemtek (RIV3) contains 45 µg recombinant influenza HA per strain (in total 135 µg) and includes similar excipient composition compared to Supemtek Tetra and former trivalent RIV candidate. The RIV3 composition can be considered as comparable to RIV4, except of the number of included HA strains as active substances.

The nonclinical pharmacology studies submitted included nonclinical immunogenicity data generated in mice with the monovalent rH3 antigen or a former version of RIV3 that was administered intraperitoneally or intramuscularly to the study animals. Based on the comparable vaccine composition and manufacturing process, nonclinical immunogenicity data from former RIV3 are considered as acceptable. The nonclinical immunogenicity data showed that RIV3 or rH3 is immunogenic in mice and can induce serum HAI and nAb antibodies against the influenza strains present in the vaccine. A clear dose effect was evident in a range of 5 - 15 – 50 µg of rH3 and the antibody response was strongly enhanced when 15 µg rH3 was formulated with aluminium adjuvant. However, it has to be noted that the dose-range and aluminium adjuvant data are from mice vaccinated via intraperitoneally route instead of the intramuscular (clinical) route. Thus, these results have to be interpreted with caution. Protection studies were not conducted with the recombinant influenza vaccine. Considering the amount of clinical and post-approval data from RIV3 and RIV4, this is accepted. These data provide important proof-of-concept and support omission of the protection studies in animals.

In addition, the applicant conducted three safety pharmacology studies in dogs and rats, respectively. In these GLP-compliant studies, animal models were injected with a single dose of RIV3 (135 µg x 3 HA strains) via subcutaneous route. No remarkable findings were observed concerning cardiovascular, respiratory and central nervous system functions. These results are in line with findings in the conducted toxicity studies. However, use of SC route is not desirable, and the relevance of the study in dogs is questioned due to absence of immunogenicity evidence from the model.

Due to the absence of any specific findings observed in toxicity studies, no secondary PD studies were conducted, which is in accordance with the WHO guidelines on nonclinical evaluation of vaccines (WHO Technical Report Series, No. 927, 2005).

Pharmacokinetic studies to demonstrate absorption, distribution, metabolism and excretion of the active ingredients of RIV3 were not performed, which is acceptable and in line with the relevant guidelines. There is no novel excipient or adjuvant included in the formulation of RIV3.

No new nonclinical toxicity studies have been performed with RIV3. All toxicity studies were conducted with former RIV3 vaccine candidates.

The applicant presented toxicity studies with RIV3 in different animal species, consisting of two single dose toxicity studies (rats, beagle dogs), a repeat-dose toxicity study (rats), a developmental and reproductive toxicity (DART) study (rats), two local tolerance studies (rabbits), and three safety pharmacology studies (beagle dogs, rats). Although all conducted under GLP and used one human dose (in 0.5 mL) of RIV3, it is noteworthy that relevance of animals was ascertained by immunogenicity data only for the DART study, and also only this study and one local tolerance study used the clinically intended IM administration route. Furthermore, the intended full human dose concentration of 45 µg/HA strain RIV3 was only tested in the DART study. In the other conducted toxicity studies, a 3-fold higher dose (135 µg per HA strain) was tested.

In single-dose toxicity studies, a single SC injection of RIV3 did not induce toxicity effects over a 14-day observation period. Limitations of these studies include use of alternative SC administration route and the small number of animals per group. The rationale to conduct two single-dose toxicity studies is not clear since single-dose toxicity studies are not recommended in the EMA Guideline on Influenza Vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) or in the WHO guidelines on nonclinical evaluation of vaccines (WHO Technical Report Series, No. 927, 2005), regarding to 3R principle.

Local tolerance studies showed that RIV3 was well tolerated upon a single IM or SC injection at the human dose, with no local reactions related to vaccine injection and no signs of systemic toxicity for a 7-day observation period. A transient microscopic inflammation at injection sites was observed after IM injection only, as expected for vaccination via IM administration route.

The repeat-dose toxicity study was conducted via the SC route. Results showed that five weekly SC injections with RIV3 were locally and systemically well tolerated in rats. There were no local reactions and no signs of systemic toxicity including clinical pathology parameters, organ weights and macroscopic findings. The main related findings were transient microscopic changes at the injection sites, which is expected. In addition, some statistically significant differences between control and treatment group were reported for some parameters (e.g., transient increase in food consumption in the male test group; a decrease in urine volume accompanied with increased osmotic pressure in the male test group; decrease in the mean corpuscular volume in the male test group; increase in fibrinogen in female test animals; increase in the adrenal weight in female test animals), but are not considered toxicologically relevant. It is noteworthy that use of alternative administration route (SC) rather than clinically intended IM route for a pivotal toxicity study is uncommon, as well as for the short dosing interval of 7-days rather than a classic 2-3-weeks interval.

In DART study conducted in female rats, three IM injections (31 and 12 days before mating and on Gestation Day 6) of RIV3 did not induce maternal toxicity, and there were no adverse effects on mating performance or fertility, embryo-foetal development (including an evaluation of teratogenicity) and early post-natal development. RIV3 at the human dose induced an active immune response to the three strains in all rat dams from the vaccine group. The exposure of foetuses and pups to vaccine-specific maternal antibodies was also demonstrated. RIV3 at the human dose induced an active immune response to the three strains in all rat dams from the vaccine group.

Despite limitations of these toxicity studies identified, it is acknowledged that extensive clinical experience with RIV3 and RIV4 from clinical studies and post-marketing surveillance safety profile did

not identify any unexpected safety signal. In this regard, the nonclinical safety package developed for RIV3 showing no issue of major safety concern complies with known clinical adverse event profile of RIV3.

No genotoxicity and carcinogenicity studies were performed with RIV3, which is in accordance with applicable regulatory guidelines.

The Applicant did not provide specific studies on the ERA but an adequate justification for not submitting such studies. This approach is acceptable for vaccines as laid down in the "Guideline on the environmental risk assessment of medicinal products for human use" – Revision 1 (EMEA/CHMP/SWP/4447/00 Rev. 1 – Corr.).

4.5.2. Conclusions

Despite several limitations within the non-clinical studies provided – as described in the discussion section - no issue of major concern was identified. Additionally, since non-clinical data are superseded by extensive clinical experience demonstrated with mainly the quadrivalent recombinant influenza vaccine (Supemtek Tetra) but also the trivalent variant RIV3 (Flublok, not authorised in Europe), the non-clinical data package is accepted.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Based on the review of clinical data, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table *3*. Clinical studies

Study ID	Enrolment status Start date Total enrolment	Design Control type	Study & control drugs Dose, route of administration	Population
PSC12	Completed; published 2014-10-22 N = 8,963	Phase III, randomised, observer-blinded, active controlled 2-arm	One injection of RIV4 containing 45 µg of rHA per strain or IIV4 (Fluarix Tetra) containing 15 µg of HA per strain (2014-2015 influenza season) Intramuscular (IM) route	Adults aged ≥ 50 years, medically stable
PSC16	Completed; published 2014-10-22 N = 1,350	Phase III, randomised, observer-blinded, active controlled 2-arm	One injection of RIV4 containing 45 µg of HA per strain or IIV4 (Fluarix Tetra) containing 15 µg of HA per strain (2014-2015 influenza season) IM route	Healthy adults aged 18 to 49 years

Study ID	Enrolment status Start date Total enrolment	Design Control type	Study & control drugs Dose, route of administration	Population
PSC04	Completed; published 2007-09-15 N = 4,648	Phase III, randomised, double-blind, placebo-controlled 2-arm	One injection of RIV3 containing 45 µg of HA per strain (2007-2008 season) or placebo IM route	Healthy adults aged 18 to 49 years
VAP00027	Completed; published 2022-10-27 N = 1,308	Phase III, non-randomised, open-label, uncontrolled	One injection of RIV4 containing 45 µg of HA per strain (2022- 2023 influenza season) IM route	Healthy subjects aged 9 to 49 years
VAP00026	Terminated (futility); published 2022-11-10 N = 366	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 influenza season) One or 2 injections 28 days apart of IIV4 containing 15 µg of HA per strain (2022-2023 influenza season) IM route	Healthy children aged 3 to 8 years
VAP00007	Completed; published N/A N = 48,781	Phase IV, post-licensure, observational, retrospective, safety surveillance study in pregnant women and their offspring	N/A	Pregnant women

5.2. Clinical pharmacology

5.2.1. Methods

Immunogenicity assessments in the main studies were supported by validated assays including haemagglutination inhibition (HAI), virus neutralisation tests (NT), real-time RT-PCR, and virus isolation in cell culture. The HAI and NT assays were validated for accuracy, precision, and specificity and deemed suitable for quantifying anti-influenza antibodies. PCR- and culture-based methods were used for virus detection and typing and followed established guidelines.

5.2.2. Pharmacokinetics

No pharmacokinetics studies have been conducted for RIV3. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Trivalent Influenza Vaccine (recombinant, prepared in cell culture) contains recombinant haemagglutinin proteins of the three strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. It provides active immunisation against three influenza virus strains: an A/(H1N1) strain, an A/(H3N2) strain, and one B strain (lineage: B/(Victoria)).

This vaccine induces humoral antibodies against the haemagglutinins. These antibodies protect against influenza infection.

Annual influenza revaccination is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

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/164653/05 Rev. 1).

5.2.3.2. Primary and secondary pharmacology

Primary pharmacology focuses on the induction of an antigen-specific immune response rather than classical receptor-mediated pharmacological effects. The mechanism of action is based on the generation of strain-specific antibodies against haemagglutinin antigens, which mediate virus neutralisation and are considered correlates of protection.

Proof-of-concept for immunogenicity was established in early-phase clinical studies by demonstrating increases in haemagglutination inhibition (HAI) titres against vaccine strains. Seroconversion and seroprotection rates were assessed at baseline and 28 days post-vaccination, in line with established surrogate endpoints for influenza vaccines. The dose selected for further clinical development was supported by a clear dose-response relationship in HAI titres.

No formal PD/PK modelling was applicable. No relevant covariate effects (e.g. age, sex, or baseline immunity) on vaccine-induced antibody responses were identified in early studies, although some age-related differences were explored in subsequent pivotal trials.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable.

5.2.5. Dose selection and therapeutic window

No dedicated dose-finding studies were conducted for RIV3. The composition and antigen content are consistent with those of the authorised quadrivalent recombinant influenza vaccine (RIV4) and other non-adjuvanted seasonal influenza vaccines.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The clinical pharmacology profile of the recombinant trivalent influenza vaccine (RIV3) is consistent with that of seasonal influenza vaccines and considered adequate to support the proposed indication. As expected for this vaccine class, no pharmacokinetic studies were performed or required, given the local mechanism of action and the absence of systemic distribution or metabolism of the antigenic components. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current Guidelines on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1). Pharmacodynamic properties are based on the induction of strain-specific humoral immune responses against recombinant haemagglutinin (rHA) antigens, which are recognised correlates of protection for influenza vaccines. This mode of action is well established and accepted as the primary pharmacological principle for prophylactic influenza immunisation.

The clinical development programme included comprehensive immunogenicity assessments using validated assays such as HAI and virus neutralisation tests (NT), which reliably quantify antibody responses. The HAI assay has been adequately described and validation reports for strains including A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), A/Texas/50/2012 (H3N2), B/Hubei Wujiagang/158/2009, B/Massachusetts/2/2012, and B/Brisbane/60/2008 have been provided. The validation covered accuracy/recovery, sensitivity, specificity, intra- and inter-assay precision, and linearity, addressing day-to-day variability as well as variability introduced by operator and RBC lot. Egg-derived antigens, sheep reference sera from NIBSC, and human sera from influenza vaccinees were used. The data demonstrate that the HAI method performs reliably and is suitable for monitoring immunogenicity in clinical studies. The surrogate endpoints applied (namely seroconversion and seroprotection rates) are in line with regulatory guidance and were assessed at standardised time points (Day 0 and Day 28). These data provide confirmatory evidence of the expected pharmacodynamic effect and support the selection of HAI-based surrogate endpoints in pivotal studies.

No dose finding was undertaken specifically for Supemtek. Initial dose selection during the development of Flublok (RIV3), authorised by FDA in 2013 was informed by two Phase II studies evaluating rHA doses in different age groups. The studies demonstrated clear immunogenicity and supported the use of 45 µg per strain as the optimal dose, which was subsequently used in pivotal efficacy and safety trials for Supemtek Tetra, authorised in the EU in 2020. The current application is based on the same clinical dossier, now excluding the B/Yamagata lineage rHA in accordance with the WHO recommendations from September 2023. No meaningful covariate effects were identified in early development, although some age-related differences in immune response were explored in later studies. The selected dose falls within the expected immunological therapeutic window and is consistent with the formulation used in the authorised quadrivalent vaccine (RIV4).

Overall, the clinical pharmacology programme is adequate in scope and methodological implementation. No additional pharmacology studies are considered necessary for this class of product.

5.2.6.2. Conclusions

The clinical pharmacology part of the Supemtek dossier is considered adequate to support a marketing authorisation.

The mechanism of action is well established for influenza vaccines and the immunogenicity data demonstrate robust antibody responses at the selected dose. No pharmacokinetic studies are required for this product class. The assays and surrogate endpoints applied are appropriate and aligned with

regulatory standards. The selected dose of 45 µg rHA per strain is consistent with the authorised quadrivalent formulation.

5.3. Clinical efficacy

5.3.1. Dose response study

Refer to section 5.2.4 Dose selection and therapeutic window.

5.3.2. Main studies

5.3.2.1. PSC12

5.3.2.1.1. Study title

Comparison of the Protective Efficacy of Flublok Quadrivalent Versus Licensed Inactivated Influenza Vaccine (IIV4) in Healthy, Medically Stable Adults ≥50 Years of Age

5.3.2.1.2. Study design

The study was a double-blind, randomised, active-controlled, parallel design Phase 3 multi-centre clinical trial designed to compare the relative vaccine efficacy (rVE), immunogenicity, reactogenicity and safety of RIV4 Quadrivalent with that of an authorised IIV4.

5.3.2.1.2.1. Treatment

In this Phase III study, ambulatory adults aged 50 years and older received a single dose of either the recombinant quadrivalent influenza vaccine (RIV4) or the authorised inactivated quadrivalent vaccine (IIV4, Fluarix Tetra). Participants received a single 0.5 mL intramuscular dose of either RIV4 (Group A) or IIV4 (Group B) on Day 0. RIV4 contained 180 µg recombinant haemagglutinin (rHA) protein (4×45 µg) covering H1N1 (A/California/07/2009), H3N2 (A/Texas/50/2012), B/Massachusetts/2/2012 (B/Victoria-lineage), and B/Brisbane/60/2008 (B/Yamagata-lineage). IIV4 (Fluarix Tetra) contained 60 µg HA (4×15 µg) derived from corresponding strains. Both vaccines were administered via pre-filled syringes in the deltoid muscle by qualified site personnel.

5.3.2.1.2.2. Randomisation

A total of 9,008 participants were randomised 1:1 to one of the two treatment arms on Day 0 using an interactive web-based response system. Randomisation was stratified and centrally managed to ensure balance across study sites.

5.3.2.1.2.3. Blinding

The trial employed an observer-blind design. Only the designated vaccine administrator was unblinded and was not involved in any post-vaccination assessments. All other study personnel and participants remained blinded to treatment allocation. Measures to maintain blinding included the use of separate

drug accountability logs, reconciliation by unblinded CRAs, and source data verification by blinded monitors. No information on emergency unblinding procedures was provided by the sponsor.

5.3.2.1.2.4. Patient population

The study targeted ambulatory, medically stable adults aged 50 years and older. Participants were required to have had no significant changes in chronic diagnoses or medication regimens in the three months preceding enrolment. All participants had to be capable of understanding and complying with study procedures and to provide written informed consent.

Subjects with known contraindications to either study vaccine, those recently vaccinated against influenza (within 180 days), or individuals with conditions or ongoing treatments likely to cause immunocompromise were excluded.

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

The primary objective in this study was to compare the clinical efficacy of RIV4 to that of IIV4, with respect to the ratio of attack rates of RT-PCR-confirmed protocol-defined influenza-like-illnesses (ILI) that begin at least 14 days after vaccination caused by any influenza viral types/subtypes.

5.3.2.1.3.2. Estimand for the primary objective

Table 4. Estimand for primary objective

Population	Patients aged ≥50 years who would not encounter the Intercurrent Event of major protocol deviations affecting efficacy assessment under any treatment assignment.
Treatment condition<s>	Assignment to RIV4, regardless of discontinuation and analysed as treated, compared to assignment to IIV4, regardless of discontinuation and analysed as treated.
Endpoint (variable)	RT-PCR-confirmed, protocol-defined ILI caused by any influenza strain that begins at least 14 days post-vaccination.
Population-level summary	Relative vaccine efficacy (rVE), calculated as: $rVE = 1\text{-}RR = 1 - (\text{Attack rate}_{RIV4} / \text{Attack Rate}_{IIV4}) \times 100$

The clinical question of interest was to assess how effectively a single dose of RIV4 prevents RT-PCR-confirmed ILI from any influenza strain, starting 14 days post-vaccination, in medically stable adults aged 50 years and older. The endpoint was a clinically confirmed infection; no surrogate markers were used.

The estimand was not formally described according to the ICH E9(R1) framework. Specifically, the handling of intercurrent events (such as receipt of non-study influenza vaccines, early study withdrawal, or protocol deviations) was not predefined. Based on the available information, the analysis was performed using a per-protocol efficacy population, reflecting the relative vaccine efficacy by comparing attack rates between groups during the influenza season.

5.3.2.1.3.3. Statistical methods for estimation and sensitivity analysis on primary estimand

Primary Endpoint Analysis Summary

The primary analysis assessed the relative vaccine efficacy (VE) of RIV4 compared to IIV4 in preventing RT-PCR-confirmed, protocol-defined influenza-like illness (ILI) from Day 14 post-vaccination onward.

Analysis Set

The analysis was conducted in the efficacy population, defined as all vaccinated subjects who provided follow-up data for ILI and had no major protocol deviations affecting efficacy assessment.

Statistical Methods

Relative VE was calculated as 1 minus the relative risk (RR), where RR was the ratio of attack rates in the RIV4 and IIV4 groups. The two-sided 95% confidence interval (CI) for VE was derived using the Farrington and Manning score method. Non-inferiority was concluded if the lower bound of the 95% CI exceeded -0.20%.

Multiplicity and Missing Data

No multiplicity adjustments were applied, as only the primary endpoint was formally tested. Missing data were not imputed; subjects with missing data were excluded from the respective analysis (while-on-treatment strategy).

Sensitivity and Supplementary Analyses

No formal sensitivity analyses were performed. Minor clarifications were introduced in the statistical analysis plan, but the primary endpoint and analytical approach remained unchanged from the original protocol.

The primary statistical hypothesis stated that "If non-inferiority is demonstrated, the efficacy of RIV4 will be tested as an exploratory analysis for superiority over licensed IIV4, based on the incidence of RT-PCR- confirmed protocol-defined ILI"

5.3.2.1.3.4. Secondary objectives

1. To compare the protective efficacy in prevention of respiratory illness and influenza infection beginning at least 14 days after vaccination among RIV4 recipients vs. IIV4 recipients using several alternative case definitions
2. To compare immunogenicity of RIV4 vs. IIV4 in a preselected subset of subjects adequate to compare post-vaccination HAI GMTs and seroconversion rates for all four antigens in each study vaccine

5.3.2.1.3.5. Estimands for the secondary objectives

Table 5. Estimand for key secondary objective

Population	Patients aged ≥50 years, enrolled at pre-selected serology sites, who received study vaccine and provided serum samples on Days 0 and 28, and who would not encounter the Intercurrent Event of major protocol deviations affecting immunogenicity assessment under any treatment assignment.
Treatment	Assignment to RIV4, analysed as treated regardless of randomisation and

condition<s>	discontinuation, compared to assignment to IIV4, analysed as treated regardless of randomisation and discontinuation.
Endpoint (variable)	Post-vaccination HAI GMTs and seroconversion rates for all four antigens, at Day 28 post-vaccination.
Population-level summary	Difference in GMTs and difference in seroconversion rates; both evaluated against CBER-specified non-inferiority criteria.

The secondary clinical questions focused on two aspects:

- the comparative protective efficacy of RIV4 versus IIV4 in preventing influenza-related respiratory illness using alternative case definitions, and
- the non-inferiority of immune responses as measured by post-vaccination antibody titres against the four vaccine strains.

Efficacy was assessed based on RT-PCR- or culture-confirmed ILI, applying both protocol-defined and CDC-defined case definitions. Immunogenicity was analysed in a predefined subset of subjects using haemagglutination inhibition (HAI) titres and seroconversion rates (SCRs) on Day 28, according to CBER non-inferiority criteria and regulatory thresholds for accelerated approval.

The estimands for these secondary objectives were not explicitly defined according to ICH E9(R1). Intercurrent events (such as influenza cases before Day 14, missing immunogenicity samples, or major protocol deviations) were addressed by excluding affected subjects from the respective analysis sets. Receipt of non-study influenza vaccines was not specifically handled. As such, while key elements of the estimand were implicitly addressed, no structured approach for intercurrent event handling was pre-specified.

5.3.2.1.3.6. Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary Endpoint Analysis Summary

Secondary endpoints focused on assessing alternative definitions of ILI for efficacy evaluation and comparing immunogenicity outcomes between RIV4 and IIV4. Efficacy endpoints included RT-PCR-confirmed CDC-defined ILI and culture-confirmed ILI due to vaccine-matched strains. Immunogenicity endpoints included post-vaccination haemagglutination inhibition (HAI) geometric mean titres (GMTs) and seroconversion rates (SCRs) for each of the four vaccine antigens.

Analysis Set

Efficacy analyses were performed in the same efficacy population used for the primary endpoint, comprising all vaccinated subjects with valid follow-up from Day 14 and no major protocol deviations. Immunogenicity analyses were based on a predefined subset of participants from selected sites who provided evaluable serum samples on Days 0 and 28 and had no deviations affecting immune assessment.

Statistical Methods

Relative vaccine efficacy for secondary efficacy endpoints was calculated using the same method as for the primary endpoint, based on attack rate ratios with 95% confidence intervals via the Farrington and Manning score method. Immunogenicity comparisons were made using GMT ratios and differences in SCRs. The GMT ratio (IIV4/RIV4) had to remain ≤1.5 and the SCR difference (IIV4 - RIV4) ≤10 percentage points to conclude non-inferiority. GMTs were log-transformed and back-transformed for confidence interval calculation.

Multiplicity and Missing Data

No adjustments for multiplicity were applied, as secondary endpoints were analysed descriptively. Missing data were not imputed; participants with missing values were excluded from the respective analyses.

Sensitivity and Supplementary Analysis

No formal sensitivity analyses were conducted. However, additional recalculations of VE and HAI outcomes using unrounded raw data were performed following FDA request. Post hoc analyses, including reverse cumulative distribution plots of HAI titres, fold-rise calculations, and virus neutralisation tests in a random subset of participants, were conducted in response to CHMP and EMA recommendations. These analyses did not impact the overall interpretation of results.

5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

The first patient was enrolled on 22 October 2014, and the last patient completed the final visit in 22 May 2015. A total of 9,003 participants were enrolled, across 40 sites in the US, and randomised equally to receive either RIV4 or IIV4. Of these, 8,988 received the assigned vaccine. Fifteen randomised participants withdrew before vaccination and were excluded from all analyses. Additionally, 25 vaccinated participants at Site 44 were excluded due to missing documentation verifying which vaccine was administered. The resulting randomised analysis population comprised 8,963 subjects (RIV: 4,474; IIV4: 4,489).

Of the 8,963 randomised participants, 8,604 (RIV4: 4,303; IIV4: 4,301) were included in the primary efficacy analysis. A total of 251 participants (2.8%) were excluded from this analysis due to major protocol deviations, most commonly missing nasopharyngeal swab data during ILI episodes. The analysis was conducted based on treatment received. In total, 314 RIV4 and 300 IIV4 recipients were analysed for the immunogenicity endpoints.

A total of 496 participants (5.5%) did not complete the full 6-month follow-up. Among them, 348 were lost to follow-up and 114 withdrew consent. Seventeen participants discontinued due to adverse events, including 16 deaths. The primary reason for voluntary withdrawal was the perceived burden of study procedures. Discontinuation and withdrawal rates were similar between treatment groups. These figures reflect overall study discontinuation; no separate treatment discontinuation was reported, as treatment consisted of a single vaccination on Day 0.

5.3.2.1.4.2. Deviations from study plan

One protocol amendment was introduced during the study (final version: Protocol v1.1, Amendment 1). However, no substantial changes to the planned study conduct were documented in the clinical study report or supporting materials. The amendment did not affect the study objectives, endpoints, target population, or core procedures. Recruitment, data collection, and follow-up were carried out as initially planned.

5.3.2.1.4.3. Baseline data

The demographic and baseline characteristics were well balanced between the RIV4 and IIV4 groups. There were no notable differences in age distribution, gender, race, or ethnicity. The majority of

participants were white and non-Hispanic, with a slightly higher proportion of females in both groups. The age distribution was consistent with the general U.S. population of adults aged 50 years and older. A detailed overview of baseline characteristics is provided in Table *9* below. No clinically relevant imbalances between treatment arms were observed.

Table 6. PSC12 - Subjects Demographics

Characteristic	**RIV4 N=4328**	**IIV4 N=4344**
Age (years) mean (range)	62.7 (50 – 96)	62.6 (50 - 94)
Age Group n (%)		
50-64 years	2,569 (59.4)	2,617 (60.2)
≥65 years	1,759 (40.6)	1,727 (39.8)
65-74 years	1,234 (28.5)	1,254 (28.9)
≥75 years	525 (12.1)	473 (10.9)
Gender, n (%)		
Male	1,796 (41.5)	1,807 (41.6)
Female	2,532 (58.5)	2,537 (58.4)
Race, n (%)		
Black or African American	773 (17.9)	753 (17.3)
White or Caucasian	3,467 (80.1)	3,493 (80.4)
Other[a]	88 (2.0)	98 (2.3)
Ethnicity, n (%)		
Hispanic	206 (4.8)	219 (5.0)
Non-Hispanic	4,122 (95.2)	4,123 (94.9)
Other	0	2 (0.0)

[a]Other = American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian or other

5.3.2.1.4.4. Outcomes and estimation

The primary efficacy analysis showed that RIV4 was non-inferior to IIV4 in preventing RT-PCR-confirmed, protocol-defined ILI from 14 days post-vaccination. The attack rate was 2.2% for RIV4 vs. 3.2% for IIV4, corresponding to an rVE of 30% (95% CI: 10%, 47%) (see Table *7*).

Table 7. PSC12 - Relative Vaccine Efficacy for RT-PCR-confirmed Protocol-defined ILI* - Efficacy Population (Primary Analysis)

RIV4 (N=4,303)		IIV4 (N=4,301)			
n	Attack Rate (%)	n	Attack Rate (%)	RR	rVE (95% CI)
96	2.2	138	3.2	0.70	30 (10, 47%)

*Meets case definition of protocol-defined influenza-like illness: At least one of the following respiratory symptoms (sore throat, cough, sputum production, wheezing, difficulty breathing) accompanied by at least one of the following systemic symptoms (temperature of >37.2º C, chills, fatigue, headache, myalgia).

Secondary analyses using alternative case definitions confirmed these findings. For culture-confirmed protocol-defined ILI, rVE was 43% (95% CI: 21%, 59%) with 58 cases (1.3% attack rate) versus 101 cases (2.3% attack rate) in the RIV4 and IIV4 respectively; and for RT-PCR-confirmed CDC-defined ILI, rVE was 35% (95% CI: 8%, 54%). Protection was primarily driven by efficacy against influenza A (rVE 36%, 95% CI: 14%, 53%), while efficacy against influenza B was low and inconclusive (Table *8*).

Table 8. PSC12 - rVE against RT-PCR-confirmed Protocol-defined ILI caused by Influenza A and B

	RIV4 (N=4,303)		IIV4 (N=4,301)			
Type	n	Attack Rate (%)	n	Attack Rate (%)	RR	rVE (95% CI)
Influenza A	73	1.7	114	2.7	0.64	36 (14, 53%)
Influenza B	23	0.5	24	0.6	0.96	4 (-72, 46%)

Immunogenicity analyses showed non-inferiority of RIV4 for A/H3N2 and B/Massachusetts (SCR and GMR), but not for A/H1N1 and B/Brisbane(cf. Table *9* and Table *10*).

Table 9. PSC12: Comparison of post-vaccination HAI GMTs – Adults ≥ 50 years of age

Antigen	**Visit**	**RIV4** (N=314) GMT (95% CI)	**IIV4** (N=300) GMT (95% CI)	**GMR** (95% CI)
A/H1N1/California	Day 0	44 (38, 51)	48 (41, 56)	1.15 (0.95, **1.41*)**
	Day 28	190 (164, 221)	220 (193, 250)	
A/H3N2/Texas	Day 0	87 (73, 103)	98 (83, 117)	0.69 (0.58, **0.81)**
	Day 28	522 (462, 589)	358 (318, 404)	
B/Massachusetts	Day 0	17 (15, 20)	18 (16, 21)	1.03 (0.86; **1.24)**
	Day 28	55 (48, 64)	57 (51, 65)	
B/Brisbane	Day 0	14 (12, 15)	14 (13, 16)	1.47 (1.23; 1.76)
	Day 28	29 (26, 33)	43 (38, 49)	

*Figures in bold meet criterion for non-inferiority

Note: For the HAI analyses in both studies PSC12 and PSC16, it was identified by CBER that intermediate rounding steps were done (e.g., rounding with one decimal digit after log-transformation). In order to obtain accurate computations, CBER requested to redo analyses without intermediate rounding (log10 and fold rise). The results are presented in the Table above.

Table 10. PSC12: HAI seroconversion rates – Adults ≥ 50 years of age

Antigen	**RIV4** (N=314) N (%)	**IIV4** (N=300) N (%)	**Difference** (95% CI)
A/H1N1/California	141 (44.9; 95% CI 39.3, 50.6)	147 (49.0; 95% CI: 43.2, 54.8)	4.1 (-3.8, 12.0)
A/H3N2/Texas	171 (54.5; 95% CI: 48.8, 60.1)	130 (43.3; 95% CI:37.6, 49.1)	-11.1 (-19.0, **-3.3***)
B/Massachusetts	122 (38.9; 95% CI: 33.4, 44.5)	115 (38.3; 95% CI: 32.8, 44.1)	-0.5 (-8.2, **7.2**)
B/Brisbane	66 (21.0; 95% CI: 16.6, 25.9)	103 (34.3; 95% CI: 29.0, 40.0)	13.3 (6.3, 20.3)

*Figures in bold meet criterion for non-inferiority

Note: For the HAI analyses in both studies PSC12 and PSC16, it was identified by CBER that intermediate rounding steps were done (e.g., rounding with one decimal digit after log-transformation). In order to obtain accurate computations, CBER requested to redo analyses without intermediate rounding (log10 and fold rise). The results are presented in the Table above.

HAI seroconversion rates were calculated by Age Category and several other pre-specified subsets. These analyses are documented in eCTD section 5.3.5.3. Seroconversion rates were calculated for each antigen in the two age categories (50-64 and ≥65 years) in an exploratory analysis. For both groups, the SCR met the CBER criterion (lower bound of two-sided 95% CI ≥40%) for A/California and A/Texas in the 50-64 years age subset and came somewhat close for B/Massachusetts. SCR for 50-64 years old subjects did not pass for B/Brisbane in both treatment groups. In the ≥65 years age subset, only the SCR for RIV4 against A/Texas met the CBER licensure criterion (lower bound of the 95% CI ≥30%). IIV4 did not meet the criterion for any of the four antigens in this age group.

5.3.2.1.4.5. Ancillary analyses

Ancillary analyses included post hoc recalculations of rVE and HAI immunogenicity endpoints based on raw, unrounded data following a request by the FDA during BLA review. Additional post hoc evaluations were performed in line with CHMP (2014) and EMA recommendations, including fold-rise analyses, reverse cumulative distribution curves, and influenza virus neutralisation testing (NT) in a subset of subjects. These analyses are documented in eCTD sections 5.3.5.3 and 5.3.5.4 and provide supportive context for interpretation of the humoral immune response.

One of these post-hoc analysis were HAI post/pre-HAI titre ratios as per the below table.

Table 11: GMTR % response to Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) for each strain in adults≥ 50 years of age - Immunogenicity analysis set

	Adults ≥ 50 years of age N=314
GMTR % (95% CI)	
A/California/7/2009 (H1N1)	4.31 (3.71; 5.02)
A/Texas/50/2012 (H3N2)	6.01 (5.03; 7.18)
B/Massachusetts/02/2012 (Yamagata lineage)	3.18 (2.81; 3.59)
B/Brisbane/60/2008 (Victoria lineage)	2.16 (1.94; 2.40)

5.3.2.2. PSC16

5.3.2.2.1. Study title

Double-Blind, Randomised, Active-Controlled Comparison of the Immunogenicity and Safety of Flublok Quadrivalent versus IIV4 in Healthy, Medically Stable Adults 18-49 Years of Age

5.3.2.2.2. Study design

The study was a double-blind, randomised, active-controlled, parallel design Phase 3 multi-centre clinical trial designed to compare the immunogenicity, reactogenicity and safety of Flublok Quadrivalent with that of US-authorised IIV4 administered during the 2014-2015 influenza vaccination season.

5.3.2.2.2.1. Treatment

Subjects received a single 0.5 mL intramuscular dose of either RIV4 (180 µg rHA; 45 µg per strain) or IIV4 (60 µg HA; 15 µg per strain). Both vaccines targeted the same four seasonal influenza strains. No booster doses or concomitant vaccinations were administered.

5.3.2.2.2.2. Randomisation

A total of 1,350 subjects were randomised in a 3:1 ratio (RIV4:IIV4) via an interactive web response system on Day 0.

5.3.2.2.2.3. Blinding

The trial used an observer-blind design. Vaccine administrators were unblinded but not involved in any subsequent assessments. All other study staff and participants remained blinded to treatment allocation throughout the study. No emergency unblinding procedures were reported.

5.3.2.2.2.4. Patient population

The study enrolled healthy, ambulatory adults aged 18 to 49 years at ten clinical sites across the United States. Subjects were required to be medically stable and capable of complying with study procedures. Women of childbearing potential had to test negative for pregnancy immediately prior to vaccination. Individuals were excluded if they had a history of severe reactions to influenza vaccines, contraindications to either study vaccine, immunocompromising conditions or therapies, or recent participation in other clinical trials or vaccination programs.

The study did not specifically target or exclude special populations beyond standard safety exclusions. No diagnostic tools were used for eligibility screening. Recruitment was aimed at a general adult population within the specified age range, with no planned population enrichment. Safety oversight included predefined halting rules for severe reactogenicity or unexpected, related SAEs, which were not triggered.

5.3.2.2.3. Objectives and estimands

5.3.2.2.3.1. Primary objective

The primary objective of study PSC16 was to demonstrate non-inferior immunogenicity of Flublok Quadrivalent (RIV4) compared to an authorised quadrivalent inactivated influenza vaccine (IIV4) with respect to the four included influenza antigens. Specifically, non-inferiority was assessed based on:

- the ratio of post-vaccination haemagglutination inhibition (HAI) geometric mean titres (GMTs), and
- the difference in HAI seroconversion rates (SCRs),

for each of the four influenza strains included in the vaccines.

5.3.2.2.3.2. Estimand for the primary objective

Table 12. Estimand for primary objective

Population	Patients aged 18–49 years in good general health who would not encounter major protocol deviations affecting immunogenicity results under any treatment assignment.
Treatment condition<s>	Assignment to RIV4, regardless of discontinuation, compared to assignment to IIV4, regardless of discontinuation.
Endpoints (variable)	HAI seroconversion rate (i) and HAI geometric mean titre (GMT) (ii) at Day 28 post-vaccination.
Population-level summary	Difference in seroconversion rates (SCR) and ratio of post-vaccination GMTs (RIV4/IIV4).

The clinical question of interest was whether RIV4 induces an immune response that is non-inferior to that of an authorised IIV4 in healthy adults aged 18–49 years. Immune response was assessed using haemagglutination inhibition (HAI) titres as a surrogate endpoint for clinical protection. Specifically, the focus was on comparing post-vaccination HAI geometric mean titres (GMTs) and seroconversion rates (SCRs) at Day 28 for each vaccine strain.

The estimand for the primary objective was not formally defined in accordance with the ICH E9(R1) framework. The study protocol did not specify strategies for handling intercurrent events such as protocol deviations, missing immunogenicity samples, or receipt of non-study influenza vaccines. Nonetheless, the available information indicates that the analysis was conducted in a per-protocol immunogenicity population and that the endpoints were based on laboratory-confirmed post-vaccination antibody titres measured at a predefined timepoint (Day 28). The effect measure was based on group-wise comparisons of GMT ratios and SCRs to determine non-inferiority for each antigen.

5.3.2.2.3.3. Statistical methods for estimation and sensitivity analysis on primary estimand

Primary Endpoint Analysis Summary

The primary objective was to demonstrate non-inferiority of RIV4 compared to IIV4 with respect to immunogenicity at Day 28 post-vaccination. The co-primary endpoints were seroconversion rates (SCR) and post-vaccination geometric mean titres (GMTs) for each of the four influenza strains

included in the vaccine. Non-inferiority was concluded only if all eight comparisons (SCR and GMT for each strain) met the predefined statistical criteria.

Analysis Set

The primary analysis was performed on the immunogenicity population, comprising all randomised subjects who received a study vaccine, had valid pre- and post-vaccination HAI titres within the defined time windows, and had no major protocol deviations likely to affect the immune response. Subjects were analysed according to the vaccine actually received.

Statistical Methods

SCR non-inferiority was assessed by calculating the two-sided 95% confidence interval for the difference (IIV4 – RIV4); non-inferiority was confirmed if the upper bound was ≤10%. For GMTs, the GMT ratio (IIV4/RIV4) was calculated, and non-inferiority was met if the upper bound of the 95% confidence interval was ≤1.5. All eight co-primary comparisons had to meet their respective criteria for overall success. No interim analyses were conducted.

Multiplicity and Missing Data

No multiplicity adjustment was applied across the eight co-primary endpoints, as all comparisons were required to meet non-inferiority criteria. Missing data were not imputed; only subjects with complete HAI data at baseline and Day 28 were included in the analysis.

Sensitivity and Supplementary Analyses

A per-protocol sensitivity analysis was conducted to confirm the robustness of the primary findings. No deviations from the planned statistical approach were made, and no unplanned or post hoc efficacy analyses were performed.

5.3.2.2.3.4. Secondary objectives

The secondary immunogenicity objective of study PSC16 was to evaluate the HAI seroconversion rates and proportion of subjects with a post-vaccination HAI titre ≥40 (%≥40) for the four rHA antigens contained in the quadrivalent formulation with respect to CBER criteria for licensure under accelerated approval regulations.

5.3.2.2.3.5. Estimands for the secondary objectives

Table 13. Estimand for key secondary objective

Population	Patients aged 18–49 years who would not encounter protocol deviations affecting immunogenicity data under any treatment assignment.
Treatment condition	Assignment to RIV4, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects achieving (i) HAI titre ≥40 and (ii) seroconversion at Day 28 for each vaccine strain.
Population-level summary	Proportion with 95% confidence intervals per CBER criteria (lower bound ≥70% for %≥40; ≥40% for SCR).

The clinical question of interest was whether a single dose of RIV4 induces an immune response sufficient to meet predefined licensure criteria in adults aged 18–49 years, as set out by CBER for

accelerated approval of seasonal influenza vaccines. These criteria serve as surrogate endpoints for vaccine efficacy and are based on:

- the proportion of subjects achieving HAI titres ≥1:40, and
- the seroconversion rate (SCR) per antigen.

These surrogate markers are accepted in regulatory practice as surrogates of protection for influenza vaccines. A response is considered sufficient if the lower bound of the 95% confidence interval is ≥70% for the % ≥40 and ≥40% for the SCR.

The estimands for these secondary objectives were not explicitly defined according to ICH E9(R1). Intercurrent events (such as influenza cases before Day 14, missing immunogenicity samples, or major protocol deviations) were addressed by excluding affected subjects from the respective analysis sets. Receipt of non-study influenza vaccines was not specifically handled. As such, while key elements of the estimand were implicitly addressed, no structured approach for intercurrent event handling was pre-specified.

5.3.2.2.3.6. Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary Endpoint Analysis Summary

Secondary immunogenicity endpoints included the proportion of subjects achieving HAI titres ≥1:40 and seroconversion rates (SCRs) according to CBER criteria for accelerated approval. These endpoints were evaluated descriptively to provide additional context to the co-primary immunogenicity findings. No formal hypothesis testing was applied, and results were not used to establish non-inferiority.

Analysis Set

Secondary endpoints were analysed in the same immunogenicity population used for the primary analysis. This population included all randomised subjects who received the study vaccine, had valid HAI titres at baseline and Day 28 within protocol-defined windows, and no major protocol deviations affecting immunogenicity.

Statistical Methods

Secondary analyses were descriptive. The proportion of subjects achieving post-vaccination HAI titres ≥1:40 and the SCRs were calculated for each vaccine strain. No confidence intervals or statistical comparisons were used to interpret these outcomes in a formal inferential framework.

Multiplicity and Missing Data

No adjustment for multiplicity was applied to secondary endpoints. Only subjects with complete serological data were included; missing values were not imputed.

Sensitivity and Supplementary Analysis

A per-protocol analysis of secondary endpoints was conducted to confirm consistency with the main results. No additional sensitivity or subgroup analyses were planned beyond descriptive summaries by gender, race, and ethnicity as per regulatory requirements. No protocol deviations or changes impacted the analysis of secondary endpoints.

5.3.2.2.4. Results

5.3.2.2.4.1. Participant flow and numbers analysed

Recruitment for study PSC16 took place between 22 October 2014 and 14 May 2015 across ten clinical sites in the United States. Immunogenicity follow-up was completed by 18 December 2014.

A total of 1,417 subjects were screened, of whom 1,350 were randomised in a 3:1 ratio to receive either RIV4 (n=1,011) or IIV4 (n=339). One subject in the IIV4 group withdrew consent prior to vaccination and did not receive study treatment. Thus, 1,349 subjects received the allocated vaccine.

All vaccinated participants were followed through Day 28 for immunogenicity assessment. Blood samples for HAI testing at both Day 0 and Day 28 within the protocol-defined windows were available for 1,316 participants (RIV4: n=975; IIV4: n=341), who comprised the immunogenicity analysis set. A total of 34 subjects were excluded due to missing or out-of-window serology or major protocol deviations with potential impact on the immune response.

There were no treatment discontinuations, as the intervention consisted of a single-dose vaccination. No subjects discontinued follow-up prematurely, and no rescue treatments, early escape procedures, or interim analyses were applied. The analysis was conducted based on actual treatment received (as-treated principle).

No intercurrent events affecting the primary objective were reported. Data points were included or excluded according to predefined criteria in the statistical analysis plan, based on a complete-case (while-on-treatment) strategy. The median follow-up time at the data cut-off was 28 days.

5.3.2.2.4.2. Deviations from study plan

No substantial changes to the planned conduct of the study affecting immunogenicity assessments were made during the trial. The protocol was implemented as approved, and no amendments relevant to efficacy endpoints occurred. All immunogenicity-related procedures, including blood sampling, assay methodology, and visit scheduling, were conducted in accordance with the protocol. No GCP inspection findings related to efficacy data were reported. Protocol compliance was high, with only 2.6% of randomised subjects excluded from the immunogenicity population due to major deviations.

5.3.2.2.4.3. Baseline data

Demographic and baseline characteristics were well balanced between the RIV4 and IIV4 groups. The mean age was approximately 33 years in both groups, with a similar distribution of sex, race, and ethnicity. A detailed overview of baseline characteristics is provided in Table *14* below. No clinically relevant asymmetries were observed across treatment arms. All subjects were healthy adults aged 18 to 49 years, consistent with the inclusion criteria. There were no baseline imbalances expected to impact immunogenicity outcomes, albeit females are slightly overrepresented in this study (approx. 65% in both cohorts), and Black/African Americans are somewhat more frequent (approx. 36%) than in study PSC12 or study PSC04 (both approx. 18%).

Table 14. PSC16 - Subjects Demographics

Characteristic	RIV4 N=998	IIV4 N=332
Age (years) mean (range)	33.3 (18 – 50)	34.0 (18 - 49)
Gender, n (%)		
Male	359 (36.0)	110 (33.1)
Female	639 (64.0)	222 (66.9)
Race, n (%)		
American Indian or Alaska Native	7 (0.7)	3 (0.9)
Asian	3 (0.3)	4 (1.2)
Black or African American	376 (37.7)	114 (34.3)
Native Hawaiian/ Pacific Islander	11 (1.1)	2 (0.6)
White or Caucasian	589 (59.0)	202 (60.8)
Other	12 (1.2)	7 (2.1)
Ethnicity, n (%)		
Hispanic	162 (16.2)	57 (17.2)
Non-Hispanic	836 (83.8)	275 (82.8)

5.3.2.2.4.4. Outcomes and estimation

Immunogenicity outcomes were assessed 28 days after a single dose of either RIV4 or IIV4. The co-primary endpoints were HAI geometric mean titres (GMTs) and seroconversion rates (SCRs) for all four vaccine strains. Non-inferiority was concluded for a given strain if the upper bound of the 95% confidence interval (CI) for the GMT ratio (IIV4/RIV4) was ≤1.5 and for the difference in SCRs (IIV4 - RIV4) was ≤10%.

Baseline GMTs were similar between groups. At Day 28, GMT increases were observed for all strains in both groups. For A/H1N1, A/H3N2, and B/Massachusetts, RIV4 met the non-inferiority criterion for both GMTs and SCRs. For B/Brisbane (B/Victoria lineage), non-inferiority was not met, with the upper bound of the 95% CI exceeding the margin for both endpoints. Full results are presented in Table *15* and Table 16.

Table 15. PSC16 – Pre- and Post-vaccination HAI GMTs – Immunogenicity population

Antigen	Visit	RIV4 N=969	IIV4 N=323	GMR	95% CI for GMR
A/H1/California	Day 0	59 (54, 65)	53 (45, 63)	0.81	(0.71, 0.92)
	Day 28	493 (460, 527)	397 (358, 441)		
A/H3/Texas	Day 0	74 (68, 82)	70 (60, 81)	0.50	(0.44, 0.57)
	Day 28	748 (700, 800)	377 (341, 417)		
B/Massachusetts	Day 0	26 (24, 29)	24 (21, 28)	0.86	(0.74, 0.99)

	Day 28	156 (145, 168)	134 (119, 151)		
B/Brisbane	Day 0	12 (11, 13)	11 (10, 12)	1.49	(1.29, 1.71)
	Day 28	43 (40, 46)	64 (57, 71)		

Source: 5.3.5.3 PSC16 Recalculation for Immunogenicity following FDA request, Table 14.2.1.1.1

Table *16*: PSC16 - HAI Seroconversion Rates at Day 28 – Immunogenicity population

Antigen	Parameter	RIV4 N=969	IIV4 N=323	Difference	95% CI for Difference
A/H1/California	n (%)	646 (66.7)	205 (63.5)	-3.2	(-9.2, 2.8)
	95% CI	(63.6, 69.6)	(58.0, 68.7)		
A/H3/Texas	n (%)	699 (72.1)	184 (57.0)	-15.2	(-21.3, -9.1)
	95% CI	(69.2, 74.9)	(51.4, 62.4)		
B/Massachusetts	n (%)	578 (59.6)	195 (60.4)	0.7	(-5.4, 6.9)
	95% CI	(56.5, 62.8)	(54.8, 65.7)		
B/Brisbane	n (%)	393 (40.6)	188 (58.2)	17.6	(11.4, 23.9)
	95% CI	(37.4, 43.7)	(52.6, 63.6)		

For A/H3N2, RIV4 showed a statistically significant advantage in SCR compared to IIV4, with the upper bound of the 95% CI for the difference below zero. In contrast, for B/Brisbane, immunogenicity in the RIV4 group was consistently lower across GMTs, SCRs, and the proportion of subjects achieving titres ≥40. For this strain, the proportion with titres ≥40 was 64.3% in the RIV4 group vs. 79.6% in the IIV4 group, with non-overlapping CIs, confirming reduced immunogenicity for this component in the RIV4 formulation.

5.3.2.2.4.5. Ancillary analyses

Ancillary analyses included post hoc recalculations of GMT and SCR values for study PSC16 following requests by FDA and EMA during the evaluation of Supemtek Tetra, to avoid intermediate rounding during log transformation and fold-rise calculations. These revised results are presented throughout this report and reflect the final dataset used for regulatory assessment (eCTD section 5.3.5.3). Additional complementary analyses were conducted in line with EMA guideline EMA/CHMP/VWP/457259/2014, including descriptive fold-rise summaries, reverse cumulative distribution curves, and neutralisation assays. Virus neutralising antibody responses were evaluated in a random subset of 100 participants per group, as documented in Table 17.

Table 17. PSC16 – Summary of seroneutralisation antibody response - Immunogenicity population

Influenza A		RIV4 (N=100)		IIV4 (N=100)	
		A/H1	A/H3	A/H1	A/H3
Pre-vaccination	M	100	100	100	100
	GMT [95% CI]	301 [200; 454]	97.0 [76.3; 123]	307 [213; 444]	81.6 [64.3; 104]
	Titres <10 n (%) [95% CI]	9 (9.0) [4.2; 16.4]	1 (1.0) [0.0; 5.4]	6 (6.0) [2.2; 12.6]	2 (2.0) [0.2; 7.0]
	Titres ≥40 n (%) [95% CI]	83 (83.0) [74.2; 89.8]	79 (79.0) [69.7; 86.5]	83 (83.0) [74.2; 89.8]	71 (71.0) [61.1; 79.6]

	M	100	99	100	98
	GMT [95% CI]	5,552 [4,201; 7,338]	736 [601; 900]	2,850 [2,317; 3,505]	324 [272; 386]
Post-vaccination	**Titres <10 n (%) [95% CI]**	0 (0.0) [0.0; 3.6]	0 (0.0) [0.0; 3.7]	0 (0.0) [0.0; 3.6]	0 (0.0) [0.0; 3.7]
	Titres ≥40 n (%) [95% CI]	99 (99.0) [94.6; 100.0]	99 (100.0) [96.3; 100.0]	100 (100.0) [96.4; 100.0]	96 (98.0) [92.8; 99.8]
	M	100	99	100	98
	GMR [95% CI]	18.4 [12.4; 27.5]	7.55 [5.69; 10.0]	9.27 [6.37; 13.5]	3.98 [3.21; 4.94]
Post/Pre-vaccination	**2-fold rise n (%) [95% CI]**	83 (83.0) [74.2; 89.8]	79 (79.8) [70.5; 87.2]	74 (74.0) [64.3; 82.3]	65 (66.3) [56.1; 75.6]
	4-fold rise n (%) [95% CI]	73 (73.0) [63.2; 81.4]	61 (61.6) [51.3; 71.2]	55 (55.0) [44.7; 65.0]	40 (40.8) [31.0; 51.2]
Influenza B		**RIV4** (N=100)		**IIV4** (N=100)	
		B/Victoria	**B/Yamagata**	**B/Victoria**	**B/Yamagata**
	M	100	100	100	100
	GMT [95% CI]	231 [166; 319]	235 [174; 319]	221 [171; 284]	205 [156; 270]
Pre-vaccination	**Titres <10 n (%) [95% CI]**	3 (3.0) [0.6; 8.5]	3 (3.0) [0.6; 8.5]	0 (0.0) [0.0; 3.6]	4 (4.0) [1.1; 9.9]
	Titres ≥40 n (%) [95% CI]	87 (87.0) [78.8; 92.9]	89 (89.0) [81.2; 94.4]	89 (89.0) [81.2; 94.4]	89 (89.0) [81.2; 94.4]
	M	100	100	100	100
	GMT [95% CI]	1,364 [1,073; 1,733]	1,923 [1,522; 2,430]	2,364 [1,966; 2,843]	1,344 [1,077; 1,677]
Post-vaccination	**Titres <10 n (%) [95% CI]**	0 (0.0) [0.0; 3.6]	0 (0.0) [0.0; 3.6]	0 (0.0) [0.0; 3.6]	0 (0.0) [0.0; 3.6]
	Titres ≥40 n (%) [95% CI]	99 (99.0) [94.6; 100.0]	100 (100.0) [96.4; 100.0]	100 (100.0) [96.4; 100.0]	100 (100.0) [96.4; 100.0]
	M	100	100	100	100
	GMR [95% CI]	5.91 [4.49; 7.78]	8.17 [5.98; 11.2]	10.7 [8.01; 14.3]	6.54 [4.96; 8.63]
Post/Pre-vaccination	**2-fold rise n (%) [95% CI]**	70 (70.0) [60.0; 78.8]	79 (79.0) [69.7; 86.5]	86 (86.0) [77.6; 92.1]	73 (73.0) [63.2; 81.4]
	4-fold rise n (%) [95% CI]	54 (54.0) [43.7; 64.0]	57 (57.0) [46.7; 66.9]	65 (65.0) [54.8; 74.3]	56 (56.0) [45.7; 65.9]

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with available data for the considered endpoint

Pre- and post-vaccination sera were analysed for all four vaccine strains. At baseline, GMTs were broadly comparable between groups, though slightly higher for A/H1 and A/H3 in the RIV4 group. All subjects had detectable neutralising titres at Day 28 post-vaccination, and post-vaccination GMTs increased across all strains.

One of these post-hoc analysis were HAI post/pre-HAI titre ratios as per the below table.

Table *18.*: GMTR % response to Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) for each strain in adults 18 to 49 years of age - Immunogenicity analysis set

	Adults 18-49 years of age N=969
GMTR % (95% CI)	
A/California/7/2009 (H1N1)	8.35 (7.59; 9.19)
A/Texas/50/2012 (H3N2)	10.1 (9.12; 11.1)
B/Massachusetts/02/2012 (Yamagata lineage)	5.89 (5.43; 6.40)
B/Brisbane/60/2008 (Victoria lineage)	3.59 (3.35; 3.85)

For the A/H1 and A/H3 strains, GMTs and GMR were higher in the RIV4 group compared to IIV4. This trend was also reflected in the proportion of subjects with ≥2-fold and ≥4-fold rises in neutralising titres. For B/Yamagata, responses were comparable between groups. For B/Victoria, GMT and GMR values were higher in the IIV4 group, with non-overlapping confidence intervals. However, the proportions of subjects with ≥2-fold and ≥4-fold titre rises were comparable between groups, as indicated by overlapping confidence intervals.

5.3.2.3. VAP00027

5.3.2.3.1. Study 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

5.3.2.3.2. Study design

Phase III, non-randomised, open-label, uncontrolled, multi-centre study with

- an active phase from Visit 1 (Day 1) until completion of Visit 2 (Day 29). A phone call to participants was also planned at Day 9;
- a 6-month safety follow-up period from completion of Visit 2 (Day 29) until 6 months after Visit 1 (at Day 181), performed by interviewing participants over the phone.

5.3.2.3.2.1. Treatment

Single dose injection of Quadrivalent Recombinant Influenza Vaccine (RIV4 season/2022-2023/NH) into the deltoid muscle of the upper arm, corresponding to 45 µg of HA of each of the following strains per dose:

- A/H1N1 strain: A/Wisconsin/588/2019
- A/H3N2 strain: A/Darwin/6/2021
- B/Victoria lineage strain: B/Austria/1359417/2021
- B/Yamagata lineage strain: B/Phuket/3073/2013

5.3.2.3.2.2. Randomisation

No randomisation

5.3.2.3.2.3. Blinding

No blinding

5.3.2.3.2.4. Patient population

The study was conducted in healthy participants 9 to 49 years of age at 36 centres in Europe and the United States. Individuals who received any vaccine in the 4 weeks preceding the study vaccination or who planned to receive any vaccine in the 4 weeks following the study vaccination (except for coronavirus disease 2019 [COVID-19] vaccination, which may be received at least 2 weeks before study intervention) were excluded. Individuals who received vaccination against influenza (either with the study vaccine or with another vaccine) in the 6 months preceding enrolment were excluded. Further inclusion/exclusion criteria are defined in VAP00027 Protocol Version 2.0.

5.3.2.3.3. Objectives and estimands

5.3.2.3.3.1. Primary objective

The primary immunogencity objective in Study VAP00027 was 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.

5.3.2.3.3.2. Estimand for the primary objective

Table 19. Estimand for key primary objective

Population	Healthy participants 9 to 49 years of age who would not encounter major protocol deviations affecting immunogenicity results.
Treatment condition<s>	RIV4
Endpoints (variable)	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)
Population-level summary	Difference in ratio of post-vaccination GMTs and seroconversion rates (SCR) (9-17 yoa/18-49 yoa,

Intercurrent events and strategy to handle them	
Violation of inclusion/exclusion criteria	Principle stratum strategy. Exclusion of participant from analysis as per the Per Protocol Analysis Set
Not vaccinated or not vaccinated according to schedule	
Vaccine preparation / administration not according to protocol	
Serological sample not collected in sampling window (D26 to D39)	
Protocol-prohibited medications with potential impact on immune response	

The clinical question of interest was to assess the non-inferior HAI immune response of a single dose of RIV4 against the 4 strains in children/adolescents aged 9 to 17 years compared to adults aged 18 to 49 years 28 days after vaccination. Intercurrent events were handled per principle stratum strategy.

Exclusion of participants from analysis was performed according to per protocol analysis set definition. For the derivation of immunogenicity endpoints, no imputation of missing values and no search for outliers was performed. For the analysis of the results of HAI assay, extreme values were managed according to lower or upper limit of quantification (LLOQ or ULOQ) policy, respectively.

5.3.2.3.3.3. Statistical methods for estimation and sensitivity analysis on primary estimand

The per-protocol analysis set was used as the primary analysis set for the primary objective. Immunogenicity parameters were 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. For each strain, the NI methodology was applied to compare the post-vaccination GMTs and the SC rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis. The primary analysis was conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains was demonstrated, then NI of the SC rates (4 strains) was tested.

No imputation of missing values and no search for outliers was performed.

No statistical adjustment for the interim analysis (immunogenicity based on the HAI data collected within 28 days after vaccination) was necessary because there were no repeated analyses of the same hypotheses.

No formal sensitivity analysis was performed.

5.3.2.3.3.4. Secondary objectives

The secondary immunogenicity objective in study VAP00027 was to summarise the HAI immune response induced by RIV4 in all participants.

5.3.2.3.3.5. Estimands for the secondary objectives

Table *20*. Estimand for clinical immunogenicity secondary objective

Population	Healthy participants 9 to 49 years of age who would not encounter major protocol deviations affecting immunogenicity results
Treatment condition	RIV4
Endpoint (variable)	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).
Population-level summary	Relative risk reduction (vaccine efficacy), calculated as 1 – RR with 95% confidence interval

The clinical question of interest was to assess the individual HAI immune response including seroconversion after a single dose of RIV4 against the 4 strains in children/adolescents aged 9 to 17 years and in adults aged 18 to 49 years 28 days after vaccination. Intercurrent events were handled

per principle stratum strategy. Exclusion of participants from analysis was performed according to per protocol analysis set definition. For the derivation of immunogenicity endpoints, no imputation of missing values and no search for outliers was performed. For the analysis of the results of HAI assay, extreme values were managed according to lower or upper limit of quantification (LLOQ or ULOQ) policy, respectively.

5.3.2.3.3.6. Statistical methods for estimation and sensitivity analysis on the secondary estimands

No imputation of missing values and no search for outliers was performed.

For the secondary immunogenicity objective, the analysis was conducted for each immunogenicity variable on the PPAS, and on FAS if the attrition rate from FAS to PPAS is greater than 10%.

5.3.2.3.4. Results

5.3.2.3.4.1. Participant flow and numbers analysed

The study started with enrolment on 27 October 2022 and lasted until 27 October 2023 (last contact last participant; end of study). A total of 1308 subjects (648 aged 9 to 17 years and 660 aged 18 to 49 years) were enrolled. Of the total number enrolled, 1264 subjects (96.6%) completed the active phase of the study: 629 subjects (97.1%) in the 9 to 17 years group and 635 subjects (96.2%) in the 18 to 49 years group. The number and percentages of those included in the PPAS and FAS are presented in Table 21.

Table 21: Participant disposition

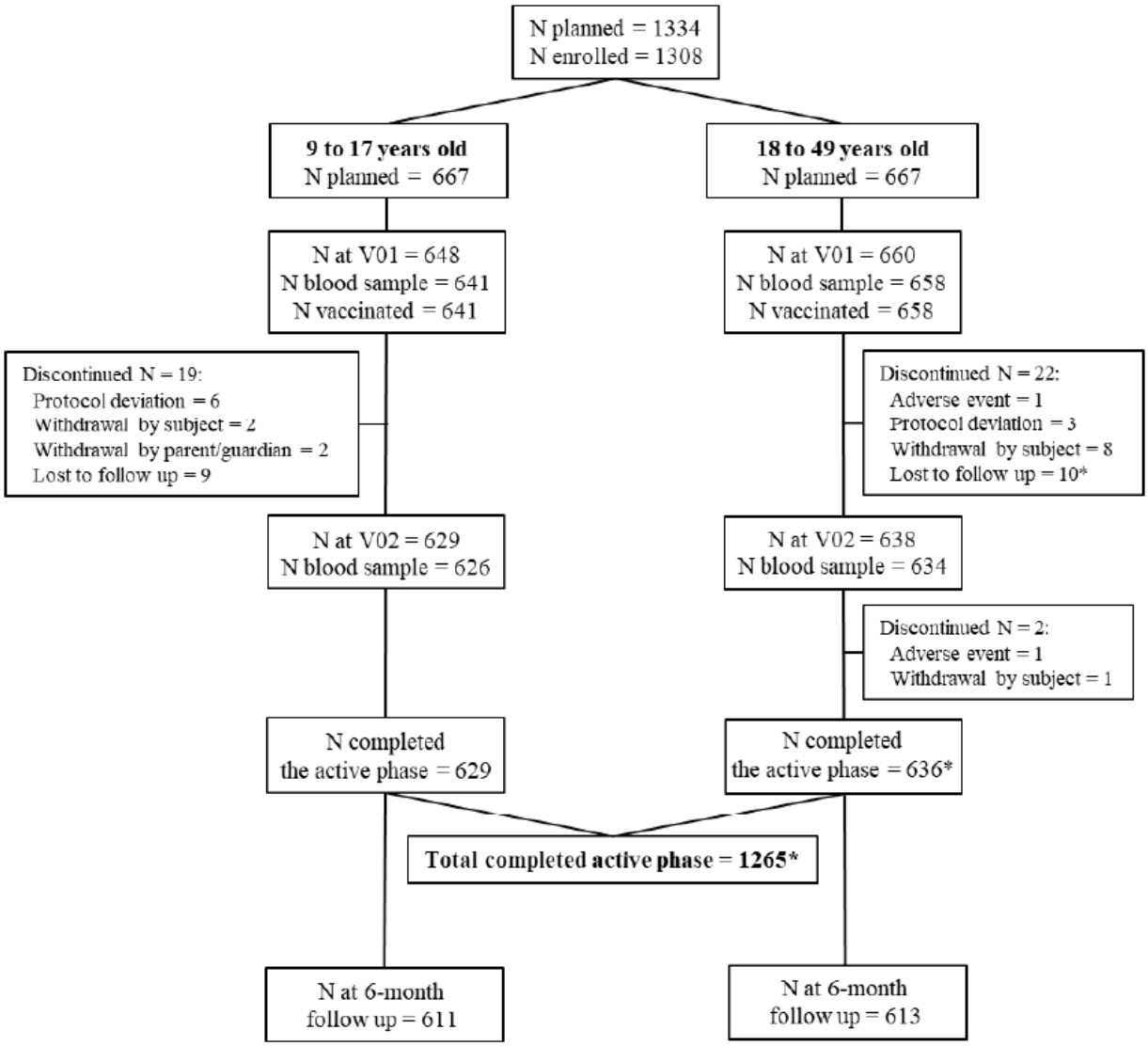
	9 to 17 years (N=648) n (%)	18 to 49 years (N=660) n (%)	All (N=1308) n (%)
Full Analysis Set (FAS)	626 (96.6)	634 (96.1)	1260 (96.3)
Not injected	7 (1.1)	2 (0.3)	9 (0.7)
Did not provide a post-dose serology sample	22 (3.4)	26 (3.9)	48 (3.7)
Per-protocol analysis set (PPAS)	609 (94.0)	606 (91.8)	1215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

n: number of study subjects fulfilling the item listed

The immunogenicity population (PPAS; N=1215) included 609 subjects in the 9 to 17 years group and 606 subjects in the 18 to 49 years group. The PPAS included all participants enrolled and vaccinated. Participants 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.

The attrition rate from FAS to PPAS was lower than 10%; therefore, the statistical outputs in the FAS were not produced. The most common protocol deviation leading to exclusion from the PPAS was "Participant did not provide the post-dose serology sample at visit 2 in the proper time window ([D26, D39]) or a post-dose serology sample was not drawn" for 78 participants (6.0%), followed by "Participant received protocol-prohibited medications impacting or that may have an impact on the immune response" for 18 participants (1.4%), and "Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria" for 8 participants (0.6%).

Figure *1*. Participant flow



* 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.

5.3.2.3.4.2. Deviations from study plan

- *Addition of a complementary analysis to assess the difference in enrolment period between age groups*

The recruitment of children and adolescents from 9 to 17 years was revealed harder than the recruitment of adults from 18 to 49 years. Hence, the last adult was enrolled on January, 5th 2023, whereas last participant from 9 to 17 years was enrolled on April, 28th 2023. To assess the impact of this delay in recruitment of participants from both age groups, a complementary analysis was performed by describing the main immunogenicity endpoints in the period where participants from both age groups were enrolled (i.e., with all participants with D01 date until January, 5th 2023).

- *Clarification of statistical blood visit window*

The Blood visit window was increased at statistical analysis level to address operational constraints whilst maintaining clinical relevance of the immunology read-outs.

- *Clarification on conducting the supportive statistical analyses on the Full Analysis Set (FAS) population, if the attrition rate from FAS to the Per Protocol Analysis Set (PPAS) is greater than 10%.*

5.3.2.3.4.3. Baseline data

There were slightly 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 subjects 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 subjects in the 18 to 34 years and 35 to 49 years age subgroups were the same (50%). Overall, the majority of subjects were White (77.4%), and 18.9% were African American/Black.

5.3.2.3.4.4. Outcomes and estimation

Primary objective

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 22. 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 subjects 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

Table 23. 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 subjects with available data for the considered endpoint

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

Secondary Objective

Pre- and post-vaccination (D29) HAI titres from all participants were analysed.

At baseline, the HAI Ab GMTs for subjects 9 to 17 years of age ranged from 48.1 for the B/Victoria lineage to 272 for 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 subjects 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 subjects were higher in subjects 9 to 17 years of age than in subjects 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 subjects 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 subjects 9 to 17 years of age than in subjects 18 to 49 years of age. At D29, the percentages of subjects 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 subjects, respectively); similarly high percentages were also seen in the 18 to 49 years age group. The seroconversion rates for subjects 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 subjects 9 to 17 years than in subjects 18 to 49 years.

5.3.2.3.4.5. Ancillary analyses

Ancillary analysis were performed by Age Group, Previous Influenza Vaccination, Serological Status at Baseline, Race and Sex. These analyses are documented in eCTD sections 5.3.5.2.

5.3.3. Supportive studies

5.3.3.1. PSC04

5.3.3.1.0. Study title

Evaluation of the Immunogenicity, Safety, Reactogenicity, Efficacy, Effectiveness and Lot Consistency of Flublok Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine In Healthy Adults Age 18 to 49 Years

5.3.3.1.1. Study design

5.3.3.1.1.1. Treatment

PSC04 was a Phase III, randomised, modified double-blind, placebo-controlled, multicentre study conducted in healthy adults aged 18 to 49 years in the United States during the 2007–2008 influenza season. The investigational product administered in the experimental arm was a trivalent recombinant influenza vaccine (RIV3, Flublok Trivalent), containing 135 µg total recombinant hemagglutinin (rHA) protein, 45 µg for each of the three included strains: A/H1N1, A/H3N2, and B/Victoria. RIV3 was supplied as a sterile, preservative-free, ready-to-use liquid formulation in 0.5 mL single-dose vials and was administered intramuscularly as a single 0.5 mL dose into the deltoid muscle. Participants in the placebo arm received a single 0.5 mL intramuscular injection of sterile saline solution. Both vaccine and placebo were visually indistinguishable and administered under blinded conditions.

5.3.3.1.1.2. Randomisation

Subjects were randomised 1:1 to receive either a single intramuscular dose of the trivalent recombinant influenza vaccine (RIV3) or placebo (saline). Within the RIV3 group, subjects were further randomised to receive one of three clinical lots (Lot A, B or C) to assess lot-to-lot consistency.

5.3.3.1.1.3. Blinding

The study was conducted in a modified double-blind manner: subjects, investigators, and outcome assessors were blinded to treatment assignment. Vaccine preparation and administration were performed by designated unblinded site staff, who had no role in subsequent assessments. The syringes were labelled with a subject-specific code but not with the treatment identity.

Emergency unblinding was permitted if knowledge of treatment assignment was necessary for appropriate medical management. The process required documentation and justification in the case report form, though no such instances were reported during the study.

5.3.3.1.1.4. Patient population

The study enrolled healthy, medically stable adults aged 18 to 49 years at multiple U.S. sites during the 2007–2008 influenza season. Participants were required to be available for follow-up over approximately six months and able to comply with study procedures. Women of childbearing potential had to test negative for pregnancy at baseline and agree to use contraception throughout the study.

The population was deliberately limited to adults without high-risk conditions for influenza complications, in accordance with CDC/ACIP definitions. Individuals for whom influenza vaccination was routinely recommended (such as those with chronic illnesses, immunodeficiency, pregnancy, or professional exposure risk) were excluded to avoid confounding the immunogenicity and safety assessments. Also excluded were subjects with recent use of immunosuppressive therapies, recent malignancy, recent receipt of authorised or experimental vaccines, and other conditions likely to interfere with study outcomes or compliance.

No special populations were specifically targeted or enriched. The exclusion of high-risk individuals ensured a homogeneous, immunocompetent study population representative of healthy adults not typically prioritised for seasonal influenza vaccination, aligning with the study's aim to evaluate vaccine immunogenicity in a baseline healthy population.

5.3.3.1.2. Objectives and estimands

5.3.3.1.2.1. Primary objective

The PSC04 study had two co-primary efficacy objectives: to evaluate the clinical efficacy of RIV3 and to assess lot-to-lot consistency in immunogenicity. The key primary efficacy objective was to demonstrate the superiority of RIV3 over placebo in preventing culture-confirmed, CDC-defined influenza-like illness caused by vaccine-represented strains in healthy adults aged 18 to 49 years.

Table 24: Estimand for key primary objective

Population	Patients aged 18–49 years without high-risk conditions for influenza, as defined by the study inclusion and exclusion criteria.
Treatment condition<s>	Assignment to RIV3, regardless of discontinuation, compared to assignment to placebo, regardless of discontinuation.
Endpoints (variable)	Occurrence of culture-confirmed CDC-defined ILI caused by vaccine-matched strains during the 2007–2008 influenza season.
Population-level summary	Relative risk reduction (vaccine efficacy), calculated as 1 − RR with 95% confidence interval.

The clinical question of interest was whether a single dose of RIV3 reduces the incidence of culture-confirmed symptomatic influenza caused by vaccine-matched strains in healthy adults aged 18–49 years, compared to placebo. The primary efficacy endpoint was based on clinical outcome data, defined as CDC-ILI with virological confirmation. HAI antibody titres were used as a surrogate marker of protection, in line with regulatory guidance.

No intercurrent events affecting the primary endpoint were reported in the study, and no specific estimand strategies were defined in the protocol.

Lot consistency (co-primary immunogencity endpoint): To demonstrate clinical consistency among three different lots of RIV3 administered during the study. The primary immunogenicity hypothesis is that for each strain contained within RIV3 the 2-sided 95% confidence interval (CI) for the ratio of post-vaccination geometric mean titres (GMTs) of HI antibody for Lot A vs. B, Lot A vs. C and Lot B vs. C will all fall within 0.67 to 1.5.

5.3.3.1.2.2. Statistical methods for estimation and sensitivity analysis on primary estimand

Primary Endpoint Analysis Summary

The primary clinical objective was to assess the efficacy of RIV3 in preventing culture-confirmed, CDC-defined influenza-like illness (CDC-ILI) caused by vaccine-matched strains in healthy adults aged 18-49 years. Vaccine efficacy was expressed as the relative reduction in influenza incidence in the RIV3 group compared to placebo.

Analysis Set

The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population, which included all randomised participants who received a dose of study vaccine and were followed during the influenza season. Subjects were analysed according to treatment received.

Statistical Methods

Vaccine efficacy was estimated as 1 minus the relative risk (RR) of confirmed influenza cases in the RIV3 group compared to placebo. Two-sided 95% confidence intervals for the point estimate were calculated using exact binomial methods. The analysis was descriptive in nature, as no formal hypothesis testing was prespecified.

Multiplicity and Missing Data

No adjustments for multiplicity were applied, as only a single primary clinical efficacy endpoint was evaluated, and no confirmatory hypotheses were tested. Missing data were not imputed; participants without clinical follow-up were excluded from the mITT population.

Sensitivity and Supplementary Analyses

No formal sensitivity analyses were performed for the primary endpoint. Supplementary analyses, such as vaccine efficacy against all culture-confirmed influenza regardless of CDC-ILI status or antigenic match, were conducted post hoc and are reported separately as exploratory.

5.3.3.1.2.3. Secondary objectives

The study included two key secondary objectives.

1. To assess the immunogenicity of RIV3 based on seroconversion and seroprotection rates for each vaccine strain, in accordance with CBER's May 2007 guidance for the authorisation of seasonal inactivated influenza vaccines.
2. To evaluate the clinical efficacy of RIV3 compared to placebo in preventing culture-confirmed symptomatic influenza (regardless of CDC-ILI case definition), caused by vaccine-matched strains. The hypothesis was that RIV3 would show superiority over placebo in reducing the incidence of virologically confirmed influenza illness attributable to vaccine strains.

5.3.3.1.2.4. Estimands for the secondary objectives

Table 25. Estimand for clinical efficacy secondary objective

Population	Patients aged 18–49 years without high-risk conditions for influenza as defined by the protocol.
Treatment condition	Assignment to RIV3, regardless of discontinuation, compared to assignment to placebo, regardless of discontinuation.
Endpoint (variable)	Occurrence of culture-confirmed influenza caused by vaccine strains, regardless of CDC-ILI definition, during the 2007–2008 influenza season.
Population-level summary	Relative risk reduction (vaccine efficacy), calculated as 1 – RR with 95% confidence interval

Table 26: Estimand for immunogenicity secondary objective

Population	Patients aged 18–49 years without high-risk conditions who received RIV3 and completed Day 28 immunogenicity assessments.
Treatment condition	Assignment to RIV3, regardless of discontinuation.
Endpoint (variable)	Seroconversion rate (as defined by CBER 2007 criteria) at Day 28 (i) and seroprotection rate (HAI titre ≥1:40) at Day 28 (ii).
Population-level summary	Proportion with 95% confidence intervals per CBER criteria (lower bound ≥70% for %≥40; ≥40% for SCR).

The clinical questions addressed by the secondary objectives were whether RIV3 reduces the incidence of culture-confirmed symptomatic influenza caused by vaccine-matched strains, regardless of whether the illness fulfils the CDC case definition for influenza-like illness, and whether a single dose of RIV3 elicits an adequate immune response against each included strain, as measured by seroconversion and seroprotection rates. The immunogenicity endpoints are considered surrogate markers of protection and are defined in accordance with the criteria set out in CBER's 2007 Guidance for the licensure of seasonal inactivated influenza vaccines.

No intercurrent events affecting the primary endpoint were reported in the study, and no specific estimand strategies were defined in the protocol.

5.3.3.1.2.5. Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary Endpoint Analysis Summary

Secondary endpoints included additional clinical efficacy and immunogenicity parameters. Clinically, an expanded case definition was applied to capture all culture-confirmed influenza cases caused by vaccine strains, regardless of whether CDC-ILI criteria were met. Immunogenicity endpoints included seroconversion rates (SCRs) and seroprotection rates (SPRs) for each vaccine strain, based on established CBER 2007 criteria.

Analysis Set

Immunogenicity analyses were conducted in the per-protocol immunogenicity (PPI) population, consisting of subjects with evaluable pre- and post-vaccination HAI titres and no major protocol deviations. The secondary clinical efficacy endpoint was assessed in the same modified intention-to-treat (mITT) population used for the primary efficacy analysis.

Statistical Methods

For immunogenicity, seroconversion was defined as a post-vaccination HAI titre ≥40 in previously seronegative subjects, or a ≥4-fold increase from baseline in subjects with baseline titres ≥10. Seroprotection was defined as a post-vaccination titre ≥40. Results were summarised descriptively. Regulatory thresholds required the lower bound of the 95% CI to be ≥40% for SCRs and ≥70% for SPRs to indicate an adequate immune response. For the secondary clinical efficacy endpoint, the same analytical method used for the primary endpoint (calculation of vaccine efficacy as 1 minus the relative risk) was applied.

Multiplicity and Missing Data

No adjustments for multiplicity were applied to secondary endpoints. Analyses were descriptive and did not involve confirmatory hypothesis testing. Missing serological or clinical data were not imputed; subjects with incomplete data were excluded from the respective analysis sets.

Sensitivity and Supplementary Analysis

No formal sensitivity or supplementary analyses were planned for secondary endpoints. However, exploratory post hoc analyses assessing vaccine efficacy against culture-confirmed influenza irrespective of antigenic match were conducted and reported separately.

5.3.3.1.3. Results

5.3.3.1.3.1. Participant flow and numbers analysed

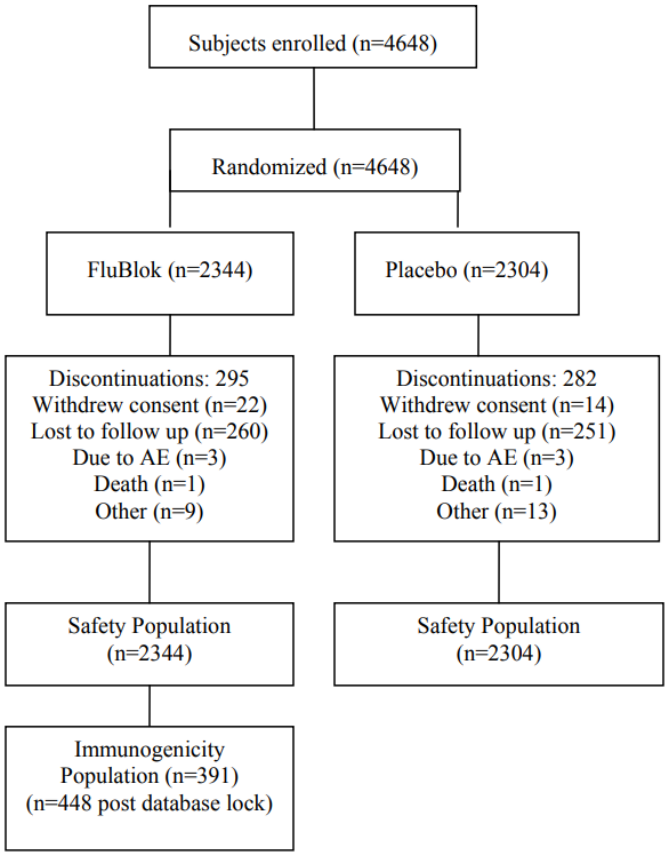
Participant recruitment for study PSC04 took place from August to October 2007, with follow-up completed in early 2008. A total of 4,648 subjects were enrolled and randomised in a 1:1 ratio to receive either RIV3 or placebo. Of these, 2,344 participants were assigned to the RIV3 group and 2,304 to the placebo group. All randomised subjects received the assigned treatment, forming the safety population (N=4,648).

A subset of 450 subjects (150 per lot) was enrolled for immunogenicity assessment. Of these, 448 completed serum sampling, and 448 samples were tested for antibody response at Day 28. A total of 391 subjects were included in the evaluable population for immunogenicity, defined as those who met all inclusion criteria and had valid Day 0 and Day 28 titre results. Reasons for exclusion from the evaluable set included missing or mislabelled samples and protocol deviations.

Throughout the study, 577 subjects discontinued follow-up: 282 in the placebo group and 295 in the RIV3 group. The most common reasons were loss to follow-up (n=511), withdrawal of consent (n=36), adverse events (n=6), death (n=2), and other reasons (n=22). The median follow-up duration was 28 days post-vaccination, as the primary immunogenicity and safety endpoints were assessed at this timepoint.

The analysis was performed on predefined populations: the safety population (all vaccinated subjects), the evaluable immunogenicity population (N=391), and for clinical efficacy, the safety population was used as a modified intention-to-treat set. All key analyses were based on absolute subject numbers rather than percentages.

Figure *2*. Participant flow



5.3.3.1.3.2. Deviations from study plan

A substantial change to the planned conduct of the study was implemented prior to the start of subject enrolment. Originally, the study aimed to enrol 630 subjects (210 per lot) for the immunogenicity subset. Following discussions with the FDA, this target was reduced to 450 subjects (150 per lot) through protocol amendments 3 and 4. This change was made to maintain sufficient power for lot consistency evaluation in accordance with the 2007 CBER guidance, while accommodating logistical constraints related to recruitment. The adjustment was implemented before the initiation of enrolment and did not impact data integrity or the primary and secondary objectives of the study.

The clinical study report also documents several protocol deviations, including violations of inclusion/exclusion criteria and procedural inconsistencies; however, these did not lead to systematic bias or compromise the overall interpretability of the results.

5.3.3.1.3.3. Baseline data

Baseline demographic and clinical characteristics were generally balanced across treatment arms. In the safety population (N=4,648), the mean age was comparable between groups (RIV3: 32.8 years; Placebo: 32.9 years), with a similar proportion of male participants (RIV3: 42.5%; Placebo: 42.2%). The majority of subjects were White/Caucasian (RIV3: 80.2%; Placebo: 79.6%) and non-Hispanic/Latino (RIV3: 89.2%; Placebo: 89.7%).

In the evaluable immunogenicity population (N=391), the demographic distribution was consistent with the overall study population, and no clinically relevant imbalances were observed across the three RIV3 manufacturing lots. No major asymmetries were detected in terms of age, sex, race, or baseline

HAI titres, suggesting that randomisation achieved an adequate distribution of covariates. The detailed data are presented in Table 27.

Table 27: PSC04 - Subjects Demographics

Characteristic	RIV3 (N=2,344)	RIV3 PPI Subset (N=391)	Placebo (N=2,304)
Age (yrs) median (range)	32 (18; 55)	31 (18; 49)	32 (18; 50)
Gender, n (%)			
Male	952 (41)	176 (45)	955 (41)
Female	1,391 (59)	215 (55)	1,249 (59)
Race/Ethnicity, n (%)			
White/Caucasian	1570 (67)	256 (65)	1530 (66)
Black/African-American	430 (18)	73 (19)	447 (19)
Latino/Hispanic	250 (11)	36 (9)	239 (10)
Asian	62 (3)	21 (5)	52 (2)
American Indian/Alaska Native	7 (<1)	1 (<1)	9 (<1)
Native Hawaiian/Pacific Islander	6 (<1)	1 (<1)	8 (<1)
Other	19 (1)	3 (1)	19 (1)

5.3.3.1.3.4. Outcomes and estimation

The first co-primary endpoint was the incidence of culture-confirmed CDC-defined ILI caused by antigenically matched influenza strains. Due to significant antigenic drift during the 2007–2008 season, case numbers were extremely low, with only one event in the RIV3 group and four in the placebo group. The calculated vaccine efficacy was 75.4% (95% CI: –148.8; 99.5). Using an expanded case definition (culture-confirmed influenza illness irrespective of CDC-ILI), 2 events occurred in the RIV3 group and 6 in the placebo group. The resulting point estimate for relative protective efficacy was 67.2% (95% CI: –83.2; 96.8) (*Table 28*).

Table 28: PSC04 – Protective efficacy of RIV3: primary and secondary endpoints

Antigen	RIV3 N=2,344	Placebo N=2,304
Primary endpoint		
Antigenically-matched culture-positive CDC-ILI, n (%)	1 (0.04)	4 (0.2)
Protective Efficacy, % (95% CI)*	75.4 (-148.8; 99.5)	
Secondary endpoint		
Antigenically-matched culture-positive CDC-ILI, n (%)	2 (0.1)	6 (0.3)
Relative Protective Efficacy, % (95% CI)*	67.2 (-83.2; 96.8)	

* Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987

Immunogenicity was evaluated by seroconversion and seroprotection rates at Day 28 in the evaluable population (N=391). For all three vaccine strains seroconversion rates met the CBER threshold of a

lower 95% CI bound ≥40%, with observed rates of 78%, 81%, and 53%, respectively. Seroprotection rates were uniformly high across all strains, ranging from 96% to 98%, with lower 95% CI bounds well above the regulatory criterion. These findings were confirmed in an extended dataset of 448 subjects. Full details are presented in Table 29 and Table 30.

Table 29: PSC04 - Seroconversion[1] or Significant Increase[2] in HAI Titres at the Day 28 Visit in Evaluable Population[3]

	RIV3 (locked database) N=391	**RIV3** (post-database lock) N=448
H1 A/Solomon Islands		
Seroconversion[1] or significant increase[2], n (%)	306 (78)	348 (78)
[2-sided 95% CI][4]	[73.8; 82.2]	[73.5; 81.5]
Lower Bound CI ≥ 40%?	**YES**	**YES**
H3 A/Wisconsin		
Seroconversion[1] or significant increase[2], n (%)	315 (81)	363 (81)
[2-sided 95% CI][4]	[76.3; 84.4]	[77.1; 84.6]
Lower Bound CI ≥ 40%?	**YES**	**YES**
B/Malaysia		
Seroconversion[1] or significant increase[2], n (%)	208 (53)	232 (52)
[2-sided 95% CI][4]	[48.1; 58.2]	[47.0; 56.5]
Lower Bound CI ≥ 40%?	**YES**	**YES**

[1] Pre-vaccination titre below limit of detection (<10) and Day 28 ≥ 40
[2] 4-fold or greater increase from pre-vaccination to Day 28.
[3] Day 28:RIV3, n=391 present in the locked database, n=448 post-database lock
[4] Confidence Intervals based on Clopper-Pearson exact method

Table 30: PSC04 - Seroprotection[1] at the Day 28 Visit in Evaluable Population[2]

	RIV3 (locked database) N=391	**RIV3** (post-database lock) N=448
H1 A/Solomon Islands		
Seroprotection (HI titre ≥40), n (%)	385 (98)	442 (99)
[2-sided 95% CI][3]	[96.7, 99.4]	[97.1, 99.5]
Lower Bound CI ≥ 40%?	**YES**	**YES**
H3 A/Wisconsin		
Seroprotection (HI titre ≥40), n (%)	377 (96)	434 (97)
[2-sided 95% CI][3]	[94.1; 98.0]	[94.8; 98.3]
Lower Bound CI ≥ 40%?	**YES**	**YES**
B/Malaysia		
Seroprotection (HI titre ≥40), n (%)	375 (96)	431 (96)
[2-sided 95% CI][3]	[93.4; 97.6]	[94.0; 97.8]
Lower Bound CI ≥ 40%?	**YES**	**YES**

[1] Post-vaccination HI titre ≥40
[2] Day 28: RIV3, n=391 present in the locked database, n=448 post-database lock
[3] Confidence Intervals based on Clopper-Pearson exact method

Lot consistency (co-primary immunogenicity endpoint)

Lot consistency could not be demonstrated for A/Wisconsin due to issues with the potency assay used for determination of rHA antigen content in the drug substance batches. Improved recalculation indicated that the H3 antigen (A/Wisconsin/67/2005) content in two of three lots was reduced by ~1/3 of the intended amount (45 µg) whereas other antigens exceeded the intended antigen amount by up to ~40% (c.f. Table 31).

Table 31: PSC04 - Clinical Lot Consistency Analysis for Geometric Mean Titres at Day 28

	GMT (95% Confidence Interval)					
	RIV3 (locked database) (N=391)			**RIV3** (post-database lock) (N=448)		
	Lot A N=131	**Lot B N=130**	**Lot C N=130**	**Lot A N=150**	**Lot B N=151**	**Lot C N=147**
A/Solomon Islands (H1N1) GMT (95% CI)	348.27 (290.80; 417.09)	341.14 (286.68; 405.96)	393.97 (328.98; 471.80)	346.15 (291.96; 410.41)	322.95 (274.80; 379.55)	381.00 (321.79; 451.10)
Difference between lots	Lot A vs. Lot B; 1.02 (0.79, 1.31) Lot A vs. Lot C; 0.88 (0.69, 1.14) Lot B vs. Lot C; 0.87 (0.67, 1.11)			Lot A vs. Lot B; 1.07 (0.85, 1.36) Lot A vs. Lot C; 0.91 (0.71, 1.15) Lot B vs. Lot C; 0.85 (0.67, 1.07)		
Distribution Equality* Meets CBER Criteria?	P=0.010 **YES**			P=0.009 **YES**		
A/Wisconsin (H3N2) GMT (95% CI)	395.43 (326.01; 479.62)	178.96 (146.75; 218.23)	241.83 (197.83; 294.14)	390.34 (324.83; 469.06)	192.25 (159.59; 231.59)	240.01 (200.14; 287.82)
Difference between lots	Lot A vs. Lot B; 2.21 (1.68, 2.91) Lot A vs. Lot C; 1.64 (1.24, 2.16) Lot B vs. Lot C; 0.74 (0.56, 0.98)			Lot A vs. Lot B; 2.03 (1.56, 2.64) Lot A vs. Lot C; 1.63 (1.26, 2.11) Lot B vs. Lot C; 0.80 (0.62, 1.04)		
Distribution Equality* Meets CBER Criteria?	P=0.111 **NO**			P=0.065 **NO**		
B/Malaysia (B/Victoria) GMT (95% CI)	175.06 (143.89, 212.98)	196.98 (165.00, 235.17)	205.57 (168.74, 250.43)	182.10 (151.95, 218.24)	205.95 (174.16, 243.55)	215.34 (179.31, 258.62)
Difference between lots	Lot A vs. Lot B; 0.89 (0.68, 1.16) Lot A vs. Lot C; 0.85 (0.64, 1.12) Lot B vs. Lot C; 0.96 (0.73, 1.25)			Lot A vs. Lot B; 0.88 (0.69, 1.13) Lot A vs. Lot C; 0.85 (0.65, 1.09) Lot B vs. Lot C; 0.96 (0.75, 1.23)		
Distribution Equality* Meets CBER Criteria?	P=0.013 **YES**			P=0.011 **YES**		

* P-values are based on statistical methods reported by Lachenbruch et al., in which the null hypothesis (i.e., lots are not equivalent) is rejected if the p-value is less than 0.05

5.3.3.1.3.5. Ancillary analyses

A post hoc analysis was conducted to evaluate clinical efficacy of RIV3 separately against influenza A and B viruses, irrespective of antigenic match. As shown in Table 32 the results were generally consistent with vaccine effectiveness estimates reported by the CDC for the 2007–2008 season.

Table 32. PSC04 - Clinical efficacy of RIV3 against all influenza strains

Antigen	RIV3 N=2,344	Placebo N=2,304
Subjects with culture-positive Influenza, n (%)[1]	64 (2.7)	114 (4.9)
Protective Efficacy, % (95% CI)[2]	44.8 (24.4; 60.0)	
Clinical Efficacy against influenza type A		
Subjects with culture-positive Influenza, n (%)[1]	41 (1.7)	79 (3.4)
Protective Efficacy, % (95% CI)[2]	49.0 (24.7; 65.9)	
Clinical Efficacy against influenza type B		
Subjects with culture-positive Influenza, n (%)[1]	23 (1.0)	36 (1.6)
Protective Efficacy, % (95% CI)[2]	37.2 (-8.9; 64.5)	

[1] All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI
[2] Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987

Source: 5.3.5.1 PSC04 Report, Table 25

In the influenza B subset, all cases were caused by antigenically drifted strains not represented in the vaccine. While numerically fewer cases were reported in the RIV3 group compared to placebo, the estimated protective efficacy against these strains was 37.2%, with a 95% confidence interval of –8.9% to 64.5%.

5.3.3.2. 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

5.3.3.2.0. Methods

Study Design and Objectives

VAP00026 study was a Phase III, randomised, modified double-blind, active-controlled trial evaluating the immunogenicity and safety of a quadrivalent recombinant influenza vaccine (RIV4) compared to a standard egg-based quadrivalent influenza vaccine (IIV4) in children aged 3 to 8 years. The study was conducted at multiple centres in the US and Europe. Participants were stratified by age (3–5 and 6–8 years) and prior influenza vaccination status, receiving one or two doses of either RIV4 or IIV4 accordingly. The study design aimed to evaluate the immunogenic profile and safety of RIV4 in a paediatric population, using both HAI and neutralising antibody endpoints.

The primary objective of the study was to demonstrate non-inferior HAI immune response of RIV4 versus authorised IIV4 for the 4 strains based on the egg-derived antigen in all participants aged 3 to 8 years.

The secondary objective of the study was to summarise the HAI immune response induced by RIV4 and IIV4 for the 4 strains based on the egg-derived antigen in subjects aged 3 to 8 years.

5.3.3.2.1. Results

An interim immunogenicity analysis conducted after approximately 25% of subjects had been enrolled and vaccinated in Study VAP00026 revealed that the posterior probability of success (PPoS) for

achieving the primary objective (non-inferior HAI response of RIV4 vs. IIV4) was less than 1%. Based on pre-defined futility criteria, the Sponsor's Firewall Internal Committee recommended stopping further enrollment.

Participant flow and numbers analysed

A total of 366 children (ages 3–8 years) were ultimately enrolled and randomised to receive either RIV4 (n = 183) or IIV4 (n = 183). Subjects were stratified by age (3–5 years vs. 6–8 years) and prior influenza vaccination status.

- Previously Vaccinated Subjects (n = 210):
    - 3–5 years: n=92 (RIV4: n=43; IIV4: n=49)
    - 6–8 years: n=118 (RIV4: n=62; IIV4: n=56)
    - Completion at Day 29 (V02): n=102 (97.1%) received RIV4; n=103 (98.1%) received IIV4
- Previously Unvaccinated Subjects (n = 156):
    - 3–5 years: n=83 (RIV4: n=39; IIV4: n=44)
    - 6–8 years: n=73 (RIV4: n=39; IIV4: n=34)
    - Completion at Day 57 (V03): n= 75 (96.2%) received RIV4; IIV4: n=74 (94.9%) received IIV4

A summary of immunogenicity analysis sets is provided in Table 33.

Table 33: Study VAP00026 – Participant disposition – Randomised study subjects

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 subjects fulfilling the item listed

M: number of subjects with available data for the corresponding group

Baseline data

The demographic characteristics of the 366 randomised subjects in Study VAP00026 were well balanced across vaccination groups (RIV4 and IIV4) and stratification factors (age and priming status):

Gender distribution:

- 178 males (48.6%) and 188 females (51.4%)
- Balanced across RIV4 and IIV4 groups

Age distribution:

- 175 subjects (47.8%) were aged 3–5 years
- 191 subjects (52.2%) were aged 6–8 years
- Mean age: 5.60 years (±1.68 SD)
- Similar age profiles between groups

Race and ethnicity:

- Majority were White (n = 280; 76.5%)
- Most subjects identified as Not Hispanic or Latino (n = 317; 86.6%)

Influenza Priming Status:

- 210 subjects (57.4%) were previously vaccinated
- 156 subjects (42.6%) were previously unvaccinated
- Within each priming group, subjects were evenly randomised (50:50) to RIV4 and IIV4

Demographic characteristics were also stratified by age groups (3–5 years and 6–8 years) and showed balanced distribution across treatment arms.

Outcomes and estimation

Primary Objective – Non-inferiority

The study did not meet its primary objective, as the RIV4 vaccine failed to demonstrate a non-inferior HAI immune response compared to the authorised IIV4 vaccine for all four influenza strains. However, non-inferiority was observed for three of the four strains (A/H1N1, A/H3N2, and B/Yamagata), but not for the B/Victoria strain, which had a GMT ratio below the required threshold (*Table 43*). Similarly, the study demonstrated that the RIV4 vaccine elicited a non-inferior HAI immune response compared to the authorised IIV4 for three of the four influenza strains (A/H1N1, A/H3N2, and B/Yamagata) based on seroconversion rates in the PPAS (*Table 44*). However, non-inferiority was not shown for the B/Victoria strain, with a seroconversion rate difference of -6.91% (95% CI: -14.02; 0.10), and similar findings were observed in the FAS.

Table 34. 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 subjects 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 was conducted on the subjects enrolled before stopping the study for futility.
The results of this analysis are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).

Table 35. 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 subjects 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 was conducted on the subjects enrolled before stopping the study for futility.
The results of this analysis are presented for each strain to illustrate differences between RIV4 and reference vaccine (IIV4).

Secondary Objective – HAI Immune Response

At D01 (baseline for all subjects), 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 subjects 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.

5.3.3.3. Others: PSC08

Evaluation of the Safety, Reactogenicity and Immunogenicity of Flublok Quadrivalent (Quadrivalent Recombinant Influenza Vaccine, Seasonal Formulation) Administered Intramuscularly to Healthy Children and Adolescents Age 6-17 Years

5.3.3.3.0. Methods

Study Design and Objectives

PSC08 was a Phase II, randomised, modified double-blind, active-controlled study comparing RIV4 vs. IIV4 to evaluate safety, reactogenicity, and immunogenicity (measured by Hemagglutination-inhibition (HAI) antibody titre at day 28 and day 56). Subjects were stratified by age and enrolled into one of two age cohorts at five sites in the US during 2013-2014 influenza season: 9-17 years of age (Cohort A) and 6-8 years of age (Cohort B). The objectives of the study were to compare the immunogenicity of RIV4 versus IIV4 in the subject population by age cohorts and to evaluate the safety and reactogenicity of RIV4 versus IIV4 in healthy children and adolescents aged 6-17 years, divided into the two age cohorts.

5.3.3.3.1. Results

The study was originally planned to be conducted as a randomised, prospective, double-blinded Phase 2/3 trial in two stages. Stage 1 was designed to evaluate the safety and preliminary immunogenicity in paediatric subjects of 6-17 years of age. Stage 2 was intended to establish non-inferior immunogenicity of RIV4 to that of IIV4 in the paediatric age groups under study and to confirm the safety and immunogenicity of RIV4 to support licensure in paediatrics. Subsequent to regulatory review, stage 2 of the protocol was placed on hold due to the circulation of wild-type influenza that was judged to possibly confound the evaluation of the safety profiles of study vaccine. Study conduct was limited to enrolment to Stage 1 only.

Participant flow and numbers analysed

Overall, 175 of 219 enrolled subjects (80%) completed the study. Twenty-eight of the 44 (64%) subjects who were classified as having discontinued the study were discontinued after their 6-month visit based on the amendment of the protocol to truncate the study at 6 months of safety follow-up. The second most common reason for discontinuation was lost to follow-up. These subjects were evenly distributed across age groups and treatment groups. There were no deaths and no discontinuations due to an adverse event.

Baseline data

The age cohorts in each treatment group were largely balanced with respect to race, gender, ethnicity and age. There was a slight predominance of female children and the study population was largely white/Caucasian, besides the younger Cohort B that received RIV4 which included a majority of black/African Americans. The mean age of Cohort A was 12.7 years, while the mean age for Cohort B was 7.1 years.

Outcomes and estimation

Serology tested for haemagglutinin inhibition antibody (HAI) titres demonstrated immunogenicity of RIV4 in older paediatric subjects in Cohort A (9-17 years of age) (Table 36). Seroconversion rates for three of the four antigens (A/H1N1, A/H3N2 and B Yamagata lineage) were numerically higher than those induced by IIV4 for the same antigens, and these response rates met CBER criterion for non-inferiority in comparison to IIV4. The seroconversion rate to the B Victoria lineage (B/Brisbane/60/2008) did not meet the criterion for non-inferiority. Seroconversion rates among the younger subjects in Cohort B (6-8 years of age) met the CBER criterion for non-inferiority only for the A/H1N1 antigen; the rates for the other 3 strains in RIV4 recipients were similar to IIV4 recipients.

Table 36. PSC08 - Seroconversion Rates[1], mPP population

HA Antigen	Cohort A		Cohort B	
	RIV4 (n=75)	IIV4 (n=77)	RIV4 (n=26)	IIV4 (n=28)
A/CALIFORNIA/7/2009	65 (87%)	52 (68%)	23 (88%)	21 (75%)
	76.8, 93.4	**55.9**, 77.8	**69.8**, 97.6	**55.1**, 89.3
Difference (95% CI)	-19% (-32.1, **-6.2**)		-13% (-33.7, **6.7**)	
B/BRISBANE/60/2008	33 (52%)	42 (67%)	18 (69%)	19 (73%)
	39.4, 65.1	**53.7**, 78.0	**48.2**, 85.7	**52.2**, 88.4
Difference (95% CI)	14% (-2.7, 31.2)		4% (-20.8, 28.5)	
A/TEXAS/50/2012	44 (59%)	38 (49%)	14 (54%)	14 (50%)
	46.7, 69.9	37.8, 61.0	33.4, 73.4	30.6, 69.4
Difference (95% CI)	-9% (-25.1, **6.5**)		-4% (-30.5, 22.8)	
B/MASSACHUSETTS/2/2012	52 (69%)	47 (61%)	20 (77%)	23 (82%)
	57.6, 79.5	**49.2**, 72.0	**56.4**, 91.0	**63.1**, 93.9
Difference (95% CI)	-8% (-23.4, **6.8**)		5% (-16.3, 26.7)	

[1] Seroconversion was measured 28 days after completion of vaccination, i.e. Day 28 for subjects who required one injection and Day 56 for subjects in Cohort B that required 2 injections.
B/BRISBANE/60/2008 – Cohort A RIV4 n=63, IIV4 n=63; Cohort B RIV4 n=26, IIV4 n=26
Bolded numbers for SCR differences indicate that CBER criterion for non-inferiority was met; **the bolded** numbers for seroconversion rates indicate that the CBER criterion for licensure under accelerated approval guidelines was met.

Geometric mean titres (GMTs) at baseline (Day 0) were unexpectedly high for the A/H3N2 antigen in both age cohorts and in both vaccine groups (Table 37). The CBER criterion for non-inferiority of post-vaccination GMTs was met for three of the four antigens in the older Cohort A and for the two influenza A antigens in the younger Cohort B.

Table 37. PSC08 - HAI GMTs by Age Cohort, mPP population

Antigen	Cohort A				Cohort B			
	RIV4 (n=75)		IIV4 (n=77)		RIV4 (n=26)		RIV4 (n=28)	
A/CALIFORNIA/7/2009								
Day 0 mean [1]	54.94		59.79		85.89		57.04	
95% CI	38.83	77.73	43.05	83.02	44.83	164.57	31.29	103.98
Day 28 mean [1 3]	914.92		564.23		1224.31		695.03	
95% CI	693.4	1207.19	449.6	708.07	749.8	1999.05	501.47	963.32
Ratio (95% CI) [2]	0.62 (0.43, **0.88**)				0.57 (0.32, **1.00**)			
Fold Rise	16.7		9.4		14.3		12.2	
B/BRISBANE/60/2008								
Day 0 mean [1]	12.49		10.56		11.43		9.36	
95% CI	10.17	15.33	8.62	12.94	8.32	15.69	7.05	12.43
Day 28 mean [1 3]	51.73		59.67		73.82		60.74	
95% CI	39.73	67.34	47.30	75.27	45.05	120.96	40.35	91.42
Ratio (95% CI) [2]	1.15 (0.81, 1.63)				0.82 (0.44, 1.54)			
Fold Rise	4.1		5.7		6.5		6.5	
A/TEXAS/50/2012								
Day 0 mean [1]	181.57		141.91		272.74		161.32	
95% CI	140.4	234.83	108.7	185.25	181.7	409.37	113.0	230.37
Day 28 mean [1 3]	852.30		531.36		1071.58		629.48	
95% CI	698.1	1040.64	449.8	627.75	776.2	1479.45	451.4	877.78
Ratio (95% CI) [2]	0.62 (0.48, **0.81**)				0.59 (0.37, **0.92**)			
Fold Rise	4.7		3.7		3.9		3.9	
B/MASSACHUSETTS 2/2012								
Day 0 mean [1]	20.44		21.17		13.89		12.19	
95% CI	16.11	25.94	16.15	27.75	9.54	20.23	8.89	16.72
Day 28 mean [1 3]	161.02		119.96		111.14		122.90	
95% CI	124.8	207.83	95.07	151.37	69.87	176.79	81.92	184.38
Ratio (95% CI) [2]	0.75 (0.53, **1.05**)				1.11 (0.61, 2.01)			
Fold Rise	7.9		5.7		8.0		10.1	

[1]Geometric mean titers (GMTs) of antibody and their 95% CIs were computed by transforming serology results to a natural logarithmic scale assuming asymptotic normality conditions were satisfied on this scale
[2]The ratio of GMTs was calculated as: GMT = (GMT_{IIV4}/$GMT_{Flublok\ Quadrivalent}$). 95% CI for GMT Ratio is based on back transformation of 95% confidence limits calculated using a t statistic for difference of log transformed HAI titers.
[3]Cohort B includes 1-Dose subjects at Day 28 and 2-Dose subjects at Day 56.
B/BRISBANE/60/2008 – Cohort A RIV4 n=63, IIV4 n=63; Cohort B RIV4 n=26, IIV4 n=26
Bolded figures indicate the CBER criterion for non-inferiority was met

Seroprotection, defined as a post-vaccination titre ≥40, also demonstrated that most subjects in each age cohort and each vaccine group were "protected" based on their response to study vaccine (Table 39). RIV4 met standards for licensure according to CBER for three of the four antigens (not including the B Victoria lineage [Brisbane]) in Cohort A and for the two influenza A antigens in Cohort B.

Table 38. PSC08 - Seroprotection Rates[1], mPP

HA Antigen	Cohort A		Cohort B	
	RIV4 (n=75)	IIV4 (n=77)	RIV4 (n=26)	IIV4 (n=28)
A/CALIFORNIA/7/2009	73 (97%)	76 (99%)	26 (100%)	28 (100%)
	90.7, 99.7	**93.0**, 100.0	**86.8**, 100.0	**87.7**, 100.0
B/BRISBANE/60/2008	49 (78%)	54 (86%)	22 (85%)	21 (81%)
	65.5, 87.3	**74.6**, 93.3	65.1, 95.6	60.6, 93.4
A/TEXAS/50/2012	75 (100%)	77 (100%)	26 (100%)	28 (100%)
	95.2, 100.0	**95.3**, 100.0	**86.8**, 100.0	**87.7**, 100.0
B/MASSACHUSETTS/2/2012	68 (91%)	69 (90%)	22 (85%)	25 (89%)
	81.7, 96.2	**80.6**, 95.4	65.1, 95.6	**71.8**, 97.7

[1] Seroprotection was measured 28 days after completion of vaccination, i.e. Day 28 for subjects who required one injection and Day 56 for subjects in Cohort B that required 2 injections
B/BRISBANE/60/2008 – Cohort A RIV4 n=63, IIV4 n=63; Cohort B RIV4 n=26, IIV4 n=26
Bolded numbers indicate that CBER criterion for licensure was met.

5.3.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

The intended indication claim for Supemtek is "Supemtek is indicated for active immunization for the prevention of influenza disease in adults and children from 9 years of age and older. Supemtek should be used in accordance with official recommendations". To support this claim, two phase 3 clinical trials with RIV4 in adults (PSC12 and PSC16), one clinical trial in paediatric patients 9-17 years of age (VAP00027) and one clinical trial (PSC04) with the initial recombinant trivalent vaccine (Flublok US); considered supportive only) have been included in the dossier. Another clinical trial, VAP00026 in paediatric patients aged 3 to 8 years, did not reach its' primary objective, but relevant data are reflected in the SmPC.

The evaluation of the clinical benefits of Supemtek in adults ≥50 years of age is based on trial PSC12. This is a large, randomised, observer-blind, active-controlled, two arm trial investigating the relative vaccine efficacy of RIV4 in comparison to IIV4 from 2 weeks to 6 months after the administration of 1 dose of quadrivalent influenza vaccine. Forty investigators in the US recruited 8963 subjects into the trial, 4474 of whom received RIV4 and 4489 of whom received IIV4. The primary endpoint was the number of rtPCR-positive cases of protocol-defined ILI. As a secondary objective, immunogenicity to all 4 antigens was determined in a subpopulation of ~300 subjects for each vaccine.

Trial PSC16 investigated the immunogenicity of RIV4 in comparison to IIV4 in adults from 18 to 49 years of age. PSC16 is a randomised, observer-blind, active-controlled, two arm trial in which ten investigators in the US recruited 1350 subjects, of whom 1011 received one injection of RIV4 and 339 received one injection of IIV4. Co-primary endpoints were the seroconversion rate for each antigen and the GMT for each antigen at Day 28 measured with the haemagglutinin assay.

PSC04 is the only trial that evaluated a trivalent formulation proposed for authorisation, but is considered supportive in terms of clinical efficacy due to the following reasons: the study was conducted during a season with pronounced antigenic drift, resulting in few matched cases and statistically inconclusive efficacy estimates. Despite an appropriate randomised, placebo-controlled, observer-blinded design, the antigenic mismatch precluded meaningful conclusions on clinical efficacy. Immunogenicity data showed consistent responses to A strains but a reduced response to B/Victoria. Additionally, variability in antigen content across lots (due to limitations of the potency assay) led to inconclusive lot-to-lot consistency results. However, this is not deemed critical to affect the overall regulatory conclusions.

In contrast, PSC12 and PSC16 provide robust immunogenicity and efficacy data for RIV4, manufactured with the same process as the proposed RIV3, apart from the exclusion of the B/Yamagata component. Both studies applied adequate designs: both pivotal trials are multi-centre, randomised, active-controlled, observer-blind clinical studies employing a non-inferiority comparison to an authorised, egg-based quadrivalent influenza vaccine. In trial PSC12, non-inferiority was defined as a lower bound of the two-sided 95% confidence interval (CI) of relative vaccine efficacy (rVE) > -20%. For trial PSC16, the proposed co-primary endpoints (GMT-ratio and SCR-difference) and NI margins were based on the FDA Guidance for Industry dating May 2007. This guideline (GL) does not cite a scientific rationale for the required cut-offs. However, the proposed co-primary endpoints and NI margins can principally be accepted in view of regulatory precedence. The design of both pivotal trials is adequate to demonstrate immunogenicity and efficacy in an adult population and in line with the requirements of the Guideline on Influenza Vaccines (Non-clinical and Clinical Module; EMA/CHMP/VWP/457259/2014). With PSC12 including clinical endpoint assessment in older adults and PSC16 focusing on immunogenicity in younger adults, the study populations were representative of the intended vaccine target groups, and the randomisation, blinding, and analytical methods adhered to established regulatory expectations. While formal estimand definitions were lacking in all studies, the endpoints were consistently derived, i.e. vaccine efficacy with regard to rtPCR confirmed influenza infection and immunogenicity parameters determined by the HAI assay, and the overall analysis framework aligns with regulatory norms to provide crucial data expected for influenza vaccines. From a planning perspective, trial PSC16 might have been underpowered to evaluate non-inferiority in the multiple primary endpoints. The comparator vaccine used in these studies was IIV4, an authorised, egg-derived influenza vaccine, which is also authorised in the EU as Fluarix Tetra. The choice of comparator is considered appropriate due to the extensive existing efficacy and immunogenicity data available for this vaccine.

The patient population defined by the in- and exclusion criteria selected individuals that are most likely healthier than influenza vaccinees in clinical practice. However, the EMA GL does not require specific studies in chronically ill subjects for the initial MA of a seasonal influenza vaccine, therefore the population included into trials PSC12 and PSC16 can be accepted. Demographic and other baseline parameters were well distributed between the RIV4 and control arms.

The results of PSC12 demonstrate clinically relevant protection against rtPCR-confirmed influenza-like illness, with supportive secondary efficacy endpoints and consistent findings across case definitions. Out of 4303 subjects included in the efficacy population in the RIV4 arm, 96 suffered rtPCR confirmed influenza infections, while out of 4301 subjects in the control arm, 138 individuals fell ill with rtPCR confirmed influenza. This results in an attack rate of 2.2% vs. 3.2% for RIV4 and IIV4, respectively, translating into a relative vaccine efficacy of +30% (95% CI: +10, +47). Analyses for alternative ILI definitions or for age, gender and other categories generally point in the same direction as the primary endpoint. The lower bound (LB) of the 95% confidence interval met the pre-specified, exploratory criterion for superior relative vaccine efficacy, LB > 9%.

Introducing uncertainty into the assessment of vaccine efficacy is the mismatch between the WHO recommended strains and the actually circulating strains. Based on epidemiology data provided by the CDC (Influenza Activity - United States, 2014–15 Season and Composition of the 2015–16 Influenza Vaccine; MMWR June 5, 2015/64(21); 583-590), more than 80% of circulating viruses were not antigenically matched to the vaccine strains in 2014-2015. The influenza season was primarily dominated by a drifted H3N2 strain, with substantial B activity occurring late in the season.

A post-hoc analysis was performed to assess the rVE for influenza A and B strains separately. For influenza A the attack rate in the RIV4 arm was 1.7% versus 2.7% in the control arm, resulting in a relative vaccine efficacy of +36% (95% CI: +14, +53). For influenza B the attack rates were 0.5% versus 0.6% for RIV4 and IIV4, respectively, resulting in a rVE of +4% (95% CI: -72, +46). These values illustrate that the overall vaccine efficacy as captured by the primary endpoint was primarily driven by the response to the H3N2 strain.

As antibody titres for the influenza A strains elicited by RIV4 in the two pivotal studies were satisfactory and the induction of cross protection is conceivable, efficacy against influenza A infection can be considered acceptably demonstrated. For influenza B infection, the confidence intervals are extremely wide due to the low incidence of cases. With regard to the B strains, more than 70% of circulating B strains in 2014/15 were of the B/Yamagata lineage, thus driving the B strain results. Clinical efficacy against infection with B/Victoria could not be shown in trial PSC12.

Immunogenicity data are available in a subset (about 7% or n~300 in each arm) of subjects from trial PSC12 and from the total population of trial PSC16.

Apart from the uncertainty of how the immunogenicity population was selected in PSC12, it is notable that the pre-defined NI criteria (seroconversion and GMT ratio according to CBER guidance) could not be met for both seroconversion as well as GMT-ratio for B/Victoria, demonstrating a substantial inferiority. For A/H1N1 seroconversion, non-inferiority was missed by a small amount. An analysis of the HAI parameters in the age groups 50-64 years and ≥65 years showed that seroconversion rates and GMTs were lower in the older age cohort for both investigated vaccines, in line with the reduced immune response usually reported in older subjects.

Immunogenicity parameters were defined as the primary outcome measure in trial PSC16, with the intention of establishing the immune response to RIV4 as non-inferior to the immune response elicited by a commercially available, egg-derived comparator as measured by the HAI assay. Seroconversion rate and GMT-ratio were co-primary endpoints and non-inferiority according to CBER criteria could be shown for both A strains as well as for B/Yamagata. For B/Victoria however, in line with results observed in trial PSC12, both seroconversion rates and GMT data were inferior to the comparator. Seroconversion was achieved by 40.6% (95% CI: 37.4, 43.7) of subjects treated with RIV4 in contrast to 58.2% (95% CI: 52.6, 63.6) of subjects who had received IIV4. GMT values were 43 (95% CI: 40, 46) for RIV4 recipients and 64 (95% CI: 57, 71) for IIV4 recipients. These results illustrate that the upper bounds of the confidence intervals for the recombinant vaccine were well below the lower bounds of the CIs for the egg-derived vaccine, leading to the conclusion that the immunogenicity for B/Victoria falls short of the magnitude of response expected from an influenza vaccine. While antibody titres are only surrogates for clinical efficacy and haemagglutinin assays may produce a different readout for an egg-derived versus a recombinant antigen, it is of concern that immunogenicity data consistently could not demonstrate NI for B/Victoria, while for B/Yamagata no such issue is evident.

Given that B/Victoria is the sole influenza B component in RIV3, this diminished response raises concerns about the level of protection in seasons with predominant B/Victoria circulation. Importantly, the removal of the B/Yamagata component does not address this weakness and may even render it more prominent. These findings are further corroborated by immunogenicity results from paediatric

study VAP00026 (see below), which did not meet non-inferiority criteria for B/Victoria either, although responses to other strains were acceptable.

Reassuringly, the applicant could further substantiate the low immunogenicity observed for B/Victoria in study PSC12 with one independent clinical trial conducted during the 2018/19 influenza season in the US (NCT03617523). RIV4 induced comparable humoral responses (GMT, GMTR, SCR) to each of the vaccine strains (including B/Victoria lineage), as did an egg-derived quadrivalent influenza vaccine, in adults aged 18-64 years. Furthermore, published data from a study performed in Hong Kong during the 2017-2018 influenza season in adults 65 to 82 years of age are available (Cowling BJ et al; Clin Infect Dis 2020). The study investigated the immunogenicity of RIV4, a IIV4-standard dose vaccine, a MF59 adjuvanted trivalent vaccine and a High Dose IIV3. HAI assay evaluations demonstrated that the immunogenicity of RIV4 was comparable to the immunogenicity of the IIV4 vaccine with regard to GMTs and fold increase for all strains including responses to the B/Victoria lineage, B/Brisbane/60/2008 strain.

Taken together, despite a potentially reduced immunogenicity towards the B/Victoria component, the totality of evidence from PSC12 and PSC16 (generated using a manufacturing process directly applicable to the RIV3 formulation) supports extrapolation of efficacy to RIV3 for the A/H1 and A/H3 components. The evidence base fulfils regulatory requirements for seasonal influenza vaccine authorisation, though it is noted that the extrapolation of B-lineage protection relies on immunogenicity data with acknowledged limitations. No additional clinical efficacy studies for RIV3 were conducted or waived, but this approach is justifiable given the well-established regulatory acceptance of HAI responses as surrogate endpoints for influenza vaccines and the comparability of manufacturing.

Paediatric data from study VAP00027 generally support extrapolation to younger age groups. Study VAP00027 was a phase 3, non-randomised, open-label, uncontrolled, multi-centre study in subjects 9 to 49 years of age in Europe and the US. 1308 subjects (648 aged 9 to 17 years and 660 aged 18 to 49 years) were enrolled and received 1 injection of RIV4. The primary objective of the study was to demonstrate the non-inferior HAI immune response of RIV4 for the 4 strains in subjects aged 9 to 17 years versus subjects aged 18 to 49 years. Non-inferiority assessment was based on GMTs and seroconversion rates with success declared if the lower limit of the 95% CIs was higher than 0.667 for the ratios of GMTs and higher than -10% for the differences of SC rates for all 4 strains. The primary analysis was conducted in 2 steps starting with testing for NI of GMTs between the age group 9-17 years and the age group 18-49 years. If NI of GMTs based on the 4 strains was demonstrated, then NI of the SC rates was also tested.

This approach is in line with the Guideline on Influenza Vaccines (Non-clinical and Clinical Module; EMA/CHMP/VWP/457259/2014) recommendations, which allows the successful comparison of immunogenicity in children from 9-17 to immunogenicity in young adults to support an indication in this paediatric age group. As the GL does not provide guidance with regard to suitable non-inferiority margins, again FDA Guideline for Industry recommendations have been implemented by the Applicant, which is accepted.

The enrolled study population was imbalanced with regard to gender and race, but this is not considered to have a meaningful impact on study outcomes.

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 with the younger age cohort achieving higher titres for all 4 strains. The HAI assay showed that comparable titres were achieved for the two A strains and the B/Yamagata strain (approx. 1900 for subjects 9-17), with much lower titres for B/Victoria (i.e. 400).

The provided subgroup analyses did not identify meaningful differences for age, race, sex, previous influenza vaccination. In the subgroup who was seronegative at baseline, the measured immune response was substantially higher than in those participants who were seropositive.

In younger children, the overall responses are considered supportive despite study VAP00026 being underpowered and stopped early.

The primary objective of study VAP00026 was to demonstrate non-inferiority of RIV4 versus IIV4 (Fluarix Tetra) in children from 3-8 years. The study was stopped for futility when approximately 25% of the planned number of participants were vaccinated. Non-inferiority could be demonstrated for 3 of the 4 strains, i.e. A/H1N1, H3N2 and B/Yamagata, but not for B/Victoria with regard to GMTs and seroconversion rates. The pertinent outcome of this study was added to section 5.1 of the SmPC.

Overall, while the clinical efficacy dataset for RIV3 is limited by the inconclusive nature of the only direct efficacy study and the suboptimal immunogenicity against B/Victoria, the broader dataset from RIV4 studies provides a coherent and supportive framework for extrapolation. The evidence is sufficient to support a positive assessment, provided that the limitations (particularly in relation to the B/Victoria response) are explicitly acknowledged in the benefit-risk discussion and product labelling.

5.3.5.2. Conclusions on the clinical efficacy

The key benefit of the trivalent recombinant influenza vaccine (RIV3) lies in its alignment with current public health recommendations, including those by WHO, FDA, and EMA, to discontinue the B/Yamagata lineage and transition to trivalent seasonal influenza vaccines. This regulatory and epidemiological context provides a strong rationale for the proposed formulation. The clinical efficacy assessment of the recombinant trivalent influenza vaccine (RIV3) relies on a combination of supportive evidence from study PSC04 and extrapolation from pivotal studies PSC12 and PSC16 conducted with the quadrivalent formulation (RIV4): Data from clinical studies conducted with the quadrivalent formulation (RIV4), which shares an identical manufacturing process and composition apart from the exclusion of B/Yamagata, allow for extrapolation of efficacy for the A/H1N1 and A/H3N2 components. Nevertheless, consistently reduced immune responses to the B/Victoria strain across studies PSC12, PSC16, and PSC04 represent a notable residual uncertainty, particularly as this is the only B-lineage component retained in RIV3. Direct clinical efficacy data from PSC04 remain inconclusive due to the antigenic mismatch during the study season and variability in antigen content across lots; however, these limitations are not considered critical for the assessment of efficacy under the current regulatory paradigm.

In participants ≥50 years of age, clinical efficacy of RIV4 has been demonstrated in pivotal study PSC12 by achieving non-inferiority to an egg-derived comparator vaccine in preventing rtPCR confirmed influenza-like illness. Efficacy of RIV4 in adults 18 - 49 years of age can be inferred based on comparative immunogenicity data from pivotal trial PSC16.

While efficacy against influenza A has been demonstrated, efficacy against influenza B remains inconclusive due to low case numbers. However, immunogenicity to the B/Yamagata strain was shown to be comparable to the egg-derived comparator, and concerns regarding inferior immunogenicity to B/Victoria may be mitigated by independent data suggesting no general weakness for this lineage.

Paediatric efficacy is supported by study VAP00027, in which the HAI immune response induced by RIV4 in participants aged 9 to 17 years was non-inferior to that in young adults. Data from study VAP00026 were added to section 5.1 of the SmPC.

In summary, the clinical efficacy data support an indication in adults and paediatric patients from 9 years of age. The outcomes of the quadrivalent vaccine can be extrapolated to the intended trivalent

formulation, as the recombinant haemagglutinin components are identical except for the omission of B/Yamagata in line with the WHO recommendation from September 2023.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2

For the purpose of this document, the following definitions apply:

- "Adverse event – AE" means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
- "Serious adverse event – SAE" means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- "Adverse drug reaction – ADR" means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

For studies PSC04 and PSC16, the assessment of safety was a primary objective. For studies PSC12, VAP00027 and VAP00026, it was a secondary objective. All objectives were to characterise the safety profile in terms of:

- Solicited injection site and solicited systemic reactions related to the vaccine during the 7 days following vaccination;
- Unsolicited adverse events (AEs) (also known as "spontaneously reported") related to the vaccine or not during the 28 days following vaccination;
- Serious adverse events (SAEs) for all studies and medically-attended adverse events (MAAEs) collected for at least 6 months following vaccination in studies PSC12 and PSC16 and up to 28 days after each vaccination in studies VAP00027 and VAP00026.

Safety follow-up included scheduled study visits at baseline and Day 28, with further safety data collection continued for at least 6 months post-vaccination. Additional contacts (e.g. telephone calls) were used as required per protocol.

Pooling of safety data was limited to studies with comparable design and study populations. While PSC12 and PSC16 used harmonised methodology allowing for meaningful comparison of RIV4 and IIV4, data from PSC04 were considered separately due to differences in study design and comparator (placebo), but carry particular weight for the assessment of RIV3 safety.

5.4.2. Patient exposure

The safety profile of RIV3 is supported by data from both RIV3 and RIV4 clinical studies. Pivotal safety data were derived from two Phase III trials with RIV4 (PSC12 and PSC16), using standardised AE collection procedures and comparing RIV4 to IIV4. Direct safety data for RIV3 originate from PSC04, a placebo-controlled trial in adults aged 18–49 years, which is considered relevant for the current application in terms of safety. Additional supportive evidence was provided by further studies in adults, children, and pregnant individuals.

Overall, 2344 subjects were exposed to RIV3 and 2304 subjects to placebo in PSC04 study, supporting the safety of RIV3 in adults 18 to 49 years.

The number of subjects exposed to RIV4 and IIV4 in each of the studies supporting the safety of RIV4 in children, adolescents, and in adults is summarised below in Table 39. These subjects constituted the "Safety Population" in each of the studies and included all subjects who received the study vaccine (RIV4 or IIV4) and provided safety data in the follow-up period.

Table 39. Number of children, adolescents, and adults exposed to RIV4 included in the safety population

Study Age Range	**RIV4**	**IIV4**
PSC12 ≥ 50 years of age	4328 50-64 years: N= 2 569 ≥ 65 years: N=1 759 65-74 years: N=1 234 ≥ 75 years: N = 525	4344 50-64 years: N=2 617 ≥ 65 years: N=1 727 65-74 years: N=1 254 ≥ 75 years: N = 473
PSC16 18-49 years of age	998	332
VAP00027 9-49 years of age	9-17 years: N = 641 18-49 years: N = 658	/
VAP00026 3-8 years of age	3-5 years: N = 81 6-8 years: N = 100	3-5 years: N = 91 6-8 years: N = 90
Total	**6806**	**4857**

5.4.3. Adverse events

An overview of the safety data (including solicited, unsolicited, serious and MAAEs) from both RIV4 studies in adults is presented below (Table *40*):

Table 40. Studies PSC16 and PSC12 - Overall safety data

	PSC12		**PSC16**	
	RIV4 N=4,328* %	**IIV4 N=4,344 %**	**RIV4 N=998 %**	**IIV4 N=332 %**
Subjects with ≥1 injection site reaction†	37.6	40.4	51.2	51.8

Local tenderness	34.3	37.1	48.0	46.7
Local pain	18.9	22.0	36.8	36.4
Firmness / Swelling	3.3	2.7	4.9	3.0
Redness	2.8	2.0	4.2	0.9
Subjects with ≥1 systemic reaction	25.0	25.6	34.1	35.8
Headache	12.7	13.5	20.3	21.1
Fatigue	12.2	12.1	16.5	16.6
Muscle pain	8.5	8.8	12.8	11.7
Joint pain	7.5	8.0	9.5	10.2
Nausea	4.9	4.9	9.0	9.3
Shivering / Chills	4.7	4.3	6.9	6.0
Fever	0.4	0.5	1.5	0.6
Subjects with ≥ 1 unsolicited Adverse Event (AE)	31.1	31.2	14.3	14.2
Subjects with ≥ 1 unsolicited Adverse Reaction (AR)	1.9	2.0	1.8	1.8
Subjects with ≥ 1 unsolicited AE leading to discontinuation	0.0	0.0‡	0.0	0.0
Subjects with ≥ 1 unsolicited severe AE	3.9	3.2	1.7	1.2
Subjects with ≥ 1 SAE	3.4	3.0	1.0	0.6
Subjects with ≥ 1 related SAE§	0.0	0.0	0.0	0.0
Death	0.2	0.3	0.0	0.0
Subjects with ≥ 1 MAE**	17.9	18.1	8.0	7.2
Subjects with ≥ 1 related MAE	0.5	0.5	0.2	0.6

* Safety population. Denominators are slightly lower for solicited events
† Reactogenicity Populations were defined as all randomised subjects who received study vaccine according to the treatment actually received and who had at least one non-missing data point for injection site, systemic or body temperature reactogenicity categories.
‡ One subject
§ SAEs and MAEs may be characterized by more than one AE term
** MAEs: Medically-Attended Adverse Events
NOTE: Results ≥ 1% reported to nearest whole percent; results > 0 but < 1% reported as < 1%.

Solicited adverse events

Solicited reactions were recorded systematically and considered related to vaccination.

The most frequently reported adverse drug reactions (ADRs) were local reactions at the injection site, particularly injection site pain, which occurred in 36.3% of RIV3 recipients in study PSC04 compared to 7.9% in the placebo group. Similar frequencies (34–40%) were observed in RIV4 studies when compared to IIV4. Injection site swelling and erythema also occurred more frequently in the RIV3 group but were mostly of mild to moderate intensity and self-limiting.

Systemic reactions such as fatigue, headache, and muscle pain (myalgia) were very common or common but occurred at similar rates across treatment groups, including placebo and IIV4 comparators. Headache and fatigue were the most frequently reported systemic symptoms, with no clear differences between study arms.

Fever was rare overall. In study PSC04, fever ≥38°C occurred in fewer than 1% of participants in both groups. A slightly higher frequency of low-grade fever was observed in RIV4 recipients in PSC16 (1.5%) compared to IIV4 (0.6%), but all cases resolved spontaneously. Other systemic events such as malaise and chills were infrequent and similarly distributed between groups, with Grade 3 events occurring in isolated cases only.

All ADRs were transient and predominantly of mild to moderate intensity. No patterns suggestive of serious, persistent, or unexpected safety signals were identified.

Studies in paediatric populations

In 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.

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.

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%, 16.1%, 7.3%, 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.

Unsolicited adverse events

Studies in adult population

Unsolicited adverse events in PSC04 study

In general, rates of unsolicited AEs were similar in both RIV3 and placebo groups. Unsolicited AEs that occurred in more than 1% of the subjects (>1%), regardless of causality or relationship to study vaccine, are summarised by body system (according to MedDRA) and treatment group in **Table 41**. The most frequently reported unsolicited AEs were pharyngo-laryngeal pain (49 [2%] participants in placebo group versus 42 [2%] in RIV3 group); cough (48 [2%] participants in RIV3 group versus 37 [2%] in placebo). Other frequently reported AEs were nasal congestion (37 participants, 2%),

headache (35 participants, 1%), and rhinorrhoea (30 subjects, 1%) for RIV3 and headache (43 subjects, 2%), nasal congestion (31 subjects, 1%), and rhinorrhoea (27 subjects, 1%) for placebo group.

There were no clinically concerning or unexpected events except for one case of pericarditis in the RIV3 group (classified as an SAE) and one case of mild Bell's palsy in RIV3 group. The event was initially classified as a treatment-related SAE, but was reclassified as "not-related" treatment-emergent event upon subsequent investigation.

Table 41. PSC04 - Treatment-Emergent (Unsolicited) Adverse Events by Body System and Preferred Term in ≥ 1% of Population - Safety Population

	Timeframe							
	Overall[1]		**Day of Vaccination**		**Days 1 to 7[2]**		**Days 8 to 28[2]**	
Body system	**Placebo**	**RIV3**	**Placebo**	**RIV3**	**Placebo**	**RIV3**	**Placebo**	**RIV3**
Preferred Term	**N=2304**	**N=2344**	**N=2304**	**N=2344**	**N=2304**	**N=2344**	**N=2304**	**N=2344**
Number of Subjects With At Least One Adverse Event	382 (17)	396 (17)	20 (1)	28 (1)	119 (5)	123 (5)	226 (10)	242 (10)
Gastrointestinal disorders	47 (2)	48 (2)	2 (<1)	6 (<1)	20 (1)	18 (1)	23 (1)	23 (1)
Diarrhoea	14 (1)	13 (1)	0	3 (<1)	10 (<1)	5 (<1)	4 (<1)	6 (<1)
Nausea	13 (1)	13 (1)	1 (<1)	0	1 (<1)	1 (<1)	11 (<1)	12 (1)
General disorders and administration site conditions[3]	47 (2)	45 (2)	7 (<1)	5 (<1)	4 (<1)	9 (<1)	33 (1)	32 (1)
Fatigue	22 (1)	13 (1)	2 (<1)	1 (<1)	1 (<1)	3 (<1)	18 (1)	9 (<1)
Pyrexia[4]	9 (<1)	16 (1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	6 (<1)	12 (1)
Infections and infestations[3]	103 (4)	101 (4)	0	1 (<1)	26 (1)	15 (1)	65 (3)	80 (3)
Nasopharyngitis	23 (1)	15 (1)	0	0	6 (<1)	0	16 (1)	13 (1)
Sinusitis	13 (1)	12 (1)	0	0	5 (<1)	3 (<1)	8 (<1)	8 (<1)
Upper respiratory tract infection	24 (1)	18 (1)	0	1 (<1)	8 (<1)	3 (<1)	15 (1)	14 (1)
Injury, poisoning & procedural complications	18 (1)	30 (1)	0	1 (<1)	6 (<1)	13 (1)	9 (<1)	12 (1)
Musculoskeletal and connective tissue disorders	36 (2)	30 (1)	1 (<1)	3 (<1)	8 (<1)	8 (<1)	25 (1)	15 (1)
Nervous system disorders[3]	57 (2)	58 (2)	4 (<1)	7 (<1)	5 (<1)	5 (<1)	43 (2)	44 (2)
Headache	43 (2)	35 (1)	0	1 (<1)	2 (<1)	1 (<1)	37 (2)	32 (1)
Pregnancy, puerperium and perinatal conditions	17 (1)	18 (1)	0	0	1 (<1)	0	1 (<1)	1 (<1)

Pregnancy	16 (1)	18 (1)	0	0	1 (<1)	0	0	1 (<1)
Psychiatric Disorders	11 (<1)	13 (1)	0	1 (<1)	4 (<1)	3 (<1)	5 (<1)	6 (<1)
Respiratory, thoracic and mediastinal disorders[5]	116 (5)	130 (6)	6 (<1)	5 (<1)	42 (2)	47 (2)	68 (3)	77 (3)
Cough	37 (2)	48 (2)	1 (<1)	3 (<1)	11 (<1)	17 (1)	23 (1)	26 (1)
Nasal congestion	31 (1)	37 (2)	0	1 (<1)	13 (1)	15 (1)	19 (1)	21 (1)
Pharyngolaryngeal pain	49 (2)	42 (2)	2 (<1)	1 (<1)	13 (1)	18 (1)	33 (1)	23 (1)
Rhinorrhea	27 (1)	30 (1)	3 (<1)	1 (<1)	11 (<1)	10 (<1)	12 (1)	18 (1)
Skin and subcutaneous tissue disorder	16 (1)	16 (1)	4 (<1)	2 (<1)	9 (<1)	8 (<1)	3 (<1)	6 (<1)

* Regardless of causality/relationship to study treatment Placebo or RIV3.

[1]Overall category includes all AEs reported through Day 28 contact and SAEs reported through the end of the study. Differences in values from those reported at
interim are due to updates to medical records following the Day 28 database lock and inclusion of SAEs reported through the end of the study (see Section 12.5 for SAE data). The incidence for pregnancy, puerperium and perinatal conditions and psychiatric disorders were <1% at the interim reporting period and were therefore not presented in the interim report.
[2]Category includes AEs with onset within timeframe
[3]This table includes, in one Placebo subject, one event of dizziness (Nervous System Disorders) and one event of chest pain (General Disorders and Administration
Site Conditions) that were later changed to the event term pneumonia (Infections and Infestations), but failed to be deleted from database used to generate the source tables listed below.
[4]Includes one case of pyrexia in the Placebo-treatment group that was later downgraded to non-serious by the Investigator, but failed to be removed from database used to generate the source tables listed below.
[5]Includes one case of pulmonary embolism (Respiratory, Thoracic and Mediastinal disorders) in the RIV3 group that was later downgraded to non-serious by the Investigator, but failed to be deleted from database used to generate the source tables listed below.

Subject experiencing multiple adverse events were counted once per body system and once per preferred term for each time period.

Unsolicited adverse reactions in PSC04 study

The most frequently reported treatment-related or possibly related AEs overall were fatigue (12 subjects, <1%), cough (16 subjects, <1%), nasal congestion (12 subjects, <1%), pharyngolaryngeal pain (16 subjects, <1%), rhinorrhoea (15 subjects, <1%) and headache reported in 21 subjects (<1%) each(source Table 31, PSC04 study report). The clinical severity of these events tended to be classified as mild or moderate, with a similar distribution in the two treatment groups. Severe adverse events (AEs) were rare across both groups. In the Placebo group, there were multiple headaches and isolated cases of photophobia, nausea, injection site pain, and arthralgia, while the RIV3 group reported one case each of headache and pharyngolaryngeal pain (source Table 32, PSC04 study report).

Unsolicited adverse events in PSC12 study

The proportion of participants reporting unsolicited adverse events was similar between the RIV4 and IIV4 vaccine groups. In total, 31.1% (1,345) of RIV4 recipients and 31.2% (1,355) of IIV4 recipients experienced at least one unsolicited AE. Adverse events reported by ≥2% of participants in either group are summarised in **Table 42**. The most frequently reported unsolicited AEs included cough, noted in 5.2% (226) of RIV4 and 5.8% (253) of IIV4 recipients; influenza-like illness, reported by 4.3% (186) and 4.6% (199), respectively; oropharyngeal pain, each at 4.1% (178 for RIV4, 177 for IIV4); headache, both at 3.3% (143 and 145); upper respiratory tract infection, at 3.0% (129) and 3.6% (156); fatigue, 2.4% (106) and 2.3% (100); myalgia, 2.2% (95) and 1.8% (79); and productive cough, 1.4% (59) and 2.2% (97), respectively. The great majority of unsolicited AEs were graded mild

or moderate and the distribution between the groups was comparable. Of the 4,328 subjects of the RIV4 588 reported mild and 590 moderate unsolicited AEs (13.6% each); in the IIV4 vaccine group including 4344 subjects it was 13.6% (591) and 14.3% (623) of participants. Only 3.9% (167) and 3.2% (141) of participants reported severe unsolicited AEs. Overall, there were no differences in the report of the most common unsolicited AEs by age category in study PSC12. In adults ≥50 years of age, most spontaneously reported AEs were also from mild to moderate severity (Grade 1-2); There were no reports of anaphylaxis, 2 reports of urticaria (1 in the RIV4 group and 1 in the IIV4 group), 13 reports of "rash" (5 in the RIV4 group and 8 in the IIV4 group) and one report of "allergic pruritus" in the RIV4 group.

Table 42. Study PSC12 – Most common unsolicited AE terms by severity – Safety Population

	RIV4 N=4328			**IIV4 N=4344**		
	%			**%**		
Preferred Term	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Cough	5.2	<1	0	5.8	<1	0
Influenza-like illness (i.e., Flu-like symptoms)	4.3	<1	0	4.6	<1	0
Oropharyngeal pain	4.1	<1	0	4.1	<1	0
Headache	3.3	<1	0	3.3	<1	0
Upper respiratory tract infection	3.0	<1	0	3.6	<1	0
Fatigue	2.4	<1	0	2.3	<1	0
Myalgia	2.2	<1	0	1.8	<1	0
Productive cough	1.4	0	0	2.2	<1	0

Unsolicited adverse reactions in PSC12 study

In PSC12 study within 28 days after vaccination, the percentages of participants who reported at least 1 unsolicited adverse reaction were 1.9% and 2.0% participants in the RIV4 and IIV4 groups, respectively. Most of the unsolicited reactions were similar in the 2 vaccine groups and were in the SOC "General disorders and administration site conditions" for 0.7% participants in the 2 groups, and in the SOC "Respiratory, thoracic and mediastinal disorders" for 0.6% and 0.7% participants in the RIV4 and IIV4 groups, respectively.

Unsolicited adverse events in PSC16 study

The proportion of participants who reported unsolicited adverse events (AEs) was similar between the RIV4 and IIV4 vaccine groups. In total, 14.3% (143) of participants in the RIV4 group and 14.2% (47) in the IIV4 group experienced at least one unsolicited AE. Adverse events reported by ≥1% of participants in either group are presented in **Table 43**. The most frequently reported unsolicited AEs included headache, reported by 2.0% (20) of RIV4 recipients and 1.5% (5) of IIV4 recipients; nasopharyngitis (1.3% \ [13] vs. 1.5% \ [5]); upper respiratory tract infection (1.0% \ [10] vs. 1.5% \ [5]); sinusitis (0.6% \ [6] vs. 1.5% \ [5]); and cough (1.4% \ [14] vs. 1.2% \ [4]). The majority of unsolicited adverse events (AEs) reported were of mild or moderate severity, with a similar distribution observed across the RIV4 and IIV4 vaccine groups. Among the 998 participants receiving RIV4, 7.2%

experienced mild and 5.4% moderate unsolicited AEs, while in the IIV4 group (n=332), 7.2% and 5.7% of participants reported mild and moderate unsolicited AEs, respectively. Severe unsolicited AEs were infrequent, occurring in 1.7% of RIV4 recipients and 1.2% of IIV4 recipients.

Table 43. Study PSC16 – Common unsolicited AE terms by severity - Safety Population

Adverse Event	**RIV4 N=998 %**			**IIV4 N=332 %**		
	Any	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Infections and Infestations						
Nasopharyngitis	1.3	0	0	1.5	0	0
Upper respiratory tract infection	1.0	1	0	1.5	0	0
Sinusitis	<1	0	0	1.5	0	0
Respiratory Disorders						
Cough	1.4	0	0	1.2	0	0
Nervous System Disorders						
Headache	2.0	1	0	1.5	0	0

PSC16 Report, Table 14.3.2.3.1 and Table 14.3.2.2.1

Unsolicited adverse reaction in PSC16 study

Within 28 days after vaccination in PSC16 study, the percentages of participants who reported at least 1 unsolicited adverse reaction were 1.8% in the 2 vaccine groups. Most of the unsolicited reactions were similar in both vaccine groups and were in the SOC "Gastrointestinal disorders" for 0.5% and 0.6% participants in the RIV4 and IIV4 groups respectively, and in the SOC "General disorders and administration site conditions" for 0.6% and 0.3% participants in the RIV4 and IIV4 groups, respectively.

Studies in paediatric population

Unsolicited adverse events in VAP00027 study

In study VAP00027, RIV4 was generally well tolerated by participants aged 9 to 49 years. Unsolicited adverse events were reported by 14.5% of participants in the 9–17-year age group and by 18.1% in the 18–49-year age group, with the majority of these events being mild to moderate in severity. Grade 3 AEs were rare, occurring in 1.6% of participants in the 9–17 age group and 2.1% in the 18–49 age group.

In the 9–17-year group, the most commonly reported System Organ Classes (SOCs) were "Infections and infestations" (4.8% of participants), "Respiratory, thoracic and mediastinal disorders" (4.1%), and "Gastrointestinal disorders" (2.5%). In the 18–49-year group, the most frequently reported SOCs included "Infections and infestations" (7.4%), "Respiratory, thoracic and mediastinal disorders" (4.4%), and "Nervous system disorders" (2.3%).

The most commonly reported AEs by preferred term included upper respiratory tract infections (1.1% in the 9–17-year group vs. 3.3% in the 18–49-year group), oropharyngeal pain (1.6% vs. 1.7%), and cough (1.7% vs. 1.2%). AEs typically occurred within the first four days post-vaccination, with a

similar incidence in both age groups (5.9% in the younger group vs. 5.6% in the older group). The majority of AEs lasted between 1 and 3 days (5.6% vs. 5.8%).

Unsolicited adverse reactions in VAP00027 study

Unsolicited adverse reactions were reported by 4.7% of participants aged 9 to 17 years and 4.0% of those aged 18 to 49 years. Most adverse reactions were mild to moderate, typically began between days 1 and 4, and resolved within 1 to 3 days (source: 5.3.5.2 VAP00027 Report, Table 8.42). Grade 3 ARs occurred in 1.1% of participants aged 9–17 years and 0.9% of those aged 18–49 years. Within 28 days of vaccination, 1.4% and 1.2% of participants in the 9 to 17 and 18 to 49 age groups, respectively, reported at least one unsolicited injection site adverse reaction, while 3.3% and 2.9% reported at least one unsolicited systemic adverse reaction. Specifically, for both age groups, Grade 3 unsolicited injection site ARs were observed in 0.9% of participants (source: 5.3.5.2 VAP00027 Report, Table 8.38). One participant (0.2%) in the 9–17 age group experienced one unsolicited systemic AR rated as Grade 3 within 28 days post-vaccination (grade 3 nausea). No further participants in the 9–17 age group reported any Grade 3 unsolicited systemic ARs within 28 days following vaccination.

In participants aged 9–17 years, unsolicited systemic adverse reactions were most commonly reported in "General disorders and administration site conditions" (1.7%), "Respiratory, thoracic and mediastinal disorders" (1.7%), and "Gastrointestinal disorders" (1.1%), while in those aged 18–49 years, the most common SOCs were "Respiratory, thoracic and mediastinal disorders" (1.5%) and "General disorders and administration site conditions" (1.2%).

The most commonly reported ARs, categorised by Preferred Term, included 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%). In the 9–17 years age group, one participant with a history of asthma experienced an asthma exacerbation on Day 2, which was determined by the investigator to be related to the vaccination. The frequency of subjects experiencing at least 1 unsolicited AR within 28 days of vaccination per SOC and PT in the SafAS is presented in **Table 44**.

Table 44. Study VAP00027 – Unsolicited ARs within 28 days after vaccine injection, by SOC and PT – Safety population

	9 to 17 years (N=641)				18 to 49 years (N=658)			
Subjects experiencing at least one:	**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
Gastrointestinal disorders	7	1.1	(0.4 ; 2.2)	9	6	0.9	(0.3 ; 2.0)	7
Abdominal discomfort	1	0.2	(0 ; 0.9)	1	1	0.2	(0 ; 0.8)	1
Diarrhoea	1	0.2	(0 ; 0.9)	2	4	0.6	(0.2 ; 1.5)	4
Nausea	5	0.8	(0.3 ; 1.8)	5	2	0.3	(0 ; 1.1)	2
Vomiting	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
General disorders and administration site conditions	11	1.7	(0.9 ; 3.0)	14	8	1.2	(0.5 ; 2.4)	13
Fatigue	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Injection site bruising	3	0.5	(0.1 ; 1.4)	3	3	0.5	(0.1 ; 1.3)	3
Injection site erythema	1	0.2	(0 ; 0.9)	1	2	0.3	(0 ; 1.1)	2
Injection site induration	2	0.3	(0 ; 1.1)	2	3	0.5	(0.1 ; 1.3)	3
Injection site pain	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1
Injection site pruritus	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1
Injection site swelling	2	0.3	(0 ; 1.1)	2	3	0.5	(0.1 ; 1.3)	3
Swelling	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Vaccination site induration	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Vaccination site rash	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Infections and infestations	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1
Rhinitis	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Upper respiratory tract infection	1	0.2	(0 ; 0.9)	1	1	0.2	(0 ; 0.8)	1
Metabolism and nutrition disorders	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Decreased appetite	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Nervous system disorders	2	0.3	(0 ; 1.1)	2	1	0.2	(0 ; 0.8)	1
Dizziness	2	0.3	(0 ; 1.1)	2	0	0	(0 ; 0.6)	0
Dysgeusia	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1
Respiratory, thoracic and mediastinal disorders	11	1.7	(0.9 ; 3.0)	15	10	1.5	(0.7 ; 2.8)	11
Asthma	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Cough	4	0.6	(0.2 ; 1.6)	4	1	0.2	(0 ; 0.8)	1
Nasal congestion	2	0.3	(0 ; 1.1)	2	4	0.6	(0.2 ; 1.5)	4
Oropharyngeal pain	2	0.3	(0 ; 1.1)	2	4	0.6	(0.2 ; 1.5)	4
Productive cough	1	0.2	(0 ; 0.9)	1	0	0	(0 ; 0.6)	0
Rhinorrhoea	5	0.8	(0.3 ; 1.8)	5	2	0.3	(0 ; 1.1)	2
Skin and subcutaneous tissue disorders	0	0	(0 ; 0.6)	0	2	0.3	(0 ; 1.1)	2
Rash	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1
Urticaria	0	0	(0 ; 0.6)	0	1	0.2	(0 ; 0.8)	1

n: number of subjects experiencing the endpoint listed in the first column
n ARs: number of ARs
Percentages are based on N

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.

Unsolicited adverse events in VAP00026 Study

In study VAP00026, both RIV4 and IIV4 were generally well tolerated in children aged 3-8 years. The occurrence of unsolicited AEs was similar between the two groups, with 24.3% in the RIV4 group and 26.0% in the IIV4 group reporting at least one AE. For the 3–5 years subgroup, 28.4% of the RIV4 group and 29.7% of the IIV4 group reported unsolicited AEs, while the 6–8 years subgroup had rates of 21.0% for RIV4 and 22.2% for IIV4. Most AEs were mild to moderate, with Grade 3 AEs being rare (3.3% in RIV4 vs. 3.9% in IIV4). Unsolicited AEs were most common in the categories of "Infections and infestations," "Respiratory disorders," and "Gastrointestinal disorders." Upper respiratory tract infections were the most frequent AEs in both groups (4.4%), followed by pharyngitis streptococcal, rhinorrhoea, and cough. Following the first vaccination, 16.9% of RIV4 recipients and 15.4% of IIV4 recipients reported unsolicited AEs. The onset of AEs after the first dose was more delayed in the RIV4 group (mostly days 5–8), while AEs in the IIV4 group appeared earlier and resolved faster (for further details, please refer to 5.3.5.1 VAP00026 Report).

Unsolicited adverse reactions in VAP00026 Study

In study VAP00026, the frequency of subjects experiencing at least 1 unsolicited AR within 28 days after any vaccination is presented by SOC and PT in the SafAS in Table 45.

Table 45. Study VAP00026 – Unsolicited ARs – Safety population

	RIV4											
	3 to 5 years (N=81)				**6 to 8 years (N=100)**				**3 to 8 years (N=181)**			
Subjects 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
Gastrointestinal disorders	1	1.2	(0 ; 6.7)	1	0	0	(0 ; 3.6)	0	1	0.6	(0 ; 3.0)	1
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)**			
Subjects 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

n: number of subjects experiencing the endpoint listed in the first column
n ARs: number of ARs
Percentages are based on N
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.

In the RIV4 group, a total of 6 unsolicited ARs were reported by 4 (2.2%) participants (2 participants in each age subgroup); and in the IIV4 group, a total of 2 unsolicited ARs were reported by 2 (1.1%) participants (1 participant in each age subgroup).

In the RIV4 group, unsolicited ARs were reported in the SOCs of "General disorders and administration site conditions" by 2 participants (1 in each age subgroup), "Gastrointestinal disorders" by 1 participant (3 to 5 years age subgroup), "Respiratory, thoracic and mediastinal disorders" by 1 participant (6 to 8 years age subgroup), and "Vascular disorders" by 1 participant (6 to 8 years age subgroup).

In the IIV4 group, unsolicited ARs were reported by 1 participant each in the SOCs of "Ear and labyrinth disorders" (6 to 8 years age subgroup) and "Gastrointestinal disorders" (3 to 5 years age subgroup). A total of 2 Grade 3 unsolicited ARs were reported by 1 previously vaccinated participant who experienced injection site induration and injection site erythema 1 day after the vaccination with RIV4. Both events resolved spontaneously (source: 5.3.5.1 VAP00026 Report, Table 8.38 and Appendix 16.7, Listing 7.1).

5.4.3.1. Adverse drug reactions

The adverse drug reactions (ADRs) included in the SmPC are based on pooled clinical data from studies PSC04, PSC12, PSC16, and VAP00027 and are presented per System Organ Class (SOC) as shown in **Table 46.** The classification of events as ADRs was based on clinical judgement, considering the temporal association, frequency, biological plausibility, and consistency across studies. Solicited reactions were recorded systematically and are generally considered related to vaccination, while unsolicited events were only included if assessed as related by the investigator. Not all AEs were classified as ADRs; events lacking consistent association with the vaccine or considered unrelated were excluded. The frequency categories were derived from the pooled safety database and assigned according to standard EMA guidance.

Table 46: ADRs proposed for inclusion in the SmPC

Immune System disorders		**Link to data***
Frequency not known	Hypersensitivity including anaphylactic reaction	
Nervous system disorders		
Very Common	Headache, Malaise / Fatigue	PSC04, PSC12, PSC16, VAP00027
Rare	Dizziness	PSC12, VAP00027

Frequency not known	Guillain-Barré syndrome	
Respiratory, thoracic and mediastinal disorders		
Uncommon	Asthma, Cough, Oropharyngeal pain, Rhinorrhoea	PSC04, VAP00027
Metabolism and nutrition disorders		
Uncommon	Decreased appetite	VAP00027
Gastrointestinal disorders		
Common	Nausea	VAP00027, PSC16
Uncommon	Abdominal discomfort, Diarrhoea, Vomiting	PSC16, PSC12, VAP00027
Skin and subcutaneous tissue disorders		
Uncommon	Dermatitis, Pruritus, Rash	PSC16, VAP00027
Rare	Urticaria	PSC12
Musculoskeletal and connective tissue disorders		
Very Common	Myalgia, Arthralgia	PSC12, PSC16
General disorders and administration site conditions		
Very Common	Local tenderness, Local pain / Injection site pain	PSC04, PSC12, PSC16, VAP00027
Common	Fever, Shivering / Chills, Firmness / Swelling, Redness / Injection site erythema, Bruising, Induration	PSC04, PSC12, PSC16, VAP00027
Uncommon	Flu-like symptoms, Injection site pruritus, Rash	PSC12, PSC16, VAP00027

* include the link to source data

The presentation of ADRs in the SmPC is considered acceptable. The listed reactions are consistent with those observed in clinical studies conducted with both RIV3 and RIV4. Frequencies are appropriately classified based on pooled data where applicable, and the terminology used aligns with MedDRA preferred terms. Importantly, the ADRs already included in the SmPC of RIV4 are also applicable to RIV3, as no relevant differences in the safety profile were identified. The overall structure and content of the table in section 4.8 of the SmPC are in line with regulatory expectations, and no clinically relevant ADRs appear to be missing. Therefore, the current presentation is deemed adequate to inform healthcare professionals and supports safe use of the vaccine.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

AEs of special interest

In study PSC12, the collection of potential hypersensitivity events was not pre-specified but was evaluated post hoc. Events were mostly mild in severity and non-serious, and, for many, causality is uncertain. Rates were low. Hypersensitivity was experienced by 4 subjects in PSC12 Study (1 subject in RIV4 group and 3 subjects in IIV4 group).

RIV4 vaccine group

A subject in the RIV4 group experienced hypersensitivity not related to the vaccine classified as an allergy. The subject was treated with salbutamol sulfate since 2006. The episode presented mild severity and was recovered within 2 days.

IIV4 vaccine group

A subject in the IIV4 group experienced hypersensitivity not related to the vaccine classified as an environmental allergy. The subject was treated with montelukast sodium . The episode presented mild severity and was not recovered.

A subject in the IIV4 group experienced hypersensitivity not related to the vaccine classified as an allergy exacerbation. The subject was treated with cetirizine hydrochloride since 2000 and salbutamol since 1995. The episode presented mild severity was recovered within a week.

A subject in the IIV4 group experienced a hypersensitivity not related to the vaccine classified as an allergy attack. The subject was treated with montelukast sodium . The episode presented mild severity and was recovered on the same day.

One case of Bell's palsy has been reported in study PSC12 after vaccination with RIV4. A brief case narrative about the subject who reported with Bell's palsy in PSC12 Study was provided. The subject received RIV4 vaccine and had a relevant medical history including hypercholesterolemia, hypertension and cataract. 85 days after vaccination, the subject was diagnosed with Bell's Palsy and treated with valacyclovir and prednisone. The event was reported as VIIth nerve paralysis and classified as a moderate treatment emergent adverse event (TEAE) in PSC12 Report, [Table 14.3.2.2.1.1]. The event occurred beyond the risk window, considering the risk window period of 8 to 30 days for cranial nerve disorders. The AE was described as moderate, non-serious and not related to the vaccine. The event resolved 17 days after diagnosis.

In study VAP00027 and VAP00026, there were no reports of AESIs.

Serious Adverse Events (SAE)

In study PSC04, a total of 66 subjects reported at least one SAE throughout duration of study: 30 subjects (1%) in the RIV3 group and 36 subjects (2%) in the placebo group (Table 47). None of the SAEs were considered to be related, and only one, "pericardial effusion", in a subject receiving RIV3, was judged to be "possibly related".

Table 47: Study PSC04 – Summary of all deaths and serious TEAE - Safety Population

MedDRA System Organ Class	**RIV3** **N=2,344** **n (%)**	**Placebo** **N=2,304** **n (%)**
Number of Subjects with >=1 AE	30 (1)	36 (2)
Blood and lymphatic system disorders	1 (<1)	1 (<1)
Cardiac disorders	2 (<1)	2 (<1)
Congenital, familial, and genetic disorders	0	1 (<1)
Eye disorders	0	1 (<1)

Gastrointestinal disorders	3 (<1)	3 (<1)
General disorders and administration site conditions	1 (<1)	4 (<1)
Hepatobiliary disorders	1 (<1)	1 (<1)
Infections and infestations	4 (<1)	12 (1)
Injury, poisoning, and procedural complications	5 (<1)	2 (<1)
Metabolism and nutrition disorders	0	3 (<1)
Musculoskeletal and connective tissue disorders	2 (<1)	2 (<1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (<1)	1 (<1)
Nervous system disorders	1 (<1)	2 (<1)
Pregnancy, puerperium, and perinatal conditions	0	3 (<1)
Psychiatric disorders	3 (<1)	4 (<1)
Renal and urinary disorders	0	1 (<1)
Reproductive system and breast disorders	5 (<1)	2 (<1)
Respiratory, thoracic, and mediastinal disorders	3 (<1)	0

In study PSC12, there were 277 subjects with at least one SAE reported overall during the 6 months of follow-up after vaccination, 145 (3.4%) of the RIV4 subjects and 132 (3%) of the IIV4 subjects (Table 48). SAEs may have been characterised by more than one adverse event term. Brief narratives of each SAE were provided in Appendix 14 of the PSC12 Report (5.3.5.1 PSC12 Report, [Section 14.3.3]). No SAEs were considered related to study vaccine. There was no notable difference between the 2 treatment groups with respect to the profile of events reported as SAEs. The SAE terms are tabulated by System Organ Class (SOC). There was no difference between vaccine groups with respect to all SAE terms (p=0.43) (5.3.5.1 PSC12 report), and no difference in the overall profile of SAEs in this older adult population. Overall, SAEs were infrequent and appeared to reflect expected events in the older adult population.

Table 48: Study PSC12 – Number of subjects with at least one SAE and total number of SAEs reported - Safety Population

MedDRA System Organ Class	**RIV4 N=4,328 n (%)**	**IIV4 N=4,344 n (%)**
Any SAE	145 (3.4)	132 (3.0)
Infections and infestations	19 (0.4)	26 (0.6)
Cardiac disorders	23 (0.5)	19 (0.4)
Musculoskeletal and connective tissue disorders	22 (0.5)	16 (0.4)
Nervous system disorders	19 (0.4)	14 (0.3)

Gastrointestinal disorders	21 (0.5)	9 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (0.2)	20 (0.5)
General disorders and administration site conditions	14 (0.3)	10 (0.2)
Respiratory, thoracic and mediastinal disorders	11 (0.3)	9 (0.2)
Injury, poisoning and procedural complications	9 (0.2)	8 (0.2)
Metabolism and nutrition disorders	7 (0.2)	7 (0.2)
Vascular disorders	5 (0.1)	6 (0.1)
Surgical and medical procedures	7 (0.2)	3 (0.1)
Renal and urinary disorders	7 (0.2)	1 (0.0)
Hepatobiliary disorders	2 (0.0)	4 (0.1)
Reproductive system and breast disorders	1 (0.0)	3 (0.1)
Blood and lymphatic system disorders	3 (0.1)	0
Investigations	2 (0.0)	1 (0.0)
Psychiatric disorders	0	3 (0.1)
Ear and labyrinth disorders	0	1 (0.0)
Skin and subcutaneous tissue disorders	0	1 (0.0)

In study PSC16, SAEs were reported from 12 subjects in the full duration of follow-up. SAEs may have been characterised by more than one AE term. Ten of the subjects were RIV4 subjects (1% of RIV4 subjects) and 2 were IIV4 subjects (0.6% of IIV4 subjects). A serious adverse event may have been characterised by more than one adverse event terms. The most commonly involved SOCs were gastrointestinal, cardiac disorders and infections and infestations. Only myocardial infarction was reported from > 1 subject (n=2) and none of the SAEs was considered related to study vaccine. Brief narratives of the 12 subjects with SAEs were provided in the PSC16 Report (5.3.5.1 PSC16 Report).

Table 49. Study PSC16 – Number of subjects with at least one SAE and total number of SAE terms reported - Safety Population

MedDRA System Organ Class	**RIV4 N=998 n (%)**	**IIV4 N=332 n (%)**
Subjects with any SAE	10 (1.0)	2 (0.6)
Gastrointestinal disorders	1 (0.1)	2 (0.6)
Gastrointestinal haemorrhage	0	1 (0.3)
Pancreatitis	0	1 (0.3)
Small intestinal obstruction	1 (0.1)	0

Cardiac disorders	2 (0.2)	0
Myocardial infarction	2 (0.2)	0
Infections and infestations	2 (0.2)	0
Appendicitis	1 (0.1)	0
Periumbilical abscess	1 (0.1)	0
Hepatobiliary disorders	0	1 (0.3)
Cholecystitis	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.1)	0
Road traffic accident	1 (0.1)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0
Neck pain	1 (0.1)	0
Nervous system disorders	1 (0.1)	0
Metabolic encephalopathy	1 (0.1)	0
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0
Abortion spontaneous	1 (0.1)	0
Reproductive system and breast disorders	1 (0.1)	0
Ovarian cyst	1 (0.1)	0
Surgical and medical procedures	1 (0.1)	0
Arm amputation	1 (0.1)	0

In study VAP00027, there were 10 subjects (0.8%) who reported at least 1 SAE (6 subjects [0.5%] within 28 days of vaccination and 4 subjects [0.3%] during the 6-month follow-up. Results were similar between age groups with 3 (0.5%) subjects who reported 4 SAEs in the 9 to 17 years age group and 7 (1.1%) subjects who reported 9 SAEs in the 18 to 49 years age group (source: 5.3.5.2 VAP00027 Report, Table 8.45).

In study VAP00026, one SAE was reported during the study for a subject in the IIV4 group. There were no SAEs in the RIV4 group.

Deaths

There were 2 deaths in study PSC04: one subject in the RIV3 group experienced a fatal pulmonary embolism, and one subject in the placebo group died due to a motor vehicle accident. Both events were considered SAEs. In the opinion of the Investigators, neither event was considered to be related to the vaccine.

There were 20 deaths throughout the duration of study PSC12 in adults ≥ 50 years of age. Eight were deaths among RIV4 subjects and 12 were among IIV4 subjects. The causes of death were of no particular concern nor appeared to reflect pathophysiology not common to the age group of subjects that were enrolled in this trial. The single IIV4 subject who died of respiratory failure resulting from

pneumonia was not among the subjects with a RT-PCR-confirmed case of influenza. None of the deaths was considered related to study vaccine.

No deaths were reported in study PSC16 or in paediatric studies VAP00027 and VAP00026.

Other significant adverse events

MAAEs

All AEs that required attention of a medical professional (MAAEs) were reported during the 6 months following vaccination for both studies PSC12 and PSC16. MAAEs may have been characterised by more than one AE term. There was no notable difference between treatment groups with respect to the number or types of events: for study PSC12, there were 4.8% of subjects reporting MAAEs in the RIV4 group and 5.4% in the IIV4 group; for study PSC16, there were 8.0% of subjects reporting MAAEs in the RIV4 group and 7.2% in the IIV4 group. There were 19 MAAEs attributed to "influenza-like illness", 6 among RIV4 subjects and 13 among IIV4 subjects. These events were not necessarily evaluated by the investigative sites at the time of the event or tested for rtPCR confirmation of influenza infection. The MAAEs reported in the 28 days following vaccination are described by MedDRA preferred terms and SOC in **Table 50.**

Treatment related MAAEs reported during PSC12 study were similarly distributed across the vaccine groups through the 6 months of follow-up. Treatment related MAAEs were reported from 774 (17.9%) and 785 (18.1%) subjects in the RIV4 and IIV4 vaccine groups, respectively. MAAEs were reported by fewer subjects in the RIV4 group however, the difference was not statistically significant (p = 0.82). Most of MAAEs were reported from only one or two individuals; the only MAAEs that were reported from ≥ 1% of subjects in either treatment group were upper respiratory infection, sinusitis, bronchitis, cough and influenza-like illness and were consistent with the expected AEs in the ≥ 50 years age group enrolled in this study. These MAAEs are part of the related treatment-emergent AE, also known as unsolicited AEs.

Table 50. Study PSC12 - Treatment related MAAEs by SOC/PT – Safety Population

	RIV4 (N=4328)				**IIV4 (N=4344)**			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Any	21	0.5	(0.3 ; 0.7)	29	21	0.5	(0.3 ; 0.7)	30
Infections and infestations	14	0.3	(0.2 ; 0.5)	16	8	0.2	(0.1 ; 0.4)	8
Upper respiratory tract infection	5	0.1	(0.0 ; 0.3)	5	2	0.0	(0.0 ; 0.2)	2
Bronchitis	3	0.1	(0.0 ; 0.2)	3	1	0.0	(0.0 ; 0.1)	1
Nasopharyngitis	2	0.0	(0.0 ; 0.2)	3	1	0.0	(0.0 ; 0.1)	1
Sinusitis	1	0.0	(0.0 ; 0.1)	1	1	0.0	(0.0 ; 0.1)	1
Viral upper respiratory tract infection	1	0.0	(0.0 ; 0.1)	1	1	0.0	(0.0 ; 0.1)	1
Cellulitis	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0

Hordeolum	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Pharyngitis streptococcal	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Respiratory tract infection	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Respiratory tract infection bacterial	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Respiratory, thoracic and mediastinal disorders	4	0.1	(0.0 ; 0.2)	8	7	0.2	(0.1 ; 0.3)	8
Cough	0	0	(0.0 ; 0.1)	0	3	0.1	(0.0 ; 0.2)	3
Tonsillar disorder	2	0.0	(0.0 ; 0.2)	2	1	0.0	(0.0 ; 0.1)	1
Nasal congestion	1	0.0	(0.0 ; 0.1)	1	1	0.0	(0.0 ; 0.1)	1
Rhinorrhoea	2	0.0	(0.0 ; 0.2)	2	0	0	(0.0 ; 0.1)	0
Wheezing	2	0.0	(0.0 ; 0.2)	2	0	0	(0.0 ; 0.1)	0
Nasal oedema	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Oropharyngeal pain	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Pharyngeal erythema	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Sinus congestion	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
General disorders and administration site conditions	1	0.0	(0.0 ; 0.1)	1	5	0.1	(0.0 ; 0.3)	5
Influenza like illness	1	0.0	(0.0 ; 0.1)	1	2	0.0	(0.0 ; 0.2)	2
Pyrexia	0	0	(0.0 ; 0.1)	0	2	0.0	(0.0 ; 0.2)	2
Injection site pruritus	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Nervous system disorders	2	0.0	(0.0 ; 0.2)	2	2	0.0	(0.0 ; 0.2)	2
Dizziness	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Headache	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Migraine	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Sinus headache	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Blood and lymphatic system disorders	1	0.0	(0.0 ; 0.1)	1	1	0.0	(0.0 ; 0.1)	1
Lymphadenopathy	1	0.0	(0.0 ; 0.1)	1	1	0.0	(0.0 ; 0.1)	1
Skin and subcutaneous tissue disorders	0	0	(0.0 ; 0.1)	0	2	0.0	(0.0 ; 0.2)	2

Drug eruption	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Pruritus	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Cardiac disorders	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Cardiac failure congestive	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Gastrointestinal disorders	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	2
Diarrhoea	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Vomiting	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Immune system disorders	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Seasonal allergy	0	0	(0.0 ; 0.1)	0	1	0.0	(0.0 ; 0.1)	1
Metabolism and nutrition disorders	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0
Vitamin D deficiency	1	0.0	(0.0 ; 0.1)	1	0	0	(0.0 ; 0.1)	0

N: number of subjects experiencing the endpoint listed in the first column
n ARs: number of ARs

During study PSC16, both MAAEs recorded in RIV4 group were classified as infections and infestations such as bronchitis and pharyngitis streptococcal. Infections and infestations ADRs such as bronchitis and pharyngitis are unlikely to be caused by the vaccine since RIV4 is a recombinant vaccine. In IIV4 group, one MAAE was classified as infections and infestations, specifically as a vulvovaginal mycotic infection and the other one was classified as skin and subcutaneous disorders, precisely as acne (Table 51).

Table 51: Study PSC16 - Treatment related MAAEs by SOC/PT - Safety Population

	RIV4 (N=998)				**IIV4 (N=332)**			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Any	2	0.2	(0.0 ; 0.7)	2	2	0.6	(0.1 ; 2.2)	2
Infections and infestations	2	0.2	(0.0 ; 0.7)	2	1	0.3	(0.0 ; 1.7)	1
Bronchitis	1	0.1	(0.0 ; 0.6)	1	0	0	(0.0 ; 1.1)	0
Pharyngitis streptococcal	1	0.1	(0.0 ; 0.6)	1	0	0	(0.0 ; 1.1)	0
Vulvovaginal mycotic infection	0	0	(0.0 ; 0.4)	0	1	0.3	(0.0 ; 1.7)	1
Skin and subcutaneous tissue disorders	0	0	(0.0 ; 0.4)	0	1	0.3	(0.0 ; 1.7)	1
Acne	0	0	(0.0 ; 0.4)	0	1	0.3	(0.0 ; 1.7)	1

n: number of subjects experiencing the endpoint listed in the first column
n ARs: number of ARs

During study VAP00027, there were 66 subjects (5.1%) who reported at least 1 MAAE (62 subjects [4.8%] within 28 days of vaccination and 6 subjects [0.5%] during the 6-month follow-up). Results were similar between age groups with 29 (4.5%) subjects who reported 39 MAAEs in the 9 to 17 years age group and 37 (5.6%) subjects who reported 47 MAAEs in the 18 to 49 years age group. None of these MAAEs were considered as related to the vaccine by the Investigator and the Sponsor (5.3.5.2 VAP00027 Report, [Table 8.53]).

In study VAP00026, one previously unvaccinated subject experienced a Grade 3 bacterial infection categorized in the SOC "Infections and infestations" (infectious agent unspecified). The event occurred 2 days after the 1st vaccination with IIV4 and lasted 7 days. Hospitalisation and healthcare provider contact were required. The subject recovered with medication. The event was assessed as not related to the study vaccine and was considered as a MAAE. A total of 21 and 15 MAAEs were reported within 28 days after any vaccination with RIV4 and IIV4, respectively (5.3.5.1 VAP00026 Report, Section 8, [Table 8.117]). Within 28 days after any vaccination, at least one MAAE was reported in 9.9% of subjects in the RIV4 group and 6.6% in the IIV4 group, with higher rates observed in older age subgroups (6–8 years). None of the MAAEs were considered related to the study vaccines. Most MAAEs fell under the "Infections and infestations" system organ class, affecting 8.3% (RIV4) and 4.4% (IIV4) of participants, again with higher incidence in the 6–8-year age group. There were no Grade 3 MAAEs reported during the study.

5.4.5. Discontinuation due to adverse events

In study PSC04, 3 participants (< 1%) in each vaccine group (RIV3 and placebo) discontinued due to an AE. One participant (< 1%) in each vaccine group (RIV3 and placebo) discontinued due to an SAE leading to death. None of them was related to the vaccine.

In study PSC12, 0.2% of participants in each vaccine group discontinued due to an AE. There were no AEs that led to study discontinuation for any participant in study PSC16. In study PSC12, 20 participants were discontinued due to serious adverse events (SAEs) leading to death:

- In the RIV4 group, 8 deaths were recorded. None of them was related to the vaccine.
- In the IIV4 group, 12 deaths were recorded. None of them was related to the vaccine.

Besides these deaths, 2 other participants were discontinued due to AEs (general and psychiatric disorders) in the RIV4 group. Thus, a total of 22 participants were discontinued due to AEs/SAEs.

In study VAP00027, no participant in the 9 to 17 years age group experienced an AE leading to study discontinuation and there were 2 participants in the 18 to 49 years age group that experienced an AE leading to study discontinuation:

- One participant experienced an intentional overdose on D07, not considered as related to the vaccine by the Investigator and the Sponsor.
- One participant experienced urticaria on the day after injection, followed by chills, fever, headache, malaise, myalgia, injection site swelling, bruising, erythema, pain, and induration on D02, all considered as related to the vaccine by the Investigator and the Sponsor.

In study VAP00026, no participant experienced an AE leading to study discontinuation.

5.4.6. Safety in special populations

Data on pregnant women

A large Phase IV observational study (VAP00007) involving over 14,500 pregnant women immunised with recombinant quadrivalent influenza vaccine (RIV4) found no safety concerns related to pregnancy, birth, or neonatal/infant outcomes. Overall, 48,781 pregnant women, including those with chronic conditions, were immunised with either RIV4 (30.7%) or inactivated quadrivalent influenza vaccine (IIV4, 69.3%) during the 2018–2019 and 2019–2020 influenza seasons. The rates of major birth defects and miscarriages in women who received RIV4 either shortly before or during pregnancy were comparable to those in the IIV4 group. Frequencies of pregnancy complications such as eclampsia/preeclampsia, preterm labour, spontaneous abortion, foetal anomalies, placental abruption, and stillbirth were similar between RIV4 and IIV4 recipients. Neonatal and infant outcomes, including small for gestational age, congenital anomalies, preterm birth, low birth weight, and failure to thrive, were also comparable between the two vaccine groups.

During the clinical development of RIV3, 3 pregnancies were reported, 2 of these subjects reported elective termination while the 3rd subject had an uneventful term pregnancy. In the PSC04 study involving RIV3, 20 pregnancies were reported during follow-up with 12 live births, one spontaneous abortion, 2 elective abortions, and 5 cases were lost to follow-up. In the PSC16 study, 8 pregnancies were reported: 7 cases received during the reporting period (reporting for pregnancies within 2 months of vaccination, study duration 8 months) of the study and 1 case received after the reporting period. In study PSC16, eight women became pregnant after receiving RIV4, with seven delivering healthy full-term infants and one experiencing a miscarriage, with no evidence of adverse effects from preconception exposure.

During post-marketing surveillance, administration of RIV (RIV3/RIV4) during pregnancy was reported in 42 spontaneously reported cases.

RIV3 and RIV4 have not been studied in breastfeeding women, and safety data in this population remain unavailable.

5.4.7. Immunological events

Please refer to 5.4.4., Adverse Events of Special Interest.

5.4.8. Safety related to drug-drug interactions and other interactions

There are currently no data regarding simultaneous administration of RIV3 or RIV4 with other vaccines.

5.4.9. Vital signs and laboratory findings

Neither of the studies included routine safety laboratory evaluations (e.g., blood chemistry and standard haematology determinations) as part of routine study procedures for the evaluation of safety. Occasional abnormal laboratory test performed as part of routine medical care were reported as AE.

Complete physical examinations were not included as part of routine study procedures for the evaluation of safety. Targeted physical examinations were performed if indicated by the occurrence of an adverse event. Subjects in study PSC12 were instructed to return for evaluation and nasopharyngeal swab testing for influenza if they experienced symptoms consistent with influenza-like illness (5.3.5.1 PSC12 Report). Additional details regarding changes in physical findings are included in the individual final study reports (5.3.5.1 PSC12 Report and 5.3.5.1 PSC16 Report).

5.4.10. Post-marketing experience

The post-marketing experience with RIV3 is limited due to the temporary market withdrawal between 2018 and 2024. However, extensive post-marketing data for RIV4 are available and are considered relevant given the close similarity in composition and manufacturing. Up to 31 January 2025, 43 786 798 doses of RIV3 and RIV4 have been distributed cumulatively. The cumulative safety data, including serious adverse events, hypersensitivity reactions, and pregnancy exposure outcomes, do not indicate any new or unexpected risks not identified in the clinical development. The reporting rate for anaphylaxis is low and consistent with expectations for influenza vaccines (the estimated reporting rate from post-marketing data is ~0.24 per million doses). The types and frequencies of reported events are aligned with those observed in clinical trials and reflected in the proposed SmPC. The post-marketing data therefore support the proposed safety profile of RIV3 and provide additional reassurance. No new safety information requiring inclusion in the SmPC has been identified.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The clinical safety profile of the trivalent recombinant influenza vaccine (RIV3) is supported by an extensive and methodologically robust dataset, primarily derived from clinical studies conducted with the quadrivalent formulation (RIV4), as well as one trial conducted directly with RIV3 (PSC04). Safety data were collected using standardised tools and observation periods, and the duration of follow-up (≥6 months in pivotal studies) is adequate for capturing both common and rare adverse events. The methodology for safety data collection is considered reliable and supports the validity of the safety evaluation.

Solicited local and systemic adverse reactions were reported with expected frequency and severity, showing a consistent reactogenicity pattern across all studies and age groups. Local reactions, particularly injection site pain and tenderness, were the most commonly reported events, typically mild to moderate and self-limiting. Systemic events such as fatigue, headache, and myalgia occurred at lower frequencies and without clinically meaningful differences between RIV and comparator groups. The reactogenicity profile observed in PSC04 with RIV3 was consistent with that of RIV4 and does not raise safety concerns.

The incidence of unsolicited adverse events, medically attended events, and SAEs was low and comparable between treatment arms. Only one SAE (pericardial effusion) in study PSC04 was considered possibly related to RIV3. No concerning patterns emerged in the evaluation of AESIs or deaths, and no events were considered vaccine-related. Discontinuations due to adverse events were rare and do not indicate specific safety concerns. No trends were identified that would require additional risk minimisation measures.

Supportive safety data in paediatric and adolescent populations (VAP00026, VAP00027) confirm a similar tolerability profile in younger age groups, with no evidence of increased reactogenicity. In particular, the data in individuals aged 9 - 17 years support the proposed indication from 9 years of age. In this age group, solicited local and systemic adverse events were reported at rates similar to those in adults, and no vaccine-related serious adverse events occurred. Safety data in pregnant women derived from study VAP00007; this was an observational study that included over 14,000 pregnant women exposed to RIV4, and demonstrated a comparable rate of adverse maternal and

infant outcomes relative to a control group receiving standard-dose IIV4. No new safety concerns were identified. RIV3 and RIV4 have not been studied in breastfeeding women, and safety data in this population remain unavailable; nevertheless no different safety profile is expected.

The adverse drug reactions listed in the SmPC are consistent with those reported in the clinical programme and reflect the safety profile of recombinant influenza vaccines. The extrapolation of the ADR profile from RIV4 to RIV3 is considered justified, and no omissions or additions are warranted based on current data.

The post-marketing safety experience with RIV4 further supports the acceptable safety profile of RIV3. No new safety signals have been identified, and the overall types and frequencies of reported events remain in line with the expected class effects. The rare occurrence of anaphylaxis (~0.24 per million doses) and Guillain-Barré Syndrome in post-marketing data are noteworthy. No changes to the proposed product information are considered necessary based on post-marketing data. As of 31 January 2025, 43 786 798 doses of RIV3 and RIV4 have been distributed cumulatively, without the emergence of new safety signals.

The outcomes from PSC04 were removed following the request of the CHMP, as the rHA content varied substantially in this study due to potency assay limitations, and antigenic mismatch during this influenza season led to wide confidence intervals, rendering the data supportive only.

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 above. The proposal by the Applicant is endorsed, as it is already authorised for Supemtek Tetra (Quadrivalent).

5.4.11.2. Conclusions on clinical safety

The clinical safety data submitted are considered robust and consistent. Based on the available evidence, no additional safety concerns requiring specific risk minimisation measures have been identified. The observed safety findings do not warrant changes to the proposed product information or the inclusion of new elements in the SmPC compared to Supemtek Tetra (authorised).

The safety database for adult and paediatric subjects from 9 - 17 years is sufficiently large to support conclusions on the safety profile of Supemtek. The nature and frequency of adverse events are consistent with expectations for influenza vaccines in these populations. Additionally, a post-authorisation study provided reassuring data from a large cohort of pregnant women vaccinated with RIV4 or an egg-derived comparator. No safety signals have emerged from post-marketing reports.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 52: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Not applicable

6.1.2. Discussion on proposed safety specification

The summary of safety concerns is considered acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

Routine pharmacovigilance activities of reporting ARs and signal detection are deemed sufficient to monitor the safety profile for RIV3.

The safety profile of RIV3 will continue to be further characterised in the real-world setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to AEs, and signal detection.

To comply with the Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines (EMA/PRAC/222346/2014), (guidance included in the EU Guideline for Influenza vaccines - non-clinical and clinical module - as an addendum), and according to PRAC recommendation to MAHs (EMA/PRAC/775434/2014) and (EMA/PRAC/209591/2015), an annual enhanced passive safety surveillance (EPSS) is to be set up for each influenza vaccine brand on the EU market. The implementation of the EPSS started from the NH 2014-2015 influenza season and is to be performed every year unless there is no strain change compared to the previous influenza season or if relevant product-specific safety data are available from prior use of the vaccine in the Southern Hemisphere (SH).

This EPSS allows for near real-time detection of early signals of potentially clinically significant changes of the safety profile compared to previous seasonal composition, and relies on enhanced routine pharmacovigilance and coverage data collection. The primary objective of the EPSS is to estimate reporting rates of suspected ARs occurring within 7 days after routine vaccination during the influenza season.

The Pharmacovigilance Risk Assessment Committee [PRAC] agreed to waive the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines while the 'interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014) is being reviewed.

As part of routine safety surveillance, medical review of spontaneous individual case safety reports (ICSRs) is performed on a weekly basis in order to detect new signals. Competent authorities will be informed as per applicable standards and regulation. As per EMA requirement, any new information (from routine safety surveillance) that may affect the benefit-risk balance of the product will be communicated promptly to the competent authorities of the member states in which the product is authorized and to the agency via email.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the pharmacovigilance plan

Based on the available safety data, the proposed pharmacovigilance plan is adequate to the safety profile of RIV3.

6.3. Plans for post-authorisation efficacy studies

Not applicable, as the applicant does not propose any imposed post-authorisation efficacy study.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

Based on the available safety data, no safety concerns requiring specific risk minimisation measures have been identified. The safety information in the proposed SmPC is aligned to the reference medicinal product. Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP and PRAC consider that the risk management plan version 2.1 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

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.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The indication is aligned with the population studied in the pivotal clinical trials. The wording is aligned with the similar vaccine Supemtek Tetra (same composition with an additional B strain).

8.2. Labelling

8.2.1. User consultation

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

- The Applicant had completed a consultation with target patient groups on the Supemtek Tetra PL as part of the initial MAA that was approved on 16 November 2020 (EU/1/20/1484/001-006). Since only minor modifications in the PL of Supemtek have been made, the justification to not undertake further consultation with target patient groups is considered acceptable.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, therapeutic indication

Influenza is an acute, highly transmissible viral infection of the respiratory tract that exhibits seasonal prevalence worldwide. The claimed indication of the investigational product, Supemtek, is active immunization immunisation for the prevention of influenza disease in adults and children from 9 years of age and older. The primary objective of vaccination is to prevent influenza disease and to reduce the incidence of influenza-related complications.

9.1.2. Available therapies

There is no effective treatment for influenza, and clinical management is based mostly on symptomatic treatment. Few antiviral drugs are available which may be able to reduce disease severity and duration, but they need to be taken soon after infection in order to be effective and can induce drug-resistant mutants. Influenza antivirals target the viral NA protein (zanamivir and oseltamivir), or the M2 protein (amantadine and rimantadine). The latter two are no longer recommended due to high level of resistance (>99%) in circulating viruses since 2009. Viruses resistant to the NA inhibitors have also increased dramatically after 2007 with the majority of seasonal H1N1 viruses (pre-pandemic 2009) exhibiting oseltamivir resistance.

Vaccination is considered the best strategy to lower the burden of influenza disease. However, the efficacy of influenza vaccines in older individuals is significantly lower than in younger individuals due

to the aging of the immune system as well as underlying medical conditions, factors which increase the risk of influenza complications and interfere with immune responses.

Currently, different seasonal inactivated (split virion, surface antigen) or recombinant influenza vaccines are authorised for children aged 6 months and older, adolescents or adults, as well as a live attenuated influenza vaccine for children and adolescents from 2 years to 17 years of age.

Vaccines against seasonal influenza may need to be updated in composition on a yearly basis to include the latest circulating viruses and people need to get vaccinated accordingly. The protection afforded by conventional influenza vaccines is driven by how well the strains in the vaccine match the viruses that circulate during influenza season (antigenic match).

9.2. Main clinical studies

The clinical development programme supporting the current application was based on three pivotal studies, all conducted with RIV4 (PSC12, PSC16, and VAP00027). Data from RIV4 are relevant to RIV3 because both vaccines are manufactured using the same process and have overlapping compositions (B/Victoria is the only B-lineage component in the trivalent formulation).

PSC12 was a randomised observer-blind active-controlled multicentre study of efficacy, immunogenicity and safety of RIV4 in older medically-stable adults ≥50 years of age. Participants were randomised in a 1:1 ratio to receive either RIV4 (4 474) or IIV4 (4 489). The primary objective was to demonstrate the non-inferior efficacy of one single IM dose of RIV4 compared to a US and EU-authorised quadrivalent inactivated influenza vaccine (IIV4).

PSC16 was a randomised observer-blind active comparator-controlled multicentre study of immunogenicity and safety of RIV4 in healthy adults 18 to 49 years of age. Participants were randomised in a 3:1 ratio to receive either RIV4 (1 011) or IIV4 (339). The primary objective was to demonstrate non-inferior immunogenicity of RIV4 compared to IIV4.

VAP00027 was a Phase III, non-randomised, open-label, uncontrolled, multi-centre study to assess immunogenicity and safety of RIV4 in children and adolescents aged 9 to 17 years and adults aged 18 to 49 years. A total of 1 308 participants were recruited: 648 aged 9 to 17 years and 660 aged 18 to 49 years. The primary objective was to demonstrate the non-inferior immune response of RIV4 for the 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years.

9.3. Favourable effects

Efficacy data are available from trial PSC12 in adults 50 years of age or older. With an attack rate of 2.2% vs. 3.2% for RIV4 and IIV4, respectively, translates into a relative vaccine efficacy of +30% (95% CI: +10, +47). Analyses for alternative influenza like-illness definitions or for age, gender and other categories generally point in the same direction as the primary endpoint.

Immunogenicity data are available from the total population of trial PSC16. In study PSC16 conducted in adults 18 to 49 years of age the immunogenicity parameters seroconversion rate and GMT-ratio at day 28 were defined as co-primary endpoints. Non-inferiority according to CBER criteria could be shown for both A strains as well as for B/Yamagata. The GMT ratio's between RIV4 and IIV4 were 0.81 (95% CI: 0.71, 0.92), 0.50 (95% CI: 0.44, 0.57) and 0.86 (95% CI: 0.74, 0.99) for the A/H1N1, A/H3N2 and B/Yamagata strains respectively. The difference in SCR was -3.2% (95% CI: -9.2, 2.8), -15.1% (95% CI: -21.3, -9.1) and 0.8% (95% CI: -5.4, 6.9) for A/H1N1, A/H3N2 and B/Yamagata, respectively.

For VAP00027, 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.

9.3.1. Uncertainties and limitations about favourable effects

Efficacy data was mainly driven by influenza A (predominantly H3N2), with an attack rate in the RIV4 arm of 1.7% versus 2.7% in the IIV4 arm, resulting in a rVE of 36% (95% CI: 14, 53). For influenza B the attack rates were 0.5% versus 0.6% for RIV4 and IIV4, respectively, resulting in a rVE of +4% (95% CI: -72, +46).

The main uncertainty regarding the favourable effects concerns the consistently reduced immune response to the B/Victoria strain observed across several studies, including PSC12, PSC16, and PSC04. As B/Victoria is the only B-lineage component in the trivalent formulation, the magnitude and reliability of protection against this strain remain uncertain and may impact the overall effectiveness of the vaccine in seasons with predominant B/Victoria circulation. While supplemental data from two independent clinical trials (NCT03617523 and Cowling BJ et al., Clin Infect Dis 2020) suggest adequate immunogenicity of RIV4 against B/Victoria, these data cannot fully resolve the uncertainty regarding the effectiveness of the trivalent formulation against this lineage.

9.4. Unfavourable effects

The clinical safety database comprises over 5 300 adult participants exposed to RIV4 in studies PSC12 and PSC16, and additional participants exposed to RIV3 in study PSC04. The safety profile of RIV3 is considered comparable to that of the already authorisedRIV4. Across adult age groups, including older adults with comorbidities, the vaccine was generally well tolerated. Reactogenicity consisted primarily of injection site reactions (e.g. pain, tenderness), which occurred frequently but were mild to moderate and transient in nature. Systemic adverse events such as fatigue, headache, and myalgia were also observed, but occurred at similar frequencies to the comparator, an authorised IIV4 (Fluarix Tetra).

One case of non-infectious pericardial effusion following RIV3 administration was considered possibly related to the vaccine; the event resolved and has not recurred in subsequent studies or post-marketing surveillance. No severe allergic reactions, including anaphylaxis, were reported in clinical studies. Anaphylaxis remains a known class effect and is considered a non-important identified risk; the estimated reporting rate from post-marketing data is ~0.24 per million doses. Guillain-Barré Syndrome (GBS) is also considered a potential risk based on class effects. While no cases have been reported for RIV3 or RIV4 during clinical development, isolated cases have been observed in the post-marketing setting.

In the paediatric population, RIV4 was evaluated in 648 participants in study VAP00027. No new safety signals were observed. The vaccine was generally well tolerated.

Up to 31 January 2025, over 43 million doses of RIV3 and RIV4 have been distributed globally. The cumulative safety data post-marketing did not indicate any new or unexpected risks not identified in the clinical development.

9.4.1. Uncertainties and limitations about unfavourable effects

While the size of the safety database is considered adequate and consistent with regulatory

expectations, limitations remain in estimating the true incidence of rare or very rare adverse reactions, despite the amount of post-marketing data accrued to date. This includes events such as anaphylaxis and Guillain-Barré Syndrome, which are recognised class effects. While not observed during clinical development, both have been reported in the post-marketing setting. The single case of pericardial effusion in PSC04 is of uncertain significance, as no further cases have been reported.

9.5. Effects table

Table 53. Effects Table for Supemtek for active immunisation for the prevention of influenza disease in adults and children from 9 years of age and older.

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects				
Relative vaccine efficacy (rVE) RT-PCR-positive protocol-defined ILIs (≥14 days post-vaccination) – 50 years of age an above *n cases/ n participants at risk (attack rate)*	rVE: 30% (95% CI: 10; 47) 96/4303 (2.2%)	138/4301 (3.2%)	**SoE:** PE, statistically significant; similar estimates when rVE is calculated based on culture-confirmed protocol-defined ILI, and for RT-PCR-confirmed CDC-defined ILI. **Unc:** Effect mainly driven by H3N2. Post-hoc analysis, rVE for Influenza A of 36% (95% CI: 14; 53)	PSC12
Non-inferior immunogenicity RIV4 vs. IIV4 28 days post vaccination - 18–49 YoA	Seroconversion rate: difference (95% CI) A/H1N1:-3.2 (-9.2;**2.8**) A/H3N2:-15.2 (-21.3;**-9.1**) B/Yam:0.7 (-5.4;**6.9**) B/Vic: 17.6 (11.4;23.9) GMTs IIV4/RIV4 A/H1N1: 397 / 493 A/H3N2: 377 / 748 B/Yam: 134 / 156 B/Vic: 64 /43 GMT ratio (95% CI) A/H1N1:0.81 (0.71;**0.92**) A/H3N2:0.50 (0.44;**0.57**) B/Yam:0.86 (0.74;**0.99**) B/Vic:1.49 (1.29;1.71)		**SoE:** adequately powered (N=969 RIV4, 323 IIV4). Non-inferiority formally met for 3 of 4 strains. Immunogenicity generally higher than in PSC12 subset. **Unc:** Non-inferiority not met for B/Victoria; weak response in both groups. No persistence data >Day 28. HAI assay antigen was egg-derived, may not fully match RIV-rHA.	PSC16
Non-inferior immunogenicity of RIV4 in paediatric population (9 to 17 years) vs adults (18 to 49 years).	GMTs RIV4 (paed)/RIV4 (adults) A/H1N1: 1946 / 982 A/H3N2: 1975 / 604 B/Yam: 1941 / 1593 B/Vic: 405 /258 GMT ratio (95% CI) H1N1: 1.98 (1.73;2.27) H3N2: 3.27 (2.76;3.87) B/Yam: 1.22 (1.09;1.37) B/Vic: 1.57 (1.35;1.82) Seroconversion rate: difference (95% CI) A/H1N1: 1.92 (-2.78;6.62) A/H3N2: -0.59 (-4.41;3.23) B/Yam: 14.3 (9.17;19.3) B/Vic: 3.29 (-1.57;8.14)		**SoE:** adequately powered. Non-inferiority formally met for the 4 strains. **Unc:** B/Victoria titres much lower compared with the two A strains and the B/Yamagata strain.	VAP00027
Unfavourable effects				

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Local pain (solicited AE)	18.9% (PSC12); 36.8% (PSC16); 34.4% (VAP00027)	22.0% (PSC12); 36.4% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16 VAP00027
Local tenderness (solicited AE)	34.3% (PSC12); 48.0% (PSC16)	37.1% (PSC12); 46.7% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16
Fatigue (solicited AE)	12.2% (PSC12); 16.5% (PSC16)	12.1% (PSC12); 16.6% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16
Headache (solicited AE)	12.7% (PSC12); 20.3% (PSC16); 18.5% (VAP00027)	13.5% (PSC12); 21.1% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16 VAP00027
Joint pain (solicited AE)	7.5% (PSC12); 9.5% (PSC16)	8.0% (PSC12); 10.2% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16
Muscle pain (solicited AE)	8.5% (PSC12); 12.8% (PSC16); 19.3% (VAP00027)	8.8% (PSC12); 11.7% (PSC16)	**SoE:** Randomised, controlled, double blinded trials **Unc:** Reactogenicity tended to be higher in younger subjects	PSC12 PSC16 (VAP00027)

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PE: primary endpoint; GMT: geometric mean titres; SCR: seroconversion rates

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Extrapolation of clinical data from the quadrivalent formulation to the trivalent RIV3 without B/Yamagata is supported by the shared manufacturing process and consistent antigen content for the retained strains, in line with WHO recommendations from September 2023.

The most important favourable effect is the demonstrated protective efficacy of the vaccine against laboratory-confirmed influenza-like illness. The primary endpoint in study PSC12 showed a statistically significant relative vaccine efficacy (rVE) of 30% compared to an egg-based quadrivalent influenza vaccine, with a lower confidence bound well above the predefined non-inferiority margin. This effect is considered clinically relevant in the context of seasonal influenza prevention in adults. Although efficacy was mainly driven by the H3N2 component, the overall consistency across secondary and exploratory analyses supports the robustness of the finding.

Immunogenicity data further support the efficacy profile, particularly the seroconversion and GMT responses observed in adults aged 18 - 49 years. In study PSC16, non-inferiority versus IIV4 was formally met for three of the four influenza strains. The lack of non-inferiority for B/Victoria introduces some uncertainty; however, this is partially mitigated by the known lower immunogenicity of this strain across both vaccine groups and the supportive efficacy signal from PSC12. Immunogenicity was

generally higher in younger adults compared to the immunosenescent PSC12 population, suggesting age-related consistency in immune response. Nevertheless, persistence of antibodies beyond Day 28 was not assessed, and the relevance of the egg-derived test antigens to the recombinant formulation remains uncertain.

The unfavourable effects are predominantly mild-to-moderate reactogenicity events, such as injection site pain, local tenderness, fatigue, and headache, which were consistently reported across pivotal trials. These adverse events were self-limited and occurred with similar frequency in the RIV4 and IIV4 groups. Reactogenicity tended to be more frequent in younger age groups, which is consistent with known age-related immunoreactivity. No unexpected safety signals were identified, and serious adverse events were rare and balanced between treatment arms.

In adolescents aged 9 - 17 years, study VAP00027 demonstrated non-inferiority of the immune response to all four vaccine strains compared to younger adults, supporting extrapolation of efficacy to this age group. Pregnancy and neonatal outcomes following maternal vaccination with RIV4 were comparable to those observed with egg-derived comparator vaccines.

Concerns regarding the performance of the B/Victoria strain may be further alleviated by external data from independent studies (NCT03617523 and Cowling BJ et al., Clin Infect Dis 2020).

The cumulative global post-marketing participant exposure to RIV3 and RIV4 has been estimated to be over 43 million doses. Supemtek is expected to be safe and well tolerated, and to have the same safety profile than the authorised Supemtek Tetra.

9.6.2. Balance of benefits and risks

The benefit–risk balance of Supemtek is positive.

9.7. Benefit-risk conclusions

The overall benefit/risk balance of Supemtek is positive, subject to the conditions stated in section "Final CHMP outcome".