17 September 2020
EMA/522939/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Supemtek

Common name: influenza quadrivalent vaccine (rDNA)

Procedure No. EMEA/H/C/005159/0000

Note

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

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List of abbreviations

AcNPV	*Autographa californica* Nuclear Polyhedrosis Virus
AE	Adverse event
AESI	Adverse Events of Special Interest
AS	Active substance
BCA	Bicinchoninic acid
BVDV	Bovine viral diarrhoea virus
CBER	(US FDA) Center for Biologics Evaluation and Research
CDC	US Centers for disease control and prevention
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence of interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRO	Clinical research organisation
CT	Clinical trial
CTD	Common technical document
Da	Dalton
DART	Developmental And Reproductive Toxicity
DLS	Dynamic light scattering
DMID	National Institutes of Health Division of Microbiology and Infectious Diseases
DSP	Downstream process
E. coli	*Escherichia coli*
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EOIS	End of Influenza season
EOP	End of production
ERL	WHO essential regulatory laboratory
EU	European Union
EU	European Union
EVOH	Ethylene-vinyl alcohol
FDA	(US) Food and Drug Administration
FOB	Functional Observational Battery
FP	Finished product
GISAID	Global initiative on sharing all influenza data
GL	Guideline
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titers
HA	Haemagglutinin
HAI	Haemagglutinin inhibition
HCP	Host cell protein
HIC	Hydrophobic interaction chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEX	Ion exchange chromatography
IIV	Inactivated influenza vaccines
IIV4	Quadrivalent Inactivated Influenza Vaccine/Fluarix Quadrivalent
ILI	Influenza-like illness
IM	Intramuscular

IND	Investigational new drug applications
ISD	Influenza Sequence Database
IWRS	Interactive Web Response System
LLDPE	Linear low density polyethylene
MAA	marketing Authorisation application
MAE	Medically-attended adverse event
MCB	Master cell bank
MI	Myocardial infarction
mPP	modified per protocol
MVB	Master virus bank
NA	Neuraminidase
nAb	Neutralising antibodies
NCBI	(US) National Center for Biotechnology Information
NH	Northern Hemisphere
NIBSC	(UK) National Institute for Biological Standards and Control
NS	Nasal swab
NtA	Notice to Applicants
Ph. Eur.	European Pharmacopoeia
PP	Per protocol
PPV	Porcine parvovirus
PQ	Performance qualification
PSC	Protein Sciences Corporation
PSFM	Protein sciences formulary medium
PTC	Product technical complaints
PV	Process validation
RBC	Red Blood Cells
Reo-3	Reovirus-3
rHA	Recombinant haemagglutinin
RIV3	Trivalent recombinant influenza vaccine/ Flubok
RIV4	Quadrivalent recombinant influenza vaccine/Supemtek
RNA	Ribonucleic acid
rt-PCR	Reverse transcription polymerase chain reaction
rVE	Relative vaccine efficacy
SAE	Serious adverse event
SC	Subcutaneous
SCR	Seroconversion rate
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	Size exclusion chromatography
SH	Southern Hemisphere
SOC	System Organ Class
SPR	Seroprotection rate
SRID	Single radial immunodiffusion assay
TS	Throat swab
TSE	Transmissible spongiform encephalopathies
USA	United States of America
USP	Upstream manufacturing process
VAERS	Vaccine Adverse Event Reporting System
VSV	Vesicular stomatitis virus
WCB	Working cell bank
WHO	World Health Organisation

WVB	Working virus bank
WVS	Working virus seed
XMulV	Xenotropic murine leukaemia virus-related virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Pasteur submitted on 4 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Supemtek, 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 vaccine is indicated for active immunization for the prevention of influenza disease in persons 18 years of age and older. Supemtek should be used in accordance with official recommendations*".

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, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0219/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0219/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the four strains of recombinant haemagglutinin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 June 2018	EMEA/H/SA/3849/1/2018/III	Dr Filip Josephson, Prof Andrea Laslop

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- *Concurrence that the in-process and release testing methods, requirements and analytical characterization for the vaccine are suitable to support licensure in EU*
- *Testing requirements and qualification for master virus bank and working virus bank*
- *Concurrence with the sites of vaccine drug substance and drug product production for distribution in the EU*
- *Specifications and end of shelf-life for the final product vaccine*
- *Concurrence that the CBER, NIBSC, or TGA reagents (from approved ERLs) are acceptable for internal and official release of vaccine lots intended for the European market*
- *Changes in manufacturing post approval*
- *Preclinical package for registration*
- *Design of study PSC12 to support licensure in 50 years of age and older*
- *PSC16 study design and strategy to support licensure in adults 18-49 years of age in Europe*
- *Possibility to add statements of superiority in the SmPC*
- *Possibility to display data from PSC04 in section 5.1 of SmPC*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

For the appointed co-rapporteur it was considered exceptionally justified that the individual had previously been acting as coordinator for Scientific advice on the development relevant for the indication subject to the present application. The justification was as follows:

Within the European regulatory network, there is a confined pool of vaccine experts and this limits the options available for coordinators and rapporteurs.

The appointed rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	4 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 January 2020

The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2020
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one manufacturing and testing site in USA between 20-24 January 2020. The outcome of the inspection carried out was issued on – A GMP inspection at one manufacturing site in Taiwan between 3-5 August 2020. The outcome of the inspection carried out was issued on	17 June 2020 11 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 July 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 July 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 September 2020
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	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the northern hemisphere (NH) and southern hemisphere (SH). The influenza virus is

transmitted by respiratory droplets or aerosols containing the influenza virus particles and subsequent inhalation of infectious particles or self-inoculation from a contaminated surface. Clinical manifestation of influenza virus infection is characterised by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis.

Some individuals are more prone than others to develop complications from influenza, e.g. bacterial pneumonia or other organ dysfunction. Severe influenza and complicated influenza potentially leading to hospitalisation and death are more likely to occur in vulnerable populations, such as older people (≥65 years of age, in part due to the age related decline of the immune response (immunosenescence)), pregnant women, younger children (especially up to 24 months of age), and patients with chronic underlying diseases. These groups are considered at risk and represent the priority target for influenza vaccination programmes in the EU.

2.1.2. Epidemiology and risk factors, prevention

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the NH and SH during winter months. In temperate climates, influenza generally affects people from November to March in the NH and from May to September in the SH. It can occur all year round in tropical climates.

Influenza in humans can be caused by the influenza virus type A, B and C, of which type A and B viruses are most clinically relevant. Type A viruses are associated with annual epidemics and pandemics, and B viruses contribute to annual epidemics. The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for annual influenza disease burden. For influenza B, only a single type is known to exist, but 2 distinct genetic lineages are identified: Yamagata and Victoria. Influenza B circulates almost every year worldwide generally later in the season in comparison to influenza A-viruses. According to data from the European Influenza Network, since 2001, influenza B has circulated with variable frequency, including 2017-2018 when type B was the predominant circulating strain. From year to year, the predominating B lineage has varied, resulting in the recommendations for quadrivalent influenza vaccines.

Traditionally and until 2012, seasonal influenza vaccines included antigens from 3 influenza strains in their composition, 2 influenza A strains (largely A/H1N1 and A/H3N2), and a strain from 1 of the 2 influenza B lineages (B/Yamagata or B/Victoria). This is because the majority of global influenza disease cases in humans since 1977 have been caused by circulating A/H1N1, A/H3N2, and influenza B strains viruses. Influenza B strains from the 2 lineages have co-circulated yearly since 1980s, when they emerged, with either or both types prevalent within any given year with no cross protection between the lineages.

The burden of influenza morbidity and mortality is high with a greater burden attributable to influenza A, largely due to the greater virulence of influenza A (A/H3N2 in particular). Seasonal influenza causes 4 – 50 million symptomatic cases in EU/EEA each year, and 15,000 – 70,000 European citizens die every year of causes associated with influenza. Despite the often short duration of illness, the yearly economic and healthcare burden of influenza is substantial. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths (WHO. Influenza (Seasonal). Fact sheet. Nov 2018). The main prevention strategy to minimise influenza burden is through annual prophylactic vaccination. Influenza vaccines are designed to protect against illness from the circulating virus strains, and the most commonly used vaccines have been inactivated influenza vaccines (IIV). The World Health Organization (WHO) recommends seasonal influenza vaccination for specific group of people which are more at risk of complications and death: pregnant women, elderly individuals (≥65 years of age), individuals with

chronic medical conditions, health care workers, and children aged from 6 months to 5 years. Additionally, some public health authorities are moving towards vaccination strategies to reduce the risk of influenza in all age groups in an effort to decrease overall disease burden and spread to those in the population who are most at risk.

2.1.3. Aetiology and pathogenesis

The influenza virus is an orthomyxovirus that can be classified into 3 biologically similar, but antigenically different types, A, B, and C, of which type A and B viruses are the most clinically significant. They are characterised as enveloped, negative strand, segmented ribonucleic acid (RNA) viruses. The viral haemagglutinin (HA) and neuraminidase (NA) surface antigens are subject to continuous and sequential evolution within immune or partially immune populations. Antigenic drift results from mutation(s) affecting the RNA segment coding for either HA or – less frequently - NA. As a result, there is alteration in the protein sequence that can lead to (minor) changes in antigenicity. Antigenic variants within a subtype (e.g. H1 or H3) emerge periodically and through natural selection gradually become the more predominant circulating virus strain, usually on an annual basis, while the preceding antigenic variant is suppressed by a specific immunity in the population. In contrast to antigenic drift, antigenic shift represents the emergence of completely new subtypes, typically through gen segment reassortment with other circulating strains and acquisition of substantially different antigenic gene sequences. Antigenic shift occurs at irregular intervals and may lead to pandemics.

The influenza type A virus can be further divided into subtypes based on the HA and NA surface glycoprotein antigens. The subtype refers to major antigenic variation with respect to the HA and/or NA virion antigens. Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are the most clinically important for annual influenza disease burden. Influenza type B viruses show extensive variation in antigenicity. Although no true B subtype is known to exist, during the early part of the 1980s, 2 antigenically and genetically distinct lineages of influenza B emerged: B/Yamagata and B/Victoria.

The 3 influenza virus types share no common virus-coded antigens and differ in epidemiology and to some degree in the severity of illness caused.

2.1.4. Clinical presentation

Clinical manifestation of influenza virus infection is characterised by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis (Monto et al. 2000). Influenza is generally self-limited and an uncomplicated disease. It can, however, be associated with severe morbidity and mortality in healthy children and certain groups of children and adults who are at increased risk of severe or complicated illness from influenza. Complications such as febrile convulsions, croup, acute otitis media, lower respiratory infections and encephalitis may arise in children as a consequence of the primary influenza infection, or as a result of secondary bacterial infections (Heikkinen et al. 1991). In older adults, pulmonary complications of influenza are most common and include secondary bacterial infection. Among others, acute respiratory infections can exacerbate asthma and chronic obstructive pulmonary disease (COPD) or lead to decompensation of patients with congestive heart failure or diabetes mellitus and subsequently lead to an increased risk of myocardial infarction and cerebrovascular accident (Gordon and Reingold 2018).

2.1.5. Management

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 (peramivir, 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 approach to lower the impact and burden of influenza disease. Currently, different seasonal inactivated (split virion or subunit) influenza vaccines (quadrivalent and trivalent) are licensed for children aged 6 months and older, adolescents and adults, as well as a live attenuated influenza vaccine licensed for children and adolescents aged 2 years to 17 years of age.

In order to prevent influenza, annual vaccination against influenza is recommended in most risk groups for older adults (≥60 or ≥65 years) and individuals with underlying conditions, such as COPD, heart conditions, diabetes, that leave them at high risk of influenza disease and associated complications. In addition, some countries have general recommendations for influenza vaccination of healthy children.

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).

In the EU many licensed seasonal influenza vaccines are produced using embryonated hen's eggs. Influenza vaccine produced in eggs can only be obtained by careful advanced planning and the supply of eggs can be uncertain. Due to the antigenic drift, influenza vaccines may require an annual adjustment of vaccine strains. A potential mismatch between circulating influenza virus strains and the strains included in the vaccine because of antigenic drift poses a major challenge for vaccine production. A need for alternative production methods for influenza vaccines was identified in a World Health Organization report already in 1995. The vaccine under licensure is a quadrivalent recombinant haemagglutinin influenza vaccine, produced in patented insect cells using a baculovirus expression vector. This technology still requires the production of a high-yielding reassortant virus, but production in cell culture has its advantages from a production perspective, i.e. for example independency from eggs, and a better scalability. Influenza vaccine virus strains can mutate and the mutation be selected when passaged in eggs. In contrast, the finished product potentially yields a purified recombinant influenza haemagglutinin that is an exact genetic match to that of the influenza strains selected for the seasonal vaccine.

About the product

Quadrivalent Recombinant Influenza Vaccine (RIV4) active substances comprises recombinant haemagglutinin of the 4 strains of influenza virus recommended annually by the WHO for the Northern Hemisphere season:

- a strain A (H1N1)
- a strain A (H3N2)
- a strain B (Yamagata lineage)
- a strain B (Victoria lineage)

Influenza vaccines induce antibodies that protect against infection by influenza viruses that match or are similar to the antigen composition of the vaccine based on antigenic similarity of vaccine to circulating strains.

The RIV4 influenza vaccine contains a higher haemagglutinin antigen content (45 µg per antigen) than quadrivalent standard dose influenza vaccines (15 µg per antigen) currently licensed.

The first recombinant haemagglutinin influenza vaccine was developed as a trivalent vaccine by Protein Sciences Corporation (PSC), now a Sanofi Company, under the trade name Flublok (RIV3), and was initially licensed in the United States of America (USA) for prevention of influenza disease in individuals 18 years of age and older in 2013. Subsequently, PSC transitioned the product from a trivalent to the current quadrivalent vaccine (RIV4), approved in 2016 in the USA for use in individuals 18 years and older.

RIV4 is a sterile solution for injection and is presented in a 0.5 mL pre-filled syringe. RIV4 is administered as one single dose per influenza season via intramuscular route.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) also known as RIV4, is presented as sterile solution containing 45 µg of each of four recombinant HA (rHA) antigens as active substance.

Other ingredients are: polysorbate 20, sodium chloride, monobasic sodium phosphate (monohydrate) and dibasic sodium phosphate (dodecahydrate) for pH control and water for injection.

The product is available in a pre-filled syringe (Type I borosilicate glass) with tip cap and plunger stopper (bromobutyl rubber), with separate (CE marked) needle or without needle.

2.2.2. Active Substance

General information

The active substance (AS) included in the final finished product consists of four active substances, separately manufactured recombinant haemagglutinin (rHA) proteins:

- rHA protein, derived from Influenza A virus subtype H1N1 (named rHA H1)
- rHA protein, derived from Influenza A virus subtype H3N2 (named rHA H3)
- rHA protein, derived from Influenza B virus Victoria lineage (named rHA B-V)
- rHA protein, derived from Influenza B virus Yamagata lineage (named rHA B-Y)

The recombinant HA antigens (rHA) are full length, uncleaved glycoproteins with molecular weights of approximately 65kDa. The rHA assembles to trimers with an approximate molecular weight of 195 kDa. The functional structure comprises rosette-like complexes. 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.

Manufacture, characterisation and process controls

The active substance is manufactured at Unigen Inc., Gifu, Japan.

Major objections were raised regarding missing GMP certificates for the Unigen and Protein Sciences sites. These were addressed during the procedure and appropriate GMP authorisations are now available for all sites.

Description of manufacturing process and process controls

The manufacturing process of the active substance contains the following steps:

- Production of the rHA expressing baculovirus
- Upstream process: expansion of baculovirus and SF+ cells and expression of rHA in baculovirus-infected SF+ cells
- Downstream process: harvest of rHA expressing cells and purification of rHA protein

The manufacturing steps are appropriately described.

Upstream manufacture of the AS includes culturing of expresSF+ cells, baculovirus infection and expansion and protein production. Detailed process flow diagrams including the in-process testing and process parameters have been provided. 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. Critical in-process controls and in-process controls are suitably described.

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 container used for the storage and transport of the monovalent bulk active substance concentrate manufactured is a single use bag. Appropriate in-process controls (including critical) are defined for downstream processing.

It is acknowledged that certain parameters may change annually in response to seasonal strain variability and it is expected that the respective information is submitted together with the annual strain variations. Reprocessing is not claimed.

Control of materials

Cell banks

The source, history and generation of the *expres*SF+ cell line is described in sufficient detail. The applicant is using a two-tiered cell bank system. The master cell bank (MCB) and the two working cell bank (WCB) lots derived thereof have been characterised in line with ICH Q5D requirements. The testing of the MCB and end of production (EOP) cells is in line with Ph. Eur. 5.2.3. requirements. A protocol for establishment of new WCBs has been submitted. All new WCB will be qualified using the adventitious agents testing scheme. The WCB is stored in liquid nitrogen.

Master Virus Banks, viral vectors

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. Generation of the master parent linear baculovirus bank has been described.

The master virus bank (MVB) was generated from the parent viral vector. Qualification testing of the MVB was performed in comparison to the parent viral vector. Taken together, the MVB is considered appropriately qualified.

The history and generation of viral vectors are described in sufficient detail.

Working virus banks

The HA gene for each influenza strain included in the seasonal vaccine is added to the master virus bank (MVB) to create the working virus bank (WVB).

The WVBs are subsequently tested to ensure identity, potency and correct assembly of the WVB. Stability of each new WVB is assessed as part of the selection process.

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 since these were the most recent WVBs for which qualification data were available at the time of CTD preparation. The qualification of these WVBs is representative of the qualification of all future WVBs. The respective section in the dossier is updated on an annual basis following the recommendation by WHO of influenza strains to be included in the vaccine.

Antigens derived from the following influenza strains are included in the 2018-2019 RIV4 formulation: H1N1 (A/Michigan/45/2015), H3N2 (A/Singapore/INFIMH-16-0019/2016), B-Yamagata (B/Phuket/3073/2013), B-Victoria (B/Maryland/15/2016).

After construction of the working virus bank, the correct sequence is then verified by comparison with the sequence of a reference virus. Reference sequences are obtained from the Influenza Sequence Database (ISD, http://www.flu.lanl.gov/vaccine), GenBank (http://www.ncbi.nlm.nih.gov), or the Global initiative on sharing all influenza data -GISAID EpiFlu database (http://platform.gisaid.org). An outline of the general cloning procedure from viral isolates is provided in the dossier.

Raw materials

Raw materials have been listed by the applicant along with their compliance to relevant pharmacopoeia.

Protein Sciences Formulary Medium (PSFM) is the growth medium used for culturing of the SF+ cells. There are no ruminant-derived materials used in the manufacturing process of the PSFM. A table with the components of PSMF medium has been provided.

The information on buffers and solutions used has been provided, the procedures used for preparation, regeneration and sanitisation of chromatography resins are described in the dossier. Re-use of the chromatography resins used has been defined.

Control of critical steps and intermediates

Critical in-process controls are indicated in the section "Description of manufacturing process and process controls" (CTD section: S.2.2). The applicant outlined the 'key' process parameters and in-process tests for each manufacturing step. The classification was performed as follows: in-process tests, critical in-process tests, process parameters, critical process parameters. In addition, questions regarding the definition of critical process parameters and critical quality attributes have been suitably addressed.

Acceptance criteria and action limits have been established based on previous manufacturing experience and process validation studies and appear sufficiently justified. Storage containers have been specified. Holding times for any process intermediates are specified and justified.

Process validation

Prior to process validation (PV), performance qualification (PQ) studies were executed according to a validation master plan. All PV and PQ have been manufactured at Unigen, Gifu, using the final process at commercial scale. 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.

Adequate tests have been chosen for process validation. Validation of cell culture passage and preparation of virus suspension was also conducted. All PV reports have been submitted in the dossier. Furthermore, a comparability study was performed following scale-up and process changes at the commercial scale. In-process control parameters, critical process parameters, and quality attributes were defined for each process. All acceptance criteria were met. Shipping of AS to the FP site has been suitably validated. The presented data indicate that the process performs effectively and reproducibly to produce an active substance/intermediate meeting its predetermined specifications.

Manufacturing process development

The applicant outlined the manufacturing process development for the early development phase (1993 – 2003; studies performed under the direction of NIH, NIAID), the commercial process development phase (2003 – 2007; under direction of Protein Sciences) and final expansion of the manufacturing capacity (2007 – 2018).

RIV was initially developed as a trivalent formulation in the clinical lot manufacturing facility and licensed by the US FDA in 2013. RIV trivalent finished product was formulated and packaged for commercial distribution.

AS and FP manufacturing facilities were validated and licensed by the U.S. FDA through a combination of clinical studies and comprehensive comparability studies which included demonstration of comparability of stability of product produced at the different sites.

Development of the upstream block included several Phase 1/2 safety, immunogenicity and dose-ranging studies. The transition from serum-requiring Sf9 cells to Protein Science's (PSC) patented SF+ cells, which are grown without added serum was the most important development. In 2007, a commercial manufacturing process was established, that does not represent the final process.

After 2007, manufacturing process development focused on reduction of manufacturing cost of goods and expansion of the manufacturing scale to prepare for commercialisation and global expansion of RIV U.S. commercial scale facilities were approved by the FDA, for formulation and packaging of RIV trivalent.

RIV4 was approved by the US FDA in 2016. Approval was supported by clinical studies PSC12 and PSC16, process validation data and comparability of stability profiles from FP process validation batches to stability profiles of trivalent commercial RIV batches.

A number of facilities were used to produce phase 3 lots during clinical development of RIV. The commercial scale facility in Gifu, Japan was built for manufacture of commercial RIV AS. A number of changes have been introduced by Unigen in order to increase the production scale. 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.

Changes in the manufacturing process due to annual strain changes:

The downstream process is designed as universal process with some adaptations when necessary. The process readjustments made annually within the approved design space, which ensures that process changes do not impact safety or efficacy. The company has, upon request, agreed to update the dossier to reflect that the registered design space is now part of section 3.2.S.2.2. In case a process change out of the registered design space is needed, this would be submitted as a dossier variation.

Characterisation

The recombinant haemagglutinin (rHA) antigens 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. Full length, intact rHA molecules are referred to as rHA0. Recombinant HA0 contains two domains, HA1 and HA2, which are separable by proteolysis with trypsin. The N-terminal HA1 contains the globular head of the protein with five antigenic sites and the receptor binding domain that mediates attachment of the influenza virus to cells. The C-terminal HA2 contains the transmembrane and cytoplasmic portions of the protein. In addition, rHA proteins contain multiple cysteine residues capable of forming disulfide bonds, which contribute to the tertiary structure and antigenicity of the molecule. A battery of methods was used to characterise physicochemical properties. The results from rHA glycoform characterisation studies should be provided to further support comparability of material derived from the clinical lot manufacturing sites and the Gifu commercial site (recommendation 1). The purified rHA proteins are in a native, properly folded conformation. rHA assembles into complexes of HA trimers. The potency of each rHA is measured with the SRID. The assay is standardised with reference antigen and antiserum provided by FDA Center for Biologics Evaluation and Research CBER or any other WHO Essential Regulatory Laboratory. This assay demonstrates the potency and appropriate antigenic activity of the rHA proteins. The biological activity of rHA and the ability to form multimers have been assessed by a haemagglutination assay. The assay demonstrated that rHA proteins are competent to agglutinate red blood cells (RBCs) and is used to confirm the biological activity of the purified rHA proteins.

A series of immunogenicity studies were conducted in laboratory animals during the pre-clinical and clinical development of RIV4, primarily in CD-1 outbred mice. Additional studies were conducted in chickens, ferrets, and rats. Those studies demonstrated a robust serological response as measured by ELISA, haemagglutination inhibition (HAI), or neutralisation assays. The appropriateness of immunogenicity studies is discussed in the non-clinical assessment report.

The data presented were initially considered limited (i.e. only 1 batch per strain of the trivalent formulation was tested) and in part outdated (strains manufactured in seasons 2004/2005 and 2006/2007 and not according to the current manufacturing process). However, it is noted that additional physico-chemical characterisation data from recent batches of 3 of the 4 rHA antigens are available in section 3.2.S.2.6. Furthermore, additional characterisation data were presented for three recent commercial batches of rHA B Yamagata lineage (i.e. B/Phuket/3073/2013, manufactured in 2019). The presented results indicate a consistent manufacturing process.

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

<u>Impurities:</u>

The active substance contains impurities which derive from the cell substrate, or the cell culture or from the downstream processing of rHA proteins. Process-related impurities are controlled by release

tests at the level of the AS. For certain impurities, the maximum amount per human dose has been calculated and raises no safety concern. Other impurities are removed during the process. Other impurities are additionally controlled at the level of the FP. The polysorbate 20 assay is still in development. The polysorbate 20 method should be validated and implemented as FP release test, via variation, (see recommendation 6). All specified impurities have been present in product studied in clinical trials. Potential product-related are present at low abundance and sufficiently controlled via release tests.

Specification

The release tests and specifications for the active substance rHA are presented in the dossier. They comprise appropriate specifications tests for appearance, identity, sterility, endotoxin, process-related impurities, rHA size, protein content and biological activity. In addition to these release tests, tests for the presence of mycoplasma and spiroplasma and in vitro assays for the presence of adventitious viruses are conducted at the time of harvest.

Analytical methods

Brief descriptions have been provided for all non-compendial methods. Non-compendial methods have been validated according to ICH Q2(R1) requirements.

Batch analysis

Batch release results have been submitted for the process validation batches produced at the commercial site. In addition, batch release results for AS batches used to demonstrate comparability of the production process are shown.

All batches were manufactured according to the commercial scale (final process). The presented batch data comply with the pre-defined acceptance criteria valid at time of release and indicate a consistent manufacturing process.

Reference materials

The applicant provided information on reference materials used (and their qualification) used for identity/potency, purity, host cell protein (HCP), quantification of protein, DNA quantification and for rHA. the provided information is considered acceptable. The procedure for qualifying new reagents for identity/potency testing is outlined in the FP section of the dossier.

Container closure

The container used for the storage and transport of the monovalent bulk AS concentrate is a single use bag. Compatibility with the AS has been addressed.

Stability studies were conducted to confirm the compatibility of the components in contact with the rHA AS. An extractables study is part of the dossier. Information provided on extractables and leachables is considered sufficient.

Stability

Stability data have been provided for rHA bulk AS produced at sites used to produce clinical lots (seasons 2013/2014, 2014/2015, and 2015/2016). Stability data are also provided for the proposed commercial manufacturing site Unigen/Gifu. The batches were manufactured according to the final process and stored at long-term conditions. All stability studies are finalised. Essentially, the stability studies comply with ICH guidelines Q1A and Q5C; a statistical evaluation of stability data was performed according to ICH guideline Q1E. Data on accelerated stability has also been provided. Photostability has been adequately addressed according to ICH Q1B. The analytical program comprised the relevant stability indicating methods. All batches met the stability specifications.

Shelf life and storage conditions for the active substance have been proposed by the applicant and found acceptable. However, a stability monitoring method for assessment of active substance product-related impurities should be implemented (recommendation 2).

For each Northern Hemisphere vaccine campaign, the applicant proposes to include batches of each rHA antigen in the annual stability study. Strain specific data will be expected as part of the annual update the following season. This approach is deemed acceptable. This approach is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Quadrivalent Recombinant Influenza Vaccine (RIV4) consists of four full-length recombinant haemagglutinins (rHAs) derived from the influenza strains selected by WHO for each year's seasonal vaccine. Supemtek is supplied in a single dose syringe (Type I glass barrel with latex free elastomer stopper) containing 0.5 mL for intramuscular injection.

The 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 biological origin are not used for manufacture of RIV4. The composition is shown in Table 1.

Table 1 Composition of one dose (0.5 mL) of Supemtek

Ingredient	**Reference**	**Nominal amount per 0.5 mL**	**Function**
rHA Influenza A/H1N1	Internal	45 µg §	Active substance
rHA Influenza A/H3N2	Internal	45 µg §	Active substance
rHA Influenza B/Victoria lineage	Internal	45 µg §	Active substance
rHA Influenza B/Yamagata lineage	Internal	45 µg §	Active substance
Sodium phosphate monobasic (*monohydrate*)	USP, BP	0.195 mg	Buffer component *
Sodium phosphate dibasic (*dodecahydrate*)	USP, EP	1.3 mg	Buffer component *

Ingredient	Reference	Nominal amount per 0.5 mL	Function
Sodium chloride	EP	4.4 mg (150 mM)	Maintenance of osmolality
Polysorbate 20	USP, EP	27.5 µg (0.005%)	Stabiliser
Water for injections (WFI)	EP	q.s. 0.5 mL	Solvent

§ Strain as recommended by WHO

* Components add up to 10 mM sodium phosphate, pH 7.0 ± 0.4

Sodium phosphate is included as a buffer for pH control. Sodium chloride is added to maintain osmolality for a product intended for intramuscular injection and to maintain a physiological medium for proper conformation of the rHA protein (active pharmaceutical ingredient). rHA proteins are membrane-bound and a surfactant (polysorbate/ tween 20) is added to maintain their solubility.

The container closure system consists a pre-filled syringe (Type I borosilicate glass) with plunger stopper (grey butyl rubber), with separate needle or without needle. The container closure system was tested for integrity. Extractables and leachables of the final container have been sufficiently addressed. The applicant commits to provide the completed risk assessment report(s) for elemental impurities (see recommendation 4). The medical device (separate CE-marked needle if supplied) has been sufficiently described.

Development of RIV4 (approved by USA FDA in 2016) was based on the trivalent formulation of RIV, which is licensed in the USA since 2013. From the submitted information, it is concluded that the applicant followed a traditional/minimal development approach.

The same general procedure is used for formulation and filling of RIV4 lots as was used for trivalent RIV. All lots were formulated in phosphate buffered saline, pH 7.0 ± 0.4, with 0.005% Tween 20.

Manufacture of the product and process controls

Name and address of the manufacturer responsible for batch release: Sanofi Pasteur, Parc Industriel d'Incarville, 27100 Val de Reuil, France. A major objection was raised since a valid GMP certificate issued by an EU/EAA inspectorate was not available for one manufacturing site. This was resolved during the procedure and suitable GMP certificates/authorisations are available for all sites.

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

The four active substances (rHA of H1, H3, and two B strains) are mixed with the formulation buffer (sodium phosphate, sodium chloride, polysorbate 20) and formulated to the target rHA content /dose based on the potency of each rHA active substance batch, which is measured prior to each RIV4 formulation. The bulk finished product solution is sterile filtered and aseptically filled into syringes. Following visual inspection, the syringes are labelled, the plunger rod is inserted, and the syringes are packaged. The finished product is stored at 2 – 8°C.

For the 2018/2019 RIV4 influenza vaccine the formulation is provided. The rHA composition is changed to match the appropriate strains recommended by the WHO for each influenza season.

A traditional process validation approach was chosen by the applicant. To confirm that the manufacturing process performs reliably and delivers product of consistent quality, RIV4 lots with the 2015/2016 NH composition were manufactured at intended commercial scale at the intended

commercial site. Consecutive validation lots have been used. For the validation runs, all IPC and release tests complied with the specifications valid at time of testing and the proposed commercial release specification. Adequate mixing during formulation was demonstrated and the analytical results confirm homogenous filling of the syringes. The percentage of rejected syringes was consistent over the validation runs. In summary, the results for the validation runs indicate consistent performance of the manufacturing process.

Aseptic manufacturing is regularly confirmed by media fills. Results for three media fills performed in 2014 are presented. The filtration and filling times cover the times specified for the RIV4 process.

The results of the filter validation demonstrate that the sterile filter is suitable for the filtration of RIV4 and has a sufficient capacity for retention of bacteria. Information on extractables/leachables has been provided but leaching from other single-use process equipment (e.g. tubing) has not been addressed and a risk assessment for elemental impurities according to ICH Q3D is missing. The applicant commits to provide the completed risk assessment report(s) for leachables from single-use materials and elemental impurities (see recommendations 3 and 4).

The applicant outlined the shipping strategy for shipment of RIV4 syringes from the manufacturing site to the EU release site and summarised the corresponding shipping validations. The shipping process is considered sufficiently supported.

Product specification

The quadrivalent formulated bulk acceptance criteria and the RIV4 FP specifications are described in the dossier. The specifications include appropriate tests for appearance, identity, endotoxin, sterility, potency, total protein content, content uniformity, purity, total DNA, osmolarity pH, fill volume, Triton X 100, Tween 20. Several other concerns regarding the specification have been sufficiently clarified. The polysorbate 20 method validation, the implementation as characterisation test and finally the implementation as release test with justified specifications has been included in the list of recommendations (recommendation 6).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

In addition, the applicant commits to submit the study results to investigate the stability indicating capability of the SRID method for one B strain in the presence of the other B strain (see recommendation 5).

Batch analysis

Batch analysis results for the process validation batches and the clinical lot used for the pivotal studies PSC12 and PSC16 comply with the release specification. The results indicate that the manufacturing process is capable of delivering FP of consistent quality that meets its specifications. Compared to the AS, no new impurities are introduced during FP manufacturing.

Reference materials

The influenza reference antigen material is obtained from CBER (US FDA) or other World Health Organization Essential Regulatory Laboratories (ERLs) for each of the four seasonal haemagglutinin strains. The reference antigen is strain specific and has been standardised by CBER or other ERLs. New reagents are qualified and the qualification report is submitted as part of the strain change annual update.

Stability of the product

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

Extensive real time stability data for multiple commercial RIV lots manufactured from 2013/2014 to 2018/2019 are presented by the applicant. The stability data for RIV4 are sufficient to support the claimed shelf life. To a large extent the stability studies comply with ICH guidelines Q1A and Q5C; a statistical evaluation of stability data was performed according to ICH guideline Q1E. Photostability has been adequately addressed according to ICH Q1B. Real time data covering a period of at least 12 months at 2-8°C are available.

The photostability studies show that RIV4 in the primary packaging (pre-filled syringes) is sensitive to light but sufficiently protected by the secondary packaging.

The claimed shelf life of 12 months at 2 - 8°C is supported by the presented stability data and is acceptable.

The applicant provided a stability commitment for annual stability studies and the respective stability protocol (data expected in the next season's annual update). The analytical program includes relevant stability indicating methods and safety related tests. Taking into account the large set of stability data gathered, the annual stability studies is deemed acceptable.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, for any on-going stability studies should be reported to EMA.

Adventitious agents

Non-viral adventitious agents

The applicant presented an overview describing all measures set as regards the control of mycoplasma/spiroplasma, bacteria and fungi as well as a respective discussion, as requested. The measures set to prevent adventitious agents from entering the production process appear appropriate and include careful selecting and testing raw and starting (MCB and MVB) materials of biological origin, assessing the manufacturing process to prevent contamination (operators, equipment, and environment), assessing the ability of the production process to clear (eliminate, reduce, neutralise, or inactivate) any adventitious agents, and testing the product at appropriate stages of the production process for the absence of adventitious agents. Taken together, the measures set to assure safety with respect to non-viral contaminants are considered adequate and the risk associated with these contaminants is considered low.

TSE

The applicant states 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.

Viral adventitious agents

Cell banks

The cell banks were tested for potential viral contaminants in line with ICH Q5A requirements.

Given that bovine materials were used in cell line development and an insect cell line is used as the cell substrate, cells banks were additionally screened for relevant viruses found in those species, as

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

detailed in the dossier. Taken together, the above studies provided no evidence of contamination by adventitious viruses and the safety of cell banks with respect to adventitious viruses is considered sufficiently demonstrated.

Virus banks

The MVB was tested according to the "Points to Consider in the Characterization of Cell Lines Used to Produce Biologics" by *in vitro* assays and *in vivo* assays and is considered adequate. Adventitious agents testing is in line with Ph. Eur. 2.6.16. Testing of virus banks with respect to adventitious viruses is considered sufficient.

Testing of unprocessed and purified bulks

During routine manufacturing, each unprocessed bulk is tested for the presence of viral contaminants. Prior to infection, the production culture is additionally tested. The proposed testing is considered adequate. The absence of infectious baculovirus is a requirement for release of the AS. A respective specification has been implemented, the method to control for the absence of infectious baculovirus is considered adequate.

Virus validation studies:

The capacity of the manufacturing process for effective virus clearance has been evaluated in several studies. The virus clearance studies were conducted in line with the requirements outlined in the Note for guidance on virus validation studies (CPMP/BWP/268/95). The applicant provided the information on validation of down-scale models as requested. Based on the results provided (i.e. results of process parameters and analytical data of process intermediates), the scale-down models can be considered as representative for the commercial scale. The provided information is considered sufficient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active Substance

The MO regarding comparability of the vaccine batches used in pivotal clinical trials and the commercial product manufactured from AS produced at a different site, the Unigen site in Gifu has been solved. During the procedure, a question remained regarding a potential clinical impact of the observed differences in the rHA complex. The applicant has analysed data from AS batches manufactured between sites and found no correlation with immunogenicity. Thus, it can be concluded that no clinical impact is expected from the differences in the rHA manufactured at the different sites. The analysis of glycoforms which is required to further support comparability of material derived from the clinical lot manufacturing sites and the Gifu commercial site has been included in the list of recommendations (recommendation 1).

The applicant is recommended to introduce a stability monitoring method for assessment of active substance product-related impurities (recommendation 2). All other concerns raised have been sufficiently addressed by the applicant.

Finished Product

The GMP certificate for the manufacturing site has been provided. Therefore, the FP MO has been resolved.

All other concerns have been sufficiently addressed by the applicant. The validation of the polysorbate 20 methods and its implementation as FP release test has been included in the list of recommendations (recommendation 6).

Also, the risk assessment for leachables from single-use materials (recommendation 3) and the risk assessment for elemental impurities (recommendation 4), as well as the investigation of the stability indicating capability of the SRID method for one B strain in the presence of the other B (recommendation 5) have been included in the list of recommendations.

Risk assessment regarding Nitrosamine

The applicant has submitted the required risk assessment regarding the potential nitrosamine impurities in Supemtek. The CHMP agrees with the applicant's conclusion that no risk of presence of nitrosamines is identified.

New active substance claim

It was not agreed that the active substance in Supemtek fulfils the requirements for a new active substance as defined by indent 1 of Annex 1 of Volume 2a of Notice to Applicants (NtA) for the following reasons: although it is acknowledged that the structure of rHA might differ from conventional flu vaccines with regards to HA0/HA1+HA2 ratio and the size of the rosette clusters, this is considered not sufficient to define a new active substance. Conventional flu vaccines are highly variable. Depending on the substrate, the inactivation agent and the whole process, a wide distribution of structurally different antigens exists. Also, mutations are not considered to induce a structurally different active substance, especially not in the context of influenza vaccine viruses which change annually. Despite this variability, all HA antigens can be considered as comparable. Chemical modifications and differences in glycosylation pattern are not well defined and the high purity is not a feature of the active substance itself.

There is high variability between different influenza vaccines and also between annually updated antigens of each single vaccine. The differences described for the rHA fall within the normal range for influenza vaccines and do not generate a new active substance under indent 1 of Annex 1 of Volume 2a of Notice to Applicants (NtA) (see new active substance section of the CHMP AR for clinical considerations, under indent 3).

2.2.1. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.2. 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.

Area	Number	Description	Classification*
Quality	1	The results from rHA glycoform characterisation studies should be provided to further support comparability of material derived from the clinical lot manufacturing sites and the Gifu commercial site.	REC

Quality	2	A stability monitoring method for assessment of active substance product-related impurities should be implemented.	REC
Quality	3	The completed risk assessment report(s) for leachables from all single-use process materials used in the finished product manufacturing should be submitted.	REC
Quality	4	The completed FP risk assessment report(s) for elemental impurities according to ICH Q3D should be provided.	REC
Quality	5	The study results to investigate the stability indicating capability of the SRID method for one B strain in the presence of the other B strain should be submitted.	REC
Quality	6	The polysorbate 20 method should be validated and implemented as finished product release test, via variation.	REC

*REC- recommendation

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme for the quadrivalent recombinant influenza vaccine (RIV4) was primarily based on immunogenicity, non-clinical safety data, clinical and pharmacovigilance data obtained with trivalent recombinant influenza vaccine (RIV3). The main difference between RIV3 and RIV4 relates to an increase in the rHA content (from 135 to 180 µg/dose) due to the addition of a second lineage B strain.

2.3.2. Pharmacology

Primary pharmacodynamic studies

No specific non-clinical pharmacology studies including immunogenicity and challenge-protection studies in animal models have been performed with RIV4. There is large amount of pharmacodynamics data available in humans with both RIV3 and RIV4, both licensed in the US and manufactured using the same manufacturing process as that intended for EU. In addition, immunogenicity of RIV3 was established in mice.

The applicant presented non-clinical immunogenicity data generated in mice with the monovalent rH3 antigen (studies M0117 and M0139) and with the RIV3 (study M0163) that were administered intraperitoneally, intramuscular and subcutaneously, respectively.

Table 2: Immunogenicity studies performed with RIV3

Type of Study (Study Number)	Animal Species	Vaccine Formulation	Results
Immunogenicity (M0117)	Mouse	Monovalent rH3 from strain A/Beijing/32/92 **(H3N2)** ± Aluminum Phosphate	Immune responses were dose-dependent; a 10-fold increase in antigen resulted in approximately a three-fold increase over baseline in ELISA and HAI antibody titers.
Immunogenicity (M0139)	Mouse	Monovalent rH3 from strain A/H3/Beijing/32/92 **(H3N2)** (no adjuvant)	rHA produced in cell culture grown in serum-free medium stimulated HAI antibodies to similar levels induced by rHA manufactured using serum in the production process.
Immunogenicity (M0163)	Mouse	Trivalent rHA from strains A/Texas/36/1991 **(H1N1)** A/Shangdong/9/1993 **(H3N2)** B/Panama/45/1990 **(B)**	A trivalent formulation of rHA vaccine (RIV3) containing the 1994-1995 Northern Hemisphere type A and B influenza strains induced functional serum HAI and neutralizing antibodies against all strains of influenza in the vaccine.

The results from these studies show that RIV3 and rH3 are immunogenic 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. These data provide important proof-of-concept and support omission of the protection studies in animals. Although these non-clinical data do not address immunogenicity of the 4th strain in the context of RIV4, the CHMP acknowledged the extensive clinical experience with RIV4 that showed immunogenicity of each of the 4 antigen compositions within the vaccine. Therefore, the absence of non-clinical pharmacology data on the Yamagata lineage is considered acceptable.

Secondary pharmacodynamic studies

No dedicated studies were performed regarding secondary pharmacodynamic. This is endorsed due to the nature of the product.

Safety pharmacology programme

No dedicated studies including RIV4 were performed regarding safety pharmacology.

Three safety pharmacology studies were performed with RIV3, even though the repeat-dose toxicity study performed in rats with this vaccine did not show effects on the cardiovascular system (no clinical signs or abnormal histopathology), respiratory system (no unusual respiratory pattern) or CNS functions (no abnormal clinical signs on behaviour and posture).

These safety pharmacology studies were performed to evaluate the effects of RIV3 (trivalent, 135µg total rHA/dose, corresponding to 45 µg rHA/strain) following a single subcutaneous injection of one human dose.

- on the cardiovascular system (blood pressure, heart rate and electrocardiogram (ECG) parameters) (Study number P081016) in unanaesthetised dogs;
- on the respiratory (breathing rate) functions (Study number P081015) in rats;
- on the central nervous system (CNS) (functional observational battery test, locomotor activity and the body temperature measurement) (Study number P081014) in rats.

Results of safety pharmacology studies showed that a single SC injection with RIV3 did not adversely affect the blood pressure, heart rate, ECG parameters (in beagle dogs), respiratory parameters (in rats) as well as FOB, locomotor activity or body temperature (in rats). However, there are limitations of this study due to the use of SC route instead of the intended IM administration in humans. In addition, relevance of the dog can be questioned due to absence of immunogenicity evidence from the model.

Pharmacodynamic drug interactions

No dedicated studies were performed regarding secondary pharmacodynamic. This is endorsed due to the nature of the product.

2.3.3. Pharmacokinetics

In accordance with current guidelines, pharmacokinetic studies are not required for the vaccine assessment. No non-clinical pharmacokinetic studies have been performed to evaluate absorption, distribution, metabolism and excretion of the active ingredients of RIV4. RIV4 does not contain novel excipient or adjuvant.

2.3.4. Toxicology

No non-clinical toxicity studies have been performed with RIV4. The applicant supports the non-clinical safety evaluation of RIV4 based on a number of toxicology studies conducted with RIV3. The only notable difference between RIV3 and RIV4 relates to an increase in the total rHA content (from 135 to 180 µg/dose) due to the addition of another lineage B rHA.

Taking into account the similarity of RIV3 to RIV4, with respect to the manufacturing process with no novel excipients or process residuals and in absence of post-marketing safety concerns with RIV3, it is agreed that the non-clinical package developed to support RIV3 is relevant to support licensure of RIV4 in the EU.

The omission of non-clinical toxicity studies with RIV4 for the licensure of RIV4 in Europe is consistent with the CHMP Scientific Advice (EMEA/H/SA/3849/1/2018/III) and the EMA guidelines on influenza vaccines.

The applicant presented toxicity studies with RIV3 in different animal species as shown in Table 3. All pivotal non-clinical toxicity studies were conducted under GLP conditions.

Table 3: Toxicology program

Study Type and Duration	Route of Administration	Species	Products Administered
Single Dose Toxicity B-6407 Single injection on Day 0 Observation period: 14 days	Subcutaneous	Rat	Trivalent Formulation (RIV3) 45 µg rHA/influenza strain / 0.5 mL corresponding to one human dose Lot number: 0973-057A Influenza strains: A/H1N1/Salomon Islands/03/2006 A/H3N2/Wisconsin/67/2005 B/Malaysia/2506/2004
Single Dose Toxicity B-6494 Single injection on Day 0 Observation period: 14 days	Subcutaneous	Dog	
Repeat-Dose Toxicity B-6408 Five injections on Days 1, 8, 15, 22 and 29 Observation period: 4 weeks	Subcutaneous	Rat	
Developmental and Reproductive Toxicity (DART) 2146-001 Three injections: twice before mating and Gestation Days 6. Observation period: 20 days post coitum or 21 days post-partum	Intramuscular	Rat	Trivalent Formulation (RIV3) 45 µg rHA/influenza strain / 0.5 mL corresponding to one human dose Lot number: 50-06020 (2006-2007 formulation used in Clinical Study PSC02) Influenza strains: A/H1N1/New Caledonia A/H3N2/Wisconsin B/Ohio
IM Local Tolerance Study I-3235 Single injection on Day 0 Observation period: 2 or 7 days	Intramuscular	Rabbit	Trivalent Formulation (RIV3) 45 µg rHA/influenza strain / 0.5 mL corresponding to one human dose Lot number: 0973-057A Influenza strains: A/H1N1/Salomon Islands/03/2006 A/H3N2/Wisconsin/67/2005 B/Malaysia/2506/2004
SC Local Tolerance Study I-3234 Single injection on Day 0 Observation period: 2 or 7 days	Subcutaneous	Rabbit	
Safety Pharmacology: cardiovascular system P081016 Single injection on Day 0	Subcutaneous	Dog	
Safety Pharmacology: respiratory functions P081015 Single injection on Day 0	Subcutaneous	Rat	
Safety Pharmacology: central nervous system P081014 Single injection on Day	Subcutaneous	Rat	

Single dose toxicity

In single-dose toxicity studies, a single SC injection of RIV3 at a human dose did not induce toxicity effects over a 14-day observation period. During each study, there were no premature deaths, no clinical signs, no effects on body weights and no macroscopic findings. In addition, local reactions and food consumption were monitored in the dog study only and there were no vaccine-related effects noted on these parameters. Limitations of these studies include use of alternative SC administration route and the small number of animals per group.

Repeat dose toxicity

The pivotal repeat-dose toxicity study was conducted with 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. It is noteworthy that use of an alternative administration route (SC) rather than the clinically intended IM route for a pivotal toxicity study is uncommon, as is the short dosing interval of 7-days rather than a classic 2-3-weeks interval. Overall, results of this study are limited, in view of the fact that RIV3 had extensive human experience at the time of conducting this study.

Genotoxicity and carcinogenicity

No genotoxicity and carcinogenicity studies were carried out in line with relevant guidelines. Studies evaluating genotoxicity and carcinogenicity are normally not required for viral vaccines. Since no adjuvants or novel excipients are used in this product absence of those studies is considered acceptable.

Reproduction toxicity

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 an 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.

Local tolerance

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. Transient microscopic inflammation at injection sites was observed after IM injection only, which was expected.

Other toxicity studies

2.3.5. Ecotoxicity/environmental risk assessment

The active substance of RIV4 is purified protein, the use of which is not expected to pose a risk to the environment. Therefore, dedicated environmental risk studies are not considered necessary.

2.3.6. Discussion on non-clinical aspects

The present MAA does not include any dedicate pharmacology or toxicology studies with RIV4. The non-clinical evaluation of RIV4 was primarily based on non-clinical obtained with RIV3 and clinical trial data and post-marketing surveillance data obtained with RIV3 and RIV4.

The main difference between RIV3 and RIV4 relates to an increase in the rHA content (from 135 to 180 µg/dose) due to the addition of a second lineage B strain. Both vaccines are manufactured using the same manufacturing process, same compositions and amounts of excipients and process residuals. Based on the similarity between RIV3 and RIV4 and availability of extensive clinical experience with RIV3, it is justified that no additional non-clinical studies with RIV4 are necessary for its MAA in the EU, in line with the EMA guidance on Guideline on Influenza Vaccines. This is also in agreement with the CHMP Scientific Advice provided confirming that sufficient non-clinical and clinical data are available for RIV3 and RIV4 so that no further non-clinical studies with RIV4 are deemed necessary for MAA in the EU.

Despite the limitations observed in the pharmacodynamic or toxicology studies, it is acknowledged that extensive clinical experience with RIV3 from pre-licensure clinical trials and post-marketing surveillance safety profile did not identify any unexpected safety signal. The absence of non-clinical immunogenicity data on the additionally added Yamagata line and the lack of dedicated pharmacodynamic data generated exclusively with the quadrivalent product was justified by available clinical data from trials and marketing/post-marketing process in US of RIV4. In particular to safety, the non-clinical safety package developed for RIV3 showing no issue of major safety concern complies with the known clinical adverse event profile of RIV3.

2.3.7. Conclusion on the non-clinical aspects

Based on the non-clinical data available from studies conducted with recombinant H3 and RIV3 and data collected from the extensive clinical experience with RIV3 from pre-licensure clinical trials and post-marketing surveillance the product, there is no specific safety concern. The product is considered approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development strategy for RIV4 followed the initial development of the trivalent product and was based on the demonstration that RIV4 was at least comparable to a licensed influenza quadrivalent vaccine in terms of safety, immunogenicity and efficacy.

The quantity of each HA antigen and excipients of RIV4 was equivalent to that of the US licensed trivalent recombinant influenza vaccine manufactured by PSC with the addition of the second B strain. Safety and immunogenicity of the RIV4 were expected to be similar to the trivalent formulation. Therefore, the clinical development plan for RIV4 did not include formal evaluation of safety in a Phase I study and dose selection in a Phase II study.

GCP

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

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

- Tabular overview of clinical studies

Table 4: Overview of clinical studies for the indication development

Study ID, Season and Location	Design and Type of Control	Population actually enrolled	Objectives	Endpoints*	Analysis populations for Efficacy and Immunogenicity
Pivotal clinical studies					
PSC12 NCT02285998 NH 2014-2015 USA	Phase III, observer-blind, active comparator-controlled, multi-centre study, randomised 1:1 to receive one IM dose of RIV4 (45 mcg rHA per strain) or IIV4 (Fluarix Tetra) (15 mcg HA per strain)	Adults aged ≥50 years, medically stable 8,963 total 4,474 RIV4 4,489 IIV4	Primary: Non-inferior vaccine efficacy Secondary: Non-inferior immunogenicity Safety	Primary: rt-PCR confirmed protocol-defined ILI caused by any influenza strain that began at least 14 days post-vaccination through the EOIS Secondary: rt-PCR confirmed, CDC defined ILI, any strain, culture-confirmed, protocol defined ILI, matched strains, culture-confirmed, CDC-defined ILI, matched strains GMT ratio and SCR difference for each strain Frequency and severity of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), and SAEs/MAEs (180 days)	Efficacy: 8,604 total 4,303 RIV4 4,301 II4 Immunogenicity: 614 total 314 RIV4 300 IIV4
PSC16 NCT02290509 NH 2014-2015 USA	Phase III, observer-blind, active comparator-controlled, multi-centre study, randomised 3:1 to receive one IM dose of RIV4 (45 mcg rHA per strain) or IIV4 (Fluarix Tetra) (15 mcg HA per strain	Healthy adults aged 18 to 49 years 1,350 total 1,011 RIV4 339 IIV4	Non-inferior immunogenicity Safety	Co-Primary: GMT ratio and SCR difference for each strain Secondary: Frequency and severity of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), and SAEs/MAEs (180 days). SCRs, % HI titer ≥1:40	Immunogenicity: 1,292 total 969 RIV4 323 IIV4
Supportive clinical study					
PSC04 NCT00539981 NH 2007-2008 USA	Phase III, observer-blind, placebo-controlled, multi-centre study, randomised 1:1 to receive one IM dose of RIV3 (45 mcg rHA per strain) or placebo (saline)	Healthy adults aged 18 to 49 years 4,648 total 2,344 RIV3 2,304 placebo	Absolute vaccine efficacy Lot consistency safety	Primary: Culture-confirmed CDC defined ILI, matched strains GMT ratio difference for each strain and lot Frequency of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), SAEs until data lock date for interim analysis Secondary: Culture-confirmed ILI regardless of CDC ILI, matched strains	Efficacy: 4,648 total 2,344 RIV3 2,304 placebo Immunogenicity: 391 (448 post database lock)

				SCRs, % HI titers ≥1:40 or ≥ 4-fold rise Exploratory: Culture-confirmed CDC defined ILI, any strain CDC defined ILI regardless of culture findings	

2.4.2. Pharmacokinetics

Pharmacokinetic studies were not conducted in the development program of RIV4, in line with current guidelines. Pharmacokinetic studies are not required for influenza vaccines as the kinetics properties of vaccines do not provide useful information for establishing adequate dosing recommendations.

2.4.3. Pharmacodynamics

Mechanism of action

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

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

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

2.4.4. Discussion on clinical pharmacology

Immunogenicity of the vaccine was assessed using a haemagglutination inhibition test (HAI). Although HAI is not a confirmed immunological correlate of protection, HAI is traditionally used for the assessment of immunogenicity of influenza vaccines. The serological analysis of the study samples from the pivotal studies PSC12 and PSC16 was performed by one central laboratory (Q2 Solutions, San Juan Capistrano (SJC), California, USA; previously Focus Diagnostics, Cypress, CA, USA), as recommended in the EMA Guideline on Influenza Vaccines - Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014.

The HAI has been described. Method validation reports for the strains 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 influenza antigens (i.e. the strains for the 2014/2015 NH season are covered) have been provided. The method validation comprised the parameters accuracy/recovery, sensitivity, specificity, intra- and inter-assay precision, and linearity. The precision experiments addressed day-to-day variability as well as variability introduced by operator and the lot of RBCs. Egg-derived antigens and corresponding sheep reference sera from

NIBSC as well as a panel of human sera from influenza vaccinees were used throughout the validation experiments.

The validation data demonstrate that the HAI method performs reliably and is suitable for monitoring of immunogenicity in clinical studies.

In the two main studies for RIV4 approval (PSC12 and PSC16), HAI antibody titers to each virus strain represented in RIV4 and IIV4 were measured as sole serologic parameter in sera obtained approximately 28 days after vaccination. HAI antibody titers were determined by an assay that used egg-derived antigens supplied by NIBSC. In contrary, the former study PSC04, now submitted supportively mainly for efficacy bridging reasons, uses a BEVS (Baculovirus-Expression Vector-System)-derived test antigen. Still, the relative values among the different included vaccine strains as well as the fact, that its respective B strain is supporting the efficacy of RIV, renders consideration of its immunogenicity results worthwhile.

Analysis of antibody responses in all studies was performed for each HA contained in the vaccine and active control according to the criteria related to post-vaccination HAI GMT, seroconversion rates and proportion of subjects with post-vaccination HAI titers ≥ 40, as specified in the FDA Guidance for Industry.

Post hoc analyses of HAI titers using additional criteria, including post-vaccination fold-increase in HAI GMT and plots of Reverse Cumulative Distribution Curves, as described in EMA Guidelines were performed for this dossier. Subsequently, the applicant also provided a subset of 100 vaccinees per arm (RIV4 and IIV4) each of PSC12 and PSC16 for seroneutralizing antibody response assessment. These post hoc analyses, as described in the EMA Guidelines in effect since 2014, show close comparability of HAI immune responses between RIV4 and IIV4 as were shown in the previous pre-specified analysis.

2.4.5. Conclusions on clinical pharmacology

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

2.5. Clinical efficacy

The applicant presented three phase III studies (PSC12, PSC16, PSC04) to be used to support the effective use of RIV4 in subjects 18 years of age and older for the present application. PSC12 and PSC16 were pivotal studies that were run with RIV4 in older adults ≥50 years and young adults 18 to 49 years of age, respectively, to demonstrate vaccine efficacy and immunogenicity of RIV4, whereas PSC04 was a supportive study conducted with RIV3 to establish vaccine efficacy in young healthy adults from 18 to 49 years of age.

The virus strains selected for the RIV4 and the RIV3 were in compliance with the seasonal influenza WHO recommendations for influenza vaccine strains chosen for each influenza seasons.

2.5.1. Dose response study

The clinical development plan for RIV4 did not include formal dose selection in a phase II study. The applicant explains that the dose of 45 mcg rHA per strain is approved in the USA for use in adults 18 years of age and older and the safety and immunogenicity of the RIV4 were expected to be similar to the US licensed trivalent formulation RIV3.

The applicant's choice of 45 mcg rHA per strain for RIV4 appears to be justifiable, considering the fact that it was a licensed dose for RIV3. The similarity of manufacturing process for RIV4 vs RIV3, and the discussion provided by the applicant regarding the results of previous clinical studies with monovalent, bivalent and trivalent rHAs.

In the frame of RIV3 development, two Phase II clinical trials were conducted to establish the optimal dose of rHA in comparison to licensed, egg-grown inactivated influenza vaccine. Dose selection was based on pharmacodynamics determined by the measured humoral immune response. The doses of rHA evaluated in the early trials were multiples of 15 µg in order to compare with licensed influenza vaccines.

Two Phase II clinical trials were conducted to establish the optimal dose of rHA (

Table 5). The first trial (DMID-03-119) was conducted in adults 65 years of age and older, due to the recognised medical need for influenza vaccines with improved efficacy in this age group. This trial, conducted by the United States of America (USA) National Institutes of Health Division of Microbiology and Infectious Diseases (DMID), evaluated rHA doses of 15, 45 and 135 µg of each antigen compared with trivalent inactivated vaccine (IIV3). Immunogenicity was determined by geometric mean HAI titers to each antigen before and approximately 28 days following a single injection.

The second dose-finding trial (PSC01), was a placebo-controlled study in adults 18-49 years of age. The RIV3 contained 15 or 45 µg rHA for influenza A/H1 and influenza B, to evaluate a dose-response for these antigens that had not been apparent in the earlier study, and 45 µg rHA for influenza A/H3 antigen, as this dose had been established as the optimal dose in the earlier study.

Table 5: Clinical Pharmacology Dose-Finding Studies

Study identifier	Location of study report	Pharmacology objective(s) of the study	Study design and type of control	Test Product(s); Batch number (s); Form; Dosage regimen; Route of administration	Number of subjects and type of population	Country(ies); Trial period (FVFS – LVLS*)
DMID – 03-119	Publication	To compare the tolerability and immunogenicity of standard and higher doses of rHA compared with conventional egg-grown influenza vaccine in adults ≥ 65 years of age	Phase II, randomized, observer-blinded, active-controlled 4-arm	One injection of RIV3 containing 15, 45 or 135 µg of rHA per strain or IIV3 containing 15 µg of HA per strain Intramuscular (IM) route	N = 99 in RIV3 15 µg group N= 100 in RIV3 45 µg group N=101 in RIV3 135 µg group N = 99 in IIV3	USA, Autumn, 2003 – Spring, 2004
PSC01 NCT00328107	Publication	To determine dose-related safety, immunogenicity and protective efficacy of RIV3	Phase II, randomized, observer-blinded, placebo-controlled 3-arm	One injection of RIV3 containing 15 or 45 µg of rHA (A/H1 and B) and 45 µg (A/H3) (2004-2005 Northern Hemisphere season) or placebo by IM route	N = 153 in RIV3 (75 µg total) N = 153 in RIV3 (135 µg total) N = 154 in placebo	17 November 2004; 26 May 2005

* FVFS – LVLS: First visit of the first subject – last visit of the last subject

Results of HAI titers in the DMID-03-119 study (adults ≥65 years of age) were reported according to GMTs within each vaccine group. The authors concluded that the HAI immune response in these older adults was dose-related for influenza A/H3 and considerably more robust than that induced by IIV3. By contrast, there was not a clear dose-response to influenza A/H1 or B. They further concluded that rHA doses of 45 µg and higher provided the optimal immune response to influenza A/H1 and B and perhaps a level of immunogenicity for influenza A/H3 superior to that of conventional inactivated vaccine.

In the 2nd study (PSC01) designed to evaluate a possible dose-response to influenza A/H1 and B versus placebo, the HAI immunogenicity was assessed by the proportion of subjects experiencing a 4-fold rise in HAI titer. Both dose levels of rHA A/H1 and B induced HAI responses (4-fold rise) in the majority of subjects, but the geometric means of titers (GMTs) were higher for the 45 µg per antigen formulation.

After conducting both studies, the authors concluded that "further development of the rHA vaccine should use a formulation of 45 µg per component, and future studies should directly compare the safety and immunogenicity of this dose with that of inactivated vaccine".

2.5.2. Main studies

2.5.2.1. PSC12

Study title: Comparison of the Protective Efficacy of Flublok[2] Quadrivalent versus Licensed Inactivated Influenza Vaccine (IIV4) in Healthy, Medically Stable Adults ≥50 Years of Age

Methods

Study Participants

A total of 8,963 subjects were randomised: 4,474 subjects in the RIV4 group and 4,489 subjects in the IIV4 group.

Selected inclusion criteria

[2] Flublok is the same vaccine as Supemtek, different trade name.

- Ambulatory non-pregnant adults aged 50 years and older, medically-stable, as determined by medical history and targeted physical examination. "Medically stable" was defined as no change in diagnosis or chronic medications (dose or class) for medical reasons in the 3 months prior to study;
- Absence of underlying conditions that make participation in the study contrary to the subject's best interest
- Able to understand and comply with planned study procedures
- Provides written informed consent prior to initiation of any study procedure

Selected exclusion criteria

- Known contraindication to either study vaccine (see product package inserts)
- Receipt of any other influenza vaccine within 180 days prior to enrolment in this study
- Underlying disease or ongoing therapy that might cause immunocompromised such that response to vaccination might be sub-optimal

Treatments

Two vaccines were tested in the trial:

- Group A: RIV4 (Flublok Quadrivalent) containing 4x45µg (180µg total) of rHA derived from influenza A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes, or
- Group B: IIV4 (Fluarix Quadrivalent) containing 4x15µg (60 µg total), of quadrivalent, inactivated influenza vaccine (licensed IIV4) containing influenza antigen derived from A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes.

IIV4 and rHAs were derived from the following influenza viruses that were identified by the FDA's Vaccines and Related Biological Products Advisory Committee as the four strains (or "like viruses") to be included in quadrivalent influenza vaccines for the 2014-2015 season:

Table 6: Influenza vaccine composition for season 2014-2015 used in the study PSC012

Flublok Quadrivalent	IIV4 (Fluarix Quadrivalent)
H1N1: A/California/07/2009	H1N1: A/ Christchurch/16/2010 (an A/California/7/2009-like virus)
H3N2: A/Texas/50/2012	H3N2: A/Texas/50/2012
B/Massachusetts/2/2012 (B/Yamagata-lineage)	B/Massachusetts/2/2012
B/Brisbane/60/2008 (B/Victoria-lineage)	B/Brisbane/60/2008

Objectives

Primary objective

- To compare the clinical efficacy of RIV4 to that of IIV4, with respect to the ratio of attack rates of rtPCR-confirmed protocol-defined ILI that begin at least 14 days after vaccination caused by any influenza viral types/subtypes.

Secondary objectives

- 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.
- To compare immunogenicity of RIV4 vs. IIV4 in a preselected subset of subjects adequate to compare post-vaccination HAI GMTs and SCRs for all four antigens in each study vaccine. All comparisons were designed to demonstrate non-inferior immunogenicity according to CBER criteria.
- To compare the safety and reactogenicity of RIV4 vs. IIV4.

Exploratory objectives

- Efficacy and safety/reactogenicity will be assessed by subgroups defined by age category, gender, and race/ethnicity, and the receipt of influenza vaccination in the prior year, as exploratory analyses.

Outcomes/endpoints

Primary efficacy endpoint:

- rtPCR-confirmed, protocol-defined ILI[3] caused by any influenza strain that begins at least 14 days post-vaccination.

Key secondary efficacy and immunogenicity endpoints:

- rtPCR-confirmed CDC-defined ILI[4] that begins at least 14 days post-vaccination caused by any influenza strain.
- culture-confirmed protocol-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain antigenically matched to those strains represented in the study vaccines.
- culture-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain antigenically matched to those in the study vaccines.
- post-vaccination HAI GMTs and SCR for all four antigens in a preselected subset of subjects.

[3] Protocol-defined ILI is defined as at least one of the following respiratory symptoms (sore throat, cough, sputum production, wheezin, difficulty breathing) accompanied by at least one of the following systemic symptoms (fever >37.2°C (99.0°F), chills (shivering), tiredness (fatigue), headache and myalgia (muscle ache).
[4] CDC-defined ILI is defined as body temperature ≥100° F accompanied by cough and/or sore throat on the same or consecutive days.

Sample size

The study was planned to be performed with 4,311 patients per group. The primary objective of the study was to demonstrate non-inferiority of rVE of RIV4 vs. IIV4. The non-inferiority margin was set to be -0.2. Assuming an influenza attack rate (AR) of 2% in IIV and 1.53% in RIV4 recipients, respectively, a significance level of 0.05, 4,311 evaluable subjects per group would be required to demonstrate non-inferiority with 80% power, with lower bound of the two-sided 95%CI around rVE of >-0.20 (-20%). A total of 9,000 subjects were enrolled to account for 4-5% loss to follow-up. The number of patients actually randomised was 4,474 for RIV4 and 4,489 patients for IIV4. The sample size for serology subset of ~520 subjects provided >80% power to determine non-inferiority.

Randomisation

Subjects were randomised 1:1 via a centralised Interactive Web Response System (IWRS) on Day 0 of their participation in the study. The IWRS system ensured balanced enrolment across the age categories of 50-64, 65-74 and ≥75 years and balanced treatment assignment across study sites.

Blinding (masking)

This was an observer-blind study. The subjects and the study personnel who performed study assessments after vaccination were blinded to treatment assignment. There was only one unblinded study member who administered study vaccine to the subject, who was not involved in subsequent assessments. Study assessments were conducted by a blinded investigator.

Statistical methods

The primary hypothesis for this trial is that the efficacy of RIV4 was non-inferior to licensed IIV4, based on the relative efficacy in prevention of rtPCR-confirmed influenza-like illness. If non-inferiority was demonstrated, the efficacy of RIV4 was tested as an exploratory analysis for superiority over licensed IIV4, based on the incidence of rtPCR-confirmed protocol-defined influenza-like illness.

Analysis set for efficacy

The efficacy population included all randomised subjects who received study vaccine and provided any follow-up documentation for ILI beginning at least 14 days following vaccine administration. Subjects were analyzed according to the vaccine received, regardless of the vaccine group to which they were randomised. The efficacy population did not include subjects with significant protocol deviations. The efficacy population was used for all analyses of efficacy endpoints.

Statistical methods for efficacy

The ILI confirmed by a positive nasopharyngeal rt-PCR test for influenza virus of any strain that begins at least 14 days after vaccination was the primary efficacy endpoint. The rVE against this endpoint was determined as rVE = 1- relative risk (RR) = 1- (attack rate (AR)RIV4/attack rate (AR)IIV4) x 100. Farrington and Manning's score method was used to compute the CI around rVE. Non-inferiority was established if the lower bound of the two-sided 95%CI for VE is greater than the non-inferiority margin of -0.20.

Analysis set for immunogenicity

The immunogenicity population included all randomised subjects at the specific study sites pre-selected for serology, who received study vaccine, provided serum samples on Days 0 and 28, and had no significant protocol deviations. Subjects were analysed according to the vaccine received, regardless of the vaccine group to which they were randomised.

Statistical methods for immunogenicity

The analyses of non-inferiority, superiority and descriptive analyses were based on results obtained with the HAI assay.

Post-vaccination HAI titers from a subset of approximately 520 subjects were compared between RIV4 subjects and IIV4 subjects using the criteria for non-inferiority defined by CBER for the difference in seroconversion rates and the ratio of GMTs of IIV4/RIV4:

- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates (% Seroconversion (licensed vaccine) - % Seroconversion(RIV4) should not exceed 10 percentage points.
- The upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT [licensed vaccine]/GMT[RIV4)) should not exceed 1.5.

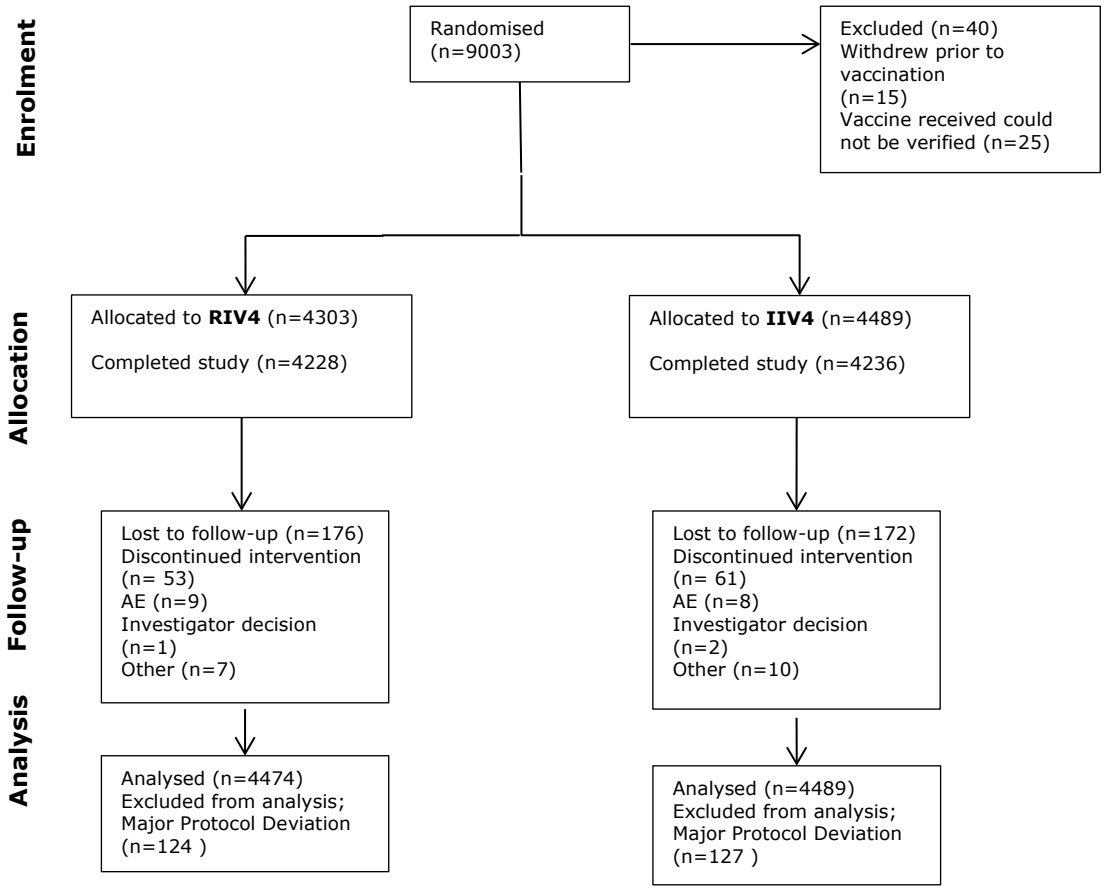
The computation of the CI for the difference in seroconversion rates utilised Farrington and Manning's score method.

The ratios of the GMTs were calculated as the antilog of the difference between 2 mean log-transformed titers. The 95% CI was calculated as the antilog of the 95% confidence limits of the log-transformed titers.

Non-inferiority of immune responses across the entire age spectrum was concluded when the criteria specified above were met.

Results

Participant flow



Of the 9,003 subjects enrolled and randomised, 8,988 received a dose of study vaccine. 15 randomised subjects did not receive study vaccine due to withdrawal before vaccination and 25 randomised subjects at study site 44 received a dose of study vaccine but the identity of which could not be verified from site records, yielding a total randomised population for final analysis of 8,963 subjects (4,474 RIV4, 4,489 IIV4).

Overall, the number of subjects included in efficacy analyses was high and only small fraction of vaccinated subjects were excluded. Of the 4,474 RIV4 recipients, 4,303 (96.2%) provided any follow-up data for ILI and had no major protocol deviations, were included for clinical efficacy analyses. 4,228 (94.5%) completed the study. Of the 4,489 IIV4 recipients, 4,301 (95.8%) were included in efficacy population and 4,236 (94.4%) completed the study.

For both treatment groups, the most common reason for discontinuation of study was lost-to-follow up (176 [3.9%] RIV4 and 172 [3.8%] IIV4 recipients), followed by voluntary withdrawal unrelated to AE (53 [1.2%] RIV4 and 61 [1.4%] IIV4 recipients).

The small subset for immunogenicity analysis was pre-selected from each treatment group, including 314 RIV4 and 300 IIV4 recipients.

Recruitment

The study was conducted at 40 sites dispersed geographically across the US during the study period from October 22, 2014 (first subject enrolled) to May 22, 2015 (last subject completed).

Conduct of the study

Of the 8,963 randomised subjects, 251 (2.8%) were categorised as having "major" protocol deviations that led to subjects being excluded from the efficacy analyses (Table 7). The most common major protocol deviations represented failure to be evaluated with NP swab in the context of symptoms of an influenza-like illness. The two treatment groups were well-balanced with respect to the number and types of protocol deviations.

Table 7: PSC12 -- Major Protocol Deviations

Deviation Category	Flublok Quadrivalent N=4474 n (%)	IIV4 N=4489 n (%)
Subjects with any Major Protocol Deviation	124 (2.8)	127 (2.8)
Concomitant Medication	0	1 (0.0)
Dosing Error	3 (0.1)	5 (0.1)
Exclusion Criteria	0	1 (0.0)
Lab Sample	28 (0.6)	27 (0.6)
Missed Study Visit	41 (0.9)	36 (0.8)
Procedure Not Per Protocol	36 (0.8)	42 (0.9)
Unblinding	1 (0.0)	0
Visit Out Of Window	6 (0.1)	4 (0.1)
Other	11 (0.2)	13 (0.3)
Subjects with any Major Protocol Deviation For Immunogenicity	24 (0.5)	25 (0.6)
Lab Sample	3 (0.1)	2 (0.0)
Missed Study Visit	23 (0.5)	24 (0.5)
Procedure Not Per Protocol	1 (0.0)	0
Visit Out Of Window	0	1 (0.0)

Baseline data

Subjects in both treatment groups were ambulatory medically-stable adults aged 50 years and older. The majority of subjects were white, non-Hispanic, and there was a slight majority of females. Approximately 40% of subjects in this trial were ≥65 years.

There were no notable differences in demographic characteristics of subjects with post-randomization data between the two treatment groups.

Table 8: PSC12 -- Subjects Demographics

Characteristic	Flublok Quadrivalent N=4328	IIV4 N=4344
Age (years) mean (range)	62.7 (50 – 96)	62.6 (50 - 94)
Age Group n (%)		
50-64 years	2569 (59.4)	2617 (60.2)
>=65 years	1759 (40.6)	1727 (39.8)
65-74 years	1234 (28.5)	1254 (28.9)
>=75 years	525 (12.1)	473 (10.9)
Gender, n (%)		
Male	1796 (41.5)	1807 (41.6)
Female	2532 (58.5)	2537 (58.4)
Race, n (%)		
Black or African American	773 (17.9)	753 (17.3)
White or Caucasian	3467 (80.1)	3493 (80.4)
Other[a]	88 (2.0)	98 (2.3)
Ethnicity, n (%)		
Hispanic	206 (4.8)	219 (5.0)
Non-Hispanic	4122 (95.2)	4123 (94.9)
Other	0	2 (0.0)

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

The baseline data for comparing the immunogenicity subset was not presented. The applicant noted the randomization via IWRS to ensure a balance of treatment group across study sites.

Numbers analysed

As part of clinical efficacy determination, 4,303 RIV4 recipients and 4,301 IIV4 recipients met the efficacy population definition (per Protocol) that was used for all clinical efficacy analyses. In total, 234 subjects, including 96 RIV4 and 138 IIV4 recipients developed protocol-defined ILI and had positive rt-PCR for influenza. Of these, 159 subjects who met the criteria for protocol-defined ILI were subsequently confirmed by culture, including 58 RIV4 and 101 IIV4 recipients.

It was mentioned that 4 ILI cases were hospitalised with documented influenza A infection, including 3 IIV4 and 1 RIV4 recipients.

In total, 314 RIV4 and 300 IIV4 recipients were analysed for the immunogenicity endpoints.

Table 9: PSC12 -- Subjects Disposition

	Flublok Quadrivalent N=4474 n (%)	IIV4 N=4489 n (%)
Randomized Population[a]	4474	4489
Efficacy Population	4303 (96.2)	4301 (95.8)
Immunogenicity Population	314 (7.0)	300 (6.7)
Safety Population	4328 (96.7)	4344 (96.8)
Reactogenicity Population	4312 (96.4)	4327 (96.4)
Reactogenicity Population 1[b]	4307 (96.3)	4319 (96.2)
Reactogenicity Population 2[c]	4306 (96.2)	4318 (96.2)
Reactogenicity Population 3[d]	4262 (95.3)	4282 (95.4)
Completed study	4228 (94.5)	4236 (94.4)
Primary Reason for Early Withdrawal		
Adverse Event	9 (0.2)	8 (0.2)
Investigator Decision	1 (0.0)	2 (0.0)
Lost to Follow-up	176 (3.9)	172 (3.8)
Sponsor Request	0	0
Voluntary withdrawal unrelated to AE	53 (1.2)	61 (1.4)
Other	7 (0.2)	10 (0.2)

[a] Excludes 40 subjects who received randomization numbers, but who either withdrew prior to vaccination (n=15) or for whom the vaccine received could not be verified (n=25; 12 assigned to Flublok Quadrivalent and 13 assigned to IIV4).
[b] Subjects with any Injection site reactogenicity data, Days 0-7
[c] Subjects with any systemic reactogenicity data, Days 0-7
[d] Subjects with any body temperature data, Days 0-7

Outcomes and estimation

Efficacy results are presented only for the per protocol population.

The primary efficacy endpoint for PSC12 was met. The attack rates of rtPCR confirmed protocol-defined ILI occurring at least 14 days after vaccination were 2.2% (n=96) among 4,303 RIV4 recipients and 3.2% (n=138) among 4,301 IIV4 recipients, yielding a **rVE of +30% (95%CI: +10, 47%)**, thus meeting the pre-specified non-inferiority criterion.

The applicant also stated that this rVE from the primary endpoint met the pre-specified criterion for superiority (lower bound of 95%CI >+9.0%). .

The key secondary efficacy endpoint – occurrence of rtPCR confirmed CDC-ILI met the non-inferiority criterion but unmet the superiority criterion. rVE was +32% (95%CI: +8, 54%).

The time to rtPCR-confirmed, protocol-defined ILI further confirmed a consistently reduced attack rate among RIV4 recipients as compared with IIV4 recipients that became apparent within 2-4 weeks of vaccination and persisted throughout the influenza season (***Figure 1***).

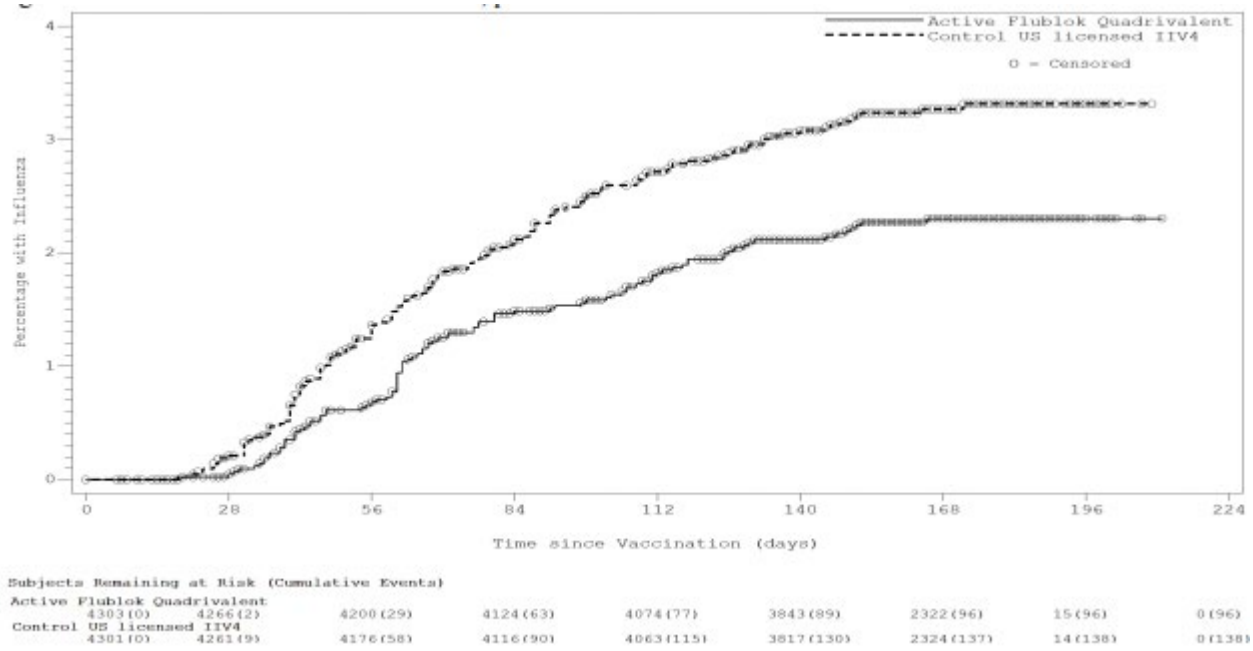


Figure 1: PSC12 – Time to rt-PCR-confirmed, protocol-defined ILI

An increase of B activity late in the season can be determined from the time to rt-PCR confirmed ILI curves provided according to vaccine and A or B strain infection (***Figure 2***).

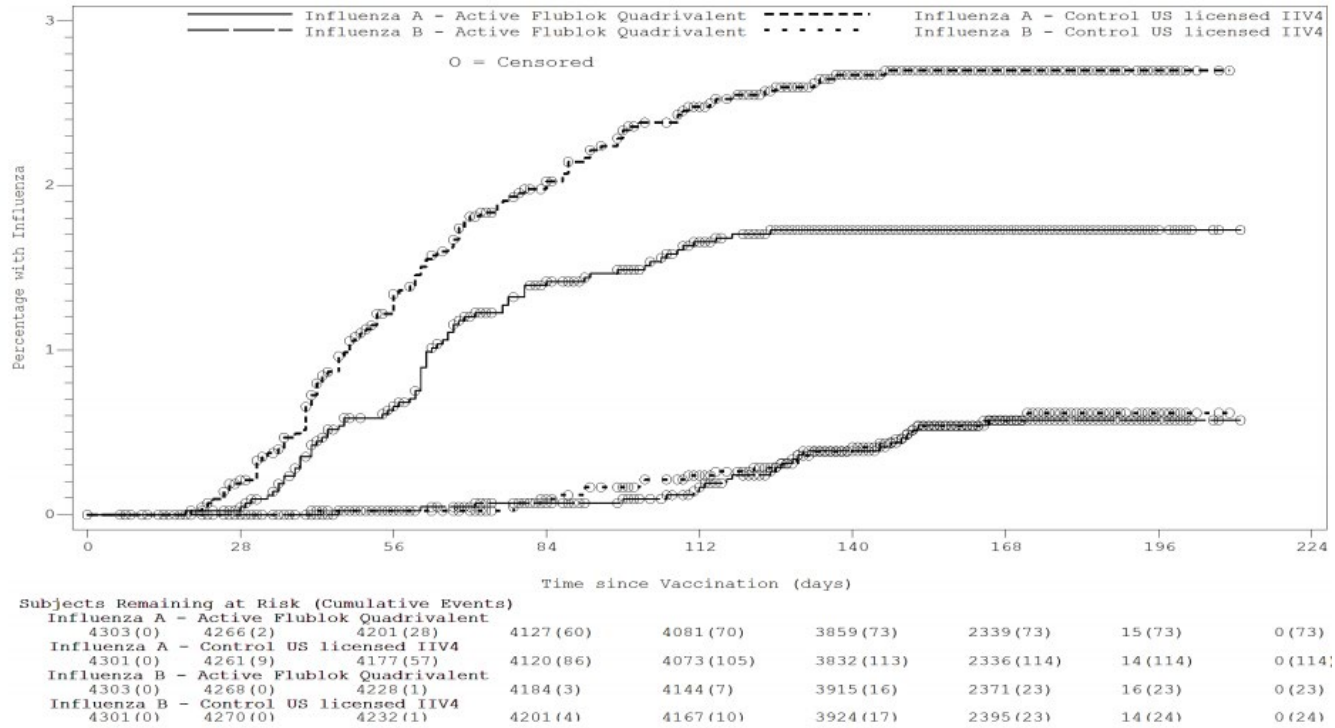


Figure 2: PSC12 – Time to rt-PCR-confirmed, protocol-defined ILI due to Influenza A and B

Two other key secondary efficacy endpoints – occurrence of culture-confirmed influenza due to antigenically matched strains in association with protocol-defined ILI or CDC-ILI, were not analyzed, as the virus cultures did not provide adequate titers of viruses for antigenic similarity testing.

For the secondary immunogenicity endpoints, pre- and post-vaccination (Day 28) HAI titers and 38 days post-vaccination for each strain, from a subset of subjects (N= 614) were analysed. The results are included in the table below.

Table 10: 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	48	1.15 (0.95; **1.41***)
		(38, 51)	(41, 56)	
	Day 28	190	220	
		(164, 221)	(193, 250)	
A/H3N2/Texas	Day 0	87	98	0.69 (0.58; **0.81**)
		(73, 103)	(83, 117)	
	Day 28	522	358	
		(462, 589)	(318, 404)	
B/Massachusetts	Day 0	17	18	1.03 (0.86; **1.24**)
		(15, 20)	(16, 21)	
	Day 28	55	57	
		(48, 64)	(51, 65)	
B/Brisbane	Day 0	14	14	1.47 (1.23; 1.76)
		(12, 15)	(13, 16)	
	Day 28	29	43	
		(26, 33)	(38, 49)	

* Figures in bold meet criterion for non-inferiority (upper limit of 2-sided 95% CI of GMR < 1.5)

Table 11: PSC12: HAI seroconversion rates – Adults ⩾ 50 years of age

Antigen	RIV4 N=314 N (%)	IIV4 N=300 N (%)	Difference (95% CI)
A/California	141 (44.9)	147 (49.0)	4.1 (-3.8; 12.0)
A/Texas	171 (54.5)	130 (43.3)	-11.1 (-19.0; **-3.3***)
B/Massachusetts	122 (38.9)	115 (38.3)	-0.5 (-8.2; **7.2**)
B/Brisbane	66 (21.0)	103 (34.3)	13.3 (6.3; 20.3)

* Figures in bold meet CBER criteria for non-inferiority

RIV4 met the pre-specified non-inferiority criterion vs IIV4 with respect to the differences in HAI SCRs for 2 of the 4 strains (A/Texas, B/Massachusetts), while the post-vaccination HAI GMT ratio endpoint met non-inferiority criterion for 3 of the 4 strains (A/California, A/Texas, B/Massachusetts), according to the CBER criteria.

Overall, RIV4 induced robust HAI response to A/H3 strain, but blunted responses to influenza B strains. The HAI response to B/Brisbane was lower in RIV4 than in IIV4 recipients. The clinical relevance of this difference is unknown. In general, these data is well consistent with clinical efficacy results.

Ancillary analyses

A *post-hoc* analysis was carried out on the occurrence of culture-confirmed protocol-defined ILI due to any influenza strain, meeting both non-inferiority and superiority criteria. The rVE was estimated to be 43% (95%CI: +21, 59%) in the efficacy population.

Additional *post-hoc* analysis on the primary efficacy endpoint showed that the rVE of RIV4 over IIV4 was apparent for influenza A strains especially A/H3 strain, whereas rVE for influenza B was not conclusive due to limited cases. The rVE against influenza A strain was estimated to be +36% (95%CI: +14, 53%), and rVE against influenza B was +4% (95%CI: -72, 46%).

Data on subgroup analyses according to age, gender and other categories of demographics generally point in the same direction as the primary analysis. The point estimates for rVE were mostly positive but with some variability between genders, races and ethnicities. The CIs were wide and no meaningful conclusion can be drawn. rVE point estimate was higher in subjects aged 50-64 years than in subjects ≥65 years, and 95% CI for older subjects was wide and encompassed zero. The applicant stated that between the RIV4 and IIV4 recipients, no conclusive difference in efficacy of two vaccines could be demonstrated based on age category.

The impact of prior influenza vaccination status was evaluated in exploratory analysis, showing greater rVE in subjects who had not received influenza vaccines in the prior year than in the study population as a whole. Among 3,994 subjects (2,006 RIV4 and 1,988 IIV4 recipients) who reported not having received a flu vaccine in the prior season, the rVE was +48% (95%CI: +16, 68%).

The impact of underlying medical illness on rVE was explored in an post-hoc analysis. RIV4 was shown to be more effective than IIV4 in subjects with underlying conditions, although this RIV4 benefit is higher in subjects with no underlying conditions than in subjects with underlying conditions.

The applicant clarified that the pre-specified exploratory efficacy analyses on the influenza-related complications such as hospitalizations, deaths and pneumonia in PSC12, were not performed, due to the absence or not sufficient data to warrant a health economic assessment. There were 4 influenza-related hospitalization cases, which were categorised as SAEs, because these subjects were not tested according to the protocol. Due to distribution of these cases (1 in RIV4 vs 3 in IIV4), it is agreed that excluding these cases from primary analysis would not bias the results towards rejecting the null hypothesis and thus study conclusion holds.

2.5.2.2. PSC16

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

Methods

Study Participants

Approximately 1,350 ambulatory, medically stable adults aged 18-49 years of age who meet the Inclusion/Exclusion Criteria will be enrolled.

Inclusion criteria

1. Adults, regardless of gender, ambulatory, in good health or medically stable, age 18-49 years of age.
2. Able to understand and comply with planned study procedures and to provide written informed consent prior to initiation of any study procedure.
3. No receipt of any other influenza or other vaccine within 180 days prior to enrolment in this study.

4. No plan to receive another licensed influenza or other vaccine during the duration of this study
5. Women of child-bearing potential must have a negative pregnancy test within 24 hours of vaccination.

Exclusion criteria

1. Prior serious or severe reaction to influenza vaccine.
2. Known contraindication to RIV4 or to IIV4 (see product package inserts).
3. Receipt of any new medication(s) (investigational or non-investigational) within 30 days prior to enrolment in this study
4. Underlying disease or therapeutic intervention that might adversely affect the immune response, e.g. cytotoxic agents, supraphysiologic doses of corticosteroids.
5. Plans to participate in any investigation involving an investigational product during this study.
6. Pregnant, lactating or planning to become pregnant within 30 days of study vaccine.
7. Any clinical or social circumstance that in the opinion of the investigator could interfere with compliance with study procedures or interfere with the interpretation of clinical data

Treatments

Two vaccines were tested in the trial:

- Group A: RIV4 (Flublok Quadrivalent) containing 4x45µg (180µg total) of rHA derived from influenza A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes, or
- Group B: IIV4 (Fluarix Quadrivalent) containing 4x15µg (60 µg total), of quadrivalent, inactivated influenza vaccine (licensed IIV4) containing influenza antigen derived from A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes.

IIV4 and rHAs were derived from the following influenza viruses that were identified by the FDA's Vaccines and Related Biological Products Advisory Committee as the four strains (or "like viruses") to be included in quadrivalent influenza vaccines for the 2014-2015 season:

Table 12: Influenza vaccine composition for season 2014-2015 used in the study PSC012

Flublok Quadrivalent	IIV4 (Fluarix Quadrivalent)
H1N1: A/California/07/2009	H1N1: A/ Christchurch/16/2010 (an A/California/7/2009-like virus)
H3N2: A/Texas/50/2012	H3N2: A/Texas/50/2012
B/Massachusetts/2/2012 (B/Yamagata-lineage)	B/Massachusetts/2/2012
B/Brisbane/60/2008 (B/Victoria-lineage)	B/Brisbane/60/2008

Objectives

Primary Objective

- To demonstrate non-inferior immunogenicity of the four antigens in the RIV4 formulation to the corresponding antigens in the licensed IIV4. This was to be accomplished through the evaluation of the ratio of post-vaccination HAI GMT to each of the four antigens and the difference in HAI seroconversion rates to the same four antigens.

  Evaluations utilised CBER criteria for non-inferiority of HAI GMTs and seroconversion rates.

- A second objective is to compare the safety profiles of RIV4 and US-licensed IIV4.

Secondary Objectives:

- To evaluate the HAI seroconversion rates and % with post-vaccination HAI titers ≥40 (seroprotection rates) against the four rHA antigens contained in the quadrivalent formulation with respect to CBER criteria for licensure under accelerated approval regulations.
- To evaluate the safety and reactogenicity of RIV4 in adults 18-49 years of age.

Outcomes/endpoints

Primary immunogenicity endpoint:

The study had eight co-primary endpoints:

- HAI seroconversion rates at Day 28 to each of the four antigens contained in the study vaccine
- HAI GMTs at Day 28 to each of the four antigens contained in the study vaccine

These measurements were compared between the two vaccine groups according to CBER criteria for non-inferiority. HAI seroconversion is defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a minimum four fold rise in post-vaccination HI antibody titer.

Secondary immunogenicity endpoints:

- Seroconversion rates and seroprotection to all four antigens in RIV4, assessed according to CBER criteria for licensure under accelerated approval regulations:
  - For adults <65 years of age, the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HAI antibody should meet or exceed 40%. The lower bound of the two-sided 95% CI for the percent of subjects achieving an HAI antibody titer ≥ 1:40 (seroprotection) should meet or exceed 70%.
- Incidence and severity of solicited local and solicited systemic events of reactogenicity and body temperature reported via Memory Aid A during Days 0-7 following vaccine administration.
- Serious adverse events (SAEs) and other unsolicited AEs and MAEs occurring during the 28 days following vaccine administration.
- SAEs and MAEs occurring up to 6 months post-vaccination.

Immunogenicity: The antigens used in the HAI assay were the egg-derived versions of the HA in RIV4, i.e. A/California/07/2009, not A/Christchurch/16/2010, an antigenically similar H1 strain that was present in the comparator IIV4.

Sample size

The sample size proposed for this study is ~1,000 for the RIV4 group and ~350 for the US-licensed IIV4 control (total 1,350 subjects). This allowed for a retention rate of ~98%, assuring adequate power for the non-inferior immunogenicity analyses. This was a reasonable retention rate based on clinical trials conducted by PSC. In order to accumulate a safety database on RIV4 of ~1,000 subjects, randomization of ~1,350 subjects in a 3:1 ratio assured at least 80% power for evaluation of the co-primary comparisons. These calculations assumed HAI titer variability ≤1.5, and the criterion for GMT ratios ≤1.5.

Randomisation

Randomization assignments were centralised. Subjects were to receive their allocated treatment of RIV4 or IIV4 according to a SAS-generated randomization schedule. Following determination of eligibility, subjects were to be randomised in a 3:1 ratio to RIV4 or US-licensed IIV4.

Blinding (masking)

Neither the investigator nor the subject was planned to be aware of the treatment assignment until the study was completed. An unblinded person (provided he or she was not involved in any study assessments) or site staff was to administer study vaccine according to the label information on the syringe. Study personnel who performed study assessments after vaccination were blinded to treatment assignment.

Statistical methods

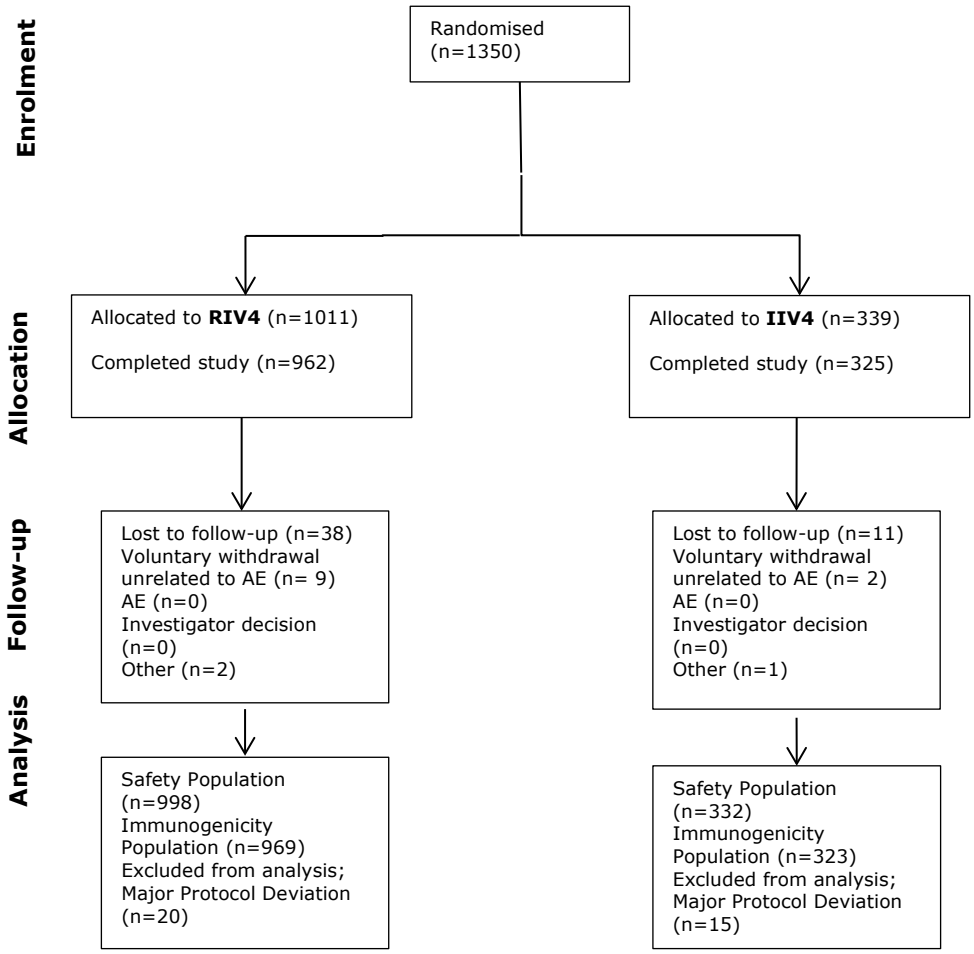
The primary non-inferiority immunogenicity analyses for this trial was based on the modified Per-Protocol (mPP) population. The primary immunogenicity population (mPP) included all randomised subjects who received a dose of study vaccine, provided serum samples for baseline (Day 0) and Day 28 HAI titers within specified time frames for those study days and had no major protocol deviations that might be expected to adversely affect the immune response.

For the primary endpoint of the GMT ratio, non-inferiority was planned to be established for each antigen if the upper bound of a two-sided 95% CI for ratio of 2 vaccine groups GMT ratios did not exceed 1.5. The ratio of the GMTs were to be calculated as the antilog of the difference between two mean log-transformed titers. The 95% CI were to be calculated as the antilog of the 95% confidence limits of the log transformed titers.

For the primary endpoint of the seroconversion rate, non-inferiority for each antigen was planned to be established if the upper bound of a two-sided 95% CI for the difference in seroconversion rates did not exceed 10 percentage points. The computation of the confidence interval for the difference in seroconversion rates was planned following Farrington and Manning's score method. To control the experiment wise error rate, all eight null hypotheses needed to be rejected at a nominal significance level of 0.025 to achieve statistical significance for any single endpoint.

Results

Participant flow



Of the 1,350 subjects who were enrolled and randomised, all received a dose of study vaccine. Overall, the rate of retention of subjects was very high (>95%); of the 63 subjects who did not complete the study, 49 were lost to follow-up, 11 withdrew consent and 3 terminated for other reasons. No subject discontinued due to an adverse event.

Recruitment

The study was conducted at 10 sites dispersed geographically across the US during the study period from October 22, 2014 (first subject enrolled) to May 14, 2015 (last subject completed).

Conduct of the study

No changes from the original protocol were made in the conduct of this study and no changes were implemented from the original Statistical Analysis Plan.

Of the 1,350 randomised subjects, 35 (2.6%) represented a major protocol deviation that excluded the subject from the immunogenicity analyses (Table 13). The most common reason for exclusion from the immunogenicity analysis was that the subject missed the visit at which serology samples were to be obtained.

Table 13: PSC16 -- Major Protocol Deviations by Category*

Deviation Category	Flublok Quadrivalent N=1011 n (%)	IIV4 N=339 n (%)
Subjects with any Major Protocol Deviation*	20 (2.0)	15 (4.4)
Dosing Error	1 (0.1)	2 (0.6)
Exclusion Criteria	1 (0.1)	0
Lab Sample missing or invalid	5 (0.5)	5 (1.5)
Missed Study Visit	14 (1.4)	11 (3.2)
Procedure Not Per Protocol	2 (0.2)	1 (0.3)
Other	1 (0.1)	1 (0.3)

Source: Table 14.1.2.2
*Leading to exclusion from immunogenicity population

Baseline data

Table 14 below summarises the demographic characteristics by treatment group for all subjects with post-randomization data. The majority of subjects were white, non-Hispanic and there was a slight majority of females. There were no notable differences in demographic characteristics of subjects with post-randomization data between the two treatment groups.

Table 14: PSC16 -- Subjects Demographics

Characteristic	Flublok Quadrivalent N=998	IIV4 N=332
Age (years)		
Mean	33.3	34.0
Range	18, 50	18, 49
Sex, 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)

Source: Table 14.1.3

Numbers analysed

Table 15: PSC16 -- Subjects Disposition

	Flublok Quadrivalent N=1011 n (%)	IIV4 N=339 n (%)
Randomized Population	1011	339
Immunogenicity Population	969 (95.8)	323 (95.3)
Safety Population	998 (98.7)	332 (97.9)
Reactogenicity Population	996 (98.5)	332 (97.9)
Reactogenicity Population 1 [a]	996 (98.5)	332 (97.9)
Reactogenicity Population 2 [b]	994 (98.3)	332 (97.9)
Reactogenicity Population 3 [c]	990 (97.9)	327 (96.5)
Completed study	962 (95.2)	325 (95.9)
Primary Reason for Early Withdrawal		
Adverse Event	0	0
Investigator Decision	0	0
Lost to Follow-up	38 (3.8)	11 (3.2)
Sponsor Request	0	0
Voluntary withdrawal unrelated to AE	9 (0.9)	2 (0.6)
Other	2 (0.2)	1 (0.3)
Subjects who returned Memory Aid A	934 (92.4)	314 (92.6)
Subjects who returned Memory Aid B	877 (86.7)	288 (85.0)

Source: Table 14.1.1

Outcomes and estimation

Primary Immunogenicity Analyses

Non-inferiority of Seroconversion Rates

The primary endpoint of seroconversion rates (SCR) for each of the four antigens represented in the study vaccines and the differences between SCR in the two treatment groups are shown Table 16.

Non-inferiority, defined as an upper bound of the 95% confidence interval for the difference in SCR [IIV4 minus RIV4] ≤10%, was demonstrated for seroconversion among RIV4 recipients for A/H1/California, A/ H3/Texas and B/Massachusetts. The seroconversion rate to B/Brisbane among RIV4 was less robust and did not meet the criterion for non-inferiority.

Table 16: PSC16: HAI Seroconversion rates at Day 28 – Subjects 18 to 49 Years of Age – Immunogenicity population

Category	Parameter	Flublok Quadrivalent 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)	-15.1	(**-21.3**, **-9.1**)
	95% CI	(69.2, 74.9)	(51.4, 62.4)		
B/Massachusetts					
	n (%)	578 (59.6)	195 (60.4)	0.8	(**-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)		

Figures in **bold** meet CBER criteria for non-inferiority
Source: Table 14.2.1.2

Non-inferiority of post-vaccination HAI GMTs

The co-primary endpoint of non-inferior post-vaccination HAI GMTs demonstrated satisfactory rises in GMT among RIV4 recipients for A/H1/California, A/H3/Texas and B/Massachusetts (Table 17). The

post-vaccination GMTs for these three antigens were non-inferior by the criterion of an upper bound of the 95% confidence interval around the ratio of GMT IIV4 / GMT RIV4 ≤1.5.

Table 17: PSC16: Pre- and post-vaccination HAI GMTs – Immunogenicity population

Antigen	Visit	Parameter	Flublok Quadrivalent (N=969)	IIV4 (N=323)	GMR	95% CI for GMR
A/H1/California	Day 0					
		GMT	60	54	0.90	(0.75, 1.09)
		95% CI	(54, 65)	(46, 63)		
	Day 28					
		GMT	502	407	0.81	(0.71, **0.92**)
		95% CI	(469, 537)	(367, 451)		
A/H3/Texas	Day 0					
		GMT	75	70	0.93	(0.78, 1.13)
		95% CI	(68, 83)	(60, 82)		
	Day 28					
		GMT	757	385	0.51	(0.45, **0.58**)
		95% CI	(709, 808)	(348, 425)		
B/Massachusetts	Day 0					
		GMT	27	24	0.89	(0.77, 1.06)
		95% CI	(25, 29)	(21, 28)		
	Day 28					
		GMT	159	136	0.86	(0.74, **1.00**)
		95% CI	(147, 171)	(121,153)		
B/Brisbane	Day 0					
		GMT	12	11	0.92	(0.82, 1.05)
		95% CI	(11, 13)	(10, 12)		
	Day 28					
		GMT	43	64	1.49	(1.30, 1.71)
		95% CI	(40, 46)	(58, 72)		

Figures in **bold** meet CBER criteria for non-inferiority
Source: Table 14.2.1.1.1

Seroconversion rate and GMT-ratio for each strain 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 and GMT data were markedly worse than for 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: 58, 72) for IIV4 recipients. These results illustrate that the upper bounds of the confidence intervals for the recombinant vaccine were 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, immunogenicity data consistently cannot demonstrate NI for B/Victoria. This issue is not evident for B/Yamagata.

Additional data subsequently submitted by the applicant however indicate, that there is not a general weakness regarding B/Victoria lineage immunogenicity in RIV4.

In a study, performed in Hong Kong during the 2017-2018 influenza season in adults 65 to 82 years of age (Cowling BJ *et al*), immunogenicity of RIV 4 was compared with the immunogenicity of an IIV4 standard dose vaccine, a MF59 adjuvanted trivalent vaccine, and a High Dose IIV3. HAI showed that

RIV4 immunogenicity was comparable to the immunogenicity of the IIV4 vaccine for all strains including responses to the B/Victoria lineage, B/Brisbane/60/2008 strain.

Table 18: Summary of pre- and post-vaccination antibody titers and fold rises in each vaccination group

2017-2018 Subjects 65 through 82 years of age	Vaccine (N=200 for each group)	GMTs D30 (95% CI)	% with ≥4-fold rise from D0 to D30* (95% CI)
A/Michigan/45/2015 (H1N1)	SD-IIV4	69 (58, 83)	42% (36, 50)
	aIIV3	94† (78, 114)	60%† (53, 67)
	HD-IIV3	125† (102-152)	59%† (52, 66)
	RIV4	85 (69, 105)	60%† (53, 67)
A/Hong Kong/4801/2014 (H3N2) egg-like	SD-IIV4	158 (135, 186)	41% (34, 48)
	aIIV3	207† (178, 241)	48% (40, 55)
	HD-IIV3	214† (183, 250)	54%† (46, 61)
	RIV4	254† (218, 295)	56%† (48, 63)
B/Brisbane/60/2008 (Victoria lineage)	SD-IIV4	89 (75, 105)	48% (41, 56)
	aIIV3	95 (81, 112)	44% (37, 51)
	HD-IIV3	132† (112, 157)	52% (45, 60)
	RIV4	90 (76, 107)	44% (37,51)
B/Phuket/3073/2013‡ (Yamagata lineage)	SD-IIV4	121 (104, 141)	42% (36, 50)
	aIIV3	63† (54, 74)	12%† (8, 18)
	HD-IIV3	68† (57, 81)	15%† (10, 21)
	RIV4	131† (111, 155)	42% (36, 50)

* At least a 4-fold rise from D0 to D30 with D30 titer ≥40.
† Values that are significantly different from the corresponding value in the standard-dose group. Statistical significance was designated at P value <.05.
‡ Note that a B/Yamagata lineage virus was not included in the MF59-adjuvanted TIV and the high-dose TIV
Source: Table 3. (7)

Another study (Belongia *et al* 2020. Clinical Trial number: NCT02872311) evaluated the immunogenicity performance of RIV4 compared to Fluzone high dose IIV3 and adjuvanted-IIV3 after standard-dose IIV3 the season prior, in individuals 65-74 years of age. The study was performed over 2 seasons 2016-2017, 2017-2108 when the B/Victoria lineage strain in vaccine TIV and QIV formulations was the same strain used in the pivotal RIV4 trials, B/Brisbane/60/2008. HAI titers were measured at 28 days post vaccination in the second season of the study as well as influenza attack rates, both stratified by vaccine types. The results for the influenza B strain, B/Brisbane/60/2008 were comparable to the Fluzone HD and adjuvanted IIV3 results in this older age group.

Whilst a potential for underpowering is given, it needs to be noted that sample size eventually sufficed to bring up statistical evidence for RIV4 being not non-inferior to IIV4 in terms of immunogenic response for strain B/Victoria.

In order to complete assessment of the primary non-inferiority investigations, an ITT analysis was performed, and results were submitted subsequently. Due to the small difference in subject numbers between the ITT set and the mPP set, no noteworthy divergencies appear.

Secondary Immunogenicity Analyses

Seroconversion Rates to each Study Vaccine

Seroconversion rates were also assessed by CBER criteria under accelerated approval regulations (Table 19). The criterion for an acceptable magnitude of seroconversion (lower bound of the 95% confidence interval ≥40%) was met in the RIV4 group for A/H1/California, A/H3/Texas and B/Massachusetts. The criterion was not met for B/Brisbane.

Table 19: PSC16 -- Seroconversion rates at day 28

Category	Flublok Quadrivalent N=969	IIV4 N=323
A/H1/California		
n (%)	646 (66.7)	205 (63.5)
95% CI	(**63.6**, 69.6)	(**58.0**, 68.7)
A/H3/Texas		
n (%)	699 (72.1)	184 (57.0)
95% CI	(**69.2**, 74.9)	(**51.4**, 62.4)
B/Massachusetts		
n (%)	578 (59.6)	195 (60.4)
95% CI	(**56.5**, 62.8)	(**54.8**, 65.7)
B/Brisbane		
n (%)	393 (40.6)	188 (58.2)
95% CI	(37.4, 43.7)	(**52.6**, 63.6)

Figures in **bold** meet CBER criterion for licensure under accelerated approval regulations
Source: Table 14.2.1.2

Proportion of Subjects with Post Vaccination HAI Titer ≥40

Another criterion for approval of seasonal influenza vaccines under accelerated approval regulations is the proportion of individuals who have a post-vaccination HAI titer of ≥40 (Table 20). The criterion for this parameter in adults <65 years of age is a lower bound of the 95% confidence interval that meets or exceeds 70%.

Table 20: PSC16 -- Proportion of Subjects with Post Vaccination HAI Titer ⩾40 at Day 28

Antigen	Flublok Quadrivalent N=969	IIV4 N=323
A/H1/California	952 (98.2)	320 (99.1)
Titer ≥40 n (%)	(**97.2**, 99.0)	(**97.3**, 99.8)
95% CI		
A/H3/Texas	966 (99.7)	320 (99.1)
Titer ≥40 n (%)	(**99.1**, 99.9)	(**97.3**, 99.8)
95% CI		
B/Massachusetts	882 (91.0)	297 (92.0)
Titer ≥40 n (%)	(**89.0**, 92.7)	(**88.4**, 94.7)
95% CI		
B/Brisbane	623 (64.3)	257 (79.6)
Titer ≥40 n (%)	(61.2, 67.3)	(**74.8**, 83.8)
95% CI		

Figures in **bold** meet CBER criterion for licensure under accelerated approval regulations
Source: Table 14.2.2.1

The secondary immunogenicity analyses demonstrate that the B/Victoria component of RIV4 is not able to meet the FDA immunogenicity criteria as defined in the FDA Guidance for Industry. Results for seroconversion and seroprotection rates are consistently below those of the comparator vaccine. The B/Yamagata component on the other hand has no such difficulties, even though it is evaluated against an egg-derived antigen in a similar fashion.

Ancillary analyses

The Per Protocol population was defined in the protocol, but that analysis was overlooked by the CRO statisticians in their initial analysis of the trial. The PP analysis was performed as a sensitivity analysis during the review period at the reminder of the FDA. The results apparently confirmed the mPP population analysis.

An analysis of the GMTs of IIV4/RIV4 (GMRs) at day 28, and difference between groups for seroconversion rates for the immunogenicity population, was provided, as well as for the revised immunogenicity population and the per-protocol immunogenicity population. The values for GMTs and seroconversion rates do not reveal meaningful differences. It is agreed, that there is no effect on the study "noninferiority" outcome. All endpoints are met in all populations, except B/Brisbane (B/Victoria-lineage), which was not met in all population.

Clinical studies in special populations

The elderly were included in study PSC12. The table below, details the numbers of adult subjects in the development program per age category. There have been no non-controlled studies.

Table 21: Study PSC12 – Age group repartition in the different populations

		Age 50-64 years n (%)	Age 65-74 years n (%)	Age 75-84 years n (%)	Age 85 years and above n (%)
Randomized Population (N=8963)	RIV4 (N=4474)	2684 (60.0%)	1255 (28.1%)	476 (10.6%)	59 (1.3%)
	IIV4 (N=4489)	2728 (60.8%)	1277 (28.4%)	433 (9.6%)	51 (1.1%)
Efficacy Population (N=8604)	RIV4 (N=4303)	2571 (59.7%)	1210 (28.1%)	465 (10.8%)	57 (1.3%)
	IIV4 (N=4301)	2591 (60.2%)	1239 (28.8%)	422 (9.8%)	49 (1.1%)

Supportive study

2.5.2.3. PSC04

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

Methods

Study Participants

Healthy, medically stable adult males and females, aged 18-49 years who met all Inclusion Criteria, did not meet any of the Exclusion Criteria, agreed to comply with all of the study procedures and be available for follow-up for the duration of the influenza season for a total of approximately 6 months.

Women of child-bearing potential had to have a negative urine pregnancy test results at the time of randomization and had to be willing to use an adequate form of contraception during the course of the study.

Treatments

Two vaccines were tested in the trial:

- RIV3 (Flublok): each 0.5 mL dose of RIV3 contained 135µg of rHA, consisting of 45µg each of rHA derived from the respective influenza viruses for the 2007-2008 formulation: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004.

  Note: Flublok assignment will be further stratified into three lots: A, B and C at all sites.

- Placebo consisted of normal saline for injection, USP.

According to treatment assignment, a single IM injection of the RIV3 (total 135 mcg rHA from 3 strains containing 45 mcg per strain) or placebo, in a total volume of 0.5 mL, will be administered into the non-dominant deltoid muscle.

Objectives

Primary

- **Efficacy**: to determine the absolute efficacy of a single dose of RIV3 containing 135µg of total recombinant haemagglutinin (rHA) (45µg per strain) in the prevention of culture-confirmed symptomatic influenza meeting the case definition of CDC-ILI due to strains represented in the vaccine in a population of healthy adults aged 18-49 years.
- Lot consistency: to demonstrate clinical consistency among three different lots of FluBlok administered during the study. The primary immunogenicity hypothesis is that for each strain contained within FluBlok, the 2-sided 95% CI for the ratio of post-vaccination geometric mean titers (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.
- Safety: to determine the safety relative to placebo of a single dose of RIV3 containing 135µg of total rHA as determined by the rates of adverse events (AEs) and the observation of systemic and local reactions

Secondary

- **Efficacy**: to determine the efficacy, relative to Placebo, of a single dose of RIV3 containing 135µg of total rHA in the prevention of culture-confirmed respiratory illness (regardless of CDC-ILI) due to strains represented in the vaccine
- Seroconversion rate: Post-vaccination titer of ≥1:40 in subjects with undetectable baseline antibody (HI titer <1:10) or a >4-fold rise in antibody in subjects with a baseline titer of ≥1:10, with the achievement of post-vaccination titer of at least 1:40. For adults <65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 40%
- Seroprotection rate: Post-vaccination titer of ≥1:40. For adults <65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 70%.

Exploratory

- **Efficacy**: to determine the efficacy, relative to Placebo, of a single dose of RIV3 containing 135µg of total rHA in prevention of culture-confirmed CDC-ILI due to any strain of influenza
- **Efficacy**: to determine the efficacy, relative to Placebo, of a single dose of RIV3 in prevention of all episodes of CDC-ILI or respiratory illness occurring during the surveillance period, regardless of culture results

Outcomes/endpoints

Primary endpoint:

- **Efficacy**: the development of CDC-ILI with a positive NS/TS culture for an influenza virus strain antigenically resembling a strain represented in Flublok obtained during the acute illness episode.
- Immunogenicity: for each strain represented in RIV3, equivalence in post-vaccination GMTs among the three lots administered.
- Safety: the rate and severity of solicited AEs reported within 7 days of vaccination, all AEs reported within 28 days of vaccination and all SAEs reported for the duration of study.

Secondary endpoints:

- **Efficacy**: the development of any signs and symptoms of respiratory illness with a positive NS/TS culture for an influenza virus strain antigenically resembling a strain represented in RIV3 obtained during the acute illness episode
- Immunogenicity: for all three lots combined, and for each strain represented in RIV3; SCRs defined as 4-fold or greater rises in those seropositive at baseline and attainment of a HAI titer of ≥40 in those seronegative at baseline; SPR defined as proportion of subjects achieving a HAI titer of ≥40; 28 days after vaccination

Exploratory endpoints:

- development of CDC-ILI with a positive NS/TS culture for any influenza virus strain obtained during the acute illness episode
- development of CDC-ILI during the surveillance period regardless of culture results

Sample size

Based on previous studies it was estimated that RIV3 was at least 70% efficacious relative to Placebo, as measured by protective efficacy (PE). A Placebo attack rate of 3% or greater was expected (influenza culture positive). This trial was powered to establish that the lower bound of the 95% confidence interval for PE is greater than 40%. The sample size chosen for this study was 4,318 randomised 1:1 (RIV3=2,159, Placebo= 2,159). This test has approximately 80% power with $\alpha = 0.05$ to achieve its goal assuming a total sample size of 4,318 accounting for a 5% attrition rate (post-attrition samples sizes of at least: RIV3=2,051, Placebo= 2,051).

Randomisation

All subjects were stratified prior to randomization based on whether receipt (y/n) of influenza vaccine during the 2006-2007 influenza season. All subjects were randomised 1:1 to either RIV3 or Placebo and to maintain a 1:1:1 ratio of RIV3 clinical lots A, B and C. The randomised treatment schedule was prepared by a Biostatistician using the block method with a block size of 6.

Blinding (masking)

The study is a modified double-blind. The study vaccine was administered by an unblinded person who was not involved in subsequent assessment. Neither the subjects nor the study personnel who performed study assessments after vaccination were aware of the treatment assignment until the study was over.

Statistical methods

The efficacy for subjects was computed as follows for the RIV3 and Placebo treatment groups:

VE = 100 x (1 – relative risk of subjects having culture-confirmed CDC-ILI)

CDC-ILI = 1 – attack rate RIV3/attack rate placebo

The efficacy analysis population consists of all subjects that met study entry criteria, received vaccine as assigned, and who made at least 50% of telephone contacts during the surveillance period, including the EIOS call.

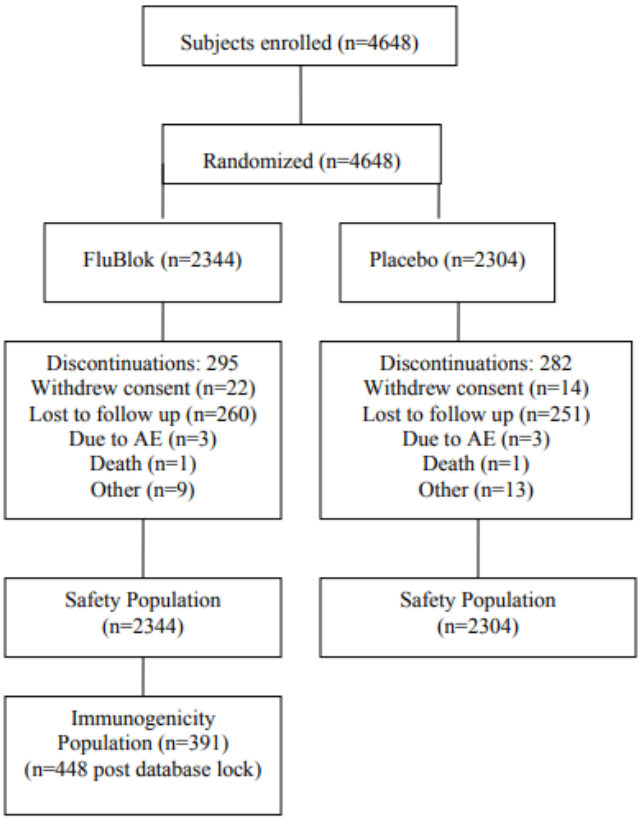
The primary efficacy hypothesis was that the efficacy of RIV3 against culture-confirmed CDC-ILI due to influenza strains antigenically resembling the vaccine exceeded 40%, with 95% confidence. This trial was powered to establish that the lower bound of the 95%CI for vaccine efficacy was greater than 40%.

Immunogenicity analysis population consists of all subjects who met the study entry criteria and had HAI titers taken at baseline (Day 0) and after vaccination (Day 28).

Safety analysis population included all randomised subjects who received study vaccine according to the treatment (RIV3 or Placebo) actually received.

Results

Participant flow



All 4,648 randomised subjects received the treatments, including 2,344 RIV3 recipients and 2,304 Placebo recipients, and were used as efficacy population for clinical efficacy analyses.

Recruitment

The study was conducted in the US during the study period from September 2007 (first subject enrolled) to May 2008 (last subject completed).

Conduct of the study

The protocol deviation that occurred during the study was provided.

Baseline data

The study subjects that constitute safety population (and efficacy population) were healthy young adults. The median age was 32 years for both RIV3 and Placebo treatment groups. The majority of subjects were females (59% in each group) and white (67% RIV3, 66% Placebo). The proportions of black subjects, Hispanic subjects and other race/ethnicity were similar between RIV3 and Placebo groups.

The demographic characteristics of subjects included in immunogenicity subset for interim analysis did not show notable differences to the overall safety (and efficacy) population.

Table 22: PSC04 – Summary of Demographics and Other baseline characteristics – Safety population (N=4,648) and Immunogenicity subset (evaluable population)

Characteristics	Study Treatment		
	FluBlok N=2344	Immunogenicity Subset (Evaluable Population) FluBlok N=391	Placebo N=2304
Race/Ethnicity			
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)
Gender			
Male	953 (41)	176 (45)	955 (41)
Female	1391 (59)	215 (55)	1349 (59)
Age (years)			
Mean (SD)	32.5 (9.30)	32.9 (9.98)	32.5 (9.17)
Median	32.0	31.0	32.0
Minimum-Maximum	18, 55	18, 49	18, 50
Data source: Table 14.1.3 and 14.1.4, Listing 16.2.6			

Numbers analysed

All 4,648 randomised subjects received the treatments, including 2,344 RIV3 recipients and 2,304 Placebo recipients, and were used as efficacy population for clinical efficacy analyses. The most common reason for discontinuation was lost to follow-up (251 instances [89% of all discontinuations] in the Placebo group and 260 instances [88% of all discontinuations] in the RIV3 group).

A total of 577 (12%) subjects discontinued prior to the completion of the study, including 282 Placebo recipients and 295 RIV3 recipients.

In total, 391 RIV3 recipients had serum samples and were included in interim immunogenicity analysis and 448 evaluable at end of the study for immunogenicity endpoints.

The numbers of subjects for safety analysis was 4,648, including 2,344 in RIV3 and 2,304 in Placebo treatment group.

Outcomes and estimation

During the study period, a total of 582 subjects reported a score of 2 or more on their flu symptoms Card, including 273 in RIV3 and 309 in Placebo treatment groups. Among them, positive cultures for influenza were evident in 178 subjects, including 64 RIV3 and 114 placebo recipients. Of these, a total of 122 subjects (69%), including 44 RIV3 and 78 placebo recipients, developed culture-confirmed CDC ILI, as defined by a fever of ≥100°F oral accompanied by cough and/or sore throat, on the same day or on consecutive days.

The primary efficacy endpoint of study PSC04 was unmet. Only 1 subject with a positive culture due to a strain represented in the vaccine met CDC-ILI definition among RIV3 recipients versus 4 among the Placebo group, resulting in a point estimate of RIV3 efficacy of 75.4% (95%CI: -148.0, 99.5).

The secondary efficacy endpoint of study PSC04 – development of culture-positive ILI regardless of CDC ILI definition, was unmet, either. With 2 subjects reporting culture-positive ILI due to matched strains in RIV3 vs 6 subjects in placebo recipients, giving rise to a rVE of 67.2% (95%CI: -83.2; 96.8).

Both primary and secondary efficacy endpoints required that influenza strain isolated is antigenically similar to the HA of the strain included in the vaccine. However, the 2007-2008 influenza season was proven with characteristics of a suboptimal match for Type A strains, and a different lineage (i.e. B/Yamagata) for Type B. Only 8 of all virus isolates (<5%) from 179 subjects in PSC04 were antigenically related to the strains represented in RIV3, including none of 59 B isolates. Because of so few cases of the primary and secondary efficacy endpoints, it is impossible to accurately estimate the protective efficacy of RIV3 in PSC04.

Evaluable populations for immunogenicity analysis included 391 RIV3 recipients for interim analysis and 448 recipients for additional analysis.

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 (45µg) whereas other antigens exceeded the intended antigen amount by up to ~40%.

For secondary immunogenicity endpoints, RIV3 met CBER immunogenicity criteria for all 3 strains, using both SCR (lower bound of 2-sided 95%CI exceeds 40%) and SPR (lower bound of the 2-sided 95%CI exceeds 70%):

- H1: 78% (95%CI: 73.8, 82.2) for seroconversion rate and 98% (95%CI: 96.7, 99.4) for seroprotection rate.
- H3: 81% (95%CI: 76.3, 84.4) for seroconversion rate and 96% (95%CI: 94.1, 98.0) for seroprotection rate.
- B: 53% (95%CI: 48.1, 58.2) for seroconversion rate and 96% (95%CI: 93.4, 97.6) for seroprotection rate.

However, immunogenicity results have to be interpreted with caution, as issues with the potency test to measure antigen content caused considerable variation in rHA amount contained in the different.

Ancillary analyses

Clinical efficacy of RIV3 was further explored on two pre-specified exploratory endpoints. The first - culture-positive CDC-ILI due to any strain of influenza was reported by 44 RIV3 and 78 Placebo recipients, resulting in an overall vaccine efficacy of 44.6% (95%CI: 18.8, 62.6). The second – CDC-ILI regardless of culture results, developed in 127 RIV3 and 162 placebo recipients, yielding an efficacy of 22.9% (95%CI: 2.2, 39.4).

Additional post-hoc exploratory analyses were performed on culture-positive influenza regardless of CDC-ILI and culture-positive CDC-ILI by influenza Type regardless of antigenic match, in order to compare these results with the results of published findings of vaccine efficacy reported during the 2007-2008 influenza season. Although these analyses might provide some useful information, caution

is needed to interpret these comparative data from different studies, due to differences in study design, trial population, statistical methods, and number of cases included in the subgroup analyses.

Interestingly, post-hoc analysis according to time periods showed little or no protective efficacy of RIV3 after Feb 8, 2008, corresponding to approximately 4-5 months after vaccination. The applicant is unable to explain the underlying mechanism except the assumption about a decline in cross-protective HAI antibodies. The applicant claimed that RIV3 efficacy is higher or at least comparable to other licensed influenza vaccines during the 2007/2008 influenza season, and presented the results of another study conducted in 2017/2018 influenza season with older adults aged 65-74 years (Clinical Trial number: NCT02872311), showing that the HAI response to all three vaccine strains at month 6 were similar in RIV4 vs aIIV3 and HD-IIV3.

Summary of main studies

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

Table 23: Summary of Efficacy for trial PSC12

Title: PSC12 - Comparison of the Protective Efficacy of Flublok Quadrivalent versus Licensed Inactivated Influenza Vaccine (IIV4) in Healthy, Medically Stable Adults ≥50 Years of Age		
Study identifier	PSC12 NCT02285998	
Design	Phase III, randomised, observer-blind, active-controlled, multi-centre study	
	Duration of main phase:	6 months, From Oct 2014 to May 2015
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority; Exploratory: this was not pre-specified in SAP of PSC12	
Treatments groups	RIV4	IM vaccination; n = 4,303
	IIV4	IM vaccination; n = 4,489
Endpoints and definitions	Primary endpoint	rtPCR-confirmed protocol-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain
	Key secondary endpoints	rtPCR-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain
		culture-confirmed protocol-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain antigenically matched to those strains represented in the study vaccines
		culture-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain antigenically matched to those in the study vaccines
		post-vaccination HAI GMTs and SCR for all four antigens in a preselected subset of subjects.
Database lock	17 June 2015	
Results and Analysis		
Analysis description	**Primary Analysis**	

Analysis population and time point description	Modified Per protocol: all randomised subjects who received known study vaccine and provided any follow-up for ILI beginning at least 14 days following vaccine administration		
Descriptive statistics and estimate variability	Treatment group	**RIV4**	**IIV4**
	Efficacy population, ≥50+ years	4,303	4,301
	rt-PCR confirmed protocol-defined ILI, any strain (attack rate)	96 (2.2%)	138 (3.2%)
	rt-PCR-confirmed protocol-defined influenza A (attack rate), *post-hoc*	73 (1.7%)	114 (2.7%)
	rt-PCR-confirmed protocol-defined influenza B (attack rate), *post-hoc*	23 (0.53%)	24 (0.56%)
	culture-confirmed CDC ILI, matched strain	Not performed	Not performed
	culture-confirmed protocol-defined ILI, matched strain	Not performed	Not performed
	rt-PCR confirmed CDC ILI, any strain, *post hoc*	54 (1.3%)	83 (1.9%)
	Immunogenicity population, ≥50+ years	314	300
	SCR **H1N1** 95% CI	141 (44.9%) (39.3, 50.6)	147 (49.0%) (43.2, 54.8)
	SCR **H3N2** 95% CI	171 (54.5%) (48.8, 60.1)	130 (43.3%) (37.6, 49.1)
	SCR **B/ Yamagata** 95%CI	122 (38.9%) (33.4, 44.5)	115 (38.3%) (32.8, 44.1)
	SCR **B/ Victoria** 95% CI	66 (**21.0%**) (**16.6, 25.9**)	103 **(34.3%**) (**29.0, 40.0**)
	GMT **H1N1** 95% CI	194 (167, 226)	224 (197, 255)
	GMT **H3N2** 95% CI	530 (470, 597)	366 (325, 412)
	GMT **B/Yamagata** 95% CI	56 (49, 64)	58 (51, 66)
	GMT **B/Victoria** 95% CI	**30** **(26, 34)**	**44** **(39, 50)**
Effect estimate per comparison	Primary analysis on all protocol-defined rt-PCR confirmed influenza	rVE: 30%	
		95% CI: 10%, 47%	
		Pre-specified NI criterion: met Since LL 95%CI > +9%, pre-specified superiority (exploratory) criterion is also met	
	Post-hoc analyses	rVE against all rt-PCR positive influenza A: 36%	
		95% CI: 14%, 53%	
		rVE against all rt-PCR positive influenza B: 4%	
		95%CI: -72%, 46%	
	Second efficacy analysis on rt-PCR confirmed CDC ILI	rVE: 32%	
		95%CI: 8%, 54% Pre-specified NI criterion: met pre-specified superiority (exploratory) criterion is unmet	
	SCRs at Day 28, A/H1N1/California	Difference (95%CI): 4.1 (-3.8, **12.0**) Prespecified NI criterion unmet	
	SCRs at Day 28, A/H3N2/Texas	Difference (95%CI): -11.2 (-19.0, -3.3) Prespecified NI criterion met	

	SCRs at Day 28, B/Massachusetts	Difference (95%CI): -0.6 (-8.2, 7.2) Prespecified NI criterion met
	SCRs at Day 28, B/Brisbane	Difference (95%CI): 13.3 (6.3, **20.3**) Prespecified NI criterion unmet
	GMT ratio at Day 28, A/H1N1/California	GMTR (95%CI): 1.15 (0.95, 1.41) Prespecified NI criterion met
	GMT ratio at Day 28, A/H3N2/Texas	GMTR (95%CI): 0.69 (0.58, 0.82) Prespecified NI criterion met
	GMT at Day 28, B/Massachusetts	GMTR (95%CI): 1.04 (0.86, 1.24) Prespecified NI criterion met
	GMT at Day 28, B/Brisbane	GMTR (95%CI): 1.47 (1.24, **1.77**) Prespecified NI criterion unmet
Notes	Based on the primary endpoint and key secondary endpoints the study shows that efficacy of RIV4 is non-inferior to that of IIV4. The RIV4 was 30% more efficacious than IIV4 in preventing rt-PCR confirmed protocol-defined ILI, and this was driven primarily by predominant efficacy against A/H3N2 strain.	

Table 24: Summary of Immunogenicity for trial PSC16

Title: PSC16 - Double-Blind, Randomized, Active-Controlled Comparison of the Immunogenicity and Safety of Flublok Quadrivalent versus IIV4 in Healthy, Medically Stable Adults 18-49 Years of Age			
Study identifier	PSC16		
Design	Phase III, randomised, observer-blind, active-controlled, multi-centre study		
	Duration of main phase:		6 months
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority		
Treatments groups	RIV4		IM vaccination; n = 1,011
	IIV4		IM vaccination; n = 339
Endpoints and definitions	Primary endpoint	SCR	SCR at Day 28/HI Assay for each strain (SCR: either a pre-vaccination titer<1:10 and a post-vaccination titer ≥1:40, or a pre-vaccination titer ≥1:10 and a ≥4-fold increase in post-vaccination titer)
	Co-primary endpoint	GMT	Geometric Mean Titre at Day 28/HI Assay for each strain
Database lock	18 June 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Per protocol: all randomised subjects who received study vaccine and provided pre-vaccination and post-vaccination serology for HAI titers on Days 0 and 28 within the specified time frame, respectively, and had no significant protocol deviations that might adversely impact the immune response		
Descriptive statistics and estimate variability	Treatment group	**RIV4**	**IIV4**
	Population	N=969	N=323
	SCR **H1N1** 95% CI	646 (66.7%) (63.6, 69.6)	205 (63.5%) (58.0, 68.7)
	SCR **H3N2** 95% CI	699 (72.1%) (69.2, 74.9)	184 (57.0%) (51.4, 62.4)

	SCR **B/ Yamagata** 95%CI	578 (59.6%) (56.5, 62.8)	195 (60.4%) (54.8, 65.7)
	SCR **B/ Victoria** 95% CI	393 (40.6%) (37.4, 43.7)	188 (58.2%) (52.6, 63.6)
	GMT **H1N1** 95% CI	502 (469, 537)	407 (367, 451)
	GMT **H3N2** 95% CI	757 (709, 808)	385 (348, 425)
	GMT **B/ Yamagata** 95% CI	159 (147, 171)	136 (121, 153)
	GMT **B/Victoria** 95% CI	43 (40, 46)	64 (58, 72)
NI: The upper bound of the two-sided 95% CI on the difference between the seroconversion rates (% Seroconversion (FDA-approved IIV4) - % Seroconversion (Flublok Quadrivalent)) should not exceed **10** percentage points.	**SCR H1N1**	Comparison groups	IIV4 vs. RIV4
		SCR difference	-3.2
		95% CI	-9.2, 2.8
	SCR H3N2	Comparison groups	IIV4 vs. RIV4
		SCR difference	-15.2
		95% CI	-21.3, -9.1
	SCR B/ Yamagata	Comparison groups	IIV4 vs. RIV4
		SCR difference	0.7
		95% CI	-5.4, 6.9
	SCR B/ Victoria	Comparison groups	IIV4 vs. RIV4
		SCR difference	17.6
		95% CI	**11.4 , 23.9**
NI: The upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT[FDA-approved IIV4]/GMT[Flublok Quadrivalent)) should not exceed **1.5**	**GMT H1N1**	Comparison groups	IIV4 vs. RIV4
		GMT ratio	0.81
		95% CI	0.71, 0.92
	GMT H3N2	Comparison groups	IIV4 vs. RIV4
		GMT ratio	0.50
		95% CI	0.44, 0.57
	GMT B/ Yamagata	Comparison groups	IIV4 vs. RIV4
		GMT ratio	0.86
		95% CI	0.74, 0.99
	GMT B/ Victoria	Comparison groups	IIV4 vs. RIV4
		GMT ratio	1.49
		95% CI	1.29, **1.71**
Notes	Non-inferiority was demonstrated for SCR among RIV4 recipients for A/H1/California, A/ H3/Texas and B/Massachusetts. The SCR to B/Brisbane did not meet the criterion for non-inferiority. The co-primary endpoint of non-inferior post-vaccination HAI GMTs demonstrated satisfactory rises in GMT for A/H1/California, A/H3/Texas and B/Massachusetts.		

Table 25: Summary of Efficacy for trial PSC04

Title: Evaluation of the immunogenicity, safety, reactogenicity, efficacy, effectiveness and lot consistency of Flublok Trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine in healthy adults 18 to 49 years		
Study identifier	PSC04	
Design	Phase III, randomised, observer-blind, placebo-controlled, multi-centre study	
	Duration of main phase:	From Sept 15, 2007 to May 28, 2008
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority for primary clinical efficacy Equivalence for lot consistency	

	Exploratory: efficacy due to any strain of influenza	
Treatments groups	RIV3	IM vaccination; n = 2,344
	Placebo	IM vaccination; n = 2,304
Endpoints and definitions	Primary Efficacy endpoint	culture-confirmed CDC-ILI due to influenza virus antigenically resembling vaccine strains
	Secondary Efficacy endpoint	culture-confirmed respiratory illness (not necessarily CDC-ILI) due to influenza virus antigenically resembling vaccine strains
	Exploratory Efficacy endpoints	culture-confirmed CDC-ILI due to any strain
		CDC-ILI regardless of culture confirmation
	Primary immunogenicity endpoint	GMT ratio
	Secondary immunogenicity endpoints	SCRs, SPRs
Database lock	10 September 2008	

Results and Analysis

Analysis description	**Primary, Secondary and exploratory Analysis**			
Analysis population and time point description	All efficacy endpoints were analysed using all 4,648 randomised subjects who received the study vaccine. Immunogenicity endpoints were analysed using a subset of subjects (391*) for lot consistency			
Descriptive statistics and estimate variability	Treatment group	**RIV3**		**Saline placebo**
	Efficacy population, 18-49 years	N=2,344		N=2,304
	culture-confirmed CDC-ILI (attack rate)	64 (2.7%)		114 (4.9%)
	culture-confirmed CDC-ILI due to matched strains (attack rate)	1 (0.04%)		4 (0.2%)
	culture-confirmed respiratory illness due to matched strains (attack rate)	2 (0.1%)		6 (0.3%)
	culture-confirmed CDC-ILI due to any strain (attack rate)	44 (1.9%)		78 (3.4%)
	CDC-ILI regardless of culture results (attack rate)	127 (5.4%)		162 (7.0%)
	culture-confirmed CDC-ILI due to any influenza type A, ***post-hoc***	26 (1.1%)		56 (2.4%)
	culture-confirmed CDC-ILI due to any influenza type B, ***post-hoc***	18 (0.8%)		23 (1.0%)
	Immunogenicity population for lot consistency (391 subjects)	Lot A 131	Lot B 130	Lot C 130	-
	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)	-
	A/Wisconsin (H3N2) GMT (95%CI)	395.43 (326.01; 479.62)	178.96 (146.75; 218.23)	241.83 (197.83; 294.14)	-
	B/Malaysia GMT (95%CI)	175.06 (143.89; 212.98)	196.98 (165.00; 235.17)	205.57 (168.74; 250.43)	-
	A/Solomon Islands (H1N1) **SCRs** (95%CI)	78% (73.8, 82.2)			-
	A/Wisconsin (H3N2) **SCRs** (95%CI)	81% (76.3, 84.4)			-
	B/Malaysia **SCRs** (95%CI)	53% (48.1, 58.2)			-

	A/Solomon Islands (H1N1) **SPRs** (95%CI)	98% (96.7, 99.4)	-
	A/Wisconsin (H3N2) **SPRs** (95%CI)	96% (94.1, 98.0)	-
	B/Malaysia **SPRs** (95%CI)	96% (93.4, 97.6)	-
Effect estimate per comparison	Primary analysis on culture-positive CDC ILI due to matched strains	rVE: 75.4 % 95% CI: -148.0, 99.5 Pre-specified success criterion: **unmet**	
	Secondary efficacy analysis on culture-positive ILI due to matched strains, regardless of CDC-ILI	rVE: 67.2% 95% CI: -83.2, 96.8	
	Exploratory efficacy analysis on culture-positive CDC-ILI, any strain	rVE: 44.6% 95%CI: 18.8, 62.6	
	Exploratory efficacy analysis on CDC-ILI, regardless of culture results	rVE: 22.9% 95%CI: 2.2, 39.4	
	Post-hoc analysis on culture-positive CDC-ILI due to any influenza A	rVE: 54.4% 95%CI: 26.1, 72.5	
	Post-hoc analysis on culture-positive CDC-ILI due to any influenza B	rVE: 23.1% 95%CI: -49.0, 60.9	
	A/H1N1 Lot consistency analysis on difference between lots, GMT ratios (95%CI)	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) CBER criteria: met	
	A/H3N2 Lot consistency analysis on difference between lots, GMT ratios (95%CI)	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) CBER criteria: **unmet**	
	B/Malaysia Lot consistency analysis on difference between lots, GMT ratios (95%CI)	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) CBER criteria: met	
	SCRs at Day 28, H1 A/Solomon Islands	2-sided 95%CI: 73.8, 82.2 Lower bound CI ≥ 40% (CBER criteria): YES	
	SCRs at Day 28, H3 A/Wisconsin	2-sided 95%CI: 76.3, 84.4 Lower bound CI ≥ 40% (CBER criteria): YES	
	SCRs at Day 28, B/Malaysia	2-sided 95%CI: 48.1, 58.2 Lower bound CI ≥ 40% (CBER criteria): YES	
Notes	Primary efficacy endpoint did not meet success criteria and secondary efficacy analysis was non-conclusive. Exploratory and post-hoc analyses describe moderate efficacy of RIV3 in preventing against culture-confirmed CDC-ILI due to any strain, and this effect was driven by the predominant efficacy against influenza type A strains. Lot consistency analyses showed that three clinical lots did not meet pre-defined criteria for A/H3 strain, partially due to different amounts of Wisconsin rHA protein included in the three lots. Nonetheless, RIV3 is demonstrated immunogenic and meets CBER criteria for SCRs and SPRs.		

*using 448 subjects showed consistent results

2.5.3. Discussion on clinical efficacy

To support this application, two pivotal phase 3 studies, PSC12 and PSC16, were submitted, aiming to show clinical efficacy of RIV4 in adults ≥50 (PSC12) years and clinical immunogenicity of RIV4 in adults 18 to 49 years (PSC16). Both studies compared RIV4 with a US and EU-licensed active comparator IIV4. In addition, a supportive study PSC04 conducted with RIV3 was included for adult 18-49 years of age indication. The CHMP Scientific advice of the EMA (EMEA/H/SA/3849/1/2018/III) supported this program.

Design and conduct of clinical studies

The designs of PSC12, PSC16 and PSC04 were adequate, all were conducted in the USA in accordance with GCP.

In **PSC12**, of 9,003 randomised subjects, 8,963 received a known study vaccine and were included in the final analysis. 8,604 (96%) constituted efficacy population for the non-inferiority analysis. The number of subjects excluded from efficacy analyses was small (total 359) and well balanced between two treatment groups, including 251 subjects who had protocol deviation. In **PSC04**, a total of 4,648 eligible subjects were randomised, all vaccinated and included in the efficacy analyses.

Surveillance of lab-confirmed ILI was the key measure of efficacy endpoints of PSC12 and PSC04. In PSC04, there was inconsistent description about the time window for swabs taken. The applicant explains that only the date of the swab was reported during the study and thus the time window of up to 2 days for ILI is referred to a maximum of 72 hours. In PSC12, case definition required that lab-confirmed ILIs began at least 14 days after vaccination. However, no such a requirement was stated in CSR of PSC04.

While PSC04 was a superiority trial to compare RIV3 versus placebo, PSC12 aimed to demonstrate non-inferior efficacy of RIV4 relative to IIV4, as endorsed by the CHMP (EMEA/H/SA/3849/1/2018/III). The protocol stated that if the non-inferiority criterion was met, an exploratory superior analysis was pursued. However, this analysis was not included in the SAP of PSC12.

Both PSC12 and PSC04 included immunogenicity endpoints but focusing on only serum HAI responses. PSC12 did not include the measurement of CMI. This precluded the possibility to explore a potential immune correlate of protection for the elderly.

In study PSC12, immunogenicity data were determined in a subpopulation of ~300 subjects for each vaccine collected from subjects enrolled in 5 pre-selected study sites. Neither protocol nor CSR provide any detail regarding site- and subject- selection for serology investigations. The applicant clarified, that the three PSC12 sites (10, 14, and 39) chosen prior to study initiation to obtain serology samples were all affiliated with the same clinical site network (Benchmark Research) and selected based on previous enrolment experience and projections from prior successfully enrolled clinical trials sponsored by Protein Sciences Corporation. As the pace of enrolment indicated those three sites might not fully obtain the serology subset sample, based on previous experience, enrolment pace and likelihood of success, the two additional sites (34 and 37) were asked to participate in the PSC12 serology subset because they were appropriately prepared to undertake the additional study procedures.

The demographic and baseline characteristics were overall similar across vaccine groups. There was only a slight difference in one centre with a very limited population size. The described selection approach finally did not raise concerns related to selection bias.

The dose used in pivotal PSC12 with RIV4 was selected based on the US licensed RIV3 in terms of safety and immunogenicity at a dose of 0.5 mL (45 mcg rHA per strain) and the fact that RIV4 follows essentially the same manufacturing process as RIV3. This appears acceptable.

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 USA recruited 1,350 subjects, of whom 1,011 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.

Both pivotal trials (PSC12 and PSC16) were multi-centre, randomised, active-controlled, observer-blind clinical studies employing a non-inferiority comparison to a licensed, 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%. The size of the NI margin was discussed and justified. 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 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). From a planning perspective, trial PSC16 might have been underpowered to evaluate non-inferiority in the multiple primary endpoints.

Efficacy data and additional analyses

In pivotal **PSC12**, RIV4 is demonstrated similarly efficacious as IIV4 in the prevention against influenza in adults ≥50 years of age. Following a single IM dose, the rVE of RIV4 vs IIV4 against protocol-defined rtPCR-positive influenza in the efficacy population (per protocol) was 30% (95%CI: +10, 47%). This size of treatment effect was further confirmed by secondary and exploratory analyses using the rtPCR-confirmed CDC-ILI and culture-confirmed CDC-ILI (any match).

As shown in a *post-hoc* analysis, the observed rVE was mainly attributable to the predominant efficacy of RIV4 against influenza A strains, especially A/H3 (rVE 36%, 95%CI: 14%, 53%). However, for rVE against influenza B strains, the attack rates were 0.5% versus 0.6% for RIV4 and IIV4, respectively, resulting in a rVE of +17 (95% CI: -72, +46). The confidence intervals are extremely wide due to the low incidence of cases and no firm conclusion can be drawn. It remains unclear whether two vaccines can be intrinsically similar in efficacy against influenza B strains. Since more than 70% of circulating B strains in 2014/15 were of the B/Yamagata lineage, thus driving the B strain results, and since the non-inferiority of antibody titres against B/Yamagata could be replicated in both pivotal trials in comparison to an egg-derived licensed vaccine, efficacy of RIV4 against infection with the B/Yamagata strain can be accepted despite the scarcity of provided data. The applicant further substantiated the low efficacy observed for B/Victoria in study PSC12 with one 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 (data shown in table below). In a second trial conducted in older adults 65 to 82 years of age in Hong Kong during the influenza season 2017/18, RIV4 was demonstrated at least as immunogenic as a standard-dose quadrivalent vaccine, with respect to humoral immune response to individual vaccine strains, including B/Brisbane/60/2008 Victoria lineage.

Table 26: Summary of immune response in ages 18 to 64 by GMTs, GMRs and SCR (NCT03617523)

Parameters D28 Subjects 18 to 64 years of age	Vaccine	A/H1N1	A/H3N2	B/Victoria B/Maryland/15/2016	B/Yamagata B/Phuket/3073/2013
GMTs at D 28 (95% CI)	IIV4 N=61	525 (386 to 712)	379 (276 to 523)	588 (447 to 773)	759 (571 to 1009)
	RIV4 N=58	708 (498 to 1007)	644 (456 to 909)	525 (388 to 711)	1102 (829 to 1465)
GMTRs pre/post-vaccination (95% CI)	IIV4 N=61	2.93 (2.02 to 4.23)	3.55 (2.60 to 4.85)	3.39 (2.43 to 4.73)	2.84 (2.10 to 3.85)
	RIV4 N=58	6.34 (4.17 to 9.63)	8.19 (5.56 to 12.1)	4.40 (3.13 to 6.19)	5.20 (3.76 to 7.21)
Seroconversion (95% CI)	IIV4 N=61	32.8 (21.3 to 46.0)	44.3 (31.5 to 57.6)	32.8 (21.3 to 46.0)	27.9 (17.1 to 40.8)
	RIV4 N=58	51.7 (38.2 to 65.0)	70.7 (57.3 to 81.9)	46.6 (33.3 to 60.1)	55.2 (41.5 to 68.3)

Source: Clinicaltrials.gov NCT03617523 Results (9)

The rVE (PSC12) analysis by subject demographics showed a greater rVE in the 18-64 years of age group than in older subjects ≥65 years of age. Although a positive point estimates in sex and race strata, the applicant concluded that wide 95%CI and the limited sizes of subgroups preclude their meaningful interpretation and there was no conclusive difference in efficacy of RIV4 vs IIV4 in the ≥65 years of age subjects. These analyses might be read as aligning with the non-inferiority conclusion of the primary efficacy endpoint, but alternatively may raise a question if the effect size reported in primary efficacy analysis could be reproduced in different subgroups of subjects.

In an exploratory analysis, the magnitude of treatment effect of RIV4 vs IIV4 was smaller in subjects having received influenza vaccines in the prior season than reported in the primary efficacy analysis.

A post-hoc analysis for study PSC12 showed that RIV4 is more effective than IIV4 in subjects with underlying conditions, although this RIV4 benefit is higher in subjects with no underlying conditions than in subjects with underlying conditions.

The pre-specified exploratory efficacy analyses on the influenza-related complications such as hospitalizations, deaths and pneumonia in PSC12, were not performed, due to the absence or not sufficient data to warrant a health economic assessment.

Regarding the exploratory superiority analysis, although RIV4 met the prespecified criterion in the per protocol population, it is questionable if the observed rVE of >+9% with 95%CI for RIV4 over IIV4 could be held in various situations, such as for different influenza seasons with both a good antigenic match and apparent mismatch of A/H3, for subgroups of subjects discussed above or for A/H1 and/or influenz B strains.

Exploring potential immune correlate of protection for the older adults ≥65 years was not attempted in PSC12, as the study did not include measurements of CMI.

In **PSC04**, which is supportive in nature for this application, efficacy of RIV3 relative to saline placebo could not be reliably estimated due to so few cases of the primary and secondary endpoints. In two exploratory analyses carried out on culture-confirmed CDC-ILI or CDC-ILI, in the ITT population, one

IM dose of RIV3 could confer an overall rVE of 44.6% (95%CI: 18,8, 62.6) and 22.9% (95%CI: 2.2, 39.4), respectively, in adults 18 to 49 years of age. As shown in an *post-hoc* analysis, these treatment effects were ascribed to the predominant efficacy of RIV3 against influenza type A strains (54.4%; 95%CI: 26.1, 72.5).

The applicant intended to directly compare these descriptive analyses to data of published literatures. Caution is needed as the differences in study design, trial population, statistical methods, and the number of cases can greatly confound the interpretation of these comparisons.

Interestingly, a *post-hoc* analysis according to analysis periods showed a little or no protective efficacy of RIV3 after Feb 8, 2008, corresponding to approximately 4-5 months after vaccination. Though it has not been possible to explain the underlying mechanism except the assumption about a decline in cross-protective HAI antibodies, the applicant clarified that RIV3 efficacy is higher or at least comparable to other licensed influenza vaccines during the 2007/2008 influenza season. The applicant presented results of another study (Clinical Trial number: NCT02872311). In this study, 89 subjects aged 65-74 years were randomised 1:1:1 to receive HD-IIV3, aIIV3, or RIV4 the year after receipt of a standard dose of trivalent IIV-3 in the previous influenza season 2016-2017. Antibody persistence after 182 days after vaccination (D182) were measured. The results show that antibody titers were still present at D182 in all vaccine groups and indicate a comparable persistence of immunogenicity for all administered vaccines. It should be noted, that the sample size was small with altogether 59 subjects.

RIV3 is demonstrated immunogenic for each vaccine strain. RIV3 demonstrated satisfactory SCR and SPR that met CBER criteria for the 18 to 49 years of age.

Immunogenicity data

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 substantial inferiority. For A/H1N1 seroconversion, non-inferiority was missed by a small amount.

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 HA 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 and GMT data were markedly worse than for 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: 58, 72) for IIV4 recipients. These results illustrate that the upper bounds of the confidence intervals for the recombinant vaccine were 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 expected magnitude of response. 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 a concern that immunogenicity data consistently cannot demonstrate NI for B/Victoria, while for B/Yamagata no such issue is evident.

The HAI responses to B/Brisbane (Victoria lineage) were very low in both RIV4 and IIV4 vaccine groups. RIV4 did not meet the non-inferiority criterion for either seroconversion rates or for GMT ratios for this strain in either study. This finding was in contrast to the immune response to the recombinant B antigens observed in earlier clinical trials of the trivalent formulation of the recombinant vaccine in

which criteria for either accelerated approval (seroconversion rates) or non-inferiority to inactivated vaccine B strains were met.

The magnitude of HAI response to this antigen in both vaccine groups was low, suggesting a possibly reduced inherent immunogenicity of the B/Brisbane HA antigen in general. Another potential contributing factor proposed by the applicant may have been that most subjects were seronegative to B/Brisbane at the time of vaccination and therefore unprimed for this antigen. But although there are indeed literature hints for a generally low B/Brisbane/60/2008 immunogenicity, two other vaccines in Europe within the same season showed better B/Brisbane antigenicity, closer to A strain values, also with a mainly unprimed population (e.g. https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001042-24/results and https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000785-21/results#moreInformationSection). Furthermore, this strain has been used successfully for several years between 2010 and 2018.

In a subset of 100 vaccinees of each study arm (RIV4 and IIV4) of PSC12/16, subsequently determined seroneutralization assay data (Baseline and Day 28 post-vaccination) also showed less immunogenicity for B/Victoria in the RIV4 arms compared to the IIV4 arms, but the absolute GMTs post-vaccination at least proved to be sufficiently "protective" values (99-100% "seroprotection", ≥1:40), interestingly with already high baseline "seroprotection" rates (95-96% in elder population and 87-89% in young adults). The clinical relevance of the low B/Victoria strain immunogenicity in trial PSC12 could not be elucidated unequivocally, as no conclusive efficacy for that strain could be shown due to low B/Victoria circulation during the trial seasons (more than 70% of circulating B strains in 2014/15 were of the B/Yamagata lineage).

Additional data subsequently submitted by the applicant reinforce the notion that there is not a general weakness regarding B/Victoria lineage immunogenicity in RIV4.

In study performed in Hong Kong during the 2017-2018 influenza season in adults 65 to 82 years of age (Cowling BJ *et al*), immunogenicity of RIV4 was compared with the immunogenicity of an IIV4-standard dose vaccine, a MF59 adjuvanted trivalent vaccine, and a High Dose IIV3. HAI showed that RIV4 immunogenicity was comparable to the immunogenicity of the IIV4 vaccine for all strains including responses to the B/Victoria lineage, B/Brisbane/60/2008 strain. Another study (Belongia *et al* 2020) evaluated the immunogenicity performance of RIV4 compared to Fluzone HD IIV3 and adjuvanted-IIV3 after standard-dose IIV3 the season prior, in individuals 65-74 years of age. The study was performed over 2 seasons 2016-2017, 2017-2108 when the B/Victoria lineage strain in vaccine TIV and QIV formulations was the same strain used in the pivotal RIV4 trials, B/Brisbane/60/2008. HAI titers were measured at 28 days post vaccination in the second season of the study as well as influenza attack rates, both stratified by vaccine types. The results for the influenza B strain, B/Brisbane/60/2008 were comparable to the Fluzone HD and adjuvanted IIV3 results in this older age group.

In contrary, and consistent with the earlier RIV3 studies, RIV4 subjects in studies PSC12 and PSC16 had notably higher HAI antibody responses to the influenza A/H3N2 vaccine component relative to IIV4 subjects for all major adult age brackets (from 18 to 49 years of age, from 50 to 64 years of age, and ≥65 years of age).

The findings related to A/H3N2 are especially relevant, given that seasons in which A/H3N2 is the predominant circulating strain are known to be associated with greater morbidity and mortality than are seasons dominated by the other epidemic subtypes based on observations in recent decades. Furthermore, in study PSC12, the higher immune response to A/H3N2 in RIV4 subjects relative to IIV4 subjects and the predominance of cases with type A/H3N2 isolates (73/96, 76 %) very likely contributed to the higher relative VE demonstrated in this study. "Antigenic match" could not be evaluated within PSC12 as planned due to the predominant "antigenic mismatch" of A/H3N2 circulating strains (A/H3N2/Switzerland) and the corresponding vaccine strain (A/H3N2/Texas) for the 2014-2015

influenza season, also reported by the CDC. Similar observations were made in the study PSC04 conducted during the 2007-2008 season.

Regarding specifically elderly subjects ≥65 years of age in PSC12, the immunogenicity exploratively has been shown to be weaker than in subjects 50-64 or 18-49 years of age in all strains in both RIV4 and IIV4, with the A/H1N1 strain yielding a relatively better seroconversion rate in IIV4 (37 vs. 27%) and the A/H3N2 in turn a better result in RIV4 (41 vs 25%). In adults 50-64 years of age, the seroconversion rates ranged between the <50- and >65 year-old subjects, and did not significantly differ between the treatment groups, except for A/H3N2 with a better result for RIV4 (63 vs. 51%) and B/Brisbane in favour of IIV4 (43 vs. 26%). Thus, like in other influenza vaccines, a clear age-dependency of immune response is visible here as well.

The assessment of the performance of RIV4 in adults 18 years of age and older in comparison to an active IIV4 comparator showed that RIV4 was, in general, as immunogenic as, and for influenza A/H3N2 more immunogenic, than the licensed IIV4 Fluarix Tetra in the given season. This roughly was true, as well, for the age categories ≥50 years of age.

Furthermore, regarding the intended bridging approach, adults from 18 to 49 years of age demonstrated immune responses at least comparable to those generated by adults ≥ 50 years of age in whom protective efficacy was demonstrated.

In general, the immune responses to the B strains among both age groups were less robust than to the A strains, but this was true for both RIV4 and the active IIV4 comparator. RIV4 was non-inferior to IIV4 for B/Massachusetts for SCR and GMT in both studies (all subjects). B/Brisbane demonstrated the least robust immunogenicity with both vaccines.

At least, regarding B strains, in view of a predominant strain mismatch during the 2014-2015 influenza season (and also 2007-2008), some degree of cross-reactive effectivity of RIV4 (and RIV3) can be assumed from the efficacy results in studies PSC12 (and PSC04), albeit no exact strain differentiation could be made during their evaluations.

The immunogenicity subset of study PSC04, otherwise mainly meant to show absolute efficacy (1:1 compared to placebo) of the equivalent trivalent predecessor vaccine (RIV3) against culture-confirmed CDC- or non-CDC-defined influenza-like illness in adults 18-49 years of age, may in some respects also support the present immunogenicity considerations, albeit HAI titers determined with a different test antigen (recombinant versus egg-grown, as mentioned above).

The GMTs raised in the subpopulation of n=391 (448) originally used for the lot-to-lot consistency assessment and as secondary objectives for seroconversion and seroprotection rate calculation allows the relative conclusion, that still sufficient immunogenicity (and efficacy, albeit mismatching strains) for B/Malaysia (also a B/Victoria strain) could be shown, in order to alleviate doubts against a general insufficient immunogenicity against the B/Victoria lineage as suspected when only considering the PSC12 and PSC16 B/Brisbane-results.

Table 27: PSC04 – Geometric mean titers and 2-sided 95% confidence internals at the Day 0 and Day 28 visits in the evaluable population

	A/Solomon		*B/Malaysia*		*A/Wisconsin*	
Timepoint	**GMT**	**95% CI range**	**GMT**	**95% CI**	**GMT**	**95% CI**
Day 0	31.26	(27.22, 35.90)	49.75	(43.98, 56.27)	22.36	(19.99, 25.02)
Day 28	360.36	(325.04, 399.51)	192.05	(172.01, 214.44)	257.76	(229.04, 290.09)
1. FluBlok, n=391 present in the locked database						
Data Source: Tables 14.2.2.1; Listing 16.2.16						

However, immunogenicity results of PSC04 have to be interpreted with caution, as issues with the potency test to measure antigen content caused considerable variation in rHA amount contained in the different RIV3 lots, leading to failure of lot consistency. Improved recalculation indicated that the H3 antigen (A/Wisconsin/67/2005) content in two of three lots was reduced by ~ 1/3 (~30µg) of the intended amount (45µg) whereas the other antigens exceeded the intended antigen amount by up to 40% (51-64µg).The applicant reconfirmed that the reference reagents used for the potency measurement were essential regulatory laboratory (ERL) calibrated and relevant for recombinant HA antigens used in the vaccine lots, and they did not compromise the HA antigen content of the B/Brisbane strain contained in the vaccine formulation used in PSC12 and PSC16 studies.

In the context of seroconversion calculation, comparing A-strain seroconversion results in PSC16 (and 12) to the respective values in PSC04, the PSC16/12 values turn out to be generally lower in spite of higher GMTs with relatively narrow CIs. Comparing the lower A-strain seroconversion rates in PSC16 versus PSC04 in spite of higher post-exposure GMTs, it was hint that this discrepancy may be due of the different vaccine strains between these two seasons, different HAI methodologies, as well as different pre-exposure history and baseline titers.

Finally, according to the Guideline on Influenza Vaccines – Non-clinical and clinical module, it is not expected that any one study will be able to provide estimates of strain-specific efficacy and studies will not be powered for such analyses. It is noted that trial PSC16 has formally failed its primary objective and could not show non-inferiority of RIV4 to IIV4 in all its strains. Whilst the potential of underpowering of PSC16 was mentioned in the methodological assessment in this report, it needs to be noted that sample size eventually also sufficed to bring up statistical evidence for RIV4 being inferior to IIV4 in terms of immunogenic response in relation to strain B/Victoria.

2.5.4. Conclusions on the clinical efficacy

Clinical efficacy of RIV4 has been demonstrated in subjects ≥50 years of age in pivotal PSC12, showing 10% efficacy with 95%CI, relative to IIV4, in preventing against rt-PCR confirmed protocol defined ILI occurring >14 days after vaccination. RIV4 can also be inferred as effective in adults 18 to 49 years of age, based on immunogenicity data from pivotal PSC16 and the clinical endpoint data of the supportive PSC04 study with RIV3, taking in to account the evidence documented in PSC12 with older adults.

Regarding clinical efficacy by influenza subtype, RIV4 is demonstrated efficacious against influenza A, whereas efficacy against influenza B is inconclusive. Nonetheless, RIV4 is shown to be as immunogenic as IIV4 comparator with respect to the HAI response to B/Yamagata strain.

Though the beneficial effects of RIV4 against influenza A and B/Yamagata is demonstrated by efficacy and supported by immunogenicity data, there were uncertainties with regard to the B/Victoria component due to inferior immunogenicity. Further data from two independent clinical trials were provided to alleviate this issue, indicating that there is not a general weakness regarding the immunogenicity of the B/Victoria lineage in RIV4.

The applicant commits to continue to monitor the performance of this vaccine during the post-authorisation phase by means of an effectiveness study, as specified in the RMP.

2.6. Clinical safety

The safety of the quadrivalent recombinant influenza vaccine Supemtek (RIV4) to support registration in adults ≥18 years of age has been studied in 2 completed phase III studies:

- Study PSC12 was a Phase III observer-blind, randomised, active-controlled, parallel design, multicentre clinical trial in adults ≥ 50 years of age designed to assess relative vaccine efficacy, and to compare the immunogenicity, reactogenicity and safety of RIV4 with that of an EU-licensed IIV4 (Fluarix Tetra).
- Study PSC16 was a Phase III observer-blind, randomised, active-controlled, parallel design, multicentre clinical trial in subjects from 18 to 49 years of age designed to compare the safety, reactogenicity and immunogenicity of RIV4 to EU-licensed IIV4 (Fluarix Tetra).

The safety data from these two studies were not pooled for an integrated safety analysis as the age groups enrolled were not overlapping. Therefore, safety data were presented separately according to the 2 age strata covered by these studies (18 to 49 years of age and ≥50 years of age). Additionally, safety data from study PSC12 conducted in elderly subjects ≥ 50 years of age were also presented by the age categories 50-64 years of age and ≥ 65 years of age.

The RIV4 development is based on the manufacturing process and controls of the trivalent recombinant influenza vaccine (RIV3). The quantity of each HA antigen and excipients of RIV4 was equivalent to that of RIV3 but with the addition of the second B strain. Safety data from one clinical study performed with the trivalent vaccine RIV3 has been provided:

- Study PSC04 was a Phase III double-blind, randomised, placebo-controlled clinical trial designed to evaluate the immunogenicity, safety, reactogenicity, efficacy, effectiveness and lot consistency of FluBlok trivalent recombinant baculovirus-expressed haemagglutinin influenza vaccine in healthy adults 18 to 49 years.

The RIV3 safety program provided includes results from a number of additional clinical trials (e.g. PSC01, PSC03, PSC04, PSC06 and PSC11) demonstrating the safety of RIV3 compared to either placebo or active comparators in adult and elderly subjects.

Patient exposure

The study population in both trial included ambulatory and medically stable adults ≥50 years of age (trial PSC12) or 18-49 years of age (trial PSC16) without contraindication to the vaccines, and who did not have underlying conditions that might complicate the evaluation of the primary efficacy and safety endpoint. Individuals with underlying disease or therapeutic intervention that might adversely affect the immune response, e.g. cytotoxic agents or supraphysiologic doses of corticosteroids were excluded. Also pregnant or lactating women and women planning to become pregnant within 30 days after vaccine administration were excluded (applicable only for trial PSC16 including subjects 18-49 years of age).

The safety population included all randomised subjects who received study vaccine or control (i.e. RIV4 or IIV4) and provided any safety data. The safety population from trial PSC12 and PSC16 included altogether 10,002 subjects. 8,672 subjects were included in the safety population of trial PSC12 and 1,330 subjects in the safety population of trial PSC16. A total of 5,326 subjects received one dose of RIV4 in the two studies, i.e. 998 adults 18 to 49 years of age in study PSC16, and 4,328 adults from ≥50 years of in study PSC12. The safety population of RIV4 included 2,569 individuals 50-64 years of age, 1,234 individuals 65 to 74 years, and 525 individuals ≥75 years of age. 4,676 subjects received IIV4 in the two trials.

Adverse events

Solicited adverse events

In trial PSC12 and PSC16, local solicited reactions were more frequently recorded than solicited systemic reactions in both vaccine groups. The incidence of solicited local and systemic reactogenicity was comparable in both vaccine groups in both trials. The most frequently reported local solicited reaction in both vaccine groups was local tenderness, followed by local pain. The most frequently reported solicited systemic reactions were headache, fatigue, joint and muscle pain. The majority of local and systemic solicited reactions was mild to moderate in both vaccine groups. Also the incidence of fever was comparable in the two groups.

Differences in the frequency of solicited injection site reactions were observed in both trials, and in both vaccine groups related to gender, race, and ethnicity. In trial PSC12, reactogenicity differences were additionally observed related to age. In both trials and both vaccine groups, local reactogenicity events occurred within the same range, but tended to be more frequently reported by females compared with males, by white subjects compared with non-white subjects, and by non-hispanic subjects compared with hispanic subjects. Reactogenicity also tended to be higher in individuals 50 to 64 years of age, compared to those older than 64 years of age (trial PSC12). It is known from other vaccines, that demographic parameters might have an impact on immune response. Age related differences are well known for vaccines. The lower reactogenicity in elderly is associated with a lower immune response due to immunosenesence. The observed different reactogenicity in demographic subgroups is not large and not considered clinically meaningful in respect to safety.

Solicited local adverse reactions

Trial PSC12

Overall, 48.0% of subjects (2,071) in the RIV4 vaccine group and 51.0% of subjects (2,206) in the IIV4 vaccine group recorded one or more solicited reactogenicity event (local or systemic), p-value 0.006, [95 % CI (46.5,49.5) and (49.5, 52.5)].

Overall, 37.6% of subjects (1,621) in the RIV4 vaccine group versus 40.4% of subjects (1,745) in the IIV4 vaccine group recorded one or more solicited local reaction, p-value 0.009, [95 % CI (36.2, 39.1) and (38.9, 41.9)]. The most frequently reported solicited local reaction in both vaccine groups was local tenderness reported by 34.3% (1,479) of subjects [95% CI (32.9, 35.8)] in the RIV4 vaccine group and by 37.1% (1,604) of subjects in the IIV4 vaccine group [95% CI (35.7, 38.6)], followed by local pain reported by 18.9% (813) of subjects [95% CI (17.7, 20.1)], versus 22.0% (950) of subjects [95% CI (20.8, 23.3)], in the two vaccine groups. The majority of solicited local reactions were mild to moderate. 13 subjects each in the two vaccine groups reported grade 3 solicited local reactions and 3 subjects reported grade 4 reactions (1 in the RIV4 group and 2 in the IIV4 group).

Trial PSC16

Overall, 51.2% of subjects (510) in the RIV4 vaccine group versus 51.8% of subjects (172) in the IIV4 vaccine group recorded one or more solicited local reaction, p-value 0.90, [95% CI (48.1, 54.4) and (46.3, 57.3)]. The most frequently reported solicited local reactions in both vaccine groups were local tenderness reported by 48.0% of subjects (478) in the RIV4 vaccine group and by 46.7% of subjects (155) in the IIV4 vaccine group [CI 95% (44.8, 51.1) and (41.2, 52.2)], followed by local pain reported by 36.8% of subjects (367), and by 36.4% of subjects (121) in the two vaccine groups, [95% CI (33.8, 39.9) and (31.3, 41.9)]. P-values for the events of tenderness and local pain were 0.70 and 0.95. The majority of solicited local reactions were mild to moderate. A total of 16 subjects reported grade 3 solicited local reactions, 11 (1.1%) in the RIV4 and 5 (1.5%) in the IIV4 vaccine group. Overall, only 1 subject (in the RIV4 vaccine group) reported a grade 4 solicited local reactogenicity event.

Local reactogenicty by demography

Demographic differences reagarding local reactogenicity have been observed. Since the reactogenicity events occurred within the same range, they do not negatively impact the B/R ratio of RIV4 in any of the demographic subgroups.

Trial PSC12

In both treatment groups injection-site reactions were within the same range, but tended to be reported more frequently in younger subjects (50-64 years of age), females, whites, and non-hispanics, compared with older subjects ≥65 years of age, males, blacks, and hispanics. The proportion of subjects reporting at least one solicited local reactogenicity event in the 50-64 years of age group in trial PSC12 was 42.3% (1080) of subjects (95% CI [40.3, 44.2] in the RIV4 group and 44.6% (1159) of subjects in the IIV4 group (95% CI [(42.6,46.5]), as compared with 30.9% (541) of subjects (95% CI [28.7, 33.1]), and 34.1% (586) of subjects (95% CI [31.9, 36.4]) in adults ≥ 65 years of age in the two vaccine groups, p-value <0.001 in both groups (statistically significant). The proportion of subjects who reported at least one solicited local reactogenicity event was higher in females compared with males in both vaccine groups. Overall, 45.4% (95% CI [43.4, 47.4]) of females (1145 subjects) in the RIV4 and 48.4% of females (95% CI [46.5, 50.4]) in the IIV4 vaccine group (1221 subjects) reported at least one solicited local reactogenicity event compared with 26.7% (95% CI [24.6,28.8]) of male subjects (476) and 29.1% (95% CI [27.1, 31.3] of male subjects (524) in the two vaccine groups. The difference was statistically significant in both groups (p-value <0.001). Local reactogenicity was higher in white subjects compared with non-white subjects in both vaccine groups. At least one solicited local reactogenicty event was reported by 39.9% (1378) of white subjects in the RIV4 vaccine group (95% CI [38.3, 41.6]), and by 42.8% (1486) of white subjecsts in the IIV4 vaccine group (95% CI [41.1, 44.4]), compared with 28.5% (243) and 30.7% (259) of non-white subjects (95% CI [25.4,31.6] and [27.6, 33.9]) in the two vaccine groups (p-value <0.001, statistically significant). Regarding to ethnicity, local reactogenicty was lower in hispanic subjects compared with non-hispanic subjects in both vaccine groups. 27.3% (56) and 31.7% (69) of hispanic subjects (95% CI [21.3,34.0] and [25.5,38.3]) in the RIV4 and the IIV4 vaccine group, compared with 38.2% (1565) and 40.9% (1676) of non-hispanic subjects (95% CI [36.7,39.7] and [39.4,42.4]), p-value 0.002 in the RIV4 and 0.007 in the IIV4 vaccine group.

Trial PSC16

The proportion of subjects reporting at least one solicited local reactogenicity event was 56.7% (361) and 57.2% (127) of female subjects in the RIV4 and the IIV4 vaccine group (95% CI [52.7,60.6] and [50.4,63.8]), versus 41.5% (149) and 40.9% (45) of male subjects (95% CI [36.4,46.8] and [31.6,50.7]). Overall 59.7% (351) and 56.4% (114) of white subjects in the RIV4 and the IIV4 vaccine group (95% CI [55.6,63.7] and [49.3,63.4]), versus 39.0% (159) and 44.6% (58) of non-white subjects (95% CI [34.2,43.9] and [35.9,53.6]), reported at least one local reactogenicity event, p-value <0.001 in the RIV 4 vaccine group (statistically significant) and 0.037 in the IIV 4 vaccine group. 53.7% (87) and 52.6% (30) of hispanic subjects (95% CI [45.7,61.6] and [39.0,66.0]), versus 62.7% (523) and 63.6% (175) of non-hispanic subjects, (95% CI [59.3,66.0] and [57.6,69.3]) reported at least one solicited local reactogenicity, p-value 0.034 and 0.14 in the RIV4 and the IIV4 vaccine group.

Solicited systemic adverse reactions

Trial PSC12

Overall, 25.0% (1,077) of subjects in the RIV4 and 25.6% (1,106) of subjects in the IIV4 vaccine group recorded one or more solicited systemic reaction, p-value 0.54, [95% CI (23.7, 26.3) and (24.3, 26.9)]. The most frequently reported solicited systemic reactions in the RIV4 and the IIV4 vaccine group were fatigue reported by 12.2% (526) versus 12.1% (521) of subjects, p-value 0.84, [95% CI

(11.3,13.2) and (11.1, 13.1)], and headache reported by 12.7% (549) versus 13.5% (582) of subjects, p-value was 0.32, [95% CI (11.8, 13.8) and (12.5, 14.5)]. This was followed by joint (7.5% versus 8.0% of subjects) and muscle pain (8.5% versus 8.8% of subjects). p-values for joint and muscle pain were 0.40 and 0.7, respectively, [95% CIs were (6.8, 8.4) versus (7.2, 8.9)], and [(7.7, 9.4) versus (7.9, 9.6)] for the two symptoms in the two vaccine groups. The majority of solicited systemic reactions were mild to moderate. Grade 3 solicited systemic reactions were reported by 1.3% of subjects each in the two vaccine groups (58 and 55 subjects in the RIV4 and the IIV4 vaccine group). Grade 4 solicited systemic reactions were reported by 4 subjects (0.1%) in the RIV4 and by 8 subjects (0.2%) in the IIV4 vaccine group.

In relation to fever, only 0.4% (19) and 0.5% (21) of subjects in the RIV4 and the IIV4 vaccine group reported fever events ≥100.4°F (38.0° C). Grade 3 body temperature, i.e. 102.1°F (38.9°C) to 104°F (40°C) was recorded for 7 (0.2%) and 6 (0.1%) subjects in the two vaccine groups. No subject reported a grade 4 fever event, i.e. body temperature >104°F (40°C).

Trial PSC16

Overall, 34.1% (339) of subjects in the RIV4 and 35.8% (119) of subjects in the IIV4 vaccine group recorded one or more solicited systemic reaction, p-value 0.59, [95% CI (31.2, 37.1) and (30.7, 41.3)]. The most frequently reported solicited systemic reactions in the RIV4 and the IIV4 vaccine group was headache, reported by 20.3% (202) versus 21.1% (70) of subjects, p-value 0.75, [95% CI (17.9, 23.0) and (16.8, 25.9)], followed by fatigue reported by 16.5% (164) versus 16.6% (55) of subjects, p-value > 0.99, [95% CI (14.2,19.0) and (12.7, 21.0)], respectively. Joint and muscle pain were reported by less than 13% of subjects in both groups. The majority of solicited systemic reactions were mild to moderate. Grade 3 solicited systemic reactions were reported by 2.3% and 2.7% of subjects in the two vaccine groups (23 and 9 subjects). Grade 4 solicited systemic reactions were reported by 2 subjects, one in the RIV4, and one in the IIV4 vaccine group.

In relation to fever, only 1.5% (15) and 0.6% (2) of subjects in the RIV4 and the IIV4 vaccine group reported fever events ≥100.4° F (38.0° C). Grade 3 body temperature, i.e. 102.1° F (38.9° C) to 104° F (40° C) was recorded for 4 (0.4%) and 1 (0.3%) subject in the two vaccine groups. No subject reported a grade 4 fever event, i.e. body temperature >104°F (40°C).

Unsolicited adverse events

The safety population to assess unsolicited adverse events was 4,328 subjects in the RIV4 and 4,344 subjects in the IIV4 vaccine group in trial PSC12, and 998 subjects and 332 subjects in trial PSC16. The most common unsolicited AE terms reported from the RIV4 and IIV4 groups in both studies were respiratory tract infection symptoms like nasopharyngitis, upper respiratory tract infection, sinusitis, and cough/productive cough, in the SOCs of "infection and infestations" and "respiratory disorders". Other commonly reported unsolicited AE were headache, fatigue, and myalgia. The tabled unsolicited adverse events did not indicate any difference in the safety profile of the two vaccines. Frequency and nature of AEs was balanced.

A subgroup analysis by age, gender and racial/ethnic origin was performed in each population. Elderly subjects tended to report unsolicited AE with higher frequency compared to non-elderly (31.1% versus 14.3%). Unsolicited non-serious AEs were reported by higher percentages of female subjects than male subjects. Caucasian/white subjects tended to report unsolicited non-serious AEs more frequently than non-white subjects.

Trial PSC12

Overall, 31.1% (1,345) and 31.2% (1,355) of subjects recorded at least one unsolicited AE. The most common recorded unsolicited AEs were cough recorded by 5.2% (226) and 5.8% (253) of subjects in

the RIV4 and the IIV4 vaccine group, influenza like illness (4.3% [186] and 4.6% [199]), oropharyngeal pain (4.1% each [178, 177]), headache (3.3% each [143, 145]), upper respiratory tract infection (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]).

Trial PSC16

Overall, 14.3% (143) and 14.2% (47) of subjects recorded at least one unsolicited AE. The most common recorded unsolicited AEs were headache recorded by 2.0% (20) and 1.5% (5) of subjects in the RIV4 and the IIV4 vaccine group, nasopharyngitis (1.3% [13] and 1.5% [5]), upper respiratory tract infection (1.0% [10] and 1.5% [5]), sinusitis (0.6% [6] and 1.5% [5[), and cough (1.4% [14] and 1.2% [4]). All other events were reported from less than 1% of subjects in either treatment group.

Adverse Events of Special Interest

The study protocol did not define AESIs as specific safety endpoints. However, study protocols were screened for AEs potentially associated with influenza vaccination including neuritis, convulsion, encephalitis, vasculitis, Guillain-Barré syndrome, Bell´s palsy and demyelinating disorders.

Overall, the incidence of AESIs potentially associated with influenza vaccination was low across the RIV4 clinical development program and generally balanced between the vaccine groups. However, one case of Bell´s palsy has been reported in study PSC12 in a 79-year old female subject 85 days after vaccination with RIV4. This event resolved within 17 days after the diagnosis and was judged as not related to study vaccine by the investigator. However, based on the information provided a causal relationship between the event of Bell´s palsy and vaccination cannot be excluded. The applicant argued that the causal relationship between Bell´s palsy and RIV4 vaccination seems unlikely as the occurrence of this event was beyond the risk window of cranial nerve disorders which was published to be between 8 to 30 days in girls receiving HPV4 vaccination. With regard to the time periods used to investigate the increased risk of Bell´s palsy after influenza vaccination, different risk periods up to 3 months were found in literature (e.g. Greene et al., 2010, Stowe et al., 2006, Wijnans et al., 2017). No temporal relationship between administration of influenza vaccines and the occurrence of Bell´s Palsy have been reported, however, the available evidence favours that a causal relationship between Bell´s palsy and influenza vaccinations seems to be low considering the late onset of this event. No event of Bell´s palsy has been reported in study PSC16 in adults 18 – 49 years of age. Bell´s palsy has also been reported in study PSC04 in a 35-year old subject who received the trivalent vaccine RIV3. This subject had a history of multiple prior episodes of Bell´s palsy. The event was initially classified as treatment-related SAE, but then reclassified as "not related" upon subsequent investigation. The subject had prodromal symptoms (watery eyes) one day prior to vaccination, which was consistent with the prodrome in her previous episodes of Bell's palsy. In addition, onset of the Bell's palsy had occurred within one hour of vaccination, which is incompatible with the known pathophysiology of this disorder. The symptoms resolved without treatment or sequelae within 3 days after vaccination, and did not recur by the time of the Day 28 contact.

In study PSC12 conducted in elderly ≥50 years of age, 2 subjects (0.0%) in the RIV4 treatment arm and 1 subject (0.0%) in the IIV4 treatment arm reported an AE of convulsion 14, 133 and 70 days after vaccination, respectively. None of these events was considered related by the Investigator. However, one of these AEs experienced by a 52-year old subject 133 days post-vaccination was fatal. Since this subject had a medical history of seizure disorders, the cause of death might be attributable to the underlying comorbid condition. In study PSC16, one case (0.1%) of convulsion was reported in the RIV4 vaccine group compared to none in the IIV4 arm. This event occurred 114 days post-vaccination and it is agreed that this event is considered unrelated to study vaccine due to the lack of temporal relationship.

Among elderly, 3 subjects (0.1%) in the RIV4 treatment arm and 1 subject (0.0%) in the IIV4 treatment arm reported an AE of peripheral neuropathy 53, 175, 107 and 58 days after vaccination, respectively. Due to the late onset of these events after vaccination, it is agreed that these AEs might not be related to the study vaccine.

No events of neuritis, vasculitis, demyelinating disorders or Guillain-Barré Syndrome (GBS) have been reported across the clinical development program of RIV4. However, the annual incidence rate of GBS ranges from 0.8 to 1.9 per 100,000 persons and it might be difficult to detect a small increase in risk for a rare disease such as GBS in the clinical studies (Fadrigue et al., 2019). Therefore, the addition of GBS in section 4.8 of the SmPC is endorsed.

Serious adverse event/deaths/other significant events

The proportion of subjects who recorded a SAE was in general comparable in the two vaccine groups in both trials. No notable differences could be observed with regard to the nature of SAEs in the two vaccine groups. It was however noted, that the SAE of myocardial infarction was slightly more frequently reported in the RIV4 group compared to the IIV4 arm. In study PSC12, 4 subjects (0.1%) exposed to RIV4 and 3 subjects (0.1%) in the IIV4 treatment arm experienced myocardial infarction. In study PSC16, 2 subjects (0.2%) in the RIV4 and 0 subjects (0%) in the IIV4 arm experienced myocardial infarction. In study PSC12, all of the subjects who suffered from MI had comorbidities that are associated with increased risk for cardiovascular events including increased age, hypertension, hyperlipidaemia, hypercholesterolemia and/or diabetes mellitus and thus reflect a population of high risk of MI. However, in study PSC16 conducted in adults 18 to 49 years of age, the subjects who suffered from MI were <45 years of age (37 and 44 years of age). The 37-year old subject who suffered from myocardial infarction on day 88 received concomitant medications of steroid injections (since 01 May 2012), tramadol (since 06 January 2014) and Flexeril (since 06 July 2014). Cyclobenzaprine (Flexeril) is closely related to tricyclic antidepressants which are known to produce arrhythmias, sinus tachycardia, prolongation of conduction time leading to myocardial infarction and stroke. The 44-year old subject had comorbidities of hypertriglyceridemia (since 2012) and diabetes mellitus type II (since 2011) which are associated with an increased risk for cardiovascular events. These were judged as not related to the vaccination.

No SAEs considered being vaccine related were recorded in the clinical trial protocols of trial PSC12 and PSC16. Subgroup analysis for SAEs by age (age categories 50-64, 65-74, ≥65 and ≥75), gender and race/ethnicity were submitted for study PSC12. These data was not provided for study PSC16 conducted in adults 18 to 49 years of age. However, considering that subgroup analyses by race and ethnicity need to be interpreted with caution because the number of subjects belonging in racial groups other than whites or blacks/African American or subjects with Hispanic/Latino ethnicity were underrepresented, subgroup analyses by race and ethnicity for study PSC16 might be less informative. This is acceptable. The number of subjects experiencing at least one SAE after vaccination was 2.5% among subjects 50-64 years of age, 3.7% among subjects 65-74 years of age, 4.6% among subjects ≥65 years of age and 6.7% among subjects ≥75 years of age. The incidence of SAE was comparable in the age categories of both vaccine groups (RIV4 and IIV4). As expected, the incidence of SAE tended to increase with age. The number of subjects with at least one SAE was slightly higher in male subjects (4%) compared to female subjects (2.9%) in the RIV4 arm. In subjects vaccinated with IIV4, the incidence of SAE was comparable between male and female subjects (3% in both groups). The number of subjects with at least one SAE were slightly lower in Caucasian/white subjects (3.3%) compared to blacks/African American (3.9%). Subgroup analysis by ethnicity showed a slightly higher incidence of SAE in non-Hispanic (3.4%) compared to Hispanic (2.4%) subjects vaccinated with RIV4. In subjects

vaccinated with IIV4, Hispanic subjects (5.5%) reported a higher incidence of at least one SAE compared to non-Hispanic (2.9%). Overall, no safety concerns arise from the provided data.

Trial PSC12

Overall, 145 (3.4%) and 132 (3.0%) of the 4,328 and 4,344 subjects of the safety population in the RIV4 and the IIV4 vaccine group of trials PSC12 recorded SAEs during the 6-months follow-up period.

Trial PSC16

Overall, 15 SAEs were reported from 10 out of 998 subjects (1.0%) in the safety population of the RIV 4 vaccine group, and from 2 out of 332 subjects (0.6%) in the safety population of the IIV4 vaccine group, during the 6-months follow-up period in trial PSC16.

Deaths

Overall, 20 deaths were recorded throughout the duration of trial PSC12; 8 in the RIV4 and 12 in the IIV4 vaccine group. None of the deaths were considered being vaccine related. There were no deaths reported throughout the duration of trial PSC16.

Medically-attended adverse events (MAEs)

Among elderly, MAEs reported throughout the study period of 6 months were 17.9% in the RIV4 and 18.1% in the IIV4 treatment arm. The most commonly reported MAEs were in the SOCs "Infections and Infestations" (8.45% RIV4 and 8.2% IIV4), "Respiratory, thoracic and mediastinal disorders" (2.5% RIV4 and 2.6% IIV4), "General disorders and administration site conditions" (2.4% RIV4 and 2.7% IIV4), "Musculoskeletal and connective tissue disorders" (2.2% RIV4 and 2.3% IIV4) and "Injury, poisoning and procedural complications" (2.1% RIV4 and 1.9% IIV4). Within these categories, the specific preferred terms of respiratory infection, sinusitis, bronchitis, cough and influenza-like illness were reported by ≥1% of subjects. The frequency of MAEs reported within 28 days post-vaccination was 4.8% in the RIV4 and 5.4% in the IIV4 treatment arm and was almost balanced between the vaccine groups. The incidence of vaccine-related MAEs was 0.5% in both treatment groups.

In study PSC12, the applicant stated that treatment related MAEs were reported from 774 (17.9%) and 785 (18.1%) subjects in the RIV4 and IIV4 groups, respectively. However, the incidence of vaccine-related MAEs was 0.5% in both treatment groups. The data provided show that the most frequently reported MAEs were in the SOCs "Infections and infestations" (0.3% RIV4 and 0.2% IIV4) and "Respiratory tract infection and mediastinal disorders" (0.1% RIV4 and 0.2% IIV4). Within these SOCs, no noteworthy differences were observed in any of the preferred terms. Most of the MAEs were reported in only one or two subjects. The only MAEs that were reported from ≥2 subjects in either treatment group were upper respiratory infection, bronchitis and cough.

Overall, the incidence of vaccine-related MAEs was low in study PSC12 and no noteworthy difference was observed in any of the preferred terms between the vaccine groups.

In study PSC16, MAEs reported throughout the study period of 6 months were 8.0% in the RIV4 and 7.2% in the IIV4 group. The most frequently reported MAEs were in the SOCs "Infections and infestations" (3.5% RIV4 and 3.9% IIV4), "Injury, poisoning and procedural complications" (0.8% RIV4 and 0.3% IIV4) and "Respiratory tract infection and mediastinal disorders" (0.8% RIV4 and 0.6% IIV4). Within these SOCs no noteworthy difference was observed in any of the preferred terms. However, an imbalance has been observed in the SOC "Pregnancy and puerperium and perinatal conditions" (0.6% RIV4 versus 0% IIV4) with a notable difference in pregnancies reported for 0.5% (5 subjects) in the RIV4 arm compared to no pregnancy reported in the IIV4 arm (please refer to section Safety in Special Population). Within all other reported SOCs, the only MAE that was reported from

≥1% of subjects in a treatment group was sinusitis, reported from 1.5% IIV4 recipients. No MAE was reported by ≥1% of subjects in the RIV4 group. The frequency of MAEs reported within 28 days post-vaccination was 3.8% in the RIV4 and 3.3% in the IIV4 treatment arm. The incidence of vaccine-related MAEs in study PSC16 was 0.2% in the RIV4 and 0.6% in the IIV4 group. The data show that treatment-related MAEs were only reported in the SOCs "Infections and infestations" (0.2% RIV4 and 0.3% IIV4) and "Skin and subcutaneous tissue disorders" (0.0% RIV4 and 0.3% IIV4). Within these SOCs, each preferred term was reported by one subject each. The incidence of vaccine-related MAEs was low in study PSC16 and did not raise any safety concerns.

The incidence of MEAs increased with age (15.3% in subjects aged 50 - 64 years of age, 20.3% in subjects 65 - 74% and 24.6% in subjects ≥75 years of age). Slightly higher incidence of MAEs were reported in female subjects (19.9%) compared to male subjects (15.5%). Subpopulation analyses of SAEs by race and ethnicity revealed higher rates in whites as compared to blacks/African Americans and in non-Hispanic (18%) as compared to Hispanic (14.6%). It should be noted, that subgroup analyses by race and ethnicity need to be interpreted with caution because the number of subjects belonging in racial groups other than whites or blacks/African American or subjects with Hispanic/Latino ethnicity were underrepresented.

Laboratory findings

No routine safety laboratory testing was specified.

Safety in special populations

Pregnancy and lactation

The use of RIV4 during pregnancy has not been studied. Pregnant women were excluded from clinical study trial PSC12, and PSC16 only included individuals ≥50 years.

Post-marketing data for use of the recombinant influenza vaccines RIV3 and RIV4 during pregnancy in the USA are available from 2013/14 through 2017/18 for RIV3 and since 2017/18 for RIV4. Data are limited to reports of pregnancies occurring incidentally during clinical trials, VAERS (Vaccine Adverse Event Reporting System) reports, and pregnancy registry reports. Overall, 29 pregnancy cases are present in Sanofi pharmacovigilance database. For 20 cases the outcome is unknown, one miscarriage, one abortion, and 7 live births were recorded. In a program conducted by Center for vaccine Equity at the Task Force for Global Health, 40,000 doses of RIV3 were donated for influenza vaccine coverage in Mongolia. 333 pregnant women received RIV3. No serious AEs were reported from the passive surveillance network. No active follow-up of pregnancies has been performed, and the capability of Mongolian surveillance network to capture the pregnancy related AE are uncertain. During the clinical development of the RIV3 (PSC01 trial), three pregnancies were reported, two of these subjects reported elective termination while the third subject had an uneventful term pregnancy. In PSC04 study involving RIV3, 20 pregnancies were reported with 12 live births, one spontaneous abortion, two elective abortions, and five cases were lost to follow-up. The data do not raise safety concerns, but are overall too limited for final conclusion. The limited experience with the use of RIV4 during pregnancy is adequately reflected in the SmPC. The routine pharmacovigilance activities include an observational study (VAP00007) to address the missing information regarding use of RIV4 during pregnancy.

Paediatric population

The intended indication is active immunization for use in persons 18 years of age and older for the prevention of influenza disease. The company conducted a clinical trial to evaluate safety, reactogenicity, and immunogenicity of RIV compared with IIV4 in the paediatric population from 6 to

less than 18 years of age (PSC08). This study was conducted during the 2013/2014 northern hemisphere influenza season and completed on 28 July 2014, but is not included into the application dossier. Two other studies are not finalised yet, i.e. LIO-04-16 (completion due June 2020) and VAP0004 (completion due).

Immunological events

Events possibly reflecting hypersensitivity were identified to be of interest since commercialisation of Flublok, the trivalent formulation of RIV4. As with most vaccines, inactivated influenza vaccines are associated with a risk of serious allergic reactions. Anaphylaxis and reactions related to hypersensitivity have been reported in the post-marketing experience with RIV4. In trial PSC12 events potentially reflecting hypersensitivity were recorded infrequently and were balanced between the two vaccine groups. The most frequently recorded event potentially representing hypersensitivity was mild wheezing in 0.4% (16) versus 0.5% (22) of subjects in the RIV4 and the IIV4 vaccine group. 4 cases of hypersensitivity occurred in trial PSC12, 1 in the RIV4 and 3 in the IIV4 group. The one event of hypersensitivity in the RIV4 vaccine group was considered unrelated to the vaccine. The applicant states that no subject in study PSC16 reported an AE of anaphylaxis or other hypersensitivity events. AEs that may represent hypersensitivity reactions (e.g. rash and pruritus) were reported in subjects exposed to RIV4 within a few days following vaccination. The applicant provided a comparative table for study PSC16 showing unsolicited related and not related AEs suggesting allergic reactions. The AEs of anaphylaxis or other hypersensitivity events included pruritus, rash and dermatitis. Although the incidences of these events were rare, they were only reported in subjects vaccinated with RIV4. None of these events was reported in subjects vaccinated with IIV4. However, the AEs of pruritus, dermatitis and rash are adequately reflected in the tabulated list of AEs in section 4.8 of the updated SmPC.

Safety related to drug-drug interactions and other interactions

No interaction studies were performed for RIV4.

Discontinuation due to adverse events

The incidence of AEs leading to discontinuation was comparable in the two vaccine groups in trial PSC12 (10 cases in RIV4 group and 12 cases in IIV4 group). Overall, 20 subjects 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 subjects were discontinued due to AEs (general and psychiatric disorders) in the RIV4 group.

No subject discontinued due an AE in study PSC16.

Post marketing experience

The first marketing authorisation for the trivalent formulation of the recombinant haemagglutinin influenza vaccine (RIV3), produced within the same manufacturing process like the quadrivalent formulation RIV4, was obtained tin the USA on 16 January 2013. The RIV3 vaccine was discontinued as of March 2018 and is no longer marketed in the USA. RIV4 was licensed under the tradename Flublok Quadrivalent in the USA on 07 October 2016.

Cumulatively up to 15 January 2020, there has been no cases from post-marketing experience reporting fatal events involving RIV3 or RIV4. The total number of recorded AEs was 983 for RIV4 and 672 for RIV3. For RIV4 the AE with the highest reporting incidences were related to product use, i.e. "product administered to patient of inappropriate age" (223 events/reporting rate 2.4.2/100.000), followed by "product storage error" and "wrong product administered" (61 and 53 events, reporting rates 0.3 and 0.55, respectively). This is followed by pain, headache, pruritus, and rash with reporting rates of 0.37, 0.22, 018, and 0.15 per 100,000.

Overall, 15 SAEs RIV4 were recorded for RIV4 post licensure. This includes two cases of Guillain-Barre and one case of Steven-Johnson syndrome. The case of Steven-Johnson syndrome involves a 69 year old female who received RIV4 on 18-Oct-2019. On 26-Oct- 2019, 8 days post vaccination, patient developed unknown symptoms (not reported) and on 30- Oct-2019 the patient was diagnosed with Steven Johnson's syndrome. Co-medication included lisinopril and atorvastatin. Patient's medical history, medical condition at time of product use and laboratory test results were not reported. Steven-Johnson-syndrome is included as an AE in the SmPC of atorvastatin. Because of missing information and the co-medication a definitive conclusion of causality is not possible. In the two cases of GBS time to onset after vaccination is compatible with the role of the vaccine. The medical information is not sufficient to draw a final conclusion. GBS is a known potential risk for influenza vaccines (class risk). Both Steven-Johnson-syndrome and GBS will be followed up within the routine pharmacovigilance.

Three cluster cases of neuropathy, all from the same reporter were submitted. The cases involved three female vaccines who experience neuropathy on arm 14 days post vaccination with RIV4. From the available clinical data it is not known whether neuropathy occurred in the arm were the vaccine has been administered. For none of the three cases further clinical information is available, the symptoms were not described. In summary, it remains unclear what symptoms the females experienced. A causality assessment is not possible from the submitted information.

Two case of anaphylactic reaction were recorded, one occurred 5 minutes after vaccination and another with unknown time to onset. The first anaphylactic reactions was experienced by a female with knowns allergies who had been getting "mild hives" on her jawline, and couldn't determine what they were from, and was taking a preventative tablet of Benadryl each day. Vaccine causality cannot be ruled out. The second case cannot be assessed due to missing date of onset and missing clinical information. Anaphylactic reaction are described for vaccines and are included into the Supemtek SmPC with a frequency "not known".

In the majority of cases (beside the one with missing information on time to onset) a temporally association is given. A lack of medical information and co-medication do not allow a final causality assessment of the SAEs. Safety evaluation of Supemtek will be performed within routine pharmacovigilance. Since, a clear causality cannot be established from the clinical data available from the SAE narratives it is not considered appropriate to include any of the events into the SmPC.

2.6.1. Discussion on clinical safety

Supemtek (RIV4) is a quadrivalent recombinant influenza vaccine that contains a higher haemagglutinin antigen content (45 µg per antigen) than other licensed quadrivalent standard dose influenza vaccines (15 µg per antigen). RIV4 is licensed in the USA since 2016 for use in adults. The manufacturing process of RIV4 is based on the same as was used for the trivalent recombinant influenza vaccine, that was formerly licensed in the USA, with the addition of another B strain. The clinical trial program to support the licensure of RIV4 in the EU includes two pivotal and one supportive trial. In the two pivotal trials (PSC12 and PSC16), the safety and reactogenicity of RIV4 was compared with a licensed egg-based IIV4 (Fluarix Tetra), that contains 15 µg antigen per strain. The comparator

is considered acceptable. Both pivotal trials were conducted in the USA, which is also deemed acceptable.

Study PSC04, used as supportive in the context of this application, was conducted with RIV3 and designed with the primary object of evaluating the efficacy, relative to placebo, of a single dose of RIV3 in a population of healthy adults aged 18-49 years. This study is considered of less relevance for the evaluation of safety of the quadrivalent product.

The study population in both pivotal trials included ambulatory and medically stable adults ≥50 years of age (trial PSC12) or 18-49 years of age (trial PSC16) without contraindication to the vaccines and who did not have underlying conditions that might complicate the evaluation of the primary endpoints.

The safety database is considered sufficient for the licensure of RIV4. A total of 5,326 subjects received one dose of RIV4 in the two pivotal trials, i.e. 998 adults 18 to 49 years of age in trial PSC16, and 4,328 adults ≥50 years of age in study PSC12. The safety population of RIV4 included 2,569 individuals 50-64 years of age, 1,234 individuals 65 to 74 years, and 525 individuals ≥75 years of age. Local and systemic reactogenicity was comparable between RIV4 and the comparator vaccine group in trials PSC12 and PSC16. The majority of local and systemic solicited reactions were mild to moderate in both vaccine groups and both trials. The most frequently reported local solicited reaction in both vaccine groups was local tenderness, followed by local pain. The incidence of solicited systemic reactions was lower than the incidence of solicited local reactions in both vaccine groups and was comparable between the two groups, in both trials. The most frequently reported solicited systemic reactions in the RIV4 and the IIV4 vaccine group were fatigue and headache, followed by joint and muscle pain. Fever events were uncommon in both vaccine groups and both trials.

Differences in the frequency of solicited injection site reactions were observed in both trials related to gender, race, and ethnicity, and in trial PSC12 also related to age. Local reactogenicity occurred within the same range, but tended to be higher in females compared with males, in white subjects compared with non-white subjects, and in non-hispanic subjects compared with hispanic subjects. Reactogenicity tended to be also higher in younger individuals 50 to 64 years of age, compared with those older than 64 years of age. Like for solicited local reactions, demographic differences regarding solicited systemic reactogenicity were observed in both trials, but less notable. These effects are results of complex genetic, immunological, hormonal and environmental interactions and not yet entirely understood. A lower reactogenicity in elderly compared with younger individuals is well known for vaccines and associated with a lower immune response in the elderly caused by immunosenescence. Sex-based differences in vaccine response are also described in literature. Data about racial and ethnic disparity in vaccine immune response are limited, and underlying mechanisms and contributing factors are not well known. The demographic differences observed in the two trials were not large and were observed for both vaccines. They are not considered of clinical importance in any of the subgroups, regarding the reactogenicity profile and risk/benefit ratio of the product.

The safety profile of the two vaccines was comparable in the two trials. Frequency and nature of AEs was balanced between the two vaccine groups in both trials. In none of the two trials SAEs considered being vaccine related were recorded. However, the SAE of myocardial infarction was slightly more frequently reported in the RIV4 group compared to the IIV4 arm. All subjects who suffered from MI in study PSC12 (4 subjects in RIV4 and 3 subjects in IIV4) had comorbidities that are associated with increased risk for cardiovascular events including increased age, hypertension, hyperlipidemia, hypercholesterolemia and/or diabetes mellitus and thus reflect a population of high risk of MI. However, in study PSC16 the subjects (2 subjects in RIV4 and none in IIV4) who suffered from MI were <45 years of age (37 and 44 years of age). The 44-year old subject had comorbidities of hypertriglyceridemia (since 2012) and diabetes mellitus type II (since 2011) which are associated with an increased risk for cardiovascular events. The 37-year old subject who suffered from myocardial

infarction on day 88 received concomitant medications of steroid injections (since 01 May 2012), tramadol (since 06 January 2014) and Flexeril (since 06 July 2014). Cyclobenzaprine (Flexeril) is closely related to tricyclic antidepressants which are known to produce arrhythmias, sinus tachycardia, prolongation of conduction time leading to myocardial infarction and stroke. Considering the lack of temporal association as well as any additional inflammatory signs or symptoms indicating pathophysiology related to vaccination, it is agreed to that these events were judged as not related to the vaccination.

The use of RIV4 during pregnancy has not been studied. A high level summary of post-marketing experience with RIV3 and RIV4 from the use in the USA has been submitted within RMP and in the summary of clinical safety. Also a high level summary of pregnancy outcomes from trial PSC16 was provided. The pregnancy data are overall too limited for a final conclusion. The limited experience with the use of RIV4 during pregnancy is adequately reflected in the SmPC. An observational study (VAP00007) will be conducted after licensure. The objective of this Phase IV study is to estimate the relative vaccine effectiveness of RIV4 versus a standard dose inactivated influenza vaccine against all PCR-confirmed influenza in vaccinees aged 18–64 years. Safety data from the pregnancy effectiveness study will be reported, as per the legislation, as part of the post-marketing data with potential impact on the R/B balance, in the PSURs, if they will result in meaningful safety data.

Indication is only sought for the adult population. The company conducted a clinical trial to evaluate safety, reactogenicity, and immunogenicity of RIV4 compared with IIV4 in the paediatric population from 6 to less than 18 years of age (PSC08). This study was conducted during the 2013/2014 northern hemisphere influenza season and completed on 28 July 2014, but is not included into the application dossier. Two other studies, i.e. LIO-04-16 (completion due June 2020) and VAP0004 (completion due) are not finalised yet.

In general, the methodology for collecting safety data is deemed acceptable. The submitted clinical safety data overall indicate an acceptable reactogenicity and safety profile for RIV4.

2.6.2. Conclusions on the clinical safety

The submitted clinical safety data overall indicate an acceptable reactogenicity and safety profile for Supemtek, the recombinant quadrivalent influenza vaccine. RIV4 was not more reactogenic than IIV4, though the antigen content in RIV4 is higher. No safety concerns or major safety objections could be identified.

The safety profile of RIV4 will be further characterised through post-marketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to adverse events and signal detection.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Not applicable

Pharmacovigilance plan

Development of Robust Innovative Vaccine Effectiveness (DRIVE)

Purpose of the study:

Objectives is to measure season IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type (e.g. by antigen preparation strategy, number of virus strains, adjuvant,) then by overall influenza vaccination. To comply with the Guideline on Influenza vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) of July 2016, a supporting IMI (Innovative Medicines Initiative) program called on DRIVE. DRIVE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific influenza vaccine effectiveness data in Europe.

VAP00003: Examining vaccine effectiveness (VE) of RIV4 relative to standard dose inactivated influenza vaccine among Kaiser Permanente Northern California members aged 18-64 years

Purpose of the study: To estimate the rVE of RIV4 versus SD-IIV against all PCR-confirmed influenza in vaccinees aged 18–64 years, this study will compare the incidence of PCR-confirmed influenza and various hospitalization definitions among RIV4 vaccinees versus SD-IIV vaccinees. The primary comparison will be focused on adults aged 50–64 years at KPNC during the 2018–2019 and 2019–2020 influenza seasons. All adults aged 18–64 years will also be assessed for both influenza seasons.

Risk minimisation measures

Not applicable.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16.01.2013. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points. The PSUR cycle will be yearly.

2.9. New Active Substance

The applicant declared that quadrivalent influenza virus haemagglutinin has been previously authorised in a medicinal product in the European Union but differs significantly with regard to safety and/or efficacy due to differences in molecular structure, nature of the source material or manufacturing process.

The CHMP considers that, based on the available quality and clinical data, recombinant influenza A/H3N2 virus haemagglutinin is considered to be a new active substance as it differs significantly in properties with regard to safety and efficacy from other influenza H3N2 virus haemagglutinin contained in medicinal products previously authorised within the European Union due to differences in molecular structure, nature of the source material or manufacturing process.

The applicant claims that the improved efficacy seen against H3N2 is truly attributable to different HA glycosylation. Most probably, the higher efficacy against H3N2 is rather because the HA is expressed in insect cells and is therefore less prone to acquiring mutations during production and therefore simply better matches circulating strains (including drift variants). The data revealing a better efficacy in elderly come from a H3N2-dominated season (2014-2015, Dunkle et al., 2017) and are not representative for all four influenza strains included in the Supemtek vaccine. The same is true for the data referenced for the 2017-2018 season (Belongia et al., 2020). In the latter however a certain advantage in terms of immunogenicity for H3N2 strains is detectable in recipients of Supemtek as compared to other influenza vaccines that is even more pronounced for drifted viral strains.

From a safety perspective, the recombinant influenza virus haemagglutinin within Supemtek show a better safety profile than conventional split and subunit vaccines due to differences in the nature of source material and manufacturing process (e.g. no exposure to inactivation agents, absence of micro-aggregates or viral RNA fragments in combination with lipids).

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Supemtek (Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture)) is included in the additional monitoring list as it is a biological medicine, such as a vaccine or a medicine derived from plasma (blood), authorised in the EU after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the northern hemisphere (NH) and southern hemisphere (SH). The influenza virus is transmitted by respiratory droplets or aerosols containing the influenza virus particles and subsequent inhalation of infectious particles or self-inoculation from a contaminated surface. Clinical manifestation of influenza virus infection is characterised by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis.

Some individuals are more prone than others to develop complications from influenza, e.g. bacterial pneumonia or other organ dysfunction. Severe influenza and complicated influenza potentially leading to hospitalisation and death are more likely to occur in vulnerable populations, such as older people (≥ 65 years of age, in part due to the age related decline of the immune response (immunosenescence)), pregnant women, younger children (especially up to 24 months of age), and patients with chronic underlying diseases. These groups are considered at risk and represent the priority target for influenza vaccination programmes in the EU.

3.1.2. Available therapies

Vaccination is considered the best approach to lower the burden of influenza disease. Different seasonal inactivated (split virion or subunit) influenza vaccines (quadrivalent and trivalent) are licensed for children aged 6 months and older, adolescents and adults, as well as a Live Attenuated Influenza Vaccine licensed for children and adolescents aged 2 years to 17 years.

Differences between the circulating strains and those included in the vaccine as a result of antigenic drift poses another key challenge for conventional influenza vaccines as it decreases vaccine efficacy. This is particularly relevant since A/H3N2 shows a high rate of evolution among the influenza subtypes currently circulating with antigenically distinct strains emerging on average every 2 to 5 years.

In elderly, immune responses against conventional (trivalent) inactivated influenza vaccines has been shown to be lower than in younger adults due to immunosenescence. In line with this, clinical vaccine efficacy estimates were lower in older adults (17% to 53 %) as compared to younger adults (70% to 90%) (Goodwin et al. 2006). Therefore, there is a need for improved influenza vaccines for these age groups, i.e. children and elderly.

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.

3.1.3. Main clinical studies

Supemtek clinical development presented three phase III studies (PSC12, PSC16, PSC04) to be used to support the effective use of RIV4 in subjects 18 years of age and older for the present application. PSC12 and PSC16 were pivotal studies that were run with RIV4 in older adults ≥50 years and young adults 18 to 49 years of age, respectively, to demonstrate vaccine efficacy and immunogenicity of RIV4, whereas PSC04 was a supportive study conducted with RIV3 to establish vaccine efficacy in young healthy adults from 18 to 49 years of age.

The pivotal PSC12 trial 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 (N=8,963); the primary objective was to demonstrate the non-inferior efficacy of one single IM dose of RIV4 compared to a US and EU-licensed IIV4. The second pivotal study 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 (N=1,350); the primary objective was to demonstrate non-inferior immunogenicity of RIV4 compared to IIV4 for each vaccine strain. The supportive PSC04 was a randomised observer-blind placebo-controlled multicentre study of immunogenicity, safety, reactogenicity, efficacy, effectiveness and lot consistency of RIV3 in healthy adults 18 to 49 years of age (N=4,648).

The virus strains selected for the RIV4 and the RIV3 were in compliance with the seasonal influenza WHO recommendations for influenza vaccine strains chosen for each influenza seasons.

3.2. Favourable effects

In PSC12, the preventative efficacy of RIV4 following single 0.5 mL IM dose administration is evident by demonstrating statistically non-inferior to that of IIV4 in medically stable adults ≥50 years of age. The overall rVE against rtPCR-positive protocol-defined ILI due to any strain in per protocol population was 30% (95%CI: 10%, 47%). rVE persisted for at least 6 months.

This treatment effect was confirmed by a key secondary endpoint (culture confirmed ILI according to CDC ILI definition) and a post-hoc exploratory endpoint based on all culture-confirmed influenza.

In exploratory analysis of PSC12 using subjects having not received influenza vaccines in the prior season, a greater treatment effect than reported in the primary efficacy analysis was shown.

Further post-hoc analysis showed that the demonstrated rVE was primarily attributable to the predominant efficacy of RIV4 against influenza A strains, mostly A/H3. Whereas against influenza B strains, only the same attack rates in RIV4 recipients and IIV4 recipients were observed.

Because the rVE lower bound of 95%CI was >9% - a criterion for superiority test (exploratory analysis), the applicant concluded that this exploratory efficacy endpoint was met.

Immunogenicity data are available in a subset (about 7% or n~300 in each arm) of subjects from trial PSC12. The post-vaccination HAI GMTs among RIV4 recipients showed non-inferiority according to CBER guidance for three of the four antigens (A/H1N1, A/H3N2 and B/Yamagata). The GMT ratio's between RIV4 and IIV4 were 1.15 (95%CI: 0.95, 1.41), 0.69 (95%CI: 0.58, 0.82) and 1.04 (95%CI: 0.86, 1.24) for the A/H1N1, A/H3N2 and B/Yamagata strains respectively. Seroconversion rates (SCR) induced by RIV4 were non-inferior to those in the IIV4 group for the strains A/H3N2 and B/Yamagata. The difference in SCR was -11.2% (95% CI: -19.0, -3.3) and -0.6% (95% CI: -8.2, 7.2) for A/H3N2 and B/Yamagata, respectively.

Overall, one 0.5 mL IM dose of RIV4 is demonstrated immunogenic for each vaccine strain in subjects ≥50 years of age, where RIV4 induced more robust HAI response to A/H3 strain but blunted HAI

response to influenza B strains. This immunogenicity profile of RIV4 is consistent with demonstrated efficacy of this vaccine in PSC12.

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 and non-inferiority according to CBER criteria could be shown for both A strains as well as for B/Yamagata. The GMT ratios 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), -15.2% (95% CI: -21.3, -9.1) and 0.7% (95% CI: -5.4, 6.9) for A/H1N1, A/H3N2 and B/Yamagata, respectively.

In PSC04 conducted in healthy adults aged 18 to 49 years, one single 0.5 mL IM dose of RIV3 is demonstrated efficacious in preventing against the culture positive CDC-ILI due to any strain, with rVE estimated at 44.6% (95%CI: 18.8, 62.6) in the ITT population in an exploratory analysis. This effect was revealed to be primarily ascribed to the apparent efficacy against influenza A strains.

Data from immunogenicity subset of PSC04 demonstrate that RIV3 is immunogenic for each vaccine strain and that SCRs and SPRs induced by single dose of RIV3 met CBER criteria.

3.3. Uncertainties and limitations about favourable effects

Against influenza B strains, rVE of RIV4 relative to IIV4 has not been demonstrated in PSC12, and the same holds for RIV3 relative to saline placebo in PSC04. However, the same attack rates of influenza B strains observed in the RIV4 vs IIV4 recipients of PSC12 study may suggest similar efficacy of the two vaccines. In PSC04 supportive study, a trend towards cross-protective efficacy of RIV3 (containing A/H3, A/H1, and B/Victoria vaccine strain) against influenza B/Yamagata strain was suggested by the reduced number of influenza B cases in the RIV3 vs placebo recipients. This sign of evidence for cross-protection between influenza B strains observed in PSC04 suggests that RIV4 may be effective against B/Victoria strain.

In study PSC16, the results for the B/Victoria strain 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. Antibody titres are only surrogates for clinical efficacy and the clinical relevance of this difference is unknown. Haemagglutinin assays may produce a different readout for an egg-derived versus a recombinant antigen, but it is of concern, that immunogenicity data consistently cannot demonstrate non-inferiority for B/Victoria, while for B/Yamagata no such issue is evident. The uncertainty of immunogenicity related to B/Victoria strain has not been explicitly addressed by the clinical efficacy data provided in this dossier, as no conclusive vaccine efficacy for B/Victoria could be shown in trial PSC12. It should however be noted that PSC12 study was not designed with adequate power to demonstrate non-inferior efficacy of RIV4 vs IIV4 against each individual strain.

On subgroup analysis, the effect size seen in primary analysis of PSC12 was not reproduced in subjects ≥65 years of age or subjects having received influenza vaccines in the prior season. It remains an open question whether the >9% of rVE with 95%CI observed for RIV4 over IIV4 could hold in subjects with chronic medical conditions or in influenza seasons with good antigenic match and apparent mismatch of A/H3 strain.

3.4. Unfavourable effects

The local and systemic reactions recorded for both vaccines are not unexpected for influenza vaccines regarding nature, frequency and severity. The reactogenicity of RIV4 was comparable to the reactogenicity of the comparator. The most frequently reported local solicited reaction in both vaccine groups was local tenderness, followed by local pain. The majority of local solicited reactions were mild to moderate in both vaccine groups. The most frequently reported systemic symptoms were fatigue, headache, joint and muscle pain in both vaccine groups.

3.5. Uncertainties and limitations about unfavourable effects

Demographic differences in the frequency of solicited injection site reactions were observed in both trials, and in both vaccine groups related to gender, age, race, and ethnicity. In both trials and both vaccine groups, reactogenicity events tended to be more frequently reported by females compared with males, by white subjects compared with non-white subjects, and by non-hispanic subjects compared with hispanic subjects. Reactogenicity tended also to be higher in individuals 50 to 64 years of age, compared in those older than 64 years of age. It should be noted that, though the frequency tended to be higher, the events occurred within the same range. This observation is a result of complex genetic, immunological, hormonal and environmental interactions and not yet entirely understood. However, a lower reactogenicity in elderly compared with younger individuals is well known for vaccines and associated with a lower immune response in the elderly caused by immune-senescence.

Data including the frequency of treatment related MAEs experienced by at least one subject in PSC12 in both treatment groups was provided. The treatment related MAEs were reported from 774 (17.9%) and 785 (18.1%) subjects in the RIV4 and IIV4 groups, respectively. However, the incidence of vaccine-related MAEs was 0.5% in both treatment groups. The most frequently reported MAEs were in the SOCs "Infections and infestations" (0.3% RIV4 and 0.2% IIV4) and "Respiratory tract infection and mediastinal disorders" (0.1% RIV4 and 0.2% IIV4). Within these SOCs, no noteworthy differences were observed in any of the preferred terms. Most of the MAEs were reported in only one or two subjects. The only MAEs that were reported from ≥ 2 subjects in either treatment group were upper respiratory infection, bronchitis and cough. Overall, the incidence of vaccine-related MAEs was low in study PSC12 and no noteworthy difference was observed in any of the preferred terms between the vaccine groups. The applicant clarified that the incidence of vaccine-related MAEs in study PSC16 was 0.2% in the RIV4 and 0.6% in the IIV4 group. The treatment-related MAEs were only reported in the SOCs "Infections and infestations" (0.2% RIV4 and 0.3% IIV4) and "Skin and subcutaneous tissue disorders" (0.0% RIV4 and 0.3% IIV4). Within these SOCs, each preferred term was reported by one subject each. The incidence of vaccine-related MAEs was low in study PSC16 and did not raise any safety concerns.

In relation to age strata, the number of subjects experiencing at least one SAE after vaccination was 2.5% among subjects 50-64 years of age, 3.7% among subjects 65-74 years of age, 4.6% among subjects ≥65 years of age and 6.7% among subjects ≥75 years of age. The incidence of SAE was comparable in the age categories of both vaccine groups (RIV4 and IIV4). As expected, the incidence of SAE tended to increase with age. The number of subjects with at least one SAE was slightly higher in male subjects (4%) compared to female subjects (2.9%) in the RIV4 arm. In subjects vaccinated with IIV4, the incidence of SAE was comparable between male and female subjects (3% in both groups). The number of subjects with at least one SAE were slightly lower in Caucasian/white subjects (3.3%) compared to blacks/African American (3.9%). Subgroup analysis by ethnicity showed a slightly higher incidence of SAE in non-Hispanic (3.4%) compared to Hispanic (2.4%) subjects vaccinated with

RIV4. In subjects vaccinated with IIV4, Hispanic subjects (5.5%) reported a higher incidence of at least one SAE compared to non-Hispanic (2.9%).

The incidence of MEAs increased with age (15.3% in subjects aged 50 - 64 years of age, 20.3% in subjects 65 - 74% and 24.6% in subjects ≥75 years of age). Slightly higher incidence of MAEs were reported in female subjects (19.9%) compared to male subjects (15.5%). Subpopulation analyses of SAEs by race and ethnicity revealed higher rates in whites as compared to blacks/African Americans and in non-Hispanic (18%) as compared to Hispanic (14.6%).

Overall, no safety concerns arise from the provided data. It has to be noted that the requested subgroup analyses for SAE and MAE have only been provided for study PSC12 and not for study PSC16 conducted in adults 18 to 49 years of age. However, considering that subgroup analyses by race and ethnicity need to be interpreted with caution because the number of subjects belonging in racial groups other than whites or blacks/African American or subjects with Hispanic/Latino ethnicity were underrepresented in these studies, subgroup analyses by race and ethnicity for study PSC16 might be less informative.

The SAE of myocardial infarction (MI) was slightly more frequently reported in the RIV4 group compared to the IIV4 arm. Elderly subjects who suffered from MI had comorbidities that are associated with increased risk for cardiovascular events including increased age, hypertension, hyperlipidemia, hypercholesterolemia and/or diabetes mellitus and thus reflect a population of high risk of MI. However, in study PSC16 conducted in adults 18 to 49 years of age two subjects treated with RIV4 suffered from MI. Both subjects were <45 years of age (37 and 44 years of age) and did not have any medical history that might be associated with an increased risk for cardiovascular events. The 44-year old subject who suffered from myocardial infarction on day 146 had comorbidities of hypertriglyceridemia (since 2012) and diabetes mellitus type II (since 2011) which are associated with an increased risk for cardiovascular events. Considering the lack of temporal association, any additional inflammatory signs or symptoms indicating pathophysiology related to vaccination as well as the reported comorbid conditions of hypertriglyceridemia and type II diabetes mellitus, it is agreed to judge the event as not related to the vaccination. The 37-year old subject who suffered from myocardial infarction on day 88 received concomitant medications of steroid injections (since 01 May 2012), tramadol (since 06 January 2014) and Flexeril (since 06 July 2014). Cyclobenzaprine (Flexeril) is closely related to tricyclic antidepressants which are known to produce arrhythmias, sinus tachycardia, prolongation of conduction time leading to myocardial infarction and stroke. Although causal relationship between Flexeril (cyclobenzaprine) and the occurrence of cardiovascular events including myocardial infarction could not be established (causal relationship unknown), it is contraindicated in the acute recovery phase of myocardial infarction and patients with arrhythmias, heart block or conduction disturbance or congestive heart failure due the potential side effect on the heart. Additionally, as no other inflammatory pathophysiology have been reported as well as considering no temporal relationship it is also for the second case agreed to judge it as not related to the vaccine.

3.6. Effects Table

Table 28 Effects Table for Supemtek-indicated for active immunization for the prevention of influenza disease in adults

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Relative vaccine efficacy, rVE	rtPCR-positive protocol-defined ILIs due to any strain that began ≥ 14 days after vaccination among the vaccinees who adhered to protocol	%	RIV4	IIV4	Primary endpoint was formally powered. The pre-specified non-inferiority criterion for low bound of 95%CI around rVE of greater than -20% was met.	PSC12
			rVE: +30% 95%CI: +10, 47%			
	rtPCR-positive CDC-ILIs	%	rVE: +32% 95%CI: +8, 54%		Secondary endpoint, not formally powered	PSC12
	rtPCR-positive influenza A/H3	%	rVE: +36% 95%CI: +14, 53%		*Post-hoc*	PSC12 and 2.7.3
Immuno-genicity in subjects 18 – 49 YoA	Non-inferior immunogenicity of RIV4 to IIV4 on D28 by means of seroconversion rate (%) difference ⩽10 and GMT ratio ⩽1.5	CBER criteria: Upper bound of 95% CIs ⩽ 10 and ⩽ 1.5, resp.	RIV4	IIV4	N=969 (RIV4) and 323 (IIV4), Non-Inferiority met in 3 of 4 strains, except for B/Victoria (B/Brisbane/60/2008) with weak immunogenicity in both vaccines, primary objective (all 4 strains non-inferior) formally failed. Immunogenicity generally higher than in immunogenicity subset of PSC12 --> efficacy assumable, age-related immunogenicity. Persistence data >D28 lacking; HAI assay test antigen egg-derived.	PSC16
			Seroconversion rate(%)-Difference (95%-CI) D28: 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 D28: A/H1N1: 407 / 502 A/H3N2: 385 / 757 B/Yam: 136 / 159 B/Vic: 64 /43 GMT ratio (95%-CI) D28: 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)			
Unfavourable Effects						
	Solicited AE	%	RIV4	IIV4		
Local pain		%	18.9 36.8	22.0 36.4	The majority of solicited local reactions were mild to moderate. Reactogenicity tended to be higher in younger subjects. Differences in the frequency of solicited injection site reactions were observed in both trials related to gender, race, and ethnicity. This observation not yet entirely understood.	PSC12 PSC16
Local tenderness		%	34.3 48.0	37.1 46.7		PSC12 PSC16
fatigue		%	12.2 16.5	12.1 16.6		PSC12 PSC16
headache		%	12.7 20.3	13.5 21.1		PSC12 PSC16
Joint pain		%	7.5 9.5	8.0 10.2		PSC12 PSC16
Muscle pain		%	8.5 12.8	8.8 11.7		PSC12 PSC16

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important favourable effect is the clinical efficacy of RIV4 in the older medically stable adult subjects ≥50 years of age. The rVE of RIV4 was demonstrated statistically non-inferior to that of a US and EU-licensed standard dose of IIV4 in preventing against rtPCR-confirmed protocol-defined ILI. The overall rVE of RIV4 vs IIV4 in the efficacy population was estimated at 30% (95%CI: 10, 47%), which was primarily attributable to the predominant efficacy against influenza A strains, especially A/H3N2 strain. RIV4 is able to induce HAI response to each vaccine strain after one 0.5 mL IM dose of administration. Further favourable effect is clinical efficacy of RIV3 in healthy adults 18 to 49 years of age. RIV3 was 44.6% (95%CI: 18.8, 62.6) effective, relative to placebo, in the ITT population, in preventing against the culture positive CDC-ILI due to any strain. This effect was revealed to be primarily ascribed to its apparent efficacy against influenza A strains.

For rVE against influenza B infection in PSC12, the confidence intervals were extremely wide due to the low incidence of cases. More than 70% of circulating B strains in 2014/15 were of the B/Yamagata lineage, thus driving the B strain results. The non-inferiority of antibody titres against B/Yamagata could be replicated in both pivotal trials in comparison to an egg-derived licensed vaccine. Therefore, efficacy of Supemtek against infection with the B/Yamagata strain can be accepted despite the scarcity of provided data. However, clinical efficacy of Supemtek against the fourth strain included in the quadrivalent vaccine (B/Victoria) could neither be demonstrated by the clinical efficacy study PSC12 since the circulating strains did not include B/Victoria nor by immunogenicity data since this strain showed consistently inferior antibody levels. The available data raise considerable doubts that the B/Victoria component is adequately immunogenic. This concern is further aggravated by the evidence that the trivalent parent vaccine, FluBlok, which was never licensed in the EU, also could not elicit a substantial immune response against the B/Victoria in its clinical trials (as evidenced in the FDA Clinical Review from January 2013). Further data provided from two independent clinical trials showed that 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.

Vaccination was generally associated with a reactogenicity profile common to most vaccines. No safety concerns or major safety objections could be identified.

3.7.2. Balance of benefits and risks

Clinical benefit of RIV4 in the protection against influenza A and B/Yamagata lineage is demonstrated from the pivotal studies PSC12, PSC16 and supportive study PSC04. The concern of lack of demonstration of clinical protection against B/Victoria infection discussed in PSC12 was alleviated by further data demonstrating that 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.

The observed unfavourable effects were generally consistent with the nature and frequency of AEs expected after influenza vaccine administration and the multimorbidity of the investigated elderly population. Overall, the clinical benefit-risk balance of Supemtek is currently positive.

3.8. Conclusions

The overall B/R of Supemtek is positive.

4. Recommendations

Outcome

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:

> "Supemtek is indicated for active immunization for the prevention of influenza disease in adults.
>
> Supemtek should be used in accordance with official recommendations."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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.

Other conditions and requirements of the marketing authorisation

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

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

Not applicable.

New Active Substance Status

Based on the review of the available data, the CHMP considers that recombinant influenza A/H3N2 virus haemagglutinin is a new active substance as it differs significantly in properties with regard to safety and efficacy from other influenza A/H3N2 virus haemagglutinin contained in medicinal products previously authorised within the European Union due to differences in molecular structure, nature of the source material or manufacturing process.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0219/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.