

**EU-RISK MANAGEMENT PLAN FOR SUPEMTEK<sup>®</sup> TETRA/SUPEMTEK<sup>®</sup>  
(QUADRIVALENT INFLUENZA VACCINE/TRIVALENT INFLUENZA  
VACCINE [RECOMBINANT, PREPARED IN CELL CULTURE])**

<b>Risk Management Plan (RMP) Version number</b>	Version 2.1
<b>Data Lock Point (DLP)</b>	15-JAN-2024
<b>Date of final sign-off</b>	29-JAN-2025

**Table 1 - RMP version to be assessed as part of this application**

<b>Rationale for submitting an updated RMP</b>	<p>The Marketing Authorization Holder (MAH) finalized VAP00007, a phase IV, safety surveillance study to collect information regarding the use of Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4) in pregnant women and provides updated information on the vaccine use in pregnancy.</p> <p>Information on Trivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV3) is added to European Union (EU)-RMP due to the absence of detection of naturally occurring B/Yamagata-lineage viruses since 2020, the World Health Organization (WHO) and Food and Drug Administration (FDA)/Vaccines and Related Biological Products Advisory Committee (VRBPAC) have recommended removing a component from flu vaccines due to the no longer actively circulation of a family of viruses known as influenza B/Yamagata. RIV3 is approved for 2024-2025 season in United States (US) and will be submitted to approval in Europe.</p>
<b>Summary of significant changes in this RMP</b>	<ul style="list-style-type: none"> <li>• Added information on RIV3.</li> <li>• Update on VAP00007 study.</li> </ul>

EU: European Union; FDA: Food and Drug Administration; MAH: Marketing Authorization Holder; RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture); RMP: Risk Management Plan; US: United States; VRBPAC: Vaccines and Related Biological Products Advisory Committee; WHO: World Health Organization.

**Table 2 - Other RMP versions under evaluation**

RMP Version number	Submitted on	Submitted within
2.0	19-Dec-2024	Electronic Common Technical Document (e-CTD) sequence 0067 related sequence 0056 submitted on 19-Dec-2024 - response to questions - Grouping of a type II variation Extension of indication from 9 years of age (based on VAP00027 study data and results) and type II Variation Update of Paediatric section (based on VAP00026 study results)

e-CTD: Electronic Common Technical Document; RMP: Risk Management Plan.

**Table 3 - Details of the currently approved RMP**

<b>Version number</b>	1.0
<b>Approved with procedure</b>	EMA/H/C/005159
<b>Date of approval (opinion date)</b>	17-Sep-2020

EMA: European Medicines Agency; RMP: Risk Management Plan.

**Table 4 - QPPV name and signature**

<b>Qualified Person Responsible for Pharmacovigilance (QPPV) name</b>	[REDACTED] <sup>a</sup> , [REDACTED]
<b>QPPV signature</b>	Electronic signature on file

<sup>a</sup> Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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## ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
ACS:	Acute Coronary Syndrome
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AR:	Adverse Reaction
ATC:	Anatomical Therapeutic Chemical
BEVS:	Baculovirus Expression Vector System
BLA:	Biologics License Application
CCDS:	Company Core Data Sheet
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
CMDh:	Coordination Group for Mutual Recognition and Decentralised Procedures-Human
CNS:	Central Nervous System
COVID-19:	Coronavirus Disease-2019
DART:	Developmental and Reproductive Toxicity
DBL:	Database Lock
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DRIVE:	Development of Robust Innovative Vaccine Effectiveness
ECG:	Electrocardiogram
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMA:	European Medicines Agency
EMR:	Electronic Medical Record
EPAR:	European Public Assessment Report
EPSS:	Enhanced Passive Safety Surveillance
ER:	Emergency Room
EU:	European Union
FDA:	Food and Drug Administration
GBS:	Guillain-Barre Syndrome
GMT:	Geometric Mean Titer
GP:	General Physician
GPV:	Global Pharmacovigilance
GVP:	Good Pharmacovigilance Practices
HA:	Hemagglutinin
HAI:	Hemagglutination Inhibition
HIV:	Human Immunodeficiency Virus
HSCT:	Hematopoietic Stem Cell Transplant
ICD:	International Classification of Diseases
ICSR:	Individual Case Safety Report
ICU:	Intensive Care Unit
IIV:	Inactivated Influenza Vaccine

IIV3:	Trivalent Inactivated Influenza Vaccine
IIV4:	Quadrivalent Inactivated Influenza Vaccine
ILI:	Influenza-Like Illness
IM:	Intramuscular
IMI:	Innovative Medicine Initiative
INN:	International Nonproprietary Name
IV:	Influenza Vaccination
IVE:	Influenza Vaccine Effectiveness
KPNC:	Kaiser Permanente Northern California
LBW:	Low Birth Weight
MAAE:	Medically Attended Adverse Event
MAH:	Marketing Authorization Holder
NH:	Northern Hemisphere
O/E:	Observed-to-Expected
OR:	Odds Ratio
p:	Probability
PBRER:	Periodic Benefit-Risk Evaluation Report
PL:	Package Leaflet
PRAC:	Pharmacovigilance Risk Assessment Committee
PTC:	Product Technical Complaint
QPPV:	Qualified Person Responsible for Pharmacovigilance
rHA:	Recombinant Hemagglutinin Antigen
RIV:	Recombinant Influenza Vaccine
RIV3:	Trivalent Influenza Vaccine (recombinant, prepared in cell culture)
RIV4:	Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture)
RMP:	Risk Management Plan
RR:	Risk Rate
SAE:	Serious Adverse Event
SARI:	Severe Acute Respiratory Infections
SC:	Subcutaneous
SD-IIV4:	Standard Dose Inactivated Influenza Vaccine
SGA:	Small for Gestational Age
SH:	Southern Hemisphere
SmPC:	Summary of Product Characteristics
SOT:	Solid Organ Transplant
TIV:	Trivalent Influenza Vaccine
UK:	United Kingdom
US:	United States
USPI:	United States Prescribing Information
VAERS:	Vaccine Adverse Event Reporting System
VE:	Vaccine Effectiveness
VRBPAC:	Vaccines and Related Biological Products Advisory Committee
WHO:	World Health Organization

**PART I: PRODUCT(S) OVERVIEW**

**Table 5 - Product Overview**

<b>Active substance(s) (International Nonproprietary Name [INN] or common name)</b>	Trivalent Influenza vaccine (recombinant, prepared in cell culture) Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture)
<b>Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)</b>	J07BB02
<b>Marketing Authorization Holder (MAH)</b>	Sanofi Winthrop Industrie
<b>Medicinal products to which this RMP refers</b>	2
<b>Invented name(s) in the European Economic Area (EEA)</b>	Supemtek Supemtek Tetra
<b>Marketing authorization procedure</b>	Centralized
<b>Brief description of the product</b>	<p><u>Chemical class:</u> Recombinant vaccine.</p> <p><u>Summary of mode action:</u> Trivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV3) contains rHA proteins of the three strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4) contains rHA proteins of the four strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. These proteins function as antigens which induce a humoral immune response, measured by HAI antibody.</p> <p><u>Important information about its composition:</u> RIV3 and RIV4 are manufactured using BEVS and recombinant DNA technology. [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]</p> <p>RIV3 is formulated to contain a total rHA content of 135 µg per 0.5 mL dose, consisting of 45 µg from each of three full-length rHAs derived from the influenza strains selected by WHO and the US FDA for each year's seasonal vaccine: H1N1, H3N2, and B/Victoria.</p> <p>RIV4 is formulated to contain a total rHA content of 180 µg per 0.5 mL dose, consisting of 45 µg from each of four full-length rHAs derived from the influenza strains selected by WHO and the US FDA for each year's seasonal vaccine: H1N1, H3N2, B/Yamagata lineage, and B/Victoria lineage viral strains.</p>

	The rHA antigens are full-length, uncleaved glycoproteins with molecular weights of approximately 65 000 Daltons.
<b>Hyperlink to the product information</b>	Refer to e-CTD sequence 0060, Module 1.3.1 English proposed Product Information.
<b>Indication(s) in the EEA</b>	<u>Current:</u> RIV4 is indicated for active immunization for the prevention of influenza disease in adult.
	<u>Proposed:</u> RIV4 is indicated for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV4 should be used in accordance with official recommendations. RIV3 is indicated for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV3 should be used in accordance with official recommendations.
<b>Dosage in the EEA</b>	<u>Current:</u> 0.5 ml.
	<u>Proposed:</u> Not applicable
<b>Pharmaceutical form(s) and strength(s)</b>	<u>Current:</u> 0.5 ml/dose, Solution for injection in Pre-filled Syringe, IM injection.
	<u>Proposed:</u> Not applicable
<b>Is or will the product (be) subject to additional monitoring in the European Union (EU)?</b>	Yes

ATC: Anatomical Therapeutic Chemical; BEVS: Baculovirus Expression Vector System; DNA: Deoxyribonucleic acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; FDA: Food and Drug Administration; HAI: Hemagglutination Inhibition; IM: Intramuscular; INN: International Nonproprietary Name; rHA: Recombinant Hemagglutinin Antigen; RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture); RMP: Risk Management Plan; US: United States; WHO: World Health Organization.

## PART II: SAFETY SPECIFICATION

### PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

RIV4 is mainly indicated for active immunization for the prevention of influenza disease in adult. Newly proposed indication for RIV4/RIV3 is for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV4/RIV3 should be used in accordance with official recommendations.

The epidemiology of the disease is summarized in the following table.

**Table 6 - Epidemiology of the (untreated) target disease**

<b>Indication</b>	<b>RIV is indicated for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV should be used in accordance with official recommendations</b>
<b>Incidence</b>	According to the WHO, annual influenza epidemics result in about three to five million cases of severe illness worldwide. (1) This relatively high incidence is associated with up to 650 000 respiratory deaths annually worldwide, with up to 72 000 deaths occurring in the European Region. (2)
<b>Prevalence</b>	As influenza is an acute disease, epidemiological data usually represent incidence.
<b>Demographics of the population in the authorized indication</b>	All age groups can be affected by influenza but there are groups that are more at risk than others. People at greater risk of severe disease or complications when infected are pregnant women, children under 5 years of age, older people, individuals with chronic medical conditions and individuals with immunosuppressive conditions/treatments. (1)  Among those aged 18–64 years, influenza-associated clinical burden increased with age, including hospitalizations, intensive care unit (ICU) admissions, mortality, emergency room (ER)/outpatient visits, and use of mechanical ventilation. (3) Adults aged ≥65 years are at increased risk of severe influenza-related symptoms and complications due to chronic comorbidity and immunosenescence. (4) In Europe, the rate of deaths from the flu was 31 per 100 000 each year among those aged over 65. (5)
<b>Main existing treatment options</b>	Annual Influenza Vaccination (IV) is the most effective method for preventing seasonal influenza virus infection and its complications. (1)  Individuals who develop influenza symptoms usually receive non-specific treatment such as antipyretics and rehydration. For specific situations, antiviral medications are effective for the prevention and treatment of influenza when used early and when used for treatment they can reduce the duration and severity of illness.
<b>Natural history of the indicated condition in the untreated population including mortality and morbidity</b>	Because of their age-related weakened immune system, the elderly are particularly prone to serious complications from influenza, such as influenza-associated or secondary pneumonia, which can lead to hospitalization and death. (6) Influenza infection results in increased morbidity and mortality in elderly individuals and those with high-risk conditions, many of which are common causes of death. (7)  The risk of hospitalization and death from influenza infection is >10-fold higher in people aged 65 years and over compared to younger adults. (6)(7)

<b>Indication</b>	<b>RIV is indicated for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV should be used in accordance with official recommendations</b>
<b>Important co-morbidities</b>	Influenza associated morbidity rates begin to increase after the age of 50. This may partly result from an increased prevalence of persons with medical conditions in this age group making them prone to influenza associated complications. (8) In addition, the presence of comorbidities such as diabetes, pulmonary disease, cardiovascular disease, renal disease and liver disease are risk factors for increased morbidity and mortality. (9)

ER: Emergency Room; EU: European Union; IV: Influenza Vaccination; ICU: Intensive Care Unit; RIV: Recombinant Influenza Vaccine; WHO: World Health Organization.

## **PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION**

The preclinical development of RIV4 was conducted as following:

The non-clinical safety assessment of RIV4 is supported by data from toxicity studies conducted with RIV3 administered at one human dose (45 µg rHA/strain) by the IM or subcutaneous (SC) route:

- Three safety pharmacology studies in which RIV3 was administered by SC route (one to evaluate the cardiovascular system in dogs, one to evaluate the respiratory functions in rats and one to evaluate the central nervous system [CNS] in rats),
- Two single-dose toxicity studies in which RIV3 was administered by SC route (one in rats and the second in dogs),
- Two local tolerance studies in rabbits in which RIV3 was administered (in one) by IM route and (in another) by SC route,
- One repeat-dose toxicity study in rats by SC route,
- One developmental and reproductive toxicity (DART) study in rats by IM route.

These studies were considered supportive for RIV4, as both RIV3 and RIV4 are manufactured using a similar process. Thus, there are no significant differences between the formulations (no additional excipients), only an increase in rHA content from 135 to 180 µg/dose (corresponding to 45 µg/strain per dose). In addition, the design of these non-clinical studies confirmed the intended dosing regimen in humans.

No adverse systemic effects were observed in non-clinical safety studies (with respect to toxicology, cardiovascular, CNS and respiratory endpoints), the RIV3-related effects being limited to transient local inflammation at the injected area observed in the local tolerance studies after IM administration and repeat-dose toxicity studies following SC administration. In addition to the absence of maternal toxicity, the DART study showed no adverse effects on mating performance or fertility, embryo-fetal development (including an evaluation of teratogenicity) and early post-natal development. Trivalent Recombinant Influenza vaccine was therefore shown to be safe as observed in the non-clinical safety package showing that single and repeated administrations of RIV3 with 45 µg of rHA per strain per dose were well tolerated with only expected low local reactogenicity as part of a typical response due to vaccine administration.

Based on these data generated with RIV3 and since these non-clinical studies were considered supportive for RIV4, no safety concerns are expected with RIV4 and therefore no additional toxicity studies are considered necessary to support its licensure.

No additional non-clinical data have been collected on the use of RIV3/RIV4 in any special population.

No new non-clinical toxicity studies were performed from the last RMP (2020).

## PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

### Brief Introduction to Clinical Development:

Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) has been developed based on the experience of RIV3. Safety and immunogenicity of RIV3 have been successfully proven in randomized controlled trials including the first study in 2004-2005 season. (10) RIV4 has been developed for the same age group and indication that applied to RIV3, ie, RIV is indicated for active immunization for the prevention of influenza disease in adult. Newly proposed indication is for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV should be used in accordance with official recommendations.

A large-scale placebo-controlled study (PSC04) with RIV3 in US in adults 18-49 years of age was conducted during the 2007-2008 influenza season in US. The study concluded that RIV3 had a satisfactory safety profile and provided absolute efficacy of 75.4% (95% confidence interval (CI): -14.8 to 99.5) against influenza-like illness (ILI) caused by a small number of antigenically matched strains of influenza, and approximately 45% against all strains, most of which were antigenically mismatched to the vaccine strains. The efficacy against influenza A strains, antigenically matched or mismatched (largely H3N2, in the particular season in which the study was conducted) was even higher, ranging from 49.0 to 54.4% (95% CI: 24.7-65.9% and 26.1-72.5%, respectively), depending on the case definition used for ILI. (11)

Furthermore, studies in adults 50-64 years of age (Study PSC06) and in adults 65 years of age and older (Study PSC03) showed HAI antibody responses induced by RIV3 met the pre-specified seroconversion criterion of the lower bound of the 95% CI  $\geq 40\%$  for adults  $< 65$  years and  $\geq 30\%$  for adults  $\geq 65$  years of age for all three vaccine strains. The pre-specified criterion for the proportion of subjects with post-vaccination HAI titers of  $\geq 1:40$  (“seroprotection”) of the lower bound of the 95% CI  $\geq 70\%$  for adults  $< 65$  years and  $\geq 60\%$  for adults  $\geq 65$  years of age was also met for both influenza A antigens. Responses to the B antigen were commonly less robust among recipients of both recombinant vaccine and the comparator trivalent influenza vaccine (TIV) and were of similar magnitude in recipients of both vaccines. (12)(13)

As part of the strategy to switch the RIV portfolio from trivalent to quadrivalent vaccine, the clinical development plan for RIV4 included two Phase III pivotal trials (Study PSC12 and Study PSC16) conducted in the US. Both studies were head-to-head comparisons of RIV4 to a quadrivalent inactivated influenza vaccine (IIV4) licensed in US and Europe conducted during the 2014-2015 influenza season.

Clinical data generated with RIV4 in Phase III studies PSC12 and PSC16 showed RIV4 provided 30% to 43% better protection against influenza disease compared to a standard-dose IIV4 in adults 50 years of age and older during a season characterized by predominantly antigenically drifted strains of influenza A (H3N2) and was non-inferior to the same IIV4 comparator vaccine for 3 of 4 influenza vaccine strains as assessed by seroconversion rates and geometric mean titers (GMTs) in adults 18 to 49 years of age.

Vaccination with RIV4 was found to be safe and well tolerated among 5326 adults  $\geq 18$  years of

age participating in these 2 studies, with no safety concerns identified. The safety profile of RIV4 showed comparable reactogenicity (solicited injection site reactions and solicited systemic reactions) to IIV4 and no notable difference in occurrence of unsolicited adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and deaths.

Two randomized, active-controlled trials of recombinant influenza vaccine were conducted in pediatric age group in the US. A Phase I/II clinical trial PSC02 was conducted with RIV3 in 156 children aged 6 months to 5 years (98 subjects received RIV3 [among them 61 received the full dose of 45 µg per antigen] and 58 received a licensed trivalent inactivated influenza vaccine [IIV3] [Fluzone<sup>®</sup>]). A Phase II clinical trial PSC08 was conducted in 219 children and adolescents 6 years to 17 years of age who received either RIV4 or a licensed IIV4 (Fluarix tetra<sup>®</sup>). The clinical data from pediatric studies showed an acceptable safety and reactogenicity profiles of RIV3 or RIV4. By evaluating a series of age cohorts ranging from 6 years to 17 years, it was shown that HAI assay immunity appears to be induced to a greater degree as the participants become older. Therefore, Sanofi conducted Phase III studies VAP00027 and VAP00026.

Phase III study (VAP00027) was conducted to evaluate the immunogenicity and safety of RIV4 in participants aged 9 to 17 years and in participants 18 to 49 years to demonstrate that RIV4 immunogenicity in participants aged 9 to 17 years is non-inferior to participants aged 18 to 49 years and to support the immuno bridging of efficacy in adults to children/adolescents aged 9 to 17 years.

An additional Phase III study (VAP00026) assessed the non-inferiority of RIV4 compared to the standard dose IIV4, the HAI antibody response induced by RIV4 compared to the HAI antibody response induced by IIV4, the immunogenicity of RIV4 in terms of HAI titer, and the immunogenicity of RIV4 in terms of neutralization titer and documented the safety of RIV4 compared to IIV4 in children aged 3 to 8 years. It is to be noted that the study was stopped for futility; and, at the time of the final analysis, the statistical test for non-inferiority was only conducted on the participants before stopping the study for futility. Non-inferiority was not performed according to the planned sample size and study power. Therefore, descriptive data are provided as additional supportive information only.

VAP00026 entitled “Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine Compared with Egg Based Standard Dose Quadrivalent Influenza Vaccine in Children 3 to 8 Years of Age” is a Phase III, randomized, modified double blind study to assess the immunogenicity and safety of RIV4 compared with egg based standard dose IIV4 in children in Europe and the US. VAP00026 was terminated; a total of 362 subjects were vaccinated on the date of DLP.

- Main outputs of the study: Overall, the safety profile of the RIV4 vaccine was comparable to that of the IIV4 vaccine in all participants aged 3 to 8 years. No safety concerns have been identified.
- Solicited injection site and systemic reactions mostly occurred within 3 days and were mostly of Grade 1 or Grade 2 intensity. Solicited reactions were less frequently reported after the second vaccination.
- Unsolicited AEs and adverse reactions (ARs) were reported with low frequency in both vaccination groups.

- No deaths were reported and none of the participants experienced any AESIs or AEs leading to study discontinuation in any vaccination group. In the IIV4 group, one SAE was reported in 1 participant 6 years of age. This event was not related to the study vaccine.

VAP00027 entitled “Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years” is a Phase III, non-randomized, open label, uncontrolled, multi-center study to assess the immunogenicity and safety of the RIV4 in children and adolescents (9 to 17 years of age) and adults (18 to 49 years of age) in Europe and the US. Eligible participants receive a single IM injection of RIV4. The participation duration is approximately six months (181 days) for each participant. VAP00027 study was conducted during the 2022-2023 influenza season in northern hemisphere (NH). A total of 1299 participants were vaccinated on the date of DLP.

Main outputs of the study:

- Overall, vaccination with RIV4 in participants 9 to 17 years of age and 18 to 49 years of age was found to be safe and well tolerated with no safety concerns identified.
- The safety profile of the RIV4 vaccine was comparable in both age groups, with the exception of solicited reactions within 7 days of vaccination which were slightly less present in children and adolescents (44.3%) than in adults (52.9%).
- During the study, 10 participants (0.8%) reported atleast one SAE and 66 participants (5.1%) reported atleast 1 medically attended adverse event (MAAE). None of the SAEs and MAAEs were considered as related to the vaccine.
- No deaths and no AESIs were reported during the study.

There was no new clinically important information arising from VAP00026 and VAP00027 pediatric studies.

Conclusion: No safety concerns were identified in two phase III pediatric studies. The safety profile of the RIV4 vaccine was comparable to that of the IIV4 vaccine in all participants aged 3 to 8 years. Vaccination with RIV4 in participants 9 to 17 years was found to be safe and well tolerated with no safety concerns identified. No safety signals were identified for vaccinated children, and the results support the extension of the age indication to the pediatric population for children/adolescents 9 to 17 years of age.



As RIV4 development is based upon that of RIV3, please see [Table 7](#) below showing exposure during clinical development to each product.

**Table 7 - Estimated cumulative subject exposure to RIV3 and RIV4 from completed clinical trials (PSC01, PSC02, PSC03, PSC04, PSC06, PSC08, PSC11, PSC12, PSC16, GRC90, VAP00001, VAP00016, VAP00026 and VAP00027)**

Status	Treatment	Number of Subjects
Completed	RIV3 67.5 µg	37
	RIV3 75 µg	151

Status	Treatment	Number of Subjects
	RIV3 135 µg	4608
	<b>Total RIV3</b>	<b>4796</b>
Completed	RIV4 180 µg	5682
On-going and Unblinded	RIV4 180 µg	1480
	<b>Total RIV4</b>	<b>7162</b>
<b>Total</b>		<b>11 958</b>

Included in this table are subjects who had at least one injection of RIV3 or RIV4 vaccine between 17-Nov-2004 and 15-Jan-2024. RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

**Table 8 - Exposure by age group and gender**

Treatment/Vaccine Group	Age Range	Number of Subjects		
		Male	Female	Total
RIV3 67.5 µg	6 to 35 months	19	18	37
RIV3 75 µg	18 to 49 years	48	103	151
RIV3 135 µg	6 to 35 months	22	18	40
	36 to 59 months	5	16	21
	18 to 49 years	1010	1487	2497
	50 to 64 years	402	570	972
	≥65 years	503	575	1078
	<b>Total</b>	<b>1942</b>	<b>2666</b>	<b>4608</b>
RIV4 180 µg	3 to 17 years	469	461	930
	18 to 49 years	662	1121	1783
	≥50 years	1841	2608	4449
	<b>Total</b>	<b>2972</b>	<b>4190</b>	<b>7162</b>

Studies included are PSC01, PSC02, PSC03, PSC04, PSC06, PSC08, PSC11, PSC12, PSC16, GRC90, VAP00001, VAP00026 and VAP00027.

RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

**Table 9 - Cumulative Subject Exposure to recombinant influenza vaccine (RIV) from Completed Clinical Trials (PSC01, PSC02, PSC03, PSC04, PSC06, PSC08, PSC11, PSC12, PSC16, GRC90, VAP00026, VAP00027) by Racial Group**

Vaccine/Treatment Group	Ethnic Origin	Number of Subjects
RIV3 67.5 µg	Asian	0
	Black	10
	Caucasian	27
	Other	0
	<b>Total</b>	<b>37</b>

<b>Vaccine/Treatment Group</b>	<b>Ethnic Origin</b>	<b>Number of Subjects</b>
RIV3 75 µg	Asian	10
	Black	12
	Caucasian	126
	Other	3
	<b>Total</b>	<b>151</b>
RIV3 135 µg	Asian	108
	Black	667
	Caucasian	3487
	Other	346
	<b>Total</b>	<b>4608</b>
RIV4 180 µg	Asian	10
	Black	1491
	Caucasian	5300
	Other	172
	<b>Total</b>	<b>6973</b>

Studies included are PSC01, PSC02, PSC03, PSC04, PSC06, PSC08, PSC11, PSC12, PSC16, GRC90, VAP00026 and VAP00027. In study VAP00001, racial information was not collected.  
 RIV: Recombinant Influenza Vaccine; RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

## PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

### SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

During their clinical development, RIV3 and RIV4 have been studied in various populations. Studies PSC02 and PSC08 were pediatric trials, which included healthy subjects of age 6-59 months and 6-17 years of age, respectively. Studies PSC01, PSC04 and PSC16 included healthy adult participants of age 18-49 years. Studies PSC11 and PSC12 enrolled adult subjects of age  $\geq 50$  years. Studies PSC03 and PSC06 included healthy and/or medically stable adults 65 years of age and older and 50-64 years of age.

**Table 10 - Pivotal studies in the RIV3/ RIV4 development programme**

Protocol/Reference	Season	Test Product	Comparator	Study Population	End points	Number of total participants
PSC01	2004-2005	RIV3 135 µg RIV3 75 µg	Placebo	Healthy adults 18-49 years of age	Safety, immunogenicity absolute clinical efficacy	460
PSC02	2006-2007	RIV3 135 µg RIV3 67.5 µg	(IIV3) Fluzone (15 µg per Antigen)	Healthy children 6-59 months of age	Safety, immunogenicity	156
PSC03	2006-2007	RIV3 135 µg	(IIV3) Fluzone	Healthy adults 65 years of age or older	Safety, immunogenicity, relative clinical efficacy	870
PSC04	2007-2008	RIV3 135 µg	Placebo	Healthy adults 18-49 years of age	Safety, immunogenicity, absolute clinical efficacy	4648
PSC06	2007-2008	RIV3 135 µg	(IIV3) Fluzone	Healthy adults 50-64 years of age	Safety, immunogenicity, relative clinical efficacy	602
PSC08	2013-2014	RIV4 180 µg	(IIV4) Fluarix Quadrivalent®	Healthy children 6-17 years of age	Safety, immunogenicity	219
PSC11	2012-2013	RIV3 135 µg	(IIV3) Afluria®	Ambulatory and medically stable adults $\geq 50$ years of age	Safety	2640

Protocol/Reference	Season	Test Product	Comparator	Study Population	End points	Number of total participants
PSC12	2014-2015	RIV4 180 µg	(IIV4) Fluarix Quadrivalent	Medically stable adults ≥50 years of age	Safety, immunogenicity, relative efficacy	9003
PSC16	2014-2015	RIV4 180 µg	(IIV4) Fluarix Quadrivalent	Healthy adults 18-49 years of age	Safety, immunogenicity	1350
VAP00026	2022/2023	RIV4 180 µg	(IIV4) Fluarix Quadrivalent	Healthy children 3-8 years of age	Safety, immunogenicity	366
VAP00027	2022/2023	RIV4 180 µg	NA	Healthy children 9-17 years of age and healthy adult 18-49 years of age	Safety, immunogenicity	1308

IIV3: Trivalent Inactivated Influenza Vaccine 3; IIV4: Quadrivalent Inactivated Influenza Vaccine; RIV3: Trivalent Recombinant Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

**Table 11 - Important exclusion criteria in pivotal studies in the development programme**

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Experiencing immunosuppression as a result of an underlying illness or treatment or immunodeficiency	Antibody response in patient with endogenous or iatrogenic immunosuppression may be insufficient.	No	Patients with immunodeficiency are at an increased risk of complications from influenza infection and secondary infections to influenza.  Vaccination of individuals with chronic immunodeficiency with RIV4 is recommended even though the antibody response may be limited. The effects of immunosuppression are not specific to the RIV4 vaccine but they are universal to all phenomena related to immunity. Benefits of vaccination should

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			be evaluated on a case-by-case basis which is not possible in a clinical study. (14)(15)(16)(17)
Pregnant, or lactating women or women of childbearing potential <sup>a</sup>	Pregnant populations are not usually included in the clinical studies of an investigational product unless the product is specifically indicated for the pregnant women.	Yes	Were included in the missing information.

a Study PSC13 analyzed use of RIV3 in pregnant women; however, this study was an observational study and not considered a pivotal clinical trial.

RIV3: Trivalent Influenza Vaccine (recombinant, prepared in cell culture); RIV4: Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture).

## SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme may be unlikely to detect certain types of ARs such as rare or very rare ARs, ARs with a long latency, ARs caused by prolonged or cumulative exposure.

Considering the nature of the seasonal IV, which is usually administered as a single shot annually before or during the influenza season there are no ARs caused by prolonged or cumulative exposure. RIV3 was approved in US on 16 January 2013, for active immunization in adults 18-49 years of age. RIV4 was approved in US on 07 October 2016. No safety concerns have been identified with the vaccine based on its post-approval use.

Given the large clinical development programme and the postmarketing experience associated with RIV3 and RIV4, the limitations relative to adverse drug reaction (ADR) detection in clinical trials are no longer relevant for these vaccines.

## SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

**Table 12 - Exposure of special populations included or not in clinical trial development programmes**

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	

Type of special population	Exposure
<b>Patients with relevant comorbidities</b> <ul style="list-style-type: none"> <li>• Patients with hepatic impairment</li> <li>• Patients with renal impairment</li> <li>• Patients with cardiovascular impairment</li> <li>• Immunocompromised patients</li> </ul>	Not included in the clinical development program.
<b>Populations with relevant different ethnic origin</b>	Not relevant.
<b>Subpopulations carrying known and relevant genetic polymorphisms</b>	Not relevant.
<b>Other</b>	Not included in the clinical development program. Not relevant.

Very limited data are available concerning the use of RIV4 in pregnant or breastfeeding women. However, pregnant and breastfeeding women are part of the target population. Therefore, the use of RIV4 in pregnant or breastfeeding women is considered as missing information.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by RIV4.

To date, there is no information suggesting the existence of polymorphisms affecting the efficacy or safety of RIV4 in the currently proposed indication(s).

**Patients with relevant comorbidities:**

- RIV4 was not systematically studied in patients with hepatic impairment. Since vaccines are not metabolized by the liver, no specific safety issue is expected in this population.
- RIV4 was not systematically studied in patients with renal impairment. Since vaccines are not eliminated by the kidney, no specific safety issue is expected in this population.
- RIV4 was not studied in patients with known or suspected immunodeficiency, including organ transplant patients. While efficacy may be compromised in this population, no specific safety issue is expected.
- RIV3 has been studied in adults with non-Hodgkin’s lymphoma. (18) Twenty seven patients were randomized to receive commercial TIV containing 15 µg of the hemagglutinin (HA)/antigen or RIV3 at three HA concentrations (15, 45 and 135 µg of HA). The highest increase in the neutralizing antibody levels and the highest mean titers occurred in those given the 135 µg vaccine.

As RIV4 vaccine contains only a purified recombinant protein, there is no risk of infection from the vaccination itself. A systematic review and meta-analysis to assess the evidence for IV in immunocompromised patients was conducted by Beck et al. (15); results were reported according to etiology. Vaccination was generally well tolerated with variation in mild AEs between etiological groups. Limited evidence of a transient increase in viremia and decrease in the percentage of CD4+ cells in human immunodeficiency virus (HIV)-positive patients was found although not

accompanied by worsening of clinical symptoms. According to the authors, clinical judgment remains important when discussing the benefits and safety profile of influenza vaccine with immunocompromised patients. This review did not include the studies that involved use of RIV4.

Influenza vaccine responses in adult and pediatric organ transplant recipients are quite variable and dependent on time from transplant and the immunosuppressive regimen in use. There are no established epidemiologic links between allograft dysfunction and vaccination. Given the potential risks of influenza infection in solid organ transplant (SOT) recipients, influenza vaccine should be administered to SOT recipients. (16) The studies involving organ transplant patients were not conducted using RIV4.

According to the review article by Ison, (19) evaluating IV in hematopoietic stem cell transplant (HSCT) patients and SOT patients, the response rates in SOT recipients were related to the level of immune suppression in the first 6-12 months post-transplant. The review concluded that IIV is without significant enhanced risk of inducing rejection and is associated with reduced risk of influenza. Vaccination is recommended for both HSCT and SOT recipients and their close contacts annually. The associated study was not conducted using RIV4.

Patients with diabetes are also a population of patients at increased risk of influenza and its complications. Influenza vaccination for these patients is therefore recommended by the WHO and several National Immunization Technical Advisory Groups. In 2015, a systematic review and meta-analysis was performed to evaluate the effects of influenza vaccine in this patient population. Multiple types of studies reporting on the efficacy, effectiveness, and/or safety of IV in patients with type I and type II diabetes of all ages were considered for the analysis. In all 11 observational studies with a total of 170 924 participants demonstrated that in diabetic patients of working age (ie, 18-64 years), IV prevented all-cause hospitalization with a pooled vaccine effectiveness (VE) of 58% (95% CI, 6 to 81%) and hospitalization due to influenza or pneumonia VE 43%; 95% CI (28% to 54%), whereas no effects on all-cause mortality and ILI were observed. In the elderly ( $\geq 65$  years of age), IV prevented all-cause mortality (VE 38%; 95% CI, 32% to 43%), all-cause hospitalization (VE 23%; 95% CI, 1 to 40%), hospitalization due to influenza or pneumonia (VE 45%; 95% CI, 34 to 53%), and ILI (VE 13%, 95% CI, 10 to 16%). (20) However, due to strong residual confounding the quality of the evidence was low for all outcomes. This analysis was not conducted using RIV4.

### **Patients with cardiovascular impairment**

In patients with cardiac disease or at risk of cardiovascular disease influenza infection can further exacerbate cardiovascular events. Udell et al. (21) conducted a systematic review and meta-analysis to determine if IV was associated with prevention of cardiovascular events. Almost 7000 patients, with a mean age of 67 years, with and without a recent history (within 1 year) of acute coronary syndrome (ACS) were analyzed. The analysis showed that IV significantly lowered the risk of major adverse cardiovascular events (2.9% versus 4.7%; Risk rate (RR), 0.64, [95% CI, 0.48-0.86], probability (p) = 0.003) and that treatment interaction was detected between patients with (RR, 0.45 [95% CI, 0.32-0.63]) and without (RR, 0.94 [95% CI, 0.55-1.61]) recent ACS. This study was not conducted using RIV4.

Multiple studies have suggested evidence of a cardioprotective effect of IV in patients with cardiovascular disease. (22)(23)(24) Studies have demonstrated that IV reduces mortality, hospitalization, and ACSs in patients with coronary heart disease and/or heart failure. (25)(26)(27)

Additionally, a stroke cohort study in Taiwan was performed to evaluate the effects of IV on stroke outcomes. (28) Subjects enrolled included 1 48 909 hospitalized stroke patients aged 66 years and older. Using a matching procedure by propensity score, 25 248 stroke patients who received influenza vaccine and 25 248 stroke patients who did not receive influenza vaccine were selected for comparison. Logistic regression was used to calculate the odds ratios (ORs) and 95% CIs of post-stroke complications and in-hospital mortality associated with IV. Stroke patients with IV had significantly lower risks of post-stroke pneumonia (OR = 0.79; 95% CI, 0.74-0.83), septicemia (OR = 0.78; 95% CI, 0.70-0.86), urinary tract infection (OR = 0.87; 95% CI, 0.83-0.92), and 30-day in-hospital mortality (OR = 0.60; 95% CI, 0.54-0.67) compared with stroke patients not immunized with influenza vaccine.

The following non-clinical safety pharmacology studies have been conducted to evaluate the effects of RIV3 (135 µg rHA/dose, corresponding to 45 µg rHA/strain) following a single SC injection of one human dose:

- On the cardiovascular system (blood pressure, heart rate and electrocardiogram [ECG] parameters) (Study number P081016) in unanesthetized dogs,
- On the respiratory functions (breathing rate), (Study number P081015) in rats,
- On the CNS (functional observational battery test, behavioral activity test and the body temperature measurement) (Study number P081014) in rats.

No premature deaths occurred in any of these studies and there were no adverse clinical signs or significant changes compared to controls. Consequently, RIV3 was not shown to affect the cardiovascular, respiratory and CNS systems of the animals studied. The results of these studies are consistent with available clinical data.

### **Pregnant adult**

During clinical development of most drugs and biological products, pregnant women are actively excluded from trials, and if pregnancy does occur during a trial, the usual procedure is to discontinue treatment and monitor the women to assess pregnancy outcomes. Consequently, at the time of a drug or biological product's initial marketing, (except for drugs and biological products developed to treat conditions unique to pregnancy) there are no or limited human data to inform the safety of a drug or biological product taken during pregnancy. Post-approval studies using data collected in pregnancy registries may be required to assess potential risks to the pregnancy that may affect the health of the fetus or the woman due to drug or biological product use during pregnancy. Use of complementary studies with different study designs may help address the limitations inherent to a pregnancy registry. Additionally, as more postmarketing safety information becomes available from interim registry reports, spontaneous reports, or case series, a more specific safety signal may become apparent.

During the clinical development of the RIV3, in PSC01 study, 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. In PSC16 study, seven pregnancies were reported with six uncomplicated live births while one subject who reported pregnancy three weeks following immunization reported spontaneous abortion after six weeks.

Analysis of these cases didn't show any safety concern for the mother or the unborn child with spontaneous abortion rate below background incidence.

Cumulatively, administration of RIV (RIV3/RIV4) during pregnancy was reported in 42 spontaneously reported cases during postmarketing surveillance. None of these cases revealed a safety concern.

In a program conducted by Center for vaccine Equity at the Task Force for Global Health, sponsored by US Centers for Disease Control and Prevention (CDC), 40 000 doses of RIV3 were donated for influenza vaccine coverage in Mongolia. Three hundred thirty-three (333) pregnant women received RIV3. No SAEs were reported from the passive surveillance network. However, these data are limited because there was no active follow-up of pregnancies, and the capability of Mongolian surveillance network to capture the pregnancy related AE are uncertain.

According to Advisory Committee on Immunization Practices (ACIP), pregnant and postpartum women have been observed to be at higher risk for severe illness and complications from influenza, particularly during the second and third trimesters. ACIP and the American College of Obstetricians and Gynecologists recommend that "Any age appropriate IIV4 or RIV4 may be given in any trimester". (6)(29)

Use during pregnancy was studied in VAP00007 Post-licensure Database Surveillance Study to Assess the Safety of Flublok Quadrivalent (Influenza Vaccine) in Pregnant Women and Their Offspring.

Study VAP00007 was a Phase IV, post-licensure, observational, retrospective, safety surveillance study in pregnant women and their offspring designed to assess pregnancy outcomes among pregnant women who were immunized with either RIV4 or with a comparator standard dose inactivated influenza vaccine (SD-IIV4) during pregnancy or within 28 days prior to the estimated date of conception and birth and neonatal/infant outcomes in their infants (live births).

There were 2 pregnancy cohorts included:

Pregnant Cohort 1: pregnant women immunized with RIV4 and those who became pregnant after vaccination, within 28 days prior to the estimated date of conception.

Pregnant Cohort 2: pregnant women immunized with SD-IIV4 (Fluarix Quadrivalent [Influenza Vaccine] or Flulaval® Quadrivalent [Influenza Vaccine]) and those who became pregnant after vaccination, within 28 days prior to the estimated date of conception.

Two analogous infant cohorts consisted of live infants born to immunized pregnant women:

Infant Cohort 1: live infants of pregnant women immunized with RIV4 and those who became pregnant after vaccination, within 28 days prior to the estimated date of conception.

Infant Cohort 2: live infants of pregnant women immunized with SD-IIV4 (Fluarix Quadrivalent [Influenza Vaccine] or Flulaval Quadrivalent [Influenza Vaccine]) and those who became pregnant after vaccination, within 28 days prior to the estimated date of conception.

Because this study was retrospective and used electronic medical record (EMR) data collected as part of routine clinical care, no informed consent was required. There was no fixed study visit schedule and study procedures followed routine medical care as clinically indicated for the individuals involved. No specific interventions/specimen collections were dictated by the protocol.

- Results:

The final study population included 48 781 pregnant women, of whom 14 981 (30.7%) received RIV4 and 33 800 (69.3%) received SD-IIV4. A total of 47 394 infants born to these pregnant women were included, of whom 14 538 (30.7%) infants' mothers received RIV4 and 32 856 (69.3%) infants' mothers received SD-IIV4.

Pregnancy outcomes: The frequency of pregnancy outcomes was similar across both vaccine groups. The most frequently reported pregnancy outcome in the RIV4 and SD-IIV4 groups was eclampsia/pre-eclampsia (8.4% [95% CI: 7.9%; 8.8%] and 8.4% [95% CI: 8.1%; 8.7%], respectively) followed by preterm labor (3.6% [95% CI: 3.4%; 4.0%] and 3.5% [95% CI: 3.3%; 3.7%], respectively), spontaneous abortion (3.1% [95% CI: 2.9%; 3.4%] and 3.0% [95% CI: 2.8%; 3.2%], respectively), placental abruption (0.8% [95% CI: 0.6%; 0.9%] and 0.7% [95% CI: 0.6%; 0.8%], respectively), and stillbirths/fetal deaths (0.4% [95% CI: 0.3%; 0.5%] and 0.5% [95% CI: 0.4%; 0.5%], respectively). Congenital/fetal anomalies detected during pregnancy were reported in 2.4% (95% CI: 2.1%; 2.6%) of participants in the RIV4 group and 2.4% (95% CI: 2.2%; 2.5%) of participants in the SD-IIV4 group.

Birth and neonatal/infant outcomes: The most frequently reported birth outcome in infants (live births) of women immunized with RIV4 or SD-IIV4 during pregnancy was small for gestational age (SGA) (8.8% [95% CI: 8.3%; 9.3%] and 8.7% [95% CI: 8.4%; 9.0%], respectively) followed by preterm birth (7.3% [95% CI: 6.9%; 7.7%] and 7.5% [95% CI: 7.2%; 7.7%], respectively) and low birth weight (LBW) (5.9% [95% CI: 5.5%; 6.3%] and 5.8% [95% CI: 5.6%; 6.1%], respectively). For neonatal/infant outcomes, failure to thrive was reported in 1.0% (95% CI: 0.9%; 1.2%) and 1.1% (95% CI: 1.0%; 1.3%) of infants of women immunized with RIV4 or SD-IIV4 during pregnancy, respectively. There were 86 infant deaths between the day of birth and 365 days post-birth: 27 (0.2% [95% CI: 0.1%; 0.3%]) infants of women immunized with RIV4 during pregnancy and 59 (0.2% [95% CI: 0.1%; 0.2%]) infants of women immunized with SD-IIV4 during pregnancy.

In this retrospective, observational study of over 48 000 women who received either RIV4 or SD-IIV4 during pregnancy or up to 28 days preceding the estimated date of conception and their offspring, there was no association between RIV4 receipt and pregnancy, birth, or neonatal/infant outcomes compared to SD-IIV4.

- Discussion:

The frequency of pregnancy, birth, and neonatal/infant outcomes demonstrated in this study are mostly consistent with or lower than the nationally published rates. The proportion of pregnant women with placental abruption (0.7%) was similar to national rates (0.3-1.0%), (7) while the proportion with spontaneous abortion (3.0% versus 10-20%), (10) still birth/fetal death (0.4% versus 0.57%), (11) preterm labor (3.5% versus 6%), (30) and eclampsia/pre-eclampsia (8.4% versus 10%) (31) were lower than national rates. Similarly, the proportion of infants with

preterm birth (7.4% versus 12%), (30) LBW (5.8% versus 8.24%), (12) SGA (8.7% versus 11.1%), (13) and infant death (0.2% versus 0.54%) (14) was lower than national rates.

Major congenital anomalies were reported in 7.7% (95% CI: 7.2%; 8.1%) of infants of women immunized with RIV4 during pregnancy and 7.7% (95% CI: 7.4%; 8.0%) of infants of women immunized with SD-IIV4 during pregnancy. A comparison of specific major congenital anomalies such as encephalocele, spina bifida, and cleft palate reported in this study are lower than what has been reported by the National Birth Defects Prevention Network. (15) Minor congenital anomalies were reported for 39.2% (95% CI: 38.4%, 40.0%) of infants of women immunized with RIV4 during pregnancy and 38.8% (95% CI: 38.3%, 39.4%) of infants of women immunized with SD-IIV4 during pregnancy.

The major and minor congenital anomaly reporting rates in both cohorts, while similar and not statistically different, were captured at higher-than-expected rates (7.7% and 39.0%, respectively) when compared to other available published US data. The US lacks a national population-based surveillance program to track major birth defects, but most states have established systems to provide ongoing monitoring. However, variability in how programs collect and verify cases of birth defects using different data sources hampers efforts to continuously generate reliable national estimates. This study includes an exhaustive International Classification of Diseases-10 (ICD-10) code list of Q00-Q99 to capture all coded congenital malformations, deformations, and chromosomal abnormalities. Further, Kaiser Permanente Northern California's (KPNC's) EMRs are comprehensive, and infants are well tracked, ensuring that ICD-10 codes are thoroughly captured.

- Conclusion:

The pregnancy, birth, and neonatal/infant birth outcomes studied in this retrospective safety study were comparable in women who received RIV4 or SD-IIV4 during pregnancy or up to 28 days preceding the estimated date of conception and their infants. No safety signals were identified for vaccinated pregnant women and their newborns, and the results support the safety of RIV4 in pregnant adults and neonates born from vaccinated mothers.

## **PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE**

### **SV.1 POST-AUTHORIZATION EXPOSURE**

#### **SV.1.1. Method used to calculate exposure**

Internal sales have been used as the source for sales data retrieval. These data were calculated on the basis of information provided by the internal Business Warehouse, a module of the systems applications and products system. These data represent product sold by the MAH to third party wholesalers and distributors, rather than vaccines actually administered to patients.

Detailed usage data are not available therefore presentation of patient exposure by age, sex and indication is not possible.

Sales data are collected monthly. Therefore, data do not correspond precisely to the current reporting interval. The extracted figures remain an approximation of the total quantity sold.

Based upon available sales data, a total of 37 434 227 doses of RIV4 were distributed worldwide cumulatively, including 2 903 287 doses distributed worldwide during the reporting interval (sales data till 31 January 2024). Cumulatively, 595 412 doses of RIV3 were distributed worldwide (sales data till 31 December 2017). In total, 38 029 639 doses were distributed cumulatively for RIV3 and RIV4.

Assuming that each patient received one dose, in accordance with the recommended schedule in the company core data sheet (CCDS), cumulative post-approval exposure to RIV4 was estimated to be approximately 37 434 227 patients and exposure during the reporting interval is estimated to 2 903 287 patients. Cumulatively, post-approval exposure to RIV3 was estimated at 595 412 patients. Total cumulative exposure to RIV3 and RIV4 is 38 029 639 patients.

#### **SV.1.2. Exposure**

Detailed usage data are not available therefore presentation of patient exposure by age, sex and indication is not possible.

## **PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION**

### **SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES**

The properties of RIV3/RIV4 do not indicate a potential for misuse for illegal purposes.

## PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

### SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4) was approved for marketing in the US on 07 October 2016. The safety profile of RIV4 is based on the safety profile of RIV3, which was established by virtue a robust clinical program and a postmarketing surveillance program. Trivalent Recombinant Influenza Vaccine (RIV3) was first approved for marketing in the US on 16 January 2013 and was discontinued in March 2018 (withdrawal submitted to Biologics License Application [BLA] ST 125 528 on 29 September 2017).

An estimated 10 230 subjects have received RIV3 or RIV4 in clinical studies. Since the registration of recombinant influenza vaccine (RIV3/RIV4) in the US, cumulative post-approval exposure to RIV4 was estimated to be approximately 3 544 080 as of January 2019.

Cumulatively, post-approval exposure to RIV3 was estimated at 595 412.

Review of postmarketing exposure data conducted for the current periodic benefit-risk evaluation report (PBRER) with DLP of 15 January 2019 showed that the nature and frequency of reported AEs were consistent with those described in the CCDS and United States Prescribing Information (USPI).

The following safety topics and risks are discussed in this Section. These risks are also presented in [Section SVII.1.1] in detail (risks not considered important for inclusion in the list of safety concerns in the RMP):

- **Potential harm from overdose:**
  - The MAH has not become aware of any patterns of use of overdose with RIV3/RIV4 beyond that recommended in the reference product information, including drug abuse and misuse considered relevant for the interpretation of safety data. Potential harm from overdose is not considered a risk for RIV4 because vaccine is distributed as a single use pre-filled syringe directly to health care providers.
- **Potential for risks resulting from medication errors:**
  - Use in Pediatric Population due to Medication Error:
    - o Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4) is approved for active immunization in patients of age 18 years or older. Data from a randomized, controlled trial (PSC02) demonstrated that children 6 months to less than 3 years of age had diminished HI responses to RIV3 as compared to a US licensed influenza vaccine approved for use in this population, strongly suggesting that RIV3 would not be effective in children younger than 3 years of age. Safety and effectiveness of RIV4 have not been established in children 3 years to less than 18 years of age. There is a potential of vaccination in the pediatric age group due to medication error. During the reporting period 16 January 2018 to 15 January 2019, “use of RIV4 in the pediatric population due to medication error” was validated as a signal for review. RIV4 administration in the pediatric population was reported in 78 cases out of a

total of 200 cases reported to Sanofi Pasteur from 16 January 2018 to 15 January 2019, (approximately 39% of all cases in that period). Cumulatively, the postmarketing database contains 400 cases for RIV4 (224) and RIV3 (176) vaccines. Among these cases there were 85 cases involving the patients younger than 18 years of age. There are no cases of influenza like illness or influenza indicating vaccine failure reported for the pediatric cases of RIV4 and RIV (Trivalent) vaccine. Potential harm from medication error is not considered a risk for RIV4. No safety issue was identified following off-label use or misuse of RIV4. The carton of RIV4 product in US was updated to make the existing direction “**for 18 years of age and older**” in bold font more visible for health care providers.

- **Potential for transmission of infectious agents:**

- Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4) is the world’s first approved RIV and is manufactured using an insect (baculovirus) expression vector system and recombinant DNA technology, without the use of eggs or infectious influenza virus. RIV4 contains purified rHA proteins produced in continuous insect cell line (*expresSF<sup>+</sup>*) that is derived from Sf9 cells of the fall armyworm, *S. frugiperda*, and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. As each of the rHAs is expressed in this cell line using the BEVS, extracted from the cells with detergent, and further purified by column chromatography; there is no inactivated or split influenza virus or infectious agent in the vaccine. Potential for transmission of infectious agents is not considered a risk for RIV4.

#### **SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP**

##### ***Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP***

- Anaphylaxis and allergic reactions: As with most vaccines, all parenteral, inactivated influenza vaccines are associated with a risk of serious allergic reactions, including anaphylaxis and angioedema (and the signs and symptoms of such events). Listed reactions may also include range of symptoms such as urticaria, pruritus and local and generalized skin rashes. In light of the updated guidance on format of the safety concerns and risk management plan presented in the good pharmacovigilance practices (GVP) Module V section V.A.1, (released 31 October 2018, EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2) risks that are already well-known to health professionals and do not require additional pharmacovigilance activities or additional risk minimization measures may not need to be included as an important risk. (32) Hence risks like anaphylaxis, which is already well-known to health professionals, where health professionals being aware of the risk of anaphylactic reactions, have the appropriate measures in place as part of clinical practice (which is included in the “Special warnings and precautions for use” of summary of product characteristics [SmPC]), anaphylactic reactions may not need to be included as an important risk. Although such reactions can have serious clinical consequences, they occur with a low frequency and are considered to be acceptable in relation to the severity of the indication. For this reason, anaphylaxis which is an identified risk for RIV4 is not included in the list of safety concerns in the RMP.

- Guillain-Barre syndrome (GBS): RIV4 is composed with recombinant influenza antigens, considering that more than 38 million doses distributed worldwide during 11 years of postmarketing experience with RIV3 and RIV4, the weighted cumulative evidence is insufficient to support a causal association between GBS and RIV3 and RIV4. Available epidemiological studies have not found a causal association between recombinant RIV and GBS, and the balance of epidemiological evidence has arguably only confirmed an association with egg based inactivated vaccines used in the US in 1976. As these events tend to be very rare, the available evidence has been insufficient to confirm a causal association. Whilst this may still be considered as ‘potential’ risk for influenza vaccines as a class, it is listed in undesirable effects in the SmPC. Although GBS can be serious for individual patients, the very low frequency would be unlikely to have a negative impact on the balance of benefits and risks of the product. Routine pharmacovigilance activities are the only proposed method of surveillance each year and no additional risk minimization measures are required. Therefore, GBS is considered “No Risk” and is not included in the list of safety concerns for the EU-RMP.
- Missing information:
  - Use during Pregnancy “Missing Information regarding usage of RIV4 during pregnancy” is not considered a safety concern for RIV4.
  - According to ACIP, pregnant and postpartum women have been observed to be at higher risk for severe illness and complications from influenza, particularly during the second and third trimesters. ACIP and the American College of Obstetricians and Gynecologists (33)(34)(35) recommend that “all women who are pregnant or who might be pregnant during the influenza season, receive influenza vaccine. Any licensed, recommended, and age-appropriate Inactivated Influenza Vaccine (IIV) or RIV4 may be used. ACIP acknowledges that RIV4 as well as other newly licensed IIV products (eg, quadrivalent, cell culture-based, and adjuvanted vaccines) share the limitation of having substantially less experience during pregnancy as compared with previously available products. For recombinant influenza vaccines (available as RIV3 from 2013-14 through 2017-18, and as RIV4 since 2017-18), data are limited to reports of pregnancies occurring incidentally during clinical trials, Vaccine Adverse Event Reporting System (VAERS) reports, and pregnancy registry reports”.
  - Cumulatively, administration of RIV (RIV3/RIV4) during pregnancy was reported in 21 spontaneously reported cases during postmarketing surveillance. There are additional 8 cases in the Global Pharmacovigilance (GPV) database reported from legacy Protein Sciences Corporation’s PSC16 study; seven cases received during the reporting period and one case received after the reporting period.
  - 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. Three hundred thirty (330) pregnant women received RIV3. No serious AEs were reported from the passive surveillance network. However, these data are limited because there was no active follow-up of pregnancies, and the capability of Mongolian surveillance network to capture the pregnancy related AE are uncertain.
  - During the clinical development of the RIV3, in PSC01 study, 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. In PSC16 study, seven pregnancies were reported with 6 uncomplicated live births while 1 subject who reported pregnancy 3 weeks following immunization reported spontaneous abortion after 6 weeks.

- Adverse Events of Special Interest: GBS, neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis and vasculitis are not considered as 'potential' risks for the RIV4 vaccine, however as they have historically been considered potential risks for inactivated influenza vaccines based largely on the reporting of isolated cases over decades of use, these are included in monitoring of safety of all RIV4 clinical studies as AESI, as part of routine pharmacovigilance activities in due diligence. Available epidemiological studies have not found a causal association with Bell's palsy and, for GBS, the balance of epidemiological evidence has arguably only confirmed an association with those vaccines used in the US in 1976. For the other neurological events and vasculitis, as these events tend to be very rare, the available evidence has been insufficient to confirm, or exclude, a causal association. Although these events can be serious for individual patients, even if these could be confirmed as risks their very low frequency would be unlikely to have a negative impact on the balance of benefits and risks of the product. Also, given the rarity of these events reported after IV, it is unlikely that further studies will be able to further evaluate or characterized these as potential risks on a product-specific basis. Routine pharmacovigilance activities are the only proposed method of surveillance each year and no additional risk minimization measures are required for such potential risks. Therefore, these events are not included in the list of safety concerns.

#### **SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP**

There are no important identified risks for the product.

#### **SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP**

There are no new safety concerns since first RMP.

#### **SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION**

##### **SVII.3.1. Presentation of important identified risks and important potential risks**

There are no important identified risks with RIV3/RIV4 that require inclusion as a safety concern in the RMP.

There are no important potential risks with RIV3/RIV4 that require inclusion as a safety concern in the RMP.

##### **SVII.3.2. Presentation of the missing information**

There is no important missing information with RIV3/RIV4 that requires inclusion as a safety concern in the RMP.

## PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

**Table 13 - Summary of the safety concerns**

<b>Important identified risk</b>	Not applicable
<b>Important potential risk</b>	Not applicable
<b>Missing information</b>	Not applicable

## **PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)**

### **III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES**

Routine pharmacovigilance activities of reporting ARs and signal detection are deemed sufficient to monitor the safety profile for RIV3/RIV4.

The safety profile of RIV3/RIV4 will continue to be further characterized in the real-world setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to AEs, and signal detection.

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

This EPSS allows for near real-time detection of early signals of potentially clinically significant changes of the safety profile compared to previous seasonal composition, and relies on enhanced routine pharmacovigilance and coverage data collection. The primary objective of the EPSS is to estimate reporting rates of suspected ARs occurring within 7 days after routine vaccination during the influenza season. An expedited Safety Summary report should be prepared and submitted to the Competent Authority only if such a signal is detected during the EPSS.

A waiver was obtained for Supemtek Tetra (Quadrivalent Influenza Vaccine [recombinant, prepared in cell culture]) in United Kingdom (UK) due to the infeasibility of the EPSS for NH 2021-2022, 2022-2023 and 2023-2024 season. For the NH 2024-2025 season, the Pharmacovigilance Risk Assessment Committee [PRAC] agreed to waive the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines while the 'interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014) is being reviewed (PRAC meeting held from 8<sup>th</sup> to 11<sup>th</sup> April).

As part of routine safety surveillance, medical review of spontaneous individual case safety reports (ICSRs) is performed on a weekly basis in order to detect new signals. Assessment of the detected signals is usually conducted using qualitative methods. Quantitative methods include weekly descriptive analysis of suspected ARs. If there is an unusual number of cases or an increase in seriousness/severity of a suspected AR, or if there is any reason to suspect that patient safety/public health/benefit-risk balance is affected, then additional quantitative methods such as observed-to-expected (O/E) analyses may be used to complement routine signal management methods. Competent authorities will be informed as per applicable standards and regulation. As per EMA requirement, any new information (from routine safety surveillance) that may affect the benefit-risk balance of the product will be communicated promptly to the competent authorities of

the member states in which the product is authorized and to the agency via email ([PPVemerging-safety-issue@ema.europa.eu](mailto:PPVemerging-safety-issue@ema.europa.eu)).

### III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

For the database lock (DBL) VAP00003 study examining vaccine effectiveness of RIV4 relative to standard dose inactivated influenza vaccine among Kaiser Permanente members aged 18-64 years is finished, study report is published. (36) Information on milestones of the study is published in [Annex 2].

Development of Robust Innovative Vaccine Effectiveness (DRIVE) study is deferred and awaiting EMA update on guideline.

#### **Development of Robust Innovative Vaccine Effectiveness (DRIVE):**

As per the EMA guideline on Influenza Vaccines (non-clinical and clinical module), evaluation of VE is expected to be done in Europe. It is however acknowledged by the EMA that adequate brand name specific active surveillance of effectiveness may not be feasible for any vaccine in any season. Implementation of effectiveness studies in Europe started during the NH 2017-2018 influenza season through the DRIVE initiative. The main objective was to assess the feasibility to generate product specific VE data through a public private partnership under an Innovative Medicine Initiative (IMI) between vaccine manufacturers and Public Health Institutions on a five-year period.

The implementation started during the NH 2017-2018 season with a pilot phase which aimed to test the study platform (IT infrastructure, study conduct and governance). The results were considered insufficient to allow a meaningful discussion with regulators, in light of the limitations identified. Hence the EMA/Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) considered premature to request submission of formal variations for assessment by competent authorities and agreed to waive this requirement for the NH 2017-2018 season. This was also the case for the NH 2018-2019 season where the EMA/CMDh concluded that it would be premature to evaluate the currently available limited data set, in particular as not all products from all manufacturers would be equally covered by a regulatory data evaluation at this point in time.

For the NH 2019-2020 season, a report was published on 10 September 2020. According to EMA/CMDh, the sample size should be further increased for conclusive statistics and robust VE estimates. Therefore, based on the data and results presented, the EMA/CMDh concluded that no regulatory action was warranted. (37)

For the NH 2020-21 season, the final report of DRIVE was released on 30 September 2021. (38) Considering the unprecedented situation linked to the coronavirus disease-2019 (COVID-19) pandemic and the associated stringent measures and non-pharmaceutical interventions in place to address the public health crisis, the circulation of non-COVID-19 respiratory viruses (including influenza) was very limited during the 2020-2021 influenza season, phenomenon that has been well described in Europe. Consequently, the number of influenza positive cases reported in DRIVE was extremely low and did not allow to perform the Test Negative Design pooled analysis to estimate brand specific Influenza Vaccine Effectiveness (IVE). Therefore, no regulatory action was requested.

For the NH 2021-2022 season, DRIVE conducted its last IVE study, after five seasons since its first pilot study in 2017-18. (38) The low influenza virus circulation observed during the 2021-2022 season, partly due to the nonpharmaceutical interventions and lockdowns implemented to combat the COVID-19 pandemic, together with the shift of attention and resources from influenza to COVID-19, which resulted in no new study sites, largely impacted DRIVE's study. DRIVE was not able to reach the sample size required to generate robust brand-specific IVE estimates. Therefore, no regulatory action was requested.

Considering the ongoing COVID-19 pandemic and related activities and the termination of the DRIVE project on 30 June 2022, the EMA agreed in July 2022 to defer the conduct of yearly post-authorization effectiveness studies for influenza seasonal vaccines for the NH 2022-2023 season.

In September 2023, the EMA agreed for another year of deferral for the season 2023-2024 in light of the constraints highlighted by the DRIVE consortium to generate quality vaccines effectiveness data under the current circumstances (lack of engagement by public health authorities, reluctance to collaborate with private partners, other similar ongoing initiatives publicly funded affecting the number of study sites available). (36)

**Table 14 - Additional pharmacovigilance activities (category 1 to 3) summary**

<b>Development of Robust Innovative Vaccine Effectiveness (DRIVE) (Cat. 3)</b>
<b>Study short name and title</b> To comply with the guideline on influenza vaccines – Non-clinical and clinical Module (EMA/CHMP/VWP/457259/2014) of Jul-2016, a supporting IMI program called on DRIVE. DRIVE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific IVE data in Europe.
<b>Rationale and study objectives</b> As per the IMI legal framework, this is a 5 years partnership project, encompassing 4 consecutive influenza seasons. Studies are intended to be conducted annually in European sites and the data generated will be pooled across participating centers, with the first pilot seasonal studies initiated during the 2017-2018 northern hemisphere influenza season. Each year a report will be generated to synthesize data on IVE collected across participating sites including data generated from the public health surveillances contributing to DRIVE. Objectives is to measure season IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type (eg, by antigen preparation strategy, number of virus strains, adjuvant,) then by overall IV.
<b>Study design</b> Population-based database cohort studies: To reach appropriate sample size for assessing brand-specific VE, the data from individual studies will be pooled. The studies may take place in a primary care or a hospital setting. The study setting is defined by each study site depending on the available data. Test-negative design studies: <ul style="list-style-type: none"><li>• A multicentre study using data from several study sites.</li><li>• In each participating study site, an observational case-control study using the test-negative design.</li></ul>
<b>Study populations</b> The study population consists of patients seeking care (ie, subjects consulting their general physician [GPs], or an emergency department/hospital) for symptoms compatible with ILI or Severe Acute Respiratory Infections (SARI) aged 6 months and above, with no contraindication for IV. Each study site to specify the study population and the case finding procedure, please see the case finding section.

**Milestones**

As per the IMI legal framework, this is a 5 year partnership project, encompassing 4 consecutive influenza seasons. Studies were intended to be conducted annually in European sites and the data generated were pooled across participating centers, with the first pilot seasonal studies initiated during the 2017-2018 northern hemisphere influenza season. Each year a report was generated to synthesize data on IVE collected across participating sites including data generated from the public health surveillances contributing to DRIVE. Results were provided every year but did not trigger a RMP update, as per EMA agreement on 30-Apr-2019 (EMA/248552/2019 Vaccine Working Party). Sanofi Pasteur was not the study sponsor or owner of the data and did not control the scientific deliverables, which include the Study Protocol, Statistical Analysis Plan and Study Reports. Over five seasons, DRIVE collected data on >35 000 patients, more than 60 variables, and 13 influenza vaccines.

Considering the ongoing COVID-19 pandemic and related activities and the termination of the DRIVE project on 30-Jun-2022, the EMA agreed in Jul-2022 to defer the conduct of yearly post-authorization effectiveness studies for influenza seasonal vaccines for the NH 2022-2023 season.

In Sep-2023, the EMA agreed for another year of deferral for the season 2023-2024 in light of the constraints highlighted by the DRIVE consortium to generate quality vaccines effectiveness data under the current circumstances.

COVID-19: Coronavirus Disease-2019; DRIVE: Development of Robust Innovative Vaccine Effectiveness; EMA: European Medicine Agency; GP: General Physician; ILI: Influenza Like Illness; IMI: Innovative Medicines Initiative; IV: Influenza Vaccination; IVE: Influenza Vaccine Effectiveness; NH: Northern Hemisphere;; RMP: Risk Management Plan; SARI: Severe Acute Respiratory Infections; VE: Vaccine Effectiveness.

**III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES**

**Table 15 - Ongoing and planned additional pharmacovigilance activities**

<b>Study Status</b>	<b>Summary of objectives</b>	<b>Safety concerns addressed</b>	<b>Milestones</b>	<b>Due dates</b>
<b>Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization</b>				
Not applicable				
<b>Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances</b>				
Not applicable				
<b>Category 3 - Required additional pharmacovigilance activities</b>				
Development of Robust Innovative Vaccine Effectiveness Assessment of the feasibility of building a sustainable platform in Europe able to generate brand specific IVE data in Europe.  Is deferred and awaiting EMA update on guideline.	To measure seasonal IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type, then by overall IV.	This is epidemiological study for assessing effectiveness of routine IV. No data on adverse events will be collected.  The measurement of IVE support Safety Benefit Risk analyses for Influenza  The product specific vaccine effectiveness data supports benefits of IV versus risks related for AEs.	Annual reports at the end of influenza season.	Annual at the end of influenza season.

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

## **PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES**

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are ongoing for RIV3/RIV4.

## **PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)**

There are no safety concerns with RIV3/RIV4 that require specific risk minimization measures.

### **V.1 ROUTINE RISK MINIMIZATION MEASURES**

Anaphylaxis has been communicated in the proposed SmPC, in section 4.3, “Contraindications”, section 4.4 Special warnings and precautions for use”, section 4.8 “Undesirable effects” and also addressed in package leaflet (PL).

In the SmPC following information is provided. “Contraindication: Hypersensitivity to the active substances, to any of the excipients listed in section 6.1 (list of excipients) or to any trace residuals such as octylphenol ethoxylate.” And “Special warning and precautions: Hypersensitivity: Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.”

There are no safety concerns for RIV3/RIV4 that require risk minimization measures beyond the information described in the SmPC.

### **V.2 ADDITIONAL RISK MINIMIZATION MEASURES**

Routine risk minimization activities as described in Part [V.1](#) are sufficient to manage the safety concerns of the medicinal product.

### **V.3 SUMMARY OF RISK MINIMIZATION MEASURES**

There are no safety concerns for RIV3/RIV4 that require risk minimization measures beyond the information described in the draft SmPC.

## **PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN**

### **Summary of risk management plan for Supemtek Tetra (Quadrivalent Influenza Vaccine [recombinant, prepared in cell culture])**

This is a summary of the RMP for Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV4). There are no important risks or important missing information for RIV4 that are considered as safety concerns.

Supemtek Tetra's SmPC and its PL give essential information to HCPs and patients on how Supemtek should be used.

This summary of the RMP for Supemtek Tetra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Supemtek Tetra's RMP.

#### **I. THE MEDICINE AND WHAT IT IS USED FOR**

RIV4 is authorized for active immunization for the prevention of influenza disease in adult. Newly proposed indication is for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV4 should be used in accordance with official recommendations (see SmPC for the full indication). It contains RIV4 manufactured using a baculovirus expression vector system (BEVS) and recombinant deoxyribonucleic acid (DNA) technology as the active substance and it is given by intramuscular (IM) injection.

Further information about the evaluation of Supemtek Tetra's benefits can be found in Supemtek Tetra's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

*<https://www.ema.europa.eu/en/medicines/human/EPAR/supemtek>*

#### **II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS**

There are no safety concerns for the RIV4 and no risk minimization measures beyond proposed SmPC. Together, these measures constitute routine risk minimization measures.

Anaphylaxis has been communicated in the draft SmPC, in section 4.3, "Contraindications", section 4.4 "Special warnings and precautions for use", section 4.8 "Undesirable effects". In the PL following information is provided for the HCPs. "Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine".

In addition to the measure of communication via draft SmPC, the information about ARs is collected continuously and regularly analyzed and presented in the PBRER assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A List of important risks and missing information

There are no important identified risks with RIV4 that require inclusion as a safety concern in the RMP.

There are no important potential risks with RIV4 that require inclusion as a safety concern in the RMP.

There is no important missing information with RIV4 that requires inclusion as a safety concern in the RMP.

**Table 16 - List of important risks and missing information**

<b>Important identified risk</b>	Not applicable
<b>Important potential risk</b>	Not applicable
<b>Missing information</b>	Not applicable

## II.B Summary of important risks

The safety information in the proposed SmPC is aligned to the reference medicinal product. There are no safety concerns for RIV4 or no additional risk minimization measures.

## II.C Post-authorization development plan

### II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation.

### II.C.2 Other studies in post-authorization development plan

**Table 17 - Other studies in post-authorization development plan**

<b>Development of Robust Innovative Vaccine Effectiveness (DRIVE) (Cat. 3)</b>
<p><b>Purpose of the study:</b></p> <p>Objectives is to measure season IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type (eg, by antigen preparation strategy, number of virus strains, adjuvant,) then by overall IV. To comply with the Guideline on Influenza vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) of Jul-2016, a supporting IMI program called on DRIVE. Development of Robust Innovative VE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific IVE data in Europe.</p> <p>DRIVE: Development of Robust Innovative Vaccine Effectiveness; IV: Influenza Vaccination; IVE: Influenza Vaccine Effectiveness; IMI: Innovative Medicines Initiative; VE: Vaccine Effectiveness.</p>

## **Summary of risk management plan for Supemtek (Trivalent Influenza Vaccine [recombinant, prepared in cell culture])**

This is a summary of the RMP for Trivalent Influenza Vaccine (recombinant, prepared in cell culture) (RIV3). There are no important risks or important missing information for RIV3 that are considered as safety concerns.

Supemtek's SmPC and its PL give essential information to HCPs and patients on how Supemtek should be used.

This summary of the RMP for Supemtek should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Supemtek's RMP.

### **III. THE MEDICINE AND WHAT IT IS USED FOR**

RIV3 proposed indication is for active immunization for the prevention of influenza disease in persons from 9 years of age and older. RIV3 should be used in accordance with official recommendations (see SmPC for the full indication). It contains RIV3 manufactured using a baculovirus expression vector system (BEVS) and recombinant deoxyribonucleic acid (DNA) technology as the active substance and it is given by intramuscular (IM) injection.

Further information about the evaluation of Supemtek's benefits can be found in Supemtek's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

*<https://www.ema.europa.eu/en/medicines/human/EPAR/supemtek>*

### **IV. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS**

There are no safety concerns for the RIV3, and no risk minimization measures beyond proposed SmPC. Together, these measures constitute routine risk minimization measures.

Anaphylaxis has been communicated in the draft SmPC, in section 4.3, "Contraindications", section 4.4 "Special warnings and precautions for use", section 4.8 "Undesirable effects". In the PL following information is provided for the HCPs. "Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine".

In addition to the measure of communication via draft SmPC, the information about ARs is collected continuously and regularly analyzed and presented in the PBRER assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

#### **IV.A List of important risks and missing information**

There are no important identified risks with RIV3 that require inclusion as a safety concern in the RMP.

There are no important potential risks with RIV3 that require inclusion as a safety concern in the RMP.

There is no important missing information with RIV3 that requires inclusion as a safety concern in the RMP.

**Table 18 - List of important risks and missing information**

<b>Important identified risk</b>	Not applicable
<b>Important potential risk</b>	Not applicable
<b>Missing information</b>	Not applicable

#### **IV.B Summary of important risks**

The safety information in the proposed SmPC is aligned to the reference medicinal product. There are no safety concerns for RIV3 or no additional risk minimization measures.

#### **IV.C Post-authorization development plan**

##### **IV.C.1 Studies which are conditions of the marketing authorization**

There are no studies which are conditions of the marketing authorization or specific obligation.

##### **IV.C.2 Other studies in post-authorization development plan**

There are no ongoing studies in post-authorization development plan.

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## **PART VII: ANNEXES**

## **ANNEX 4      SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS**

**NOT APPLICABLE**

## **ANNEX 6      DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES**

**NOT APPLICABLE**