EU Risk Management Plan (EU RMP)

for

Trivalent and Quadrivalent Influenza Vaccine

(surface antigen, inactivated, prepared in cell cultures)

(Flucelvax® and Flucelvax® Tetra)

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RMP version number:	4.0
Data lock point for this RMP:	27 May 2024
Date of final sign-off:	27 November 2024
Rationale for submitting an updated RMP:	Indication extension for use in persons 6 months of age and older (TIVc)
Summary of significant changes in this RMP:	Removal of safety concerns (Missing information); DRIVE deferral; Update per proposed indication extension
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	Version number: 3.2 Approved with procedure: Centralised procedure EMEA/H/C/006532/0000 Date of approval (opinion date): 15 November 2024
Qualified Person Pharmacovigilance (QPPV) name:	Juergen Zorn, MD
QPPV (deputy) signature:	PPD
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the QPPV of CSL Seqirus. The electronic signature is available on file.

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Abbreviations

Term / Abbreviation	Description
ATC	Anatomical Therapeutic Chemical
AF-HTV	Health Threats and Vaccines Strategy
ALRI	ALRI
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
aQIVc	Adjuvanted cell-based Quadrivalent Influenza Vaccine
CDC	Centers for Disease Control and Prevention
DLP	Data Lock Point
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPSS	Enhanced Passive Safety Surveillance
ETF	Emergency Task Force
EU	European Union
GBS	Guillain-Barré Syndrome
GLP	Good laboratory practice
GVP	Good Pharmacovigilance Practices
IMI	Innovative Medicines Initiative
ITP	Immune thrombocytopenia
NH	Northern Hemisphere

PL	Package Leaflet
PMC	Post-marketing commitment
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
QIVc	Cell-based Quadrivalent Influenza Vaccine
QIVr	Recombinant Quadrivalent Influenza Vaccine
RMP	Risk Management Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SH	Southern Hemisphere
SmPC	Summary of Product Characteristics
TIVc	Cell-based Trivalent Influenza Vaccine
UK	United Kingdom
US	United States
WHO	World Health Organisation

Part I: Product(s) Overview

Table Part I.1 Product(s) Overview

Active substance(s) (INN or common name):	Trivalent Influenza Vaccine (TIVc; surface antigen, inactivated, prepared in cell cultures) Quadrivalent Influenza Vaccine (QIVc; surface antigen, inactivated, prepared in cell cultures)
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Influenza vaccine ATC code: J07BB02
Marketing Authorisation Holder or Applicant:	Seqirus Netherlands B.V.
Medicinal products to which this RMP refers	Two (2)
Invented name(s) in the European Economic Area (EEA)	TIVc: Flucelvax® QIVc: Flucelvax® Tetra
Marketing Authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Influenza vaccine
	Summary of mode of action: TIVc provides active immunisation against three influenza virus strains (two A subtypes and one B type) by inducing humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses. QIVc provides active immunisation against four influenza virus strains (two A subtypes and two B types) by inducing humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.
	Important information about its composition: Influenza virus surface antigens (haemagglutinin and neuraminidase), of strains*: TIVc: A/H1N1, A/H3N2 and B/Victoria QIVc: A/H1N1, A/H3N2, B/Yamagata and B/Victoria *Propagated in Madin Darby Canine Kidney cells
Hyperlink to the Product Information	TIVc: Proposed SmPC link

	QIVc: Flucelvax Tetra, Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) (europa.eu)
Indication(s) in the EEA	Current: TIVc: Prophylaxis of influenza for adults and children from 2 years of age. QIVc: Prophylaxis of influenza for adults and children from 2 years of age.
	Proposed: TIVc: Prophylaxis of influenza for adults and children from 6 months of age and older. QIVc: Prophylaxis of influenza for adults and children from 6 months of age.
Dosage in the EEA	Current: TIVc: Adults from the age of 18 years: One dose of 0.5 mL *Paediatric population:* Children 9 years of age and older: One dose of 0.5 mL Children from 2 years to less than 9 years of age: 1 or 2 doses of 0.5 mL. Children who have not been previously vaccinated should receive a second dose after an interval of at least 4 weeks. QIVc: *Adults:* Adults from the age of 18 years: One dose of 0.5 mL *Paediatric population:* Children 9 years of age and older: One dose of 0.5 mL Children from 2 years to less than 9 years of age: 1 or 2 doses of 0.5 mL. Children who have not been previously vaccinated should receive a second dose after an interval of at least 4 weeks.
	Proposed: TIVc: *Adults:* Adults from the age of 18 years: One dose of 0.5 mL *Paediatric population:*

	Children 9 years of age and older: One dose of 0.5 mL Children from 6 months to less than 9 years of age: 1 or 2 doses of 0.5 mL. Children who have not been previously vaccinated should receive a second dose after an interval of at least 4 weeks. QIVc: Adults: Adults from the age of 18 years: One dose of 0.5 mL Paediatric population: Children 9 years of age and older: One dose of 0.5 mL Children from 6 months to less than 9 years of age: 1 or 2 doses of 0.5 mL. Children who have not been previously vaccinated should receive a second dose after an interval of at least 4 weeks.
Pharmaceutical form(s) and strengths	Current: TIVc: Suspension for injection in pre-filled syringe Clear to slightly opalescent liquid One dose of 0.5 mL contains 15 mcg haemagglutinin per influenza strain • 10 pre-filled syringes (0.5 mL) with or without needles • 1 pre-filled syringe (0.5 mL) with or without needle QIVc: Suspension for injection in pre-filled syringe Clear to slightly opalescent liquid One dose of 0.5 mL contains 15 mcg haemagglutinin per influenza strain • 10 pre-filled syringes (0.5 mL) with or without needles • 1 pre-filled syringe (0.5 mL) with or without needle
	Proposed: TIVc: No change QIVc: No change
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety Specification

Part II: Module SI – Epidemiology of The Indication(s) and Target Population

Indications and Vaccine Strain Composition

The proposed indication for Cell-based Trivalent Influenza Vaccine (TIVc) is prophylaxis of influenza for adults and children from 2 years of age. The Cell-based Quadrivalent Influenza Vaccine (QIVc) is currently licensed for use in adults and children from 2 years of age in the EU. The proposed indication for Cell-based Quadrivalent Influenza Vaccine (QIVc) is prophylaxis of influenza in adults and children from 6 months of age.

Influenza virus strains included in TIVc are A/H1N1, A/H3N2, and a B strain (from the B/Victoria strain lineage). Influenza virus strains included in QIVc are A/H1N1, A/H3N2, and two B strains (B/Victoria and B/Yamagata).

Influenza infection

Influenza is an infectious acute respiratory disease of global importance caused by an influenza virus. In temperate climates, influenza generally affects people from November to March in the Northern Hemisphere (NH) and from May to September in the Southern Hemisphere (SH). It can occur all year round in tropical climates (World Health Organisation [WHO], 2023a).

Type A viruses are associated with annual epidemics and pandemics, and type B viruses contribute to the annual epidemics (WHO, 2023a). The influenza type A virus can be further divided into subtypes based on the haemagglutinin and neuraminidase surface glycoprotein antigens. Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are the most clinically important for annual influenza disease burden.

Influenza epidemiology

Overall, the WHO estimates that worldwide annual influenza epidemics result in around 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths (WHO, 2023a). In the European Union (EU) / European Economic Area EEA region, seasonal influenza is estimated to cause up to 50 million symptomatic cases each year, and 15,000 to 70,000 European citizens die every year of causes associated with influenza (European Centre for Disease Prevention and Control (ECDC, 2022a). In the United States (US), the Centers for Disease Control and Prevention (CDC) estimate that influenza has resulted in 9.3 million to 41 million illnesses, between 100,000 to 710,000 hospitalizations and between 4,900 to 51,000 deaths annually between 2010 and 2023 (CDC, 2024). Across age groups, the burden of

influenza disproportionately falls on individuals < 5 years of age and ≥ 65 years of age (Neuzil et al, 2000; Thompson et al, 2004; Rolfes et al, 2018).

There are currently 2 known influenza B strains from 2 separate lineages, B/Yamagata and B/Victoria, that have circulated during previous influenza seasons. However, circulation of the B/Yamagata lineage has not been confirmed since March 2020 (Paget et al, 2022). Given this status, the risk of future B/Yamagata lineage epidemics is considered low and, in September 2023, the WHO influenza vaccine composition advisory committee determined that the inclusion of B/Yamagata lineage antigens in influenza vaccines is no longer warranted (WHO, 2023b). EMA's Emergency Task Force (ETF) recommended a well-planned transition to trivalent influenza vaccines with continuous monitoring considered important to confirm the disappearance of B/Yamagata. ETF recommended that antigens of the B/Yamagata lineage should be removed from the live attenuated influenza vaccines for the 2024/2025 influenza season; for all other influenza vaccines the recommended target is the 2025/2026 season (EMA Emergency Task Force (ETF), 2024).

Further information regarding the epidemiology of influenza in key age groups recommended for annual influenza vaccination, namely paediatric and elderly populations, are provided below.

Paediatric population – epidemiology, morbidity and mortality

Influenza disease is associated with substantial morbidity and mortality in children. The higher attack rate of influenza in children is attributed to a lack of prior exposure to influenza virus and an immature immune system, both of which increase susceptibility to infection (Black et al, 2011; Izurieta et al, 2000; Munoz, 2002; Simon et al, 2015). In children < 5 years of age, the average yearly attack rate of influenza disease ranges between 10% to 30%, with even higher rates documented during certain epidemic years (Neuzil et al, 2002; Somes et al, 2018). In comparison, the attack rate in the overall (unvaccinated) adult population is estimated to be an average of 4% (Jayasundara et al, 2014; Somes et al, 2018).

Globally, the annual incidence of influenza associated hospitalisations in children < 5 years of age was estimated as 135 per 100,000. (Lafond et al, 2016). In Europe, the incidence of influenza-associated hospitalisations of < 5 years of age was estimated at 53 per 100,000 (Lafond et al, 2016). In the same age group in the US, the average hospitalisation rate estimated over 15 influenza seasons (1993 to 2008) was 94 per 100,000 (Zhou et al, 2012). A systematic review and modelling study showed that in 2018, among children under 5 years globally, there were an estimated 109 million influenza virus episodes, 10 million influenza-virus-associated acute lower respiratory infection (ALRI) cases; 870,000 influenza-virus-associated ALRI hospital admissions, 15,300 in-hospital deaths, and up to 34,800 overall influenza-virus-

associated ALRI deaths. Influenza virus accounted for 7% of ALRI cases, 5% of ALRI hospital admissions, and 4% of ALRI deaths in children under 5 years. About 23% of the hospital admissions and 36% of the in-hospital deaths were in infants under 6 months. About 82% of the in-hospital deaths occurred in low-income and lower-middle-income countries (Wang et al, 2020). From the NH 2004/2005 to the NH 2019/2020 season, flu-related deaths in children reported to CDC during regular flu seasons have ranged from 37 to 199 deaths (CDC, 2023b). During 2019–2020, for example, 199 flu-related deaths in children were reported to CDC, but statistical modelling suggests that approximately 434 deaths may have occurred. Importantly, among reported flu-related deaths in children, about 80% occurred in children who were not fully vaccinated (CDC, 2023b).

Furthermore, hospitalisation and deaths represent only a fraction of the total burden of influenza on the medical system and therefore do not represent the full social and economic impact. Approximately 5% of children presenting to medical care require hospitalisation. In Europe, confirmed influenza cases in the paediatric population of 18 years of age were estimated to include multiple medical visits (1.7 to 2.8 visits per case), antibiotic prescriptions (7% to 55%), and antipyretic or other medications for symptomatic relief (76% to 99%). Influenza also leads to absence from school or childcare ranging from 2.8 to 12.0 days for the infected children, 1.3 to 6.0 days for their siblings, and from 1.3 to 6.3 days for their parents (Antonova et al, 2012).

Adults ≥ 65 years – epidemiology, morbidity and mortality

The higher burden of influenza among adults aged ≥ 65 years relative to younger adults is, in part, attributable to the age-related decline of the immune system (immunosenescence) (Lambert et al, 2012). Additionally, as individuals surpass 65 years, the prevalence of underlying medical conditions increases, as does frailty, and declines in functional status. This leads to heightened susceptibility to influenza and risk of serious complications, leading to increased influenza related hospitalisations and deaths. Recognizing their greater vulnerability, older adults are prioritized for vaccination (Grohskopf et al, 2022).

During most influenza seasons, individuals ≥ 65 years carry the heaviest burden of severe disease. Approximately 50-70% of hospitalizations due to influenza occur among this age group. In the United Kingdom (UK), the influenza-related hospitalisation rate was estimated to be 101 per 100,000 for individuals 65 to 74 years of age, and 252 per 100,000 for individuals ≥ 75 years of age relative to the overall rate of 49 per 100,000 (Matias et al, 2016). In Norway from 2008 to 2017 the average hospitalisation rate in the age groups ranged from 62 per 100,000 for those who were 60 to 69 years of age to 241 per 100,000 in the ≥ 80 year age group (Hauge et al, 2019). In Spain between NH 2010/2011 to NH 2015/2016, relative to those 15 to

65 years of age, cumulative rates for ≥ 65 years of age were approximately three times higher for severe hospitalised confirmed influenza cases, approximately two times higher for intensive care unit admissions, and approximately six times higher for deaths in influenza hospitalised patients (Oliva et al, 2018). In the US, the influenza-related hospitalisation rate over 15 seasons was estimated to be 309 per 100,000 in individuals ≥ 65 years of age versus a mean of 63.5 per 100,000 across all age groups (Zhou et al, 2012).

Influenza also contributes substantially to the mortality rate among ≥ 65 years of age. In the WHO EU region, of the more than 44,000 deaths occurring annually (ranging between approximately 28,000 to approximately 70,000 deaths per season) from influenza related causes, approximately 75% of these deaths occur in individuals ≥ 65 years of age (Iuliano et al, 2018).

Demographics of the Population and Risk Factors for the Disease

In the US, the CDC recommends that everyone 6 months of age and older get a flu vaccine every year (CDC, 2023a). The European Centre for Disease Prevention and Control (ECDC) and the WHO recommend annual seasonal influenza for specified risk groups (ECDC, 2022b; WHO, 2023a):

Population groups at increased risk of influenza or complications due to influenza infection include:

- Older adults (ECDC), specifically aged 65 years or older (WHO)
- Younger children (ECDC), specifically children aged 6 through 59 months (WHO)
- Individuals with chronic medical conditions such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or hematologic diseases, and individuals with immunosuppressive conditions (such as Human Immunodeficiency Virus (HIV)/ Acquired immunodeficiency syndrome (AIDS), receiving chemotherapy or steroids, or malignancy)
- Individuals with any condition compromising respiratory functions eg, morbid obesity (body mass index > 40), and physical handicap in children and adults

- Pregnant women and women up to 2 weeks postpartum

Main Existing Treatment Options

Seasonal influenza vaccination

Vaccination is the most effective form of influenza prevention. The main objective of seasonal influenza vaccination is to reduce the risk for those who would be predisposed to complications if they were to become infected.

In 2003, the World Health Assembly, which includes all EU/EEA countries, recommended targeting 50% of the elderly for vaccination uptake by 2006 and 75% by 2010. Moreover, an EU target was set by the Council of all EU ministers of health of achieving 75% vaccination coverage by 2014−15 in the older age groups, and if possible, extending this to people with chronic conditions (ECDC, 2023).

Personal protective measures

Public health strategies include various personal protective measures such as regular hand washing and proper drying of the hands or alcohol-based hand sanitizers; good respiratory hygiene and cough etiquette; self-isolation for those who feel unwell, feverish or have other symptoms of influenza; avoiding close contact with sick people and avoiding touching one's eyes, nose, or mouth; wearing face masks, particularly during the period when influenza and severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 are co-circulating, especially for vulnerable categories, such as the elderly or those with underlying medical conditions (CDC, 2022a; ECDC, 2022a).

Symptomatic treatment

Most simple seasonal influenza cases are managed symptomatically, and patients are advised to stay at home and rest to minimise the risk of infecting others in the community. Treatment focuses on reducing fever and relieving the symptoms. An influenza diagnosis can be confirmed by submitting nasopharyngeal specimens for laboratory analysis. It is considered important that patients monitor themselves to detect whether their condition deteriorates, and they require medical intervention (ECDC, 2022a).

Antivirals

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalised; has severe, complicated, or progressive illness; or is

at higher risk for influenza complications. Empiric antiviral treatment should be started as soon as possible in the above priority groups (CDC, 2022b).

There are four antiviral drugs approved by the European Medicines Agency (EMA) available in the EU Member States to treat influenza. These includes oseltamivir, zanamivir, peramivir and baloxavir. For the best clinical benefit, treatment with antivirals should be given early in the infection, within 48 hours, (the earlier the better), to reduce the fever and flu-like symptoms. (ECDC, 2022a).

Part II: Module SII – Non-Clinical Part of The Safety Specification

The nonclinical program was designed based on global regulatory requirements for testing of vaccines and adjuvants. Seqirus TIVc and QIVc share the same manufacturing process and drug substance. As such, the nonclinical program is relevant to both Seqirus TIVc and QIVc. TIVc was immunogenic in mice, rabbits, and ferrets, and QIVc was immunogenic in rabbits. Protection against influenza virus challenge by TIVc was demonstrated in the ferret, based on comparisons of effects on bodyweight, body temperature, and leukocyte counts between vaccinated animals and unvaccinated control animals. TIVc was well tolerated based on viability and absence of overt signs of toxicity.

Two good laboratory practice (GLP) rabbit toxicology studies were performed with TIVc and one GLP rabbit toxicology study was performed with QIVc. In the repeat-dose toxicity studies, two or three doses of vaccine were administered one week or three weeks apart using the clinical route (intramuscular), dose (45 µg or 60 µg), and volume (0.5 mL). A comprehensive evaluation of in-life and post-mortem parameters was performed. TIVc and QIVc were immunogenic, well tolerated locally, and there were no systemic toxicological effects.

In a reproductive and developmental toxicity study in female rabbits, intramuscular injections of TIVc were administered prior to mating (three doses) and during gestation (two doses) at the clinical dose (45 µg) and volume (0.5 mL). Evaluations included potential effects of the vaccine or elicited antibodies on mating, fertility, gestation, lactation, and maternal behaviour in addition to potential effects on offspring of treated does. There was no maternal toxicity and there were no treatment-related effects on any aspect of reproductive or developmental health under the conditions of the study. TIVc was not teratogenic.

In accordance with guidelines for the non-clinical development of vaccines, genotoxicity, carcinogenicity, and safety pharmacology studies were not performed. The completed non-clinical programme complies with global guidelines for the testing of vaccines, and no additional studies are required to support use in special population. No safety concerns were identified in non-clinical studies.

Part II: Module SIII – Clinical Trial Exposure

TIVc

The clinical development programme for TIVc included a total of 20 clinical trials (Table SIII.1). Of these 20 clinical trials with TIVc, seven clinical trials were randomised, controlled studies in healthy adult subjects that were part of the initial biologic license application (BLA) for licensure of TIVc in the US: V58P1, phase I/II; V58P2, phase II; V58P4, phase III; V58P4E1, phase III extension study of V58P4; V58P5, phase II/III; V58P9, phase III, and V58P13, phase III. Following approval in the EU and US, an additional seven randomised and controlled studies were conducted as EU and US post-marketing commitments (PMCs) in adult (V58P4E2, V58P14, V58_23) and paediatric subjects (V58P12, V58P15, V58P16 and V58_31), including populations at risk. As part of annual licensure update in the EU, four open label studies in adult healthy subjects (V58P1S, V58_25S, V58_32S and V58_33S) were conducted. Two QIVc studies with TIVc as comparator have also been conducted, studies V130_01 and V130_03, respectively in adults and the paediatric population. All clinical trials in the TIVc clinical programme were completed by 31 May 2017.

Safety and immunogenicity were assessed in all studies, except for studies V58_31 and V58P15 which were safety studies only. All TIVc trials compared the effects of TIVc with egg-derived influenza control vaccines, except for the annual licensure (open label) studies V58P1S; V58_25S, V58_32S and V58_33S. The most common egg-derived control vaccine was Agrippal. This comparator was used in all studies except for studies V58P5, V58_23, V58P12 and V58_31, which had Fluvirin as comparator, and V58P16, which used Fluzone as comparator. The efficacy study V58P13 was the only study with placebo as comparator, In addition to Agrippal. Both QIVc studies used TIV1c and TIV2c (WHO recommended B strain; alternate lineage B/Victoria, respectively) as comparator vaccines.

Cumulatively from development international birth date (DIBD) up to and including the Data Lock Point (DLP) of this Risk Management Plan (RMP), approximately 15,666 subjects have received TIVc in Seqirus-sponsored (previously Novartis-sponsored) investigational clinical trials. In addition, approximately 1,249 subjects were dosed with TIV2c, which is TIVc with the alternate B-strain lineage to that recommended by the WHO for seasonal trivalent vaccine applicable to the influenza season(s) in which the trials were conducted. The clinical trial exposure details for TIVc are shown in (Table SIII.1-Table SIII.3) The clinical database includes clinical trials that were conducted in different countries, continents, and influenza seasons. The safety and immunogenicity data are representative of the clinical experience of TIVc in a diverse population.

At the DLP of this RMP, the exposure details are presented in the tables below (Table SIII.1-Table SIII.3)

Table SIII.1 Completed TIVc clinical trials

Study Number (Phase)	Study Objectives	Study Design Type of Control	Study Vaccines	Number of Subjects (Exposed)	Subjects' Ages and Geographic Location
V58P1 (Phase I/II)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeA **Total**	120 120 **240**	Subjects ≥ 18 years of age Germany
V58P2 (Phase II)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeA **Total**	110 113 **223**	Subjects ≥ 18 years of age New Zealand
V58P4 (Phase III)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeA **Total**	1,330 1,324 **2,654**	Subjects ≥ 18 years of age Poland
V58P4E1 (Phase III)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeA **Total**	1,104[1] 1,131 **2,235**	Subjects ≥ 18 years of age Poland
V58P4E2 (Phase III)	Immunogenicity, safety, revaccination, concomitant vaccine	Single-blind, extension study	TIVc TIVeA **Total**	1,108[2] 414 **1,522**	Subjects ≥ 18 years of age Poland
V58P5 (Phase II/III)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeF **Total**	309 304 **613**	Subjects 18 to < 50 years of age US
V58P9 (Phase III)	Immunogenicity, safety, lot-to-lot consistency	Observer-blind, randomised	TIVc TIVeA/F **Total**	1,028 171 **1,199**	Subjects 18 to < 61 years of age Lithuania
V58P12 (Phase II/III)	Immunogenicity and safety	Observer-blind, randomised	TIVc TIVeF **Total**	2,251 1,329 **3,580**	Subjects 3 to < 18 years of age US, Europe

Study Number (Phase)	Study Objectives	Study Design Type of Control	Study Vaccines	Number of Subjects (Exposed)	Subjects' Ages and Geographic Location
V58P13 (Phase III)	Immunogenicity, safety and efficacy	Observer-blind, randomised	TIVc TIVeA Placebo **Total**	3,813 3,669 3,894 **11,376**	Subjects 18 to < 50 years of age US, Finland, Poland
V58P14 (Phase IV)	Safety, immunogenicity in subjects at risk	Observer-blind, randomised	TIVc TIVeA **Total**	1,001 396 **1,397**	Subjects ≥ 18 years old, with or without underlying medical conditions Germany
V58P15 (Phase III)	Safety	Observer-blind, randomised	TIVc TIVeA **Total**	278 148 **426**	Subjects at risk of influenza complications, 3 to 18 years of age Italy, Spain
V58P16 (Phase I/II)	Dose finding, immunogenicity and safety.	Observer-blind, randomised	TIVc TIVeFZ **Total**	507 164 **671**	Subjects 6 months to < 48 months old Thailand, Philippines, US, Finland.
V58_23 (Phase III)	Immunogenicity, safety, lot-to-lot consistency	Double-blind, randomised	TIVc TIVeF **Total**	1,169 391 **1,560**	Subjects 18 to < 50 years of age US
V58_31 (Phase III)	Safety	Open label	TIVc TIVeF **Total**	1,370 682 **2,052**	Subjects 4 to < 18 years of age Australia, New Zealand, Thailand, Philippines, US
V130_01 (Phase III)	Immunogenicity and safety	Randomised, double-blind, multicentre, non-inferiority	QIVc TIV1c[1] TIV2c[2] **Total**	1,334 677 669 **2,680**	Subjects ≥ 18 years of age US
V130_03 (Phase III)	Immunogenicity and safety	Randomised, double-blind, multicentre, non-inferiority	QIVc TIV1c[1] TIV2c[2] **Total**	1,159 593 580 **2,332**	Subjects 4 to < 18 years of age US

Study Number (Phase)	Study Objectives	Study Design Type of Control	Study Vaccines	Number of Subjects (Exposed)	Subjects' Ages and Geographic Location
Completed TIVc clinical trials conducted in the EU (post licensure)					
V58P1S	Immunogenicity and safety	Open-label uncontrolled seasonal study	TIVc	135	Subjects ≥ 18 years of age Germany
V58_25S	Immunogenicity and safety	Open-label uncontrolled seasonal study	TIVc	126	Subjects ≥ 18 years of age Germany
V58_32S	Immunogenicity and safety	Open-label uncontrolled seasonal study	TIVc	126	Subjects ≥ 18 years of age Germany
V58_33S	Immunogenicity and safety	Open-label uncontrolled seasonal study	TIVc	126	Subjects ≥ 18 years of age Germany

Source: Individual clinical study reports for randomised studies. TIVc DSUR version 6, dated 26 July 2017, for open label studies.
Abbreviations: TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal); TIVeF = egg-based trivalent influenza vaccine (Fluvirin); TIVeFZ = egg-based trivalent influenza vaccine (Fluzone); TIV1c = TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts); TIV2c = TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage; US - United States.

Table SIII.2 TIVc exposure by age and gender

Population	Male	Female	Total
Pediatric population (< 3 years)	196	184	380
Pediatric Population (3 – 17 years)	2,362	2,259	4,621
Adult Population (18 - < 65 years)	3,958	5,162	9,120
Elderly Population (≥ 65 years)	714	831	1,545
Total	**7,230**	**8,436**	**15,666**

Source: TIVc DSUR version 6, dated 26 July 2017

Table SIII.3 TIVc exposure by racial group

Race	Number of subjects (%)
Caucasian (White)	12,210 (78%)
Black	989 (6%)
American Indian	24 (< 1%)
Asian	1,426 (9%)
Native Hawaiian/Pacific	17 (< 1%)
Hispanic	853 (5%)
Other	147 (< 1%)
Total	**15,666**

Source: TIVc DSUR version 6, dated 26 July 2017

QIVc

At the DLP of this RMP, eight Seqirus-sponsored clinical studies (V130_01, V130_03, V130_10, V130_12, V130_14, V200_10, V201_01 and V201_07) involving QIVc were completed. There are no ongoing studies with QIVc. Three adjuvanted cell-based Quadrivalent Influenza Vaccine (aQIVc) studies (V200_10, V201_01, V201_07) that have been completed used QIVc as a comparator vaccine.

Completed studies:

Study V130_01 included adult subjects (> 18 years), study V130_03 included paediatric subjects between 4 years through 17 years of age, study V130_10 included subjects aged 6 months through 47 months, study V130_12 included paediatric subjects between 2 years through 17 years of age, study V130_14 included subjects aged 6 months through 47 months. Studies V200_10, V201_01 and V201_07 included subjects 50 years of age and older with QIVc used as a comparator vaccine.

Ongoing studies:

There are no ongoing studies with TIVc/QIVc.

The exposure details of the completed studies are presented in the tables below (Table SIII.4-Table SIII.7).

Studies V130_01 and V130_03 were conducted in the US during the NH 2013/2014 influenza season and study V130_12 study was conducted over three seasons during the SH 2017

influenza season (Australia, Philippines and Thailand), the NH 2017/2018 influenza season (Estonia and Finland) and the NH 2018/2019 influenza season (Estonia, Finland, Lithuania, Poland and Spain). Study V130_10 was conducted in the US during the NH 2019/2020 influenza season. Study V130_14 was conducted over 5 seasons in 15 countries (SH 2019, NH 2019/2020; NH 2020/2021, NH 2022/2023, SH 2023).

In the V130_01, V130_03 and V130_10 studies, safety and immunogenicity were evaluated. In the V130_01 and V130_03 studies, two separate cell-based trivalent influenza vaccines (TIV1c and TIV2c) were used as comparator vaccines. TIV1c contained the same three influenza strains included in the commercial formulation as QIVc (which was formulated in accordance with WHO recommendations for NH 2013/2014 influenza use). TIV2c contained three influenza strains but the influenza B strain was the opposite B lineage as the B strain contained in TIV1c. In study V130_10, the comparator was an US-licensed quadrivalent influenza vaccine (Afluria® Tetra). In study V130_12, efficacy, safety and immunogenicity were assessed for QIVc compared to a non-influenza comparator (meningococcal [serogroup ACWY] conjugate vaccine). In study V130_14, efficacy, safety and immunogenicity were assessed for QIVc compared to a non-influenza comparator (meningococcal serogroup C polysaccharide conjugate vaccine).

Studies V200_10, V201_01 and V201_07 were completed as part of the aQIVc program in adults aged 50 years and older with QIVc used as a comparator. Study V200_10 was conducted in the US during the NH 2020/2021 influenza season, study V201_01 was conducted in Australia, New Zealand, Philippines and South Africa during the SH 2021 influenza season and study V201_07 was conducted in the US during the NH 2022/2023 influenza season. Safety and immunogenicity were evaluated in the studies. In study V200_10, adjuvanted Quadrivalent Influenza Vaccine (aQIV) and recombinant Quadrivalent Influenza Vaccine (QIVr) were used as comparators in addition to QIVc. In the antigen and adjuvant dose-ranging study V201_01, seven different aQIVc formulations were investigated and QIVc was the comparator, and in the dose confirmation study V201_07, three different aQIVc formulations were evaluated and QIVc was a comparator vaccine.

A total of 2,680 subjects were vaccinated in the V130_01 study. Of these, 1,334 subjects were enrolled to QIVc group, 677 subjects to TIV1c group, and 669 subjects in the TIV2c group (Table SIII.4). All subjects enrolled received one dose of study vaccine. All subjects received one dose of study. For study V130_01, one subject randomised to QIVc received TIV1c vaccine.

A total of 2,333 subjects were enrolled in study V130_03. Of these 2,333 subjects, 1,159 were in the QIVc group, 593 in the TIV1c group, and 581 in the TIV2c group (Table SIII.4). All

subjects enrolled, except for one subject in the TIV2c group, received a study vaccine (i.e., 580 were exposed in the TIV2c group). Of the 1,159 in the QIVc group, 834 were exposed to one dose of vaccine and 325 were exposed to 2 doses of vaccine.

A total of 2,414 subjects were enrolled in study V130_10. Of the 2,414 subjects, 2,402 received a study vaccine, of which 1,597 were in the QIVc group and 805 were in the QIV comparator group (Table SIII.4). Out of the1,597 that received QIVc, 882 were exposed to one dose of vaccine and 715 were exposed to two doses of vaccine. A total of 77 subjects who were to receive two doses of vaccine did not receive their second dose.

A total of 4,514 subjects were enrolled in study V130_12. Of the 4,514 subjects, 4,513 received a study vaccine, of which 2,258 was in the QIVc group and 2,255 was in the non-influenza comparator group (Table SIII.4). Out of the 2,258 that received QIVc, 763 subjects received two doses of QIVc given their previous influenza vaccination history.

A total of 5,723 subjects were enrolled in study V130_14. Of the 5, 723 subjects, 5,697 received a study vaccine, of which 2,856 were in the QIVc group and 2,841 were in the non-influenza comparator group (Table SIII.4). Out of the 2,856 that received QIVc, 2,761 subjects received two doses of QIVc given their previous influenza vaccination history.

A total of 471 subjects were enrolled in study V200_10. All subjects enrolled received a study vaccination. Of 471 exposed subjects, 119 subjects received QIVc, 116 subjects received aQIVc, 116 subjects received aQIV and 120 subjects received QIVr (Table SIII.4).

In study V201_01, a total of 839 subjects were enrolled. The exposed set included 838 subjects, of which 97 subjects were exposed to QIVc. In total 741 subjects received one of the aQIVc formulations: 107 subjects received aQIVc CCI 107 subjects received aQIVc CCI 103 subjects received aQIVc CCI , 106 subjects received aQIVc CCI 108 subjects received aQIVc CCI 101 subjects received aQIVc CCI and 109 subjects received aQIVc CCI (Table SIII.4).

In study V201_07, a total of 1, 056 subjects were enrolled of which 1051 were exposed to study vaccines; CCI were exposed to QIVc (licensed dosage at 15µg HA per strain) and CCI to CCI QIVc CCI CCI were exposed to one of 2 treatment arms with aQIVc (aQIVc CCI] and aQIVc CCI

Table SIII.4 Completed QIVc clinical trials

Study Number (Phase)	Study Objectives	Study Design Type of Control	Study Vaccines	Number of Subjects (Exposed)	Subjects' Ages and Geographic Location
V130_01 (Phase III)	Immunogenicity and safety	Randomised, double-blind, multicentre, non-inferiority	QIVc TIV1c[1] TIV2c[2] **Total**	1,334 677 669 **2,680**	Subjects ≥18 years of age US
V130_03 (Phase III)	Immunogenicity and safety	Randomised, double-blind, multicentre, non-inferiority	QIVc TIV1c[1] TIV2c[2] **Total**	1,159 593 580 **2,332**	Subjects 4 to <18 years of age US
V130_10 (Phase III)	Immunogenicity and safety	Randomised, double-blind, multicentre, non-inferiority	QIVc QIV[3] **Total**	1,597 805 **2,402**	Subjects 6 to <48 months of age US
V130_12 (Phase III/IV)	Efficacy, immunogenicity and safety	Randomised, observer-blind, multicentre,	QIVc Non-influenza comparator[4] **Total**	2,258 2,255 **4,513**	Subjects 2 to <18 years of age Australia, Estonia, Finland, Lithuania, Philippines, Poland, Spain, Thailand
V130_14 (Phase III)	Efficacy, immunogenicity and safety	Randomised, observer-blind, multicentre	QIVc Non-influenza comparator[8] **Total**	2856 2841 **5697**	Subjects 6 to <48 months of age Bangladesh, Bulgaria, Czech Republic, Estonia, Honduras, Latvia, Malaysia, New Zealand, Pakistan, Philippines, Poland, Romania, South Africa, Thailand, Ukraine

Study Number (Phase)	Study Objectives	Study Design Type of Control	Study Vaccines	Number of Subjects (Exposed)	Subjects' Ages and Geographic Location
V201_01 (Phase II)	Dose-ranging study to evaluate safety and immunogenicity of aQIVc (using QIVc as a comparator)	Randomised, stratified, controlled, observer-blind	aQIVc[5] QIVc **Total**	~~741~~ 97 **838**	Subjects aged ≥50 years of age Australia, New Zealand, Philippines, South Africa
V200_10 (Phase II)	Immunogenicity and safety (using QIVc as a comparator)	Randomised, stratified, controlled, observer-blind	aQIVc aQIV[6] QIVr[7] QIVc **Total**	116 116 120 119 **471**	Subjects aged ≥50 years of age US
V201_07 (Phase II)	Dose-ranging study to evaluate safety and immunogenicity of aQIVc (using QIVc as a comparator)	Randomised, stratified, controlled, observer-blind	aQIVc[5] QIVc QIVc CCI CCI **Total**	CCI CCI CCI **1051**	Subjects aged ≥50 years of age US

Source: Individual study clinical study reports

[1] TIV1c = TIVc formulation containing all three WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts)

[2] TIV2c = TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage

[3] The QIV comparator used was US-licensed quadrivalent influenza vaccine (Afluria® Tetra)

[4] The non-influenza comparator was a *Neisseria meningitides* serogroup A, C, W-135, Y conjugate vaccine (Menveo®, Glaxosmithkline Biologicals, S.A.)

[5] aQIVc = adjuvanted cell-based Quadrivalent Influenza Vaccine

[6] aQIV = adjuvanted Quadrivalent Influenza Vaccine

[7] QIVr = recombinant Quadrivalent Influenza Vaccine

[8] The non-influenza comparator was a *Neisseria meningitides* serogroup C polysaccharide conjugate vaccine (NeisVac-C®, Pfizer Limited)

Table SIII.5 QIVc exposure by age

Age group	V130_01	V130_03	V130_10	V130_12	V130_14	V200_10	V201_01	V201_07	Total Subjects (n)
Paediatric Population									
Children 6 months through 8 years*	N/A	575	1,597	1,146	2,856	N/A	N/A	N/A	**6,174**
• *One dose*		*235*	*810*	*383*	*95*				
• *Two doses*		*340*	*787*	*763*	*2761*				
Adolescents 9 through 17 years (one dose)		584		1,112					**1,696**
Adult Population									
Adults 18 to <65 years (one dose)	674					57	51	CCI	**1,056**
Elderly people 65+ years (one dose)	660					62	46	CCI	**1,020**
Total	**1,334**	**1,159**	**1,597**	**2,258**	**2,856**	**119**	**97**	CCI	**9,946**

Source: Individual study clinical study reports

* The subjects not previously vaccinated received two administrations of QIVc at least 4 weeks apart while the rest of the subjects received only one dose of QIVc. Subjects 9 years and older were considered 'previously influenza vaccinated against influenza' and were randomised to receive one study vaccine. Please also note, for V130_10, 77 subjects did not get exposed to their second dose and only exposed to the first dose. In V201_07, numbers include exposure to QIVc (15µg per HA) and CCI QIVc (CCI).

N/A – not applicable

Table SIII.6 QIVc exposure by age and gender

Population	Male	Female	Total
Paediatric Population	3,998	3,872	7,870
Adult Population	903	1,173	2,076
Total	**4,901**	**5,045**	**9,946**

Source: Individual study clinical study reports

Table SIII.7 QIVc exposure by racial group

Race	Adult	Paediatric	Total
Caucasian (White)	1,727	4,256	5,983
Black	280	1,064	1,344
American Indian	14	15	29
Asian	31	2,224	2,255
Native Hawaiian	2	13	15
Other	22	298	320
Total	**2,076**	**7,870**	**9,946**

Source: Individual study clinical study reports

Part II: Module SIV – Populations Not Studied In Clinical Trials

The populations not studied in clinical studies were those excluded from the studies according to eligibility criteria defined for the studies. For TIVc and QIVc, populations not studied in pre-authorisation clinical trials included pregnant or lactating women, patients with co-morbidities, immunocompromised patients, and very young children (less than 6 months of age).

For QIVc, in the post-authorisation phase, an observational pregnancy registry study has been conducted. The pregnancy registry study was a PMC for TIVc and QIVc; by the time of initiation of the study, TIVc was no longer being marketed in the US and thus all exposures during pregnancy in this observational study were QIVc.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

In general, the immunogenicity and safety of TIVc and QIVc was studied in healthy populations prior to first approval. The table below provides an overview of exclusion criteria considered important across the development programme of TIVc and QIVc.

Table SIV.1 Important exclusion criterion, which will remain as contraindications, warnings and precautions

Criteria	Implications for target population
Hypersensitivity to the active substances, components of the adjuvant, excipients, residues	Persons with hypersensitivity must use alternative methods of prevention
Individuals with body temperature measurement ≥38°C (≥ 100.4°F) within 3 days prior to vaccination	Immunisation shall be postponed in patients with febrile illness or acute infection

Table SIV.2 Important exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for exclusion	Justification for not being a contraindication
Exposure during pregnancy or breast feeding	The impact of influenza vaccination in pregnant or breastfeeding women is not known.	The data from the pregnancy registry V130_11OB has revealed no evidence of adverse foetal, newborn or pregnancy outcomes at any stage of pregnancy. It is unknown whether TIVc and QIVc is excreted in human milk. However, public health agencies recommend that all women who are pregnant, postpartum, or who might be pregnant during influenza season should receive inactivated influenza vaccines, which can be used in all stages of pregnancy and may be used during breastfeeding.
History of Guillain-Barré Syndrome (GBS)	Potential confounder. The 1976 swine influenza vaccine was associated with an elevated risk of GBS.	Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case per one million persons vaccinated.
Bleeding disorder	Ensure safety of subjects participating in the study. Subjects with bleeding disorders might be at increased risk of haematoma formation at the vaccination site.	Benefit-risk is positive in this population with adequate warnings in the prescribing information.
Immunocompromised subjects	May have impaired response and the efficacy of influenza vaccination in this setting is not known.	Benefit-risk is positive in this population with adequate warnings in the prescribing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3 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 programme for both TIVc and QIVc, however a pregnancy registry study (V130_11OB) with QIVc was conducted post-licensure in the US (completed).
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme for both TIVc and QIVc.
Children	Limited data available for TIVc in children aged < 3 years. Currently available data in subjects aged 3 to 17 years in clinical development programmes. Influenza vaccine is not recommended for children < 6 months of age, therefore, no data are available for QIVc in children < 6 months of age at the date of vaccination. Currently available data in subjects aged ≥ 6 months is in QIVc clinical development programmes.
Elderly	Vaccination is currently recommended in the elderly population for both TIVc and QIVc.
Population with relevant different ethnic origin	For TIVc and QIVc, a majority of subjects in clinical studies were Caucasian; experience with other ethnicities is limited. The limited experience in non-Caucasians is not felt to have important implications for the use of the product in the target population.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable to both TIVc and QIVc.

Part II: Module SV – Post-Authorisation Experience

TIVc was registered in the EU under the tradename Optaflu® (EMEA/H/C/000758) with the indication for persons 18 years of age and older. Optaflu® was granted a marketing authorisation in the EU on 01 June 2007. The marketing authorisation for Optaflu® expired on 05 June 2017. Marketing authorization for Flucelvax in EU was issued on 15 November 2024.

QIVc was first granted marketing authorisation in the US on 23 May 2016, for prevention of influenza in persons 4 years of age and older. On 12 December 2018, QIVc was approved in the EU for prophylaxis of influenza in adults and children from 9 years of age, and then an extension of the indication from 2 years of age and older was granted in the EU on 22 October 2020. Positive opinion for the extension of the indication from 6 months of age and older is expected on 12 December 2024.

Cumulatively up to the DLP of this RMP, QIVc has been approved worldwide in the following 40 countries: 28 EU countries, Iceland, Norway, Lichtenstein, Argentina, Australia, Brazil, Canada, Great Britain, New Zealand, Switzerland, Taiwan and the US. Refer to the most recent PSUR for additional registration information (Flucelvax QIVc PSUR number 6).

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

TIVc

The immunisation schedule for TIVc in the general population is one dose. For children less than 9 years of age one or two 0.5 mL doses is recommended, depending on vaccination history. An estimate of cumulative patient exposure is calculated based on worldwide sales of number of doses sold/distributed during the period and the immunisation schedule.

QIVc

The immunisation schedule for QIVc in the general population is one dose. For children less than 9 years of age one or two 0.5 mL doses is recommended, depending on vaccination history. Cumulative post-marketing exposure is estimated based on doses sold/distributed worldwide

during the period and immunisation schedule with the assumption that each subject received a single administration.

SV.1.2 Exposure

TIVc

Cumulatively from the first launch of the product up to the DLP of this RMP, the cumulative patient exposure is estimated to be approximately 12,496,666 patients exposed to TIVc assuming each patient received a single dose/distributed CCI

CCI

CCI	CCI
CCI	CCI *
CCI	CCI
CCI	CCI

CCI

QIVc

Cumulatively from the product first launch until the DLP of this RMP, over 203.5 million doses of QIVc have been sold/distributed worldwide (CCI). Therefore, it is estimated that approximately 203.5 million patients were exposed to QIVc cumulatively until the DLP of this RMP.

CCI

CCI	

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for misuse for illegal purposes

Not applicable to influenza vaccines.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial RMP submission

TIVc:

Important identified risks: None

Important potential risks: Neuritis, Convulsion, Anaphylaxis, Encephalitis, Vasculitis, GBS, Demyelination, Bell's palsy, and Immune thrombocytopenia (ITP).

Important missing information:

- Use in infants and toddlers
- Safety in subjects with underlying diseases or immunocompromised patients
- Use in pregnant women

QIVc:

The following potential risks are considered important for QIVc: neuritis, convulsion, encephalitis, vasculitis, GBS, ITP, demyelination and Bell's palsy.

The following missing information is also included: safety in subjects with underlying diseases, safety in immunocompromised patients, and use in pregnant and breastfeeding women.

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

The risks below are not considered important for inclusion in the list of safety concerns in the RMP because they are listed adverse reactions and/or have minimal clinical impact. These include solicited local and systemic adverse reactions that are commonly reported during vaccine clinical trials and infrequently are adverse reactions that meet seriousness criteria, and class effects common to all influenza vaccines.

Local (injection site) reactions: injection site pain/tenderness, injection site erythema, injection site induration, and injection site ecchymosis.

Systemic reactions: loss of appetite, headache, nausea, diarrhoea, vomiting, myalgia, arthralgia, fatigue and fever (≥ 38°C), change in eating habits, sleepiness, irritability, and chills.

Other reactions that have been observed with influenza vaccines: syncope, presyncope, paraesthesia, generalised skin reactions including pruritus, urticaria or non-specific rash, and extensive swelling of injected limb.

Anaphylaxis: Anaphylaxis is already well-known to health professionals and does not require additional pharmacovigilance (PV) activities or additional risk minimisation measures as health professionals are already aware of the risk of anaphylactic reactions and have the appropriate measures in place as part of clinical practice. Anaphylactic reactions therefore have not been included as an important risk. It will be followed up via routine PV activity namely through signal detection and adverse reaction reporting.

Class effects: neuritis, encephalitis, vasculitis, GBS, demyelination, Bell's palsy, and ITP.

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

There are no identified or potential risks considered important for both TIVc and QIVc.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Since the TIVc and QIVc vaccines are both manufactured using the same process, and with overlapping compositions, it is considered that the data generated during the development of QIVc to support its safety are relevant to TIVc. Furthermore, as summarised in the most recent QIVc PSUR number 5 with DLP 15 March 2023, post-marketing experience with QIVc has

not identified any safety concerns. Therefore, the important identified and potential risks, and important missing information, are aligned for both TIVc and QIVc.

Whilst TIVc was licensed in the EU for use in adults 18 years of age and older, QIVc is licensed for use in adults and children from 2 years of age in the EU, and in adults and children 6 months of age and older in the US and several other countries. No new safety concerns for QIVc have been identified through safety monitoring in clinical trials and in the post-market setting for children 6 months to < 8 years of age. The marketing experience for both TIVc and QIVc to date is consistent with the favourable safety and tolerability profile demonstrated in the clinical development programme for TIVc and QIVc. Therefore, the previously classified missing information of 'Use in infants and toddlers (6 months of age, < 3 years of age) in TIVc EU-RMP version 3.3, dated 04 June 2014, has been removed.

Safety in immunocompromised patients and safety in subjects with underlying diseases, previously classified as missing information, have been removed from the list of safety concerns in EU RMP v4.0. This is in alignment with the proposal received from the EMA during assessment of procedure EMEA/H/C/006532/0000 to remove these as missing information from the EU RMP on the basis that there is no evidence to suspect the possibility of a safety issue with use of influenza vaccine in immunocompromised patients and in populations with underlying diseases.

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

At the DLP of this RMP, there are no important identified or important potential risks for TIVc and QIVc.

SVII.3.2 Presentation of the missing information

At the DLP of this RMP, there are no missing information for TIVc and QIVc.

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1 Summary of the safety concerns

Summary of the safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine PV activities for Seqirus products comply with Good Pharmacovigilance Practices (GVP) and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004.

Specific adverse reaction follow-up questionnaires for safety concerns:

None.

Other forms of routine pharmacovigilance activities for adverse events following immunisation:

The "Interim guidance on Enhanced Safety Surveillance for seasonal influenza vaccines in the EU" (EMA/PRAC/222346/2014) requires the implementation of annual Enhanced Safety Surveillance for influenza vaccines. It should be noted, however, that at the DLP of this RMP this interim guidance is under review by the EMA (Health Threats and Vaccines strategy (AF-HTV, 2023). In addition, at the Pharmacovigilance Risk Assessment Committee (PRAC) plenary meeting in April 2024, it was agreed to waive the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines (both national and centrally approved) while the 'Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' (EMA/PRAC/222346/2014) is under review (PRAC, 2024). Seqirus still implemented the Enhanced Passive Safety Surveillance (EPSS) for QIVc during the NH 2024/2025 influenza season. In subsequent NH influenza seasons, implementation of EPSS for QIVc or TIVc in the EU will depend on the applicable guidance and any waivers in place at the time.

The passive approach of the Enhanced Safety Surveillance is classified as a routine PV activity and in accordance with chapter "V.B.6.1.2 RMP part III section Routine PV activities of the GVP Module V". A full description of the methodology, including the specific mechanisms to raise awareness with and facilitate spontaneous reports of adverse events for vaccine recipients, estimate near real-time vaccine exposure and its implementation is described in the EPSS Plan for each NH influenza season.

III.2 Additional Pharmacovigilance Activities

Required additional pharmacovigilance activities

There are no additional PV activities required for TIVc or QIVc by the EMA.

Additional pharmacovigilance activities recommended under EMA guidelines

To comply with the Guideline on Influenza vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) of July 2016, a supporting Innovative Medicines Initiative (IMI) programme called on Development of Robust Innovative Vaccine Effectiveness (DRIVE) has been launched in July 2017. GSK, Sanofi Pasteur, Abbott and Seqirus, as vaccine manufacturers with marketed influenza vaccines in Europe, contributed to the genesis of the project. This project is a unique public-private partnership involving in addition to manufacturers, 11 partners including academic and public health institutes. DRIVE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific influenza vaccine effectiveness data in Europe. As per the IMI legal framework, this is a 5 year partnership project, encompassing four consecutive influenza seasons. Studies are intended to be conducted annually in European sites and the data generated will be pooled across participating centres, with the first pilot seasonal studies initiated during the NH 2017/2018 influenza season. Each year a report will be generated to synthesise data on influenza vaccine effectiveness collected across participating sites including data generated from the public health surveillances contributing to DRIVE. Results will be provided every year but will not trigger an RMP update unless the results impact public health or alter the benefit-risk profile of Seqirus vaccines, as per EMA agreement on 30 Apr 2019 (EMA/248552/2019 Vaccine Working Party). Seqirus will not be the study sponsor or owner of the data, and will not control the scientific deliverables, which include the Study Protocol, Statistical Analysis Plan and Study Reports. Timelines are driven by the overall project and conditioned notably by logistics associated with existing surveillances. Over its lifetime, the project is expected to progressively expand the existing infrastructure to enhance the opportunities for Seqirus to document vaccine effectiveness of its marketed influenza vaccines in Europe. It should be noted that the EMA granted a deferral on the requirement to provide

brand-specific influenza vaccine effectiveness data for the 2022–2023, 2023-2024 and 2024-2025 NH seasons, and therefore no data from DRIVE has or will be generated for these seasons.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.3.1 Summary table of additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
None				
Additional pharmacovigilance activities recommended under EMA guidelines				
A non-interventional study of vaccine effectiveness; TIVc/QIVc versus no vaccination (DRIVE sub-analysis)	To perform an analysis of influenza vaccine effectiveness of TIVc/QIVc vaccination versus no vaccination in persons of an age aligned with the applicable age indication	None	Conducted annually during the influenza season	First annual availability of results planned before Q42020 and annually thereafter

Part IV: Plans for Post-Authorisation Efficacy Studies

There are no planned post-authorisation efficacy studies for TIVc and QIVc.

Part V: Risk Minimisation Measures (Including Evaluation of The Effectiveness of Risk Minimisation Activities)

V.1 Routine Risk Minimisation Measures

Table Part V.1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks:	
None	
Important potential risks:	
None	
Missing Information:	
None	

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Section V.1 above are sufficient to manage the safety concerns of TIVc and QIVc.

V.3. Summary of Risk Minimisation Measures

Table Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern and population

Safety concern	Risk minimisation measures	Pharmacovigilance (PV) activities
Important identified risks:		
None		
Important potential risks:		
None		
Missing information:		
None		

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for TIVc (Flucelvax®)

This is a summary of the Risk Management Plan (RMP) for TIVc (Flucelvax). The RMP details important risks of TIVc, how those risks can be minimised, and how more information will be obtained about TIVc's risks and uncertainties (missing information).

TIVc's Summary of Product Characteristics (SmPC) and its package insert give essential information to healthcare professionals and patients on how TIVc should be used.

It should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 TIVc's RMP.

I. The medicine and what it is used for

TIVc is proposed for prophylaxis of influenza for adults and children of 6 months of age and older. It contains trivalent influenza vaccine (surface antigen, inactivated, prepared in cell cultures) as the active substance and it is a suspension for injection in pre-filled syringe. It is given by intra-muscular injection.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TIVc together with measures to minimise such risks and the proposed studies for learning more about TIVc's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of TIVc is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TIVc are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TIVc. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1 Summary of TIVc safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Table Part VI.2 Description of TIVc routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk:	
None	
Important potential risk:	
None	
Missing information:	
None	

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Summary of Risk Management Plan for QIVc (Flucelvax® Tetra)

This is a summary of the Risk Management Plan (RMP) for QIVc (Flucelvax Tetra). The RMP details important risks of QIVc, how those risks can be minimised, and how more information will be obtained about QIVc's risks and uncertainties (missing information).

QIVc's Summary of Product Characteristics (SmPC) and its package insert give essential information to healthcare professionals and patients on how QIVc should be used.

It should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 QIVc's RMP.

I. The medicine and what it is used for

QIVc is authorised for prophylaxis of influenza for adults and children of 2 years of age and older and proposed for prophylaxis of influenza for adults and children of 6 months of age and older. It contains quadrivalent influenza vaccine (surface antigen, inactivated, prepared in cell cultures) as the active substance and it is a suspension for injection in pre-filled syringe. It is given by intra-muscular injection.

Further information about the evaluation of QIVc's benefits can be found in QIVc's EPAR, including its plain-language summary, available on the EMA website, under the medicine's. <https://www.ema.europa.eu/en/medicines/human/EPAR/flucelvax-tetra>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of QIVc together with measures to minimise such risks and the proposed studies for learning more about QIVc's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of QIVc is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of QIVc are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of QIVc. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1 Summary of QIVc safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Table Part VI.2 Description of QIVc routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk:	
None	
Important potential risk:	
None	
Missing information:	
None	

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Annex 4 – Specific Adverse Event Follow-Up Forms

Not applicable.

CCI [redacted]

[redacted]

Annex 6 – Details of Proposed Additional Risk Minimisation Measures (if applicable)

Not applicable.

Annex 7 – Other Supporting Data (Including Referenced Material)

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Signed By	Date (GMT)
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Approved-EU-QPPV (or delegate) Approval	

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