EU Risk Management Plan

for

Aflunov®, Foclivia®
(zoonotic and pandemic adjuvanted H5N1 influenza vaccines)
and
Zoonotic Influenza Vaccine Seqirus™
(zoonotic adjuvanted H5N8 influenza vaccine)

RMP version to be assessed as part of this application:

RMP Version number:	7.0
Data Lock Point for this RMP:	19 October 2023
Date of final sign off:	08 May 2025
Rationale for submitting an updated RMP:	The version number was updated from 6.1 to 7.0 following EMA EU-RMP v6.1 approval. The EU-RMP version 7.0 is submitted together with the closing sequence for the procedure.
Summary of significant changes in this RMP:	Updated the indication and posology for Zoonotic Influenza Vaccine Seqirus by moving the information from 'Proposed' to 'Current', following EMA EU-RMP v6.1 approval.

Details of the currently approved RMP

RMP Version number:	Aflunov, Foclivia, Zoonotic Influenza Vaccine Seqirus, RMP version 6.1*
Approved with procedure:	Approved with procedure for Zoonotic Influenza Vaccine Seqirus EMA/VR/0000249071 (25 April 2025) *Procedure for Foclivia: EMEA/H/C/001208/II/0081 (RMP version 5.0). Procedure for Aflunov: EMEA/H/C/002094/II/0086 (RMP version 6.0).
Date of approval (opinion date):	25 April 2025

QPPV name:	Juergen Zorn, MD
QPPV signature:	eSignature (See last page)

Abbreviations

Term / Abbreviation	Description
ADR	Adverse Drug Reaction
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
aTIV	Adjuvanted Trivalent Influenza Vaccines
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPSS	Enhanced Passive Safety Surveillance
ESS	Enhanced Safety Surveillance
EU	European Union
GB	Great Britain
GBS	Guillain-Barré Syndrome
HA	Haemagglutinin
IM	Intramuscular
INN	International Non-proprietary Name
ITP	Idiopathic Thrombocytopenic Purpura
IRR	Incidence Rate Ratio
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
PIV	Prepandemic Influenza Vaccine
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
SARS	Severe Acute Respiratory Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
S-PSUR	Simplified Periodic Safety Update Report
QPPV	Qualified Person responsible for Pharmacovigilance
US	United States
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organisation

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Part I: Product(s) overview

Table Part I-1: Product(s) Overview

Active substance(s) (INN or common name)	Influenza virus surface antigens of strain: A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) (Zoonotic influenza vaccine (H5N1)) A/Vietnam/1194/2004 (H5N1) (Pandemic influenza vaccine (H5N1)) A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (clade 2.3.4.4b) (Zoonotic Influenza Vaccine H5N8)
Pharmacotherapeutic group(s) (ATC Code)	Group: Influenza vaccine ATC Code: J07BB02
Name of Marketing Authorisation	Seqirus S.r.l., Via del Pozzo 3/A, S. Martino 53035 Monteriggioni (SI) Italy
Medicinal products to which this RMP refers	Aflunov® [A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23)] Foclivia® [A/Vietnam/1194/2004 (H5N1)] Zoonotic Influenza Vaccine Seqirus™ [A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (clade 2.3.4.4b)]
Invented name(s)	Aflunov® Foclivia® Zoonotic Influenza Vaccine Seqirus ™
Marketing authorisation procedure	Centralised procedure (Aflunov and Foclivia); Zoonotic Influenza Vaccine Seqirus is a duplicate of Aflunov, submitted through Informed Consent Application, therefore all data cross-refer to Aflunov.
Brief description of the product	Aflunov, and Foclivia are monovalent (H5N1), inactivated, egg-derived, purified surface antigen vaccines, adjuvanted with MF59. They contain: Influenza virus surface antigens*, inactivated: A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) or

	A/Vietnam/1194/2004 (H5N1) 7.5 mcg** per 0.5 mL dose Zoonotic Influenza Vaccine Seqirus is a monovalent (H5N8), inactivated, egg-derived, purified surface antigen vaccine, adjuvanted with MF59. It contains influenza virus surface antigen*, inactivated: A/Astrakhan/3212/2020 (H5N8) (CBER-RG8A) (clade 2.3.4.4b) 7.5 mcg** per 0.5 mL dose ** propagated in eggs* *** expressed in microgram haemagglutinin* Adjuvant MF59C.1 contains: squalene 9.75 milligrams polysorbate 80 1.175 milligrams sorbitan trioleate 1.175 milligrams sodium citrate 0.66 milligrams citric acid 0.04 milligrams The MF59 adjuvant is an oil-in-water emulsion, composed of squalene as the oil phase, stabilised with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer. CCI [redacted] Haemagglutinin (HA) and neuraminidase (NA) antigens present in the vaccine induce a protective antibody response in vaccinated individuals after immunisation.
Hyperlink to the Product Information	*Aflunov* https://www.ema.europa.eu/documents/product-information/aflunov-epar-product-information_en.pdf *Zoonotic Influenza Vaccine Seqirus* Zoonotic Influenza Vaccine Seqirus, INN-Zoonotic influenza vaccine (h5n8) (surface antigen, inactivated, adjuvanted) (europa.eu) *Foclivia* https://www.ema.europa.eu/documents/product-information/foclivia-epar-product-information_en.pdf

Indication(s) in the EEA	Current *Aflunov* Active immunisation against H5N1 subtype of Influenza A virus in individuals 6 months of age and above *Zoonotic Influenza Vaccine Seqirus* Active immunisation against H5 subtype influenza A viruses in individuals 6 months of age and above *Foclivia* Prophylaxis of influenza in an officially declared pandemic situation
	Proposed *Aflunov* Not applicable *Zoonotic Influenza Vaccine Seqirus* Not applicable *Foclivia* Not applicable
Dosage in the EEA	Current *Aflunov* Individuals 6 months of age and older. Administer 2 doses (0.5 mL each), at least 3 weeks apart. *Zoonotic Influenza Vaccine Seqirus* Individuals 6 months of age and older. Administer 2 doses (0.5 mL each), at least 3 weeks apart *Foclivia* Individuals 6 months of age and older. Administer 2 doses (0.5 mL each), at least 3 weeks apart.
	Proposed *Aflunov* Not applicable *Zoonotic Influenza Vaccine Seqirus* Not applicable *Foclivia* Not applicable

Pharmaceutical form(s) and strengths	Suspension for injection in pre-filled syringe and/or single or multidose vials 7.5 mcg per 0.5 mL dose
Is / will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population

Indication

Aflunov and Foclivia, collectively referred to as aH5N1 influenza vaccine throughout this Risk Management Plan (RMP), are indicated for active immunisation against H5N1 subtype of influenza A virus (Aflunov), or for prophylaxis of influenza in an officially declared pandemic situation (Foclivia), in individuals 6 months of age and above.

Due to recent dominance of clade 2.3.4.4b lineage of H5 viruses, strain change from H5N1 to H5N8 (A/Astrakhan/3212/2020 (clade 2.3.4.4b)) is requested, in order for Zoonotic Influenza Vaccine Seqirus to be able to match with the circulating H5 virus. Zoonotic Influenza Vaccine Seqirus (copy product of Aflunov), is referred to as aH5N8 in this RMP, indicated for active immunisation against H5 subtype influenza A viruses in individuals 6 months of age and above.

Influenza type A viruses

Influenza type A viruses are of most significance to public health due to their potential to cause an influenza pandemic. Influenza type A viruses are classified into subtypes according to the combinations of different virus surface proteins HA and NA. Currently, there are 18 known different HA subtypes and 11 known different NA subtypes (CDC, 2024). Depending on the origin host, influenza A viruses can be classified as avian influenza, swine influenza, or other types of zoonotic influenza viruses. Examples include avian influenza ‘bird flu’ virus subtypes A(H5N1) and A(H9N2) or swine influenza ‘swine flu’ virus subtypes A(H1N1) and A(H3N2) (WHO, 2017a). All of these zoonotic influenza type A viruses are distinct from human influenza viruses and do not easily transmit among humans (WHO, 2023c).

Aquatic birds are the primary natural reservoir for most subtypes of influenza A viruses. Most cause asymptomatic or mild infection in birds, where the range of symptoms depends on the virus properties (Echaubard et al, 2018).

Influenza pandemics

An influenza pandemic occurs when a novel influenza virus emerges against which the majority of the world’s population has no immunity. Outbreaks of influenza in animals,

especially when they occur during annual outbreaks in humans, result in the merging of zoonotic and human influenza viruses and increase the chances of a pandemic. In the last few years, the world has faced several threats with influenza pandemic potential, making the occurrence of the next pandemic likely (VRBPAC, 2007).

This phenomenon has been observed only with Influenza A viruses and results from the emergence of a new antigenic variant (antigenic shift) caused by substitution of the HA antigen on the surface of the virus, with or without a concomitant change in NA, the other major surface antigen (Rubino and Choi, 2017; Webster and Govorkova, 2014; WHO, 2024). If such a virus demonstrates the ability to transmit efficiently from person to person, the result is a global outbreak of disease that affects a high percentage of individuals in a short period of time and is likely to cause substantially increased morbidity and mortality in all countries of the world (VRBPAC, 2007).

The estimated number of deaths caused by the 'Asian flu' of 1957 was 1.1 million worldwide and 116,000 in the United States (US) alone (Viboud et al, 2016). Experience with previous influenza pandemics (1918, 1957 and 1968), has shown that a pandemic spread in recurrent waves of infections occurring over several years (Miller et al, 2009). As the volume and speed of international travel has increased during the 20th and early 21st centuries, successive pandemics have disseminated worldwide in ever decreasing amounts of time. The evidence from the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 suggested that the next influenza pandemic may disseminate from its point source with extreme rapidity, although it is impossible to be certain of the exact timeframe (Fedson 2003a; Gellin and Qadri, 2016; Institute of Medicine, 2005). There have been 4 influenza pandemics since the beginning of 20th century: 1918 H1N1 more than 50 million deaths; 1957 H2N2 approximately 1.1 million deaths; 1968 H3N2 approximately 1 million deaths and in 2009 H1N1 more than 18,000 deaths (CDC, 2018b; WHO, 2022).

The H2, H5, H7 and H9 subtypes of influenza A have been identified as those most likely to be transmitted to humans and therefore present a potential pandemic threat. Outbreaks of avian influenza, occurred in 1999 in China (H9N2 outbreak); in 2003 in the Netherlands (H7N7 outbreak) and from 1997 to 2006 in Asia (H5N1 outbreak), posed serious risks for the emergence of a human pandemic influenza virus, since sometimes fatal bird-to-human transmission occurred, at a time when human Influenza A virus was also circulating (De Jong et al, 2005; Fouchier et al, 2004; Greco et al, 2012; Peiris et al, 1999). As of today, the H5 strains continue to circulate in domestic poultry in a number of countries and result in human infections and deaths (WHO, 2023a). As of 06 October 2023, the cumulative number of confirmed human cases of avian Influenza A / (H5N1) reported to World Health Organisation

(WHO) were 878 cases and 458 (52%) deaths (WHO, 2023b). The occurrence of an influenza pandemic before adequate preparations are in place could result in a public health emergency of unprecedented scale, an economic crisis due to excess morbidity and mortality in adults of working age, social disruption and panic. As an example, it has been estimated that the total expenditure cost of SARS in Asia was close to US dollar 60 billion, representing about US dollar 2 million per person infected (Institute of Medicine, 2004). In order to assist medical and public health leaders to optimise the response to the potential threat of pandemic influenza, the US Government (CDC, 2017; Scorza, 2017), individual states in the US and countries in the European Union (EU) have developed Influenza Pandemic Preparedness plans (Cox et al, 2003; WHO, 2017b).

The WHO has provided detailed guidance on the content of such plans (Palkonyay and Fatima, 2016; Stöhr, 2003; WHO, 2017b). The 56th World Health Assembly adopted a specific resolution on 28 May 2003 to ensure that all WHO Member States give priority to influenza pandemic preparedness planning (WHO, 2003). In particular, the need to ensure adequate supplies of pandemic vaccine must be addressed (Fedson, 2003b; WHO, 2006) and on 22 May 2009 following the H1N1 pandemic in the context of pandemic influenza preparedness, the need of sharing of influenza viruses and access to vaccines and other benefits increased. Vaccines form the main prophylactic measure against pandemic influenza and play an important role in national pandemic preparedness plans.

Once a pandemic begins, it will be too late to accomplish the many key activities required to minimise the impact (Manini et al, 2017). Therefore, planning and implementation of preparatory activities must start well in advance (WHO, 2017b). Indeed, in the event of a pandemic, a specific monovalent vaccine against the emerging strain will have to be developed rapidly, then registered and produced in very large quantities (EMA, 2021). The emergence of H5N1 virus as a human pathogen in 2003 and its subsequent genetic diversity have led to worldwide concerns over the possibility of an H5N1 pandemic. Widespread circulation and pathogenicity of the H5N1 influenza virus in birds, direct transmission of H5N1 influenza viruses to mammals, and the high case fatality rate in humans suggest that H5N1 influenza virus has important pandemic potential. As the H5N1 influenza virus cannot be eradicated or prevented in bird flocks, it remains a persistent public health threat and one for which protective measures are desired (Webster et al, 2006).

Demographics of the population and risk factors for influenza

The target population is represented by the general adult population from the age of 18 years and above. The majority of human infections with H5N1 have occurred among children and

adults younger than 40 years old (CDC, 2018a). Although most human populations are thought to have little or no immunity to influenza A (H5N1) viruses, based on the available data, mortality has been highest in people aged 10-19 years old and in young adults, which might be related to the immunological reaction of virus in different age groups (CDC, 2018a; Lai et al, 2016). The epidemiology of H5N1 influenza varies globally and populations of certain race or ethnic origin may be affected depending on where outbreaks of H5N1 occur (Lai et al, 2016).

The following population groups are at high risk for influenza (WHO, 2023d):

- Adults 65 years or older and children under 5 years of age.
- Individuals with underlying chronic medical conditions such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver, or haematologic diseases.
- Individuals with secondary immunodeficiency conditions such as human immunodeficiency virus / Acquired Immunodeficiency Syndrome, malignancy, or receiving immunosuppressive therapies, such as chemotherapy or steroids.
- Individuals with any condition compromising respiratory functions, e.g., morbid obesity (body mass index > 40), and physical handicap in children and adults.
- Health care workers are at high risk acquiring influenza virus infection due to increased exposure to the patients and risk further spread particularly to vulnerable individuals.

Though studies show that immunosuppressive conditions may contribute to a decline in immune responses and consequently compromise influenza vaccine effectiveness (compared to healthy population), the risks for influenza-like illness are reduced by vaccination (Danziger-Isakov et al, 2019; Rubin et al, 2014). The immunogenicity of the influenza vaccine is overall reduced in immunocompromised individuals, although a significant clinical protection from influenza is expected to be obtained with vaccination. Epidemiological data obtained from the 2009 influenza pandemic confirmed that immunocompromised patients remain at high risk of influenza-associated complications, namely viral and bacterial pneumonia, hospitalisation and even death (Zbinden and Manuel, 2014). Since immunosuppression includes a heterogeneous range of conditions, risk levels for severe influenza infection vary across different populations (Osterholm et al, 2012). Similarly, the systemic review and meta-analysis of 219 studies including immunocompromised subjects confirmed evidence of effectiveness for these group of patients, although of lower rate that in healthy individuals (Beck et al, 2012).

Inactivated vaccines can be generally used without risks for immunocompromised patients; live vaccines, if indicated, should be administered with care because of the risk of vaccine-associated disease (Righi et al, 2021).

Main existing treatment options

Influenza vaccination is the main preventive measure against flu. Recent studies show that flu vaccination reduces the risk of flu illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine (CDC, 2025a). A 2018 study showed that from 2012 to 2015, flu vaccination among adults reduced the risk of being admitted to an intensive care unit with flu by 82% (CDC, 2025b).

In addition to Foclivia, 3 pandemic preparedness vaccines were authorised in the EU at the Data Lock Point (DLP) for this RMP, which can be modified into pandemic influenza vaccines in a future pandemic (EMA, 2021):

- Adjupanrix (previously pandemic influenza vaccine [H5N1]; [split virion, inactivated, adjuvanted] GlaxoSmithKline Biologicals)
- Pandemic Influenza Vaccine H5N1 Baxter AG
- Pandemic Influenza Vaccine H5N1 AstraZeneca (previously pandemic influenza vaccine H5N1 Medimmune)

Besides Aflunov and Zoonotic Influenza Vaccine Seqirus, no other zoonotic influenza vaccines were licensed in the EU at the DLP for this RMP.

Evidence suggests that some antiviral drugs, notably NA inhibitors (oseltamivir, zanamivir) and cap-endonuclease inhibitor (baloxavir marboxil) can reduce the duration of viral replication and improve prospects of survival. Emergence of oseltamivir resistance has been reported (WHO, 2004). In practice, antiviral drugs are not an alternative to influenza vaccination, but may be a useful adjunct in some situations. It is best to limit their use to short-term prophylaxis of vulnerable persons in situations where the risk of contracting influenza virus infection is high (Prescrire Int, 2006).

Apart from antiviral treatments, public health management includes personal protective measures such as (WHO, 2023d):

- Regular hand washing with proper drying of the hands

- Good respiratory hygiene – covering mouth and nose when coughing or sneezing, using tissues and disposing of them correctly
- Early self-isolation of those feeling unwell, feverish and having other symptoms of influenza
- Avoiding close contact with sick people
- Avoiding touching one's eyes, nose or mouth

Part II: Module SII - Non-clinical part of the safety specification

Non-clinical studies were performed to support the development of the aH5N1/aH5N8 influenza vaccines. Aflunov and Zoonotic Influenza Vaccine Seqirus are zoonotic vaccines, intended for use before a pandemic to protect against the strain of influenza that experts believe could cause a future pandemic. Foclivia is a pandemic influenza vaccine, which can only be used once a pandemic has been declared and the strain of influenza virus responsible is identified. Although these vaccines were developed for use in different situations, the same non-clinical program supports them, as the components are the same. The H5N1/H5N8 influenza strain used to manufacture the vaccines may differ, however the H5N1 and H5N8 antigens are manufactured using the same manufacturing process and all vaccines contain MF59 adjuvant.

Non-clinical studies demonstrated that aH5N1 influenza vaccine formulations are immunogenic in mice, rabbits, and ferrets. Efficacy was evaluated in mice and ferrets vaccinated with aH5N1 influenza vaccine formulations followed by lethal challenge with virus homologous or heterologous to the vaccine. In vaccinated animals, serological cross reactivity was demonstrated by haemagglutination inhibition and microneutralisation assays, mortality was reduced or eliminated, and clinical observations consistent with viral infection were less severe or absent. These studies strongly support the protective and cross-protective efficacy of aH5N1 influenza vaccines against a lethal dose of highly pathogenic avian influenza virus.

A reproductive toxicology study in rabbits was performed where aH5N1 influenza vaccine was well-tolerated, did not cause maternal or embryofoetal toxicity, was not teratogenic, and had no effects on post-natal development. Additionally, the vaccine was immunogenic in maternal rabbits, developing foetuses had comparable titres, and antibodies persisted through the first 4 weeks of life in offspring.

Studies using Fluad®-like formulations (the 'parent' seasonal MF59-adjuvanted trivalent influenza vaccine [aTIV]) support the aH5N1/aH5N8 influenza vaccine program, as the manufacturing process used to produce antigen is the same. Studies with Fluad® include immunogenicity in mice, rabbit toxicology studies, and sensitisation in Guinea pigs. Fluad® was immunogenic, well tolerated locally and systemically, and not a skin sensitiser when tested using intradermal induction followed by a topical challenge.

There is a comprehensive package of toxicology studies evaluating the safety of MF59, as well as numerous non-clinical studies using this adjuvant in combination with a variety of antigens other than influenza. MF59 is not associated with any potential for systemic toxicity and it has a low order of local reactogenicity. In repeat-dose rabbit studies, clinical pathology findings of increased fibrinogen and minor inflammatory and degenerative changes at the injection site are consistent with the effects of intramuscular (IM) injections of an immunological adjuvant. These findings are readily reversible within days to 1 to 2 weeks. In repeat-dose toxicology studies in dogs, there were no effects on cardiovascular or central nervous system (safety pharmacology) parameters. MF59 is not genotoxic (Ames test) or clastogenic (mouse micronucleus), is not a dermal sensitiser (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

Table Part II SII-1: Key safety findings from nonclinical studies

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity findings include:	
Toxicity program supporting Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia: • Repeat-dose toxicity • Reproductive and developmental toxicity • Sensitisation	No safety concerns identified in any study. No effects on reproductive and developmental parameters, not a dermal sensitiser.
Pivotal toxicity studies evaluating MF59 alone: • Single-dose toxicity • Repeat-dose toxicity • Reproductive and developmental toxicity • Genotoxicity • Sensitisation • Cardiovascular and nervous system	No safety concerns identified in any study. No effects on reproductive and developmental parameters, not genotoxic or clastogenic, not a dermal sensitiser. No effects on cardiovascular or nervous system parameters.

No need for additional non-clinical data has been identified for any special populations. There have been no safety concerns identified from non-clinical data.

Part II: Module SIII - Clinical trial exposure

Overall, approximately 12,722 subjects have been enrolled into the aH5N1 influenza vaccine clinical program, of which 10,443 subjects have received aH5N1 influenza vaccine (Aflunov,

CCI [redacted]
CCI [redacted]

Prepandemic Influenza Vaccine [PIV][1] and Foclivia), and 2,279 a comparator vaccine and/or placebo since the Development International Birth Date of 27 March 2006. The characteristics of the subjects exposed to aH5N1 influenza vaccine and comparator/placebo in studies (age, gender, race distribution) are described below, in light of the expected characteristics of the target population for the indication. Estimates of overall cumulative subject exposure are provided in the table below, based upon actual exposure data from completed studies. The clinical studies were performed using different dose combinations: 1.875 to 15 mcg HA antigen and 0 to 100% MF59-adjuvant in a large population of healthy children, adults and elderly. In addition, 2 aH5N1 influenza vaccine studies were conducted in adults and elderly with underlying medical conditions/immunosuppressive conditions. Safety and immunogenicity were assessed with 2 A/H5N1 influenza vaccine strains: A/Vietnam/2004 and A/turkey/Turkey/2005. Various dose schedules (two doses separated by 1, 2, 3 and 6 weeks) were studied, as well as booster administration with the same or different pandemic influenza strains, and long-term immune memory. In addition, interactions with concomitant vaccines, mixed or separately administered for seasonal vaccines, were evaluated (Studies V87P5 and V101P1).

Table SIII-1: Estimated subject exposure in completed clinical studies[a]

Vaccination	Number of subjects[b]
aH5N1 influenza vaccine in different formulations: A/Vietnam/1194/2004 H5N1 3.75 mcg_half MF59[a] A/Vietnam/1194/2004 H5N1 7.5 mcg_full MF59[a] A/Vietnam/1194/2004 H5N1 15 mcg_full MF59[a] A/Vietnam/1194/2004 H5N1 15 mcg non adjuvanted A/turkey/Turkey/1/2005 H5N1 1.875mcg_half MF59[a] A/turkey/Turkey/1/2005 H5N1 1.875mcg_full MF59[a] A/turkey/Turkey/1/2005 H5N1 3.75mcg_half MF59[a] A/turkey/Turkey/1/2005 H5N1 3.75 mcg_full MF59[a] A/turkey/Turkey/1/2005 H5N1 7.5 mcg_half MF59[a] A/turkey/Turkey/1/2005 H5N1 7.5 mcg_full MF59[a]	10,443
Placebo (given alone or together with one of the comparators)	23
Other comparators: aTIV without thiomersal	

[1] *Clinical data include exposure to PIV, a zoonotic, monovalent, inactivated, subunit, egg derived, purified surface antigen vaccine, adjuvanted with MF59, however with different strain of influenza virus (A/Vietnam/1194/2004 [H5N1]-like strain [NIBRG-14]) compared with Aflunov. PIV was authorised in Australia until 18 December 2020 when the license was discontinued due to the lack of commercial interest.*

Vaccination	Number of subjects[b]
aTIV with H5N1 7.5 mcg TIV (Agrippal®- like) with 15 mcg A/Vietnam/1194/2004 (H5N1)	2,256

aTIV = adjuvanted trivalent influenza vaccine; TIV = trivalent influenza vaccine

[a] Full MF59 corresponds to the amount of MF59 (9.75mg squalene, 1.175mg of polysorbate 80, 1.175mg of sorbitan trioleate, 0.66mg of sodium citrate dehydrate and 0.04mg of citric acid monohydrate) included in a dose of the seasonal influenza trivalent vaccine Fluad (aTIV); Half MF59 corresponds to half of the amount of MF59 included in a dose of the seasonal influenza trivalent vaccine Fluad.

[b] Data from 47 subjects from Study V87P1E1 are not included in the cumulative list as they already participated in Study V87P1.

An estimate of cumulative exposure to aH5N1 influenza vaccine by age and sex for completed clinical trials sponsored by Seqirus is provided in the table below.

Table SIII-0-2: Cumulative subject exposure from completed clinical trials by age and sex

Number of subjects			
Age range	**Male**	**Female**	**Total**
6-11 months	32	33	65
12-35 months	156	134	290
3-18 years	196	204	400
18-60 years	3,785	4,367	8,152
> 60 years	868	668	1,536
Total	**5,037**	**5,406**	**10,443**

An estimate of cumulative exposure to aH5N1 influenza vaccine by racial/ethnic group for completed clinical trials sponsored by Seqirus is provided in in the table below.

Table SIII-3: Cumulative subject exposure from completed clinical trials by racial/ethnic group

Racial group	Number of subjects
Asian	345 (3.3%)
Black	43 (< 1%)
Caucasian	9,644 (92.3%)
Hispanic	374 (3.6%)
Other	37 (< 1%)
Total	**10,443**

***Note:** Data from 47 subjects from study V87P1E1 are not included in the cumulative list as they were included in study V87P*

Four of the Seqirus-sponsored aH5N1 influenza vaccine studies included in the tables above (V87P6, V87_25 and V87_26, V87_30) were conducted in special populations (children

6 months to < 18 years, and adults/elderly subjects with underlying medical conditions/immunosuppressive conditions). No Seqirus-sponsored aH5N1 influenza vaccine studies were performed in pregnant or nursing women.

Clinical data for aH5N1 support the strain update for Zoonotic Influenza Vaccine Seqirus (aH5N8, (clade 2.3.4.4b). In addition, antigenic analyses indicate that the H5N8 strain cross-reacts with most recent detected H5 viruses, supporting this strain update.

Part II: Module SIV - Populations not studied in clinical trials

In general, the majority of immunogenicity and safety studies of aH5N1 influenza vaccine were conducted in healthy adult/elderly subjects, however 4 studies were conducted in special populations (children aged 6 months to < 18 years, and adults / elderly subjects with underlying medical conditions / immunosuppressive conditions).

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

In the majority of studies, the following subjects were generally excluded:

- Those with significant comorbidities or major organ insufficiencies;
- Immunocompromised subjects, or those receiving immunosuppressants;
- Pregnant or nursing women

Use in pregnancy and lactation has been identified as a safety concern (missing information) from the exclusion criteria in clinical studies within the development program.

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

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

Table SIV.2-1: Limitation of ADR detection common to clinical development programmes

Ability to detect ADRs	Limitation of trial program	Discussion of implication for target population
Which are rare	Overall, 10,443 subjects received aH5N1 influenza vaccine in Seqirus-sponsored clinical studies	A safety population of a size close to 3,000 subjects will be sufficiently large to detect rare (≤0.001%) ADRs according to the

Ability to detect ADRs	Limitation of trial program	Discussion of implication for target population
		European Medicines Agency (EMA) guideline EMA/CHMP/VWP/457259/2014 (CHMP, 2014). The aH5N1 influenza vaccine clinical trial program contained in overall 10,443 subjects; therefore, it is sufficiently large to detect rare (≤0.001%) ADRs.

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

The limitations with respect to exposure in special populations are described in the table below.

Table SIV.3-2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant or nursing women	Pregnant and nursing women were not included in the clinical development program. However, 54 subjects became pregnant while participating in clinical trials included in the clinical development program (exposed to aH5N1, n = 54). There was no safety concern from the exposure to the 54 subjects, however, this sample size is deemed insufficient exposure, therefore use in pregnancy and lactation is considered missing information.
Subjects with relevant comorbidities: • Hepatic impairment • Renal impairment • Cardiovascular impairment	Study V87_25 included 294 adult and elderly subjects with chronic pulmonary disease, cardiovascular disease, peripheral vascular disease, diabetes mellitus, and/or renal impairment, who received aH5N1. No safety concerns have been identified from these populations. There is no indication that the safety profile of aH5N1 /aH5N8 influenza vaccines in this population differs from the populations characterised so far.
Immunocompromised subjects	Study V87_26 included 295 adult and elderly subjects with immunosuppressive conditions such as human immunodeficiency virus infection, transplant recipients and those with specific cancers and/or receiving chemotherapy, who received aH5N1. No safety concerns have been identified from these populations. There is no indication that the safety profile of aH5N1/aH5N8 influenza vaccines in this population differs from the populations characterised so far.
Subjects with disease severity different from inclusion criteria in clinical trials	Not applicable to aH5N1/aH5N8 influenza vaccine
Population with relevant different ethnic origin	Per Part II. Module SIII, studies included different racial/ethnic groups; however, the majority of subjects identified as Caucasian (9,544 subjects) or Hispanic (374 subjects). Although a limited number of subjects from different racial/ethnic groups were exposed to aH5N1 in studies, there is

Type of special population	Exposure
	no indication that the safety profile of aH5N1/aH5N8 influenza vaccine in these populations differs from the populations characterised so far. No safety concerns have been identified from these populations.
Subpopulations carrying relevant genetic polymorphisms	No safety concerns have been identified from these populations.
Other • Children	Per Part II. Module SIII, studies included 65 subjects aged 6-11 months, 290 subjects aged 12-35 months, and 400 subjects aged 3-18 years. No safety concerns have been identified from the paediatric population. No data are available in children aged less than 6 months. There is no indication that the safety profile of aH5N1/aH5N8 influenza vaccines in the paediatric population (6 months to less than 18 years) differs from the adult and elderly populations characterised so far.
• Elderly	Per Part II. Module SIII, studies included 1,536 subjects aged > 60 years. There have been no safety concerns identified from the elderly population.

Use in pregnancy and lactation has been identified as a safety concern (missing information) from populations typically underrepresented in clinical trials within the development program.

Part II: Module SV – Post-authorisation experience

Aflunov was first registered in the EU, including Norway, Iceland and Liechtenstein on 29 November 2010. This marketing authorisation covers 30 countries. Outside of the EU, Aflunov is registered in Great Britain (GB) and Singapore.

Foclivia was first registered in the EU, including Norway, Iceland and Liechtenstein on 19 October 2009. This marketing authorisation covers 30 countries. Outside of the EU, Foclivia is registered in GB, Switzerland and Canada.

Zoonotic Influenza Vaccine Seqirus (aH5N1) was not marketed in any country at the DLP for this RMP. Due to recent dominance of clade 2.3.4.4b lineage of H5 viruses, a strain change from H5N1 to the H5N8 A/Astrakhan/3212/2020 (clade 2.3.4.4b) was requested in November 2023, in order for Zoonotic Influenza Vaccine Seqirus to be able to match with the circulating H5 virus.

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Aflunov is largely sold to government parties for stockpile purposes and no doses were sold to the open market. In 2021, 299,660 doses of Aflunov were distributed. Since the International Birth Date of Foclivia (first aH5N1 vaccine authorised) to the DLP (19 October 2023), the cumulative number of doses of aH5N1 supplied worldwide in postmarketing experience is estimated to be approximately 3,925,215 doses. No doses of Aflunov or Foclivia were administered to patients. Zoonotic Influenza Vaccine Seqirus was not actively marketed at the DLP for this RMP.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable. There is no potential for misuse for illegal purposes with aH5N1/aH5N8 influenza vaccine.

Part II: Module SVII - Identified and potential risks

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

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Local reactions e.g., pain, erythema, swelling, induration, ecchymosis

- Systemic reactions e.g., fatigue, headache, fever, arthralgia/myalgia, malaise, influenza-like illness, sweating, shivering, nausea, vomiting, diarrhoea
- Allergic reactions, angioedema, eye swelling, skin reactions (pruritus, urticaria, nonspecific rash)

Known risks that require no further characterisation and are followed up via routine pharmacovigilance (namely through signal detection and adverse reaction reporting), and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice):

- Anaphylaxis
- Vaccination failure

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

Table SVII.1.2-1: List of safety concerns for inclusion in the RMP

Safety Concern	Evidence for inclusion
Important potential risk: Neuritis	Although there have been no observed cases from postmarketing use or clinical trials, neuritis is considered an adverse event of special interest (AESI) for pandemic influenza vaccines (CHMP, 2009b) and a very rare potential pharmacological class effect (CHMP, 2009a). The event is considered potentially serious and severe, as although the outcome of neuritis is usually favourable, recovery can be quite prolonged, with regaining of strength and function taking weeks to months. Some patients can experience longer periods of muscle weakness, or a slight permanent weakness (Miller et al, 2000). Neuritis usually requires medical treatment (e.g., steroids, analgesia, physiotherapy), may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity (Debeer et al, 2008; Feinberg and Radecki, 2010). Based on evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, neuritis is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Convulsions	A limited number of cases of convulsions were observed from postmarketing use or clinical trials. Convulsions are also considered an AESI for pandemic influenza vaccines (CHMP, 2009b) and a rare potential pharmacological class effect (CHMP, 2009a). The event is considered potentially serious and severe, as it may impact on patient's quality of life and/or may result in emergency hospitalisation. Uncomplicated febrile convulsions in children are generally a benign condition and have not been found to be associated with increased mortality or later neurocognitive difficulties (Bakken et al, 2015). Acute medical treatment such

Safety Concern	Evidence for inclusion
	as diazepam/midazolam may be used for prolonged convulsions, and analgesia can be used to relieve any fever discomfort. Those presenting with afebrile convulsions may also require acute medical treatment such as diazepam/midazolam. After the patient is stabilised and returns to baseline function; history, examination, and diagnostic testing may be performed to determine if the event was a seizure, the cause of the event, and if any long-term follow-up or treatment is required. It is likely the event will be an isolated incident (Krumholz et al, 2007). On the basis of case reports and evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, convulsions are considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines, and are therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Encephalitis (*encephalomyelitis*)	Although there have been no observed cases from postmarketing use or clinical trials, encephalitis (*encephalomyelitis*) is considered an AESI for pandemic influenza vaccines (CHMP, 2009b) and a very rare potential pharmacological class effect (CHMP, 2009a). The event is considered potentially serious and severe, as with potential symptoms such as encephalopathy, seizures and loss of consciousness (Sejvar et al, 2007), the event has a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. The outcome in patients developing encephalitis (*encephalomyelitis*) may range widely, from complete recovery to persistent disability, coma or death. A proportion of patients developing encephalitis (*encephalomyelitis*) will be expected to have persistent neurological, functional, and cognitive sequelae lasting for months, years or indefinitely (Sejvar et al, 2007). Encephalitis (*encephalomyelitis*) requires medical treatment (e.g. steroids, immunoglobulin, plasmapheresis), generally in a hospital setting. Based on evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, encephalitis (*encephalomyelitis*) is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Vasculitis	A limited number of cases of vasculitis were observed from postmarketing use or clinical trials. Vasculitis is also considered an AESI for pandemic influenza vaccines (CHMP, 2009b) and is a very rare potential pharmacological class effect (CHMP, 2009a). The event is considered potentially serious and severe, as depending on the type, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. The outcome of vasculitis varies substantially, depending on the vessels involved, and the extent of disease and/or organ involvement. Some vasculitis may only present transient cutaneous lesions, and some can be systemic with or without cutaneous manifestation. Systemic vasculitis can be disabling or life-threatening (Schattner, 2005). For those with cutaneous lesions only, spontaneous resolution is possible (Zanoni et al, 2016). Systemic vasculitis generally require critical medical treatment (e.g. steroids/immunosuppressants, immunoglobulin) (Woerner et al, 2017).

Safety Concern	Evidence for inclusion
	Based on case reports and evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, vasculitis is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Guillain-Barré Syndrome	Although there have been no observed cases from postmarketing use or clinical trials, Guillain-Barré syndrome (GBS) is considered an AESI for pandemic influenza vaccines (CHMP, 2009b) and a very rare potential pharmacological class effect (CHMP, 2009a). The event is considered potentially serious and severe, as it has a significant impact on patient's quality of life and/or may result in death, hospitalisation, persistent or significant disability/incapacity. Overall, GBS is generally associated with eventual favourable outcome, with most patients experiencing clinical improvement over weeks to months. In infants and children, recovery is more rapid and tends to be complete, with fatalities being rare. Elderly patients have a worse prognosis. Overall, approximately 5-15% of patients die, and continued disability after 1 year has been estimated to be 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain and fatigue may be reported. GBS requires medical treatment (e.g., plasmapheresis, immunoglobulin), generally in a hospital setting (Sejvar et al, 2011). Based on evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, GBS is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Demyelination	A limited number of cases of Demyelination were observed from postmarketing use or clinical trials, demyelination is considered an AESI for pandemic influenza vaccines (CHMP, 2009b). The event is considered potentially serious and severe as it can have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity. Demyelinating disorders require medical treatment (e.g., steroids/immunosuppressants) (Wingerchuk and Weinshenker, 2005). Based on evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, demyelination is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Bell's palsy	A limited number of cases of Bell's palsy were observed from postmarketing use or clinical trials. Bell's palsy is also considered an AESI for pandemic influenza vaccines (CHMP, 2009b). The event is considered potentially serious and severe as it may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity. Bell's palsy resolves spontaneously without treatment within 6 months in most patients (Wijnans et al, 2017). On the basis of case reports and evidence from the scientific literature as described above, Bell's palsy is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.

Safety Concern	Evidence for inclusion
	Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Immune thrombocytopenia	A limited number of cases of immune thrombocytopenia were observed from postmarketing use or clinical trials. Immune thrombocytopenia is also a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). The event is considered potentially serious and severe as depending on the platelet count and clinical manifestations, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation. Children typically recover spontaneously, in several weeks to months. In adults, spontaneous remission may occur, but it is uncommon after the first year of disease. Most post-immunisation episodes resolve within 3 months, although low platelet counts may rarely persist for more than 6 months (Wise et al, 2007). However, many patients have mild and stable disease with minimal or no bleeding. Life-threatening bleeding and death are rare (Kuter, 2017). Immune thrombocytopenia generally requires medical treatment (e.g., steroids/immunosuppressants, immunoglobulin, thrombopoietin receptor agonists) (Kuter, 2017). On the basis of case reports and evidence from the scientific literature as described above, immune thrombocytopenia is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Missing information: Use in pregnancy and lactation	Use in pregnancy and lactation has not been evaluated in the Clinical Development program. There is currently insufficient exposure to determine whether the safety profile of aH5N1/aH5N8 influenza vaccines in this population differs to that characterised so far. Use in pregnancy and lactation is therefore classified as missing information, until further data becomes available.

Note: *No postmarketing experience exists with Foclivia. The postmarketing experience refers to H1N1 (licensed for use from 6 months of age during the 2009 influenza pandemic, containing the same MF59 adjuvant and manufactured with the same process as Foclivia)*

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

Not applicable

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

Table SVII.3.1-2: Presentation of important identified and important potential risks

Important identified risk: None	
Important potential risk: Neuritis	
Potential mechanisms	Aetiology is unclear, but it is theorised to be attributable to an autoimmune response to the antigen in the influenza vaccine (Debeer et al, 2008; Feinberg and Radecki, 2010).
Evidence source(s) and strength of evidence	The strength of evidence is low, as there have been no observed cases from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, neuritis is considered an AESI (CHMP, 2009b), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a), with a potential rate of 0.45 neuritis cases per million influenza vaccinations (Vellozzi et al, 2009). On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, neuritis is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, no cases were observed from postmarketing use or clinical trials. In a study of ADRs reported to Vaccine Adverse Event Reporting System (VAERS) following seasonal influenza vaccine between 1990 and 2005, a rate of 0.45 neuritis cases per million vaccinations in adults was observed (Vellozzi et al, 2009). Neuritis is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). The outcome of neuritis is usually favourable, but recovery can be quite prolonged, with regaining of strength and function taking weeks to months. Some patients can experience longer periods of muscle weakness, or a slight permanent weakness (Miller et al, 2000). Neuritis usually requires medical treatment (e.g. steroids, analgesia, physiotherapy), may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity (Debeer et al, 2008; Feinberg and Radecki, 2010).
Risk factors and risk groups	There is no evidence of any patient, dose-related or additive/synergistic risk factors; nor of a specific risk period, in relation to neuritis specifically attributed to influenza vaccine.
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although regarded as a very rare class effect, on the basis of evidence from scientific literature, and the potentially serious outcome and severe nature of the event as described above, neuritis is considered to potentially impact the benefit-

	risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered very rare with no established causal link to vaccination, and thus public health impact is limited.
Medical Dictionary for Regulatory Activities (MedDRA) terms	Preferred Terms (PTs): *Neuritis, Neuralgic amyotrophy, Mononeuritis, Radiculitis brachial, Brachial plexopathy*

Important Potential Risk: Convulsions	
Potential mechanism	There is no evidence on the mechanism of influenza vaccine directly leading to non-febrile convulsions. In children, influenza vaccines can cause pyrexia, which can in turn provoke a febrile convulsion in susceptible individuals (Bakken et al, 2015).
Evidence source(s) and strength of evidence	The strength of evidence is low, as a limited number of cases of convulsions were observed from postmarketing use or clinical trials. However, on the basis of evidence from scientific literature, convulsions are considered an AESI (CHMP, 2009b), and a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a), with a potential rate of 0.16 convulsion (febrile and afebrile) cases per million influenza vaccinations (Vellozzi et al, 2009). On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, convulsions are considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and are therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, there were no cases observed from postmarketing use; however, 6 cases were reported from clinical trials, out of which, 5 were assessed as not related to the study vaccine. In 1 case, the event of seizure was assessed as related. In a study of ADRs reported to VAERS following seasonal influenza vaccine between 1990 and 2005, a rate of 0.16 convulsion (febrile and afebrile) cases per million vaccinations in adults was observed (Vellozzi et al, 2009). Frequency data for febrile convulsions vary: Duffy et al (2016) examined the risk of febrile convulsions in children aged 6 to 23 months 0-1 day after seasonal influenza vaccine, and identified no independent risk (incidence rate ratio [IRR] 0.46, 95%CI 0.21 to 1.02); however, (Bakken et al, 2015) identified an IRR of 2.0 (95%CI 1.15-3.51) for febrile convulsions 1-3 days after an adjuvanted pandemic H1N1 influenza vaccine in children < 45 months of age. Convulsions are generally considered a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). Uncomplicated febrile convulsions in young children are generally a benign condition, and it has not been found to be associated with increased mortality or later neurocognitive difficulties (Bakken et al, 2015). Acute medical treatment such as diazepam/midazolam may be used for prolonged convulsions, and analgesia can be used to relieve any fever discomfort. Those presenting with afebrile convulsions may also require acute medical treatment such as diazepam/midazolam. After the patient is stabilised and returns to baseline function; history, examination, and diagnostic testing may be performed to determine if the event was a seizure, the cause of the event, and if

Important Potential Risk: Convulsions	
	any long-term follow-up or treatment is required. It is likely the event will be an isolated incident (Krumholz et al, 2007). The event may impact on patient's quality of life and/or may result in emergency hospitalisation.
Risk factors and risk groups	Febrile convulsions risk factors include a fever of ≥ 38 °C; however, are dependent on the seizure threshold (which can vary between patients), age, maturation, and genetic predisposition (Bakken et al, 2015). Median age of onset of a febrile seizure is 18 months, and half of children present between 12 and 30 months. The risk interval for febrile convulsions is 0 to 1 day (Duffy et al, 2016). There is an increase of incidence in the elderly for non-febrile seizures (Kotsopoulos et al, 2005). There is no evidence of a specific risk period for any age group for non-febrile seizures.
Preventability	There is no evidence on preventability or predictability of convulsions. Administration of prophylactic antipyretics is not recommended and has been found to be ineffective in preventing recurrences of febrile convulsions (Duffy et al, 2016).
Impact on benefit-risk	Although regarded as a rare class effect; on the basis of case reports and evidence from scientific literature, and the potentially serious outcome and severe nature of the event as described above, convulsions are considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and are therefore classified as an important potential risk.
Public health impact	The event is considered rare, and thus public health impact is limited.
MedDRA terms	Standardised MedDRA Query (SMQ) [narrow]: Generalised convulsive seizures following immunisation

Important potential risk: Encephalitis (*encephalomyelitis*)	
Potential mechanisms	Aetiology is unclear, but a number of mechanisms have been proposed. It is theorised that the influenza vaccines present an antigenic challenge leading to an immunological response in the form of encephalomyelitis (Sejvar et al, 2007).
Evidence source(s) and strength of evidence	The strength of evidence is low, as there have been no observed cases from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, encephalitis is considered an AESI (CHMP, 2009b), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a), with a potential rate of 0.12 encephalitis cases per million influenza vaccinations (Vellozzi et al, 2009). On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, encephalitis (*encephalomyelitis*) is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, no cases were observed from postmarketing use or clinical trials. In a study of ADRs reported to VAERS following seasonal influenza vaccine between 1990 and 2005, a rate of 0.12 encephalomyelitis cases per million vaccinations in adults was observed (Vellozzi et al, 2009). Encephalitis (*encephalomyelitis*) is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a).

Important potential risk: Encephalitis (*encephalomyelitis*)	
	The outcome in patients developing encephalitis (*encephalomyelitis*) may range widely, from complete recovery to persistent disability, coma or death. A proportion of patients developing encephalitis (*encephalomyelitis*) will be expected to have persistent neurological, functional, and cognitive sequelae lasting for months, years or indefinitely (Sejvar et al, 2007). Encephalitis (*encephalomyelitis*) requires medical treatment (e.g. steroids, immunoglobulin, plasmapheresis), generally in a hospital setting. With potential symptoms such as encephalopathy, seizures and loss of consciousness (Sejvar et al, 2007), the event has a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity.
Risk factors and risk groups	Encephalitis (*encephalomyelitis*) is found to be most common in children less than 10 years and has a higher incidence in males. Immunocompromised patients are also at an increased risk. One study described the onset of encephalitis within 6 weeks after vaccination in 65.2% of patients, and in 50.7% within 2 weeks (Qudah et al, 2012).
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although regarded as a very rare class effect and there is no established causality with vaccination; due to potentially serious outcome and severe nature of the event as described above, encephalitis (*encephalomyelitis*) is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered very rare, and thus public health impact is limited.
MedDRA terms	SMQ [narrow]: Noninfectious encephalitis

Important potential risk: Vasculitis	
Potential mechanisms	Vasculitides are a diverse group of related disorders with a wide spectrum of potential aetiologies, clinical manifestations and prognosis (Bonetto et al, 2016). Aetiology is unclear; however, it may be related to hypersensitivity, or may involve the trigger of underlying inflammatory or autoimmune disorders (Zanoni et al, 2016).
Evidence source(s) and strength of evidence	The strength of evidence is low, as a limited number of cases of vasculitis were observed from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, vasculitis is considered an AESI (CHMP, 2009b) and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a), with a potential rate of 341.8 vasculitis cases per 100,000 person-years after influenza vaccination (Gao, 2013). On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, vasculitis is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, there were no cases observed from postmarketing use, however, 1 related case was observed from clinical trials. Events reported in this case were: Henoch-Schönlein purpura nephritis (1) and cutaneous vasculitis (1).

Important potential risk: Vasculitis	
	Note: The PT: hypersensitivity vasculitis, presented in the previous RMP version, was replaced with PT: cutaneous vasculitis, as the result of the MedDRA updated. According to a surveillance study, the incidence rate of vasculitis was 341.8 per 100,000 person-years for IM influenza vaccine (Gao, 2013). Vasculitis is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). The outcome of vasculitis varies substantially, depending on the vessels involved, and the extent of disease and/or organ involvement. Some vasculitides may only present transient cutaneous lesions, and some can be systemic with or without cutaneous manifestation. Systemic vasculitides can be disabling or life-threatening (Schattner, 2005). For those with cutaneous lesions only, spontaneous resolution is possible (Zanoni et al, 2016). Systemic vasculitides generally require critical medical treatment (e.g., steroids/immunosuppressants, immunoglobulin) (Woerner et al, 2017), and depending on the type, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity.
Risk groups or risk factors	The condition is more commonly reported in elderly; however, this could be more reflective of the target population for influenza vaccine (Bonetto et al, 2016). A medical history of underlying autoimmune disorder may play a role in risk (Woerner et al, 2017). There is no evidence of a specific risk period.
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although regarded as a very rare class effect; on the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, vasculitis is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered very rare, and thus public health impact is limited.
MedDRA terms	SMQ [narrow]: Vasculitis

Important potential risk: Guillain-Barré syndrome (GBS)	
Potential mechanisms	Aetiology is unclear, influenza vaccine may trigger antigenic stimulation resulting in demyelination and damage to the peripheral nerves (Martín Arias et al, 2015).
Evidence source(s) and strength of evidence	The strength of evidence is low, as there have been no observed cases from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, GBS is considered an AESI (CHMP, 2009b), and a very rare potential pharmacological class effect of pandemic influenza vaccines. (CHMP, 2009a), with a potential rate of 0.42 and 1.75 GBS cases per million pandemic influenza vaccinations for age < 25 years and ≥ 25 years, respectively (Vellozzi et al, 2010). On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, GBS is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.

Important potential risk: Guillain-Barré syndrome (GBS)	
Characterisation of the risk	Cumulatively to DLP, no cases were observed from postmarketing use or clinical trials. In a study of ADRs reported to VAERS following seasonal influenza vaccine between 1990 and 2005, a rate of 0.78 GBS cases per million vaccinations in adults was observed (Vellozzi et al, 2009). Vellozzi (2010) identified a verified GBS case reporting rate of 0.42 and 1.75 per million pandemic H1N1 influenza vaccinations for age < 25 years and ≥ 25 years, respectively. In a systematic review and meta-analysis conducted by Martín Arias (2015) an overall relative risk of 1.41 (95% CI 1.20-1.66) for an association between any influenza vaccine and GBS was identified. Pandemic vaccines presented a higher risk (1.84, 95% CI 1.36-2.5) compared to seasonal (1.22, 95% CI 1.01-1.48). Adjuvanted pandemic vaccines were not found to be related to a higher risk compared to non-adjuvanted. GBS is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). Overall, GBS is generally associated with eventual favourable outcome, with most patients experiencing clinical improvement over weeks to months. In infants and children, recovery is more rapid and tends to be complete, with fatalities being rare. Elderly patients have a worse prognosis. Overall, approximately 5-15% of patients die, and continued disability after 1 year has been estimated to be 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain and fatigue may be reported (Sejvar et al, 2011). GBS requires medical treatment (e.g., plasmapheresis, immunoglobulin), generally in a hospital setting (Sejvar et al, 2011). The event has a significant impact on patient's quality of life and/or may result in death, hospitalisation, persistent or significant disability/incapacity.
Risk groups or risk factors	Incidence is higher in males, and increases with age (Martín Arias et al, 2015). The risk period is considered to be within 6 weeks following immunisation (Sejvar et al, 2011).
Preventability	There is no evidence on preventability or predictability of this risk. Early recognition and treatment may shorten the time required for recovery.
Impact on benefit-risk	Although regarded as a very rare class effect; on the basis of evidence from scientific literature, and the potentially serious outcome and severe nature of the event as described above, GBS is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered very rare, and thus public health impact is limited.
MedDRA terms	SMQ [narrow]: Guillain-Barre syndrome

Important potential risk: Demyelination	
Potential mechanisms	This risk describes well-recognised inflammatory demyelinating disorders of the central nervous system (CNS), which are not covered by other safety concerns in this section, i.e. multiple sclerosis and neuromyelitis optica; as well as inflammatory conditions associated with the presences of scleroses in the CNS: optic neuritis and transverse myelitis. Aetiology is unclear; however, pathophysiology is thought to be immune-mediated (Mailand and Frederiksen, 2017).

Important potential risk: Demyelination	
Evidence source(s) and strength of evidence	Cumulatively to DLP, there were no cases observed from postmarketing use, and 1 not related case was reported from clinical trials. However, on the basis of evidence from the scientific literature, inflammatory demyelinating disorders of the central nervous system are considered an AESI for pandemic influenza vaccines (CHMP, 2009b), and have been reported vary rarely in association with influenza vaccine, with a potential rate of 0.03 multiple sclerosis cases, 0.064 of transverse myelitis, 0.04 for optic neuritis per million influenza vaccinations (Vellozzi et al, 2009). On the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, demyelinating disorders are considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and are therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, no cases were observed from postmarketing use, however, 1 not related case was reported from clinical trials. The event reported in this case was multiple sclerosis (1). In a study of ADRs reported to VAERS following seasonal influenza vaccine between 1990 and 2005, a rate of 0.03 multiple sclerosis cases, 0.064 of transverse myelitis, 0.04 for optic neuritis per million vaccinations in adults was observed (Vellozzi et al, 2009). There are no estimates on the reporting rate for neuromyelitis optica following influenza vaccine, however it is predicted to be similar to that of multiple sclerosis. Depending on the type of demyelination this condition could be reversible with minimal impact on quality of life or there could be significant neurological sequelae. Treatment options vary according to the underlying cause (e.g. steroids, immunosuppressants, plasmapheresis) (Wingerchuk and Weinshenker, 2005), and have a significant impact on patient's quality of life and/or may result in hospitalisation, persistent or significant disability/incapacity.
Risk groups or risk factors	There is insufficient evidence of any patient, dose-related or additive/synergistic risk factors; or of a specific risk period, in relation to demyelinating disorders specifically attributed to influenza vaccine.
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although reported very rarely in association with influenza vaccine; on the basis of evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described in rows above, demyelinating disorders are considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and are therefore classified as an important potential risk.
Public health impact	The event is considered very rare, and thus public health impact is limited.
MedDRA terms	SMQ [narrow]: Demyelination

Important potential risk: Bell's palsy	
Potential mechanisms	Aetiology is unclear, inflammation is thought to play an important role, and an autoimmune aetiology has also been suggested (Wijnans et al, 2017)
Evidence source(s) and strength of evidence	The strength of evidence is low, as a limited number of cases of Bell's palsy were observed from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, Bell's palsy is considered an AESI for pandemic influenza vaccines (CHMP, 2009b), and have been reported vary rarely

Important potential risk: Bell's palsy	
	in association with influenza vaccines, with a potential rate of 0.29 Bell's palsy cases per million influenza vaccinations (Vellozzi et al, 2009). On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, Bell's palsy is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Characteristics of the risk	Cumulatively to DLP, there were no cases observed from postmarketing use; however, 1 related case was reported from clinical trials. The event of facial paralysis reported in this case, was assessed as not related to the study vaccine. In a study of ADRs reported to VAERS following seasonal influenza vaccine between 1990 and 2005, a rate of 0.29 cases of facial paralysis per million vaccinations in adults was observed (Vellozzi et al, 2009). Wijnans (2017) identified an incidence rate of 38.7 per 100,000 person-years during the 6 weeks following vaccination with either pandemic H1N1 or seasonal influenza vaccine. Bell's palsy resolves spontaneously without treatment in most patients within 6 months (Wijnans et al, 2017). The event may impact on patient's quality of life and/or may result in persistent or significant disability/incapacity.
Risk groups or risk factors	Risk factors include diabetes, weakened immune system and pregnancy (Wijnans et al, 2017). Risk period is generally considered to be 6 weeks (Wijnans et al, 2017).
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although reported very rarely in association with influenza vaccine; on the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described in rows above, Bell's palsy is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered very rare, and thus public health impact is limited.
MedDRA terms	PTs: *Facial paralysis, Facial paresis, Facial nerve disorder, Oculofacial paralysis, Bell's palsy*

Important potential risk: Immune thrombocytopenia	
Potential mechanisms	Aetiology is unclear, however the suggested mechanism for immune thrombocytopenia (also called idiopathic thrombocytopenic purpura [ITP]) may be molecular mimicry (Perricone et al, 2014).
Evidence source(s) and strength of evidence	The strength of evidence is low, as a limited number of cases were observed from postmarketing use or clinical trials. However, on the basis of evidence from the scientific literature, immune thrombocytopenia is considered a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a), with 1 publication identifying 22 ITP events from 3.1 million influenza vaccinations (Liu, 2014). On the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event, immune thrombocytopenia is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.

Important potential risk: Immune thrombocytopenia	
Characteristics of the risk	Cumulatively to DLP, there were no cases observed from postmarketing use, however 1 not related case was reported from clinical trials. A study by Liu et al (2014) in a large health plan database found that among 3.1 million seasonal influenza vaccinees, only 22 had an acute ITP episode within a defined risk interval during the 2006-2009 influenza season. Seasonal influenza vaccine was not associated with an increased risk of ITP (IRR 0.78, 95%CI 0.43-1.40 (post-vaccination control)). Similarly, a review of EudraVigilance data and literature for pandemic H1N1 vaccines, identified only 28 cases of ITP out of 50,221 reported cases (Isai et al, 2012). ITP is generally considered a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, 2009a). The event is considered potentially serious and severe depending on the platelet count and clinical manifestations. Platelet counts below 20,000 per µl may result in formation of purpura and petechiae, epistaxis, bleeding of the gums or menorrhagia. Low platelet counts (< 10,000 per µl) may result in hematomas in the mouth or other mucous membranes. Fatal complications, including subarachnoid or intracerebral, lower gastrointestinal or other internal bleeding can arise due to an extremely low count (< 5,000 per µl) (Perricone et al, 2014). Children typically recover spontaneously, in several weeks to months. In adults, spontaneous remission may occur, but it is uncommon after the first year of disease. Most post-immunisation episodes resolve within 3 months, although low platelet counts may rarely persist for more than 6 months (Wise et al, 2007). However, many patients have mild and stable disease with minimal or no bleeding. Life-threatening bleeding and death are rare (Kuter, 2017). Immune thrombocytopenia generally requires medical treatment (e.g., steroids/immunosuppressants, immunoglobulin, thrombopoietin receptor agonists) (Kuter, 2017), and depending on the platelet count and clinical manifestations, the event may have a significant impact on patient's quality of life and/or may result in hospitalisation.
Risk groups or risk factors	The risk period is considered to be 6 weeks after vaccination (Liu, 2014; Perricone et al, 2014). There is no evidence of any patient, dose-related or additive/synergistic risk factors, in relation to immune thrombocytopenia specifically attributed to influenza vaccine.
Preventability	There is no evidence on preventability or predictability of this risk.
Impact on benefit-risk	Although regarded as a rare class effect; on the basis of case reports and evidence from the scientific literature, and the potentially serious outcome and severe nature of the event as described above, immune thrombocytopenia is considered to potentially impact the benefit-risk profile of aH5N1/aH5N8 influenza vaccines and is therefore classified as an important potential risk.
Public health impact	The event is considered rare, and thus public health impact is limited.
MedDRA terms	High Level Term (HLT): Thrombocytopenias

Note: No postmarketing experience exists with Foclivia. The postmarketing experience refers to H1N1 (licensed for use from 6 months of age during the 2009 influenza pandemic, containing the same MF59 adjuvant and manufactured with the same process as Foclivia)

SVII.3.2 Presentation of the missing information

Table SVII.3.2-3: Missing information. Use in pregnancy and lactation

Missing information: Use in pregnancy and lactation	
Population in need of further characterisation	Use in this special population has not been evaluated in clinical trials. Inactivated influenza vaccines in general are widely accepted as safe to use in pregnancy and while breast-feeding, however currently available information on aH5N1/aH5N8 influenza vaccines is insufficient to determine if use in this population differs from that characterised for inactivated influenza vaccines so far or is associated with any risks of clinical significance. The observational cohort study V87_27OB to evaluate the safety of pandemic influenza vaccine A/H5N1* (Foclivia®) in pregnant women (pregnancy registry) is planned in case of pandemic. In addition, during pandemic, use of aH5N1/aH5N8 influenza vaccines while breast-feeding will be monitored via routine pharmacovigilance activities. **The strain is subject to change to be matched with the next pandemic strain*

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of Safety Concerns

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome (GBS) Demyelination Bell's palsy Immune thrombocytopenia (ITP)
Missing information	Use in pregnancy and lactation

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities for Seqirus products comply with Good Pharmacovigilance Practice and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004. Routine pharmacovigilance includes management of Individual Case Safety Reports, Periodic Safety Update Reports (PSURs), monitoring safety profiles, and safety signal detection and evaluation.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific targeted follow-up questionnaires related to pregnancy reporting and outcome; and to important potential risks of Neuritis, Convulsions, Encephalitis (encephalomyelitis), Vasculitis, GBS, Demyelination, Bell's palsy, Immune thrombocytopenia (Annex 4), applicable to Aflunov, Foclivia and Zoonotic Influenza Vaccine Seqirus.
- Enhanced Passive Safety Surveillance (EPSS) for Aflunov (aH5N1) and Zoonotic Influenza Vaccine Seqirus (aH5N8) to be conducted, in collaboration with the respective Public Health Agency, upon initiation of a government-directed vaccination programme (in the context of outbreaks of zoonotic influenza viruses with pandemic potential, including use in First Responders, i.e. functions critical to maintain civil infrastructure, when there is anticipation of a possible pandemic due to the same or a similar strain) if and when the vaccine is deployed to an agreed number of vaccinees.
- Outside of the pandemic period, the normal PSUR periodicity and format will be maintained. In the situation of a pandemic, resources will be concentrated on a timely and effective monitoring of the safety profile of Foclivia (pandemic vaccine) and zoonotic aH5N1/aH5N8 influenza vaccines (if used during pandemic). The normal PSUR will be replaced with simplified PSURs (S-PSURs), accompanied by a summary of vaccine distribution. S-PSURs will be prepared monthly, with clock start the first Monday after shipment of the first batch of vaccine once a pandemic is declared. First DLP is 30 days later, with submission on Day 45. The periodicity will be reviewed in collaboration with competent authorities at 6 monthly intervals.

- In the situation of a pandemic, a business continuity planning and crisis management procedure is also in place which specifically details the plans to ensure resource is prioritised and necessary technical requirements are met.

III.2 Additional pharmacovigilance activities

It is considered that for the majority of safety concerns, routine pharmacovigilance activities alone will be sufficient. However, in the situation of a pandemic, required Category 3 Study V87_27OB is planned for Foclivia to address the missing information *Use in pregnancy and lactation:*

- V87_27OB is a postmarketing, observational cohort study to evaluate the safety of adjuvanted pandemic influenza vaccine A/H5N1[2] (Foclivia) in pregnant women (pregnancy registry). This study is planned in case of pandemic and will follow from enrolment to pregnancy outcome and in live-born infants until 3 months of age.

As a specific post-authorisation pharmacovigilance requirement, in accordance with EMA/CHMP/VWP/457259/2014 Guidance on Influenza Vaccines (CHMP, 2014), the enhanced safety surveillance (ESS) for A/H5N1 (Foclivia) will be performed during the pandemic period aiming to rapidly collect the data within a month from the start of vaccination. This is a Category 2 study, imposed by the competent authority as a Specific Obligation in the context of marketing authorisation under exceptional circumstances.

An updated RMP with further details on additional pharmacovigilance activities will be submitted to competent authorities once a pandemic is declared.

[2] *The strain is subject to change to be matched with the next pandemic strain*

III.3 Summary table of additional pharmacovigilance activities

Table Part III.3-1: On-going and planned additional pharmacovigilance activities

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Enhanced surveillance of vaccine safety (Foclivia®) (Planned)	To evaluate safety and reactogenicity of Foclivia in the different age groups in terms of local and systemic adverse reactions and any adverse events (AEs) defined as important potential risks.	Neuritis, Convulsions, Encephalitis (encephalomyelitis), Vasculitis, Guillain-Barré Syndrome, Demyelination, Bell's palsy, Immune Thrombocytopenia	EPSS plan (full description outlining implementation) to be provided once pandemic is declared. Milestones to be confirmed.	To be confirmed
Category 3 - Required additional pharmacovigilance activities				
V87_27OB is a postmarketing observational cohort safety study of pandemic influenza A/H5N1[a] vaccine (Foclivia®) in pregnant women (Planned)	To evaluate the safety of pandemic influenza vaccine in pregnant women.	Use in pregnancy and lactation	Protocol to be provided once pandemic is declared. Milestones to be confirmed.	To be confirmed

[a] *The strain is subject to change to be matched with the next pandemic strain*

Part IV: Plans for post-authorisation efficacy studies

Table Part IV-1: Planned post-authorisation efficacy studies

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A non-interventional study of vaccine effectiveness for Foclivia® (Planned)	To perform an analysis of vaccine effectiveness for Foclivia® versus no vaccination	Not applicable	Protocol to be provided when pandemic is declared. Milestones to be confirmed	To be confirmed

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

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

Safety concern	Routine risk minimisation activities
Neuritis	Neuritis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus Summary of Product Characteristics (SmPC) and Section 4 of the Package Leaflet (PL).
Convulsions	Convulsions are described in Section 4.4 Special warning and precautions for use of the Foclivia SmPC and Section 4.8 Undesirable effects of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 & 4 of the PL.
Encephalitis (*encephalomyelitis*)	Neurological disorders, such as encephalomyelitis, are described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Vasculitis	Vasculitis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Guillain-Barré syndrome	Guillain-Barré syndrome is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC and Section 4 of the PL.
Demyelination	None; included as a potential safety concern based on pharmacological class effects
Bell's palsy	None; included as a potential safety concern based on pharmacological class effects
Immune thrombocytopenia	None; included as a potential safety concern based on pharmacological class effects
Use in pregnancy and lactation	Use in pregnancy and use during breast-feeding is described in Section 4.6 of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 of the PL.

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of aH5N1/aH5N8.

V.3 Summary of risk minimisation measures

Table Part V.3-1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measure	Pharmacovigilance Activity
Important Identified Risk		
None		
Important Potential Risk		
Neuritis	Routine risk minimisation measures: Neuritis is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Neuritis targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Convulsions	Routine risk minimisation measures: Convulsions are described in: *Foclivia SmPC: Section 4.4 and 4.8* *Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and, Foclivia PL: Section 2 and 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Convulsions targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Encephalitis (*encephalomyelitis*)	Routine risk minimisation measures: Neurological disorders, such as Encephalomyelitis, are described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Encephalitis (encephalomyelitis) targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*

Safety concern	Risk minimisation measure	Pharmacovigilance Activity
Vasculitis	Routine risk minimisation measures: Vasculitis is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Vasculitis targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Guillain-Barré syndrome	Routine risk minimisation measures: Guillain-Barré syndrome is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Guillain-Barré syndrome targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Demyelination	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Demyelination targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Bell's palsy	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Bell's Palsy targeted follow-up questionnaire*

Safety concern	Risk minimisation measure	Pharmacovigilance Activity
		EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus) Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Immune thrombocytopenia	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Immune thrombocytopenia targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Missing information		
Use in pregnancy and lactation	Routine risk minimisation measures: Pregnancy and breast-feeding is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.6* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 2* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Pregnancy Reporting/Outcome form (Aflunov, Zoonotic Influenza Vaccine Seqirus, Foclivia)* Additional pharmacovigilance activities: *Category 3 study - V87_27OB (Foclivia)*

Part VI: Summary of the risk management plan

Summary of risk management plan for Aflunov (aH5N1)

This is a summary of the RMP for Aflunov. The RMP details important risks of Aflunov, how these risks can be minimised, and how more information will be obtained about Aflunov risks and uncertainties (missing information).

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

This summary of the RMP for Aflunov 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 Aflunov RMP.

I. The medicine and what it is used for

Aflunov is a zoonotic influenza vaccine authorised for an active immunisation against H5N1 subtype of Influenza A virus in individuals 6 months of age and above. It contains an inactivated, surface antigen monovalent, influenza vaccine adjuvanted with MF59C.1. It is to be administered as 2 doses of 0.5 mL by IM injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older individuals. One dose of 0.5 mL should be given at an elected date and a second dose of 0.5 mL after an interval of at least 3 weeks.

Further information about the evaluation of Aflunov's benefits can be found in Aflunov's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: Aflunov | European Medicines Agency (EMA).

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

Important risks of Aflunov, together with measures to minimise such risks and the proposed studies for learning more about Aflunov 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 PL 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.

II.A List of important risks and missing information

Important risks of Aflunov 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 Aflunov. 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 safety concerns for Aflunov

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy and lactation

II.B Summary of important risks

Table Part VI-2: Summary of important risks for Aflunov

Neuritis	
Risk minimisation measures	Routine risk minimisation measures: Neuritis is described in: *Aflunov SmPC: Section 4.8* *Aflunov PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Neuritis targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Convulsions	
Risk minimisation measures	Routine risk minimisation measures: Convulsions are described in: *Aflunov SmPC: Section 4.8* *Aflunov PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Convulsions targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Encephalitis (*encephalomyelitis*)	
Risk minimisation measures	Routine risk minimisation measures: Neurological disorders, such as encephalomyelitis, are described in: *Aflunov SmPC: Section 4.8* *Aflunov PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)*

Additional Pharmacovigilance activities	*Encephalitis (encephalomyelitis) targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Vasculitis	
Risk minimisation measures	Routine risk minimisation measures: Vasculitis is described in: *Aflunov SmPC: Section 4.8* *Aflunov PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Vasculitis targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Guillain-Barré Syndrome	
Risk minimisation measures	Routine risk minimisation measures: Guillain-Barré syndrome is described in: *Aflunov SmPC: Section 4.8* *Aflunov PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Guillain-Barré Syndrome targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Demyelination	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Demyelination targeted follow-up questionnaire*

	EPSS Additional Pharmacovigilance activities: *None*
Bell's palsy	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Bell's Palsy targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Immune thrombocytopenia	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Immune thrombocytopenia targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Pregnancy and breast-feeding are described in: *Aflunov SmPC: Section 4.6* *Aflunov PL: Section 2* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Pregnancy Reporting/Outcome form* Additional Pharmacovigilance activities: *None*

II.C Post-authorisation development plan

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

Not applicable. There are no safety studies imposed as condition of the marketing authorisation (category 1), or as a specific obligation in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (category 2) or required by the competent authority (category 3).

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

Not applicable.

Summary of risk management plan for Zoonotic Influenza Vaccine Seqirus (aH5N8)

This is a summary of the RMP for Zoonotic Influenza Vaccine Seqirus. The RMP details important risks of Zoonotic Influenza Vaccine Seqirus, how these risks can be minimised, and how more information will be obtained about Zoonotic Influenza Vaccine Seqirus risks and uncertainties (missing information).

Zoonotic Influenza Vaccine Seqirus SmPC and its PL give essential information to healthcare professionals and patients on how Zoonotic Influenza Vaccine Seqirus should be used.

This summary of the RMP for Zoonotic Influenza Vaccine Seqirus 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 Zoonotic Influenza Vaccine Seqirus RMP.

I. The medicine and what it is used for

Zoonotic Influenza Vaccine Seqirus is a zoonotic influenza vaccine authorised for an active immunisation against H5 subtype influenza A viruses in individuals 6 months of age and above. It contains an inactivated, surface antigen monovalent, influenza vaccine adjuvanted with MF59C.1. It is to be administered IM as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose at least 3 weeks after the first dose.

Further information about the evaluation of Zoonotic Influenza Vaccine Seqirus benefits will be available in Zoonotic Influenza Vaccine Seqirus EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: Zoonotic Influenza Vaccine Seqirus | European Medicines Agency (europa.eu).

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

Important risks of Zoonotic Influenza Vaccine Seqirus, together with measures to minimise such risks and the proposed studies for learning more about Zoonotic Influenza Vaccine Seqirus 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 PL 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.

II.A List of important risks and missing information

Important risks of Zoonotic Influenza Vaccine Seqirus 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 Zoonotic Influenza Vaccine Seqirus. 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-3: Summary of safety concerns for Zoonotic Influenza Vaccine Seqirus

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy and lactation

II.B Summary of important risks

Table Part VI-4: Summary of important risks for Zoonotic Influenza Vaccine Seqirus

Neuritis	
Risk minimisation measures	Routine risk minimisation measures: Neuritis is described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Zoonotic Influenza Vaccine Seqirus PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Neuritis targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Convulsions	
Risk minimisation measures	Routine risk minimisation measures: Convulsions are described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Zoonotic Influenza Vaccine Seqirus PL: Section 2 and 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Convulsions targeted follow-up questionnaire*

Additional Pharmacovigilance activities	*EPSS* Additional Pharmacovigilance activities: *None*
Encephalitis (*encephalomyelitis*)	
Risk minimisation measures	Routine risk minimisation measures: Neurological disorders, such as encephalomyelitis, are described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Zoonotic Influenza Vaccine Seqirus PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Encephalitis (encephalomyelitis) targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Vasculitis	
Risk minimisation measures	Routine risk minimisation measures: Vasculitis is described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Zoonotic Influenza Vaccine Seqirus PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Vasculitis targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Guillain-Barré Syndrome	
Risk minimisation measures	Routine risk minimisation measures: Guillain-Barré syndrome is described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Zoonotic Influenza Vaccine Seqirus PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Guillain-Barré Syndrome targeted follow-up questionnaire*

Additional Pharmacovigilance activities	*EPSS* Additional Pharmacovigilance activities: *None*
Demyelination	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Demyelination targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Bell's palsy	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Bell's Palsy targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*
Immune thrombocytopenia	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Immune thrombocytopenia targeted follow-up questionnaire* *EPSS* Additional Pharmacovigilance activities: *None*

Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Pregnancy and breast-feeding are described in: *Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.6* *Zoonotic Influenza Vaccine Seqirus PL: Section 2* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Pregnancy Reporting/Outcome form* Additional Pharmacovigilance activities: *None*

II.C Post-authorisation development plan

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

Not applicable. There are no safety studies imposed as condition of the marketing authorisation (category 1), or as a specific obligation in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (category 2) or required by the competent authority (category 3).

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

Not applicable.

Summary of risk management plan for Foclivia (aH5N1)

This is a summary of the RMP for Foclivia. The RMP details important risks of Foclivia, how these risks can be minimised, and how more information will be obtained about Foclivia risks and uncertainties (missing information).

Foclivia SmPC and its PL give essential information to healthcare professionals and patients on how Foclivia should be used.

This summary of the RMP for Foclivia 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 Foclivia RMP.

I. The medicine and what it is used for

Foclivia is a pandemic influenza vaccine authorised for the prophylaxis of influenza in an officially declared pandemic situation. It contains an inactivated, surface antigen monovalent, influenza vaccine adjuvanted with MF59C.1. It is to be administered as 2 doses of 0.5 mL by IM injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older individuals. One dose of 0.5 mL should be given at an elected date and a second dose of 0.5 mL after an interval of at least 3 weeks.

Further information about the evaluation of Foclivia benefits can be found in Foclivia 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/foclivia.

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

Important risks of Foclivia, together with measures to minimise such risks and the proposed studies for learning more about Foclivia 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 PL 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.

II.A List of important risks and missing information

Important risks of Foclivia 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 Foclivia. 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-5: Summary of safety concerns for Foclivia

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy and lactation

II.B Summary of important risks

Table Part VI-6: Summary of important risks for Foclivia

Neuritis	
Risk minimisation measures	Routine risk minimisation measures: Neuritis is described in: *Foclivia SmPC: Section 4.8* *Foclivia PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Neuritis targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Convulsions	
Risk minimisation measures	Routine risk minimisation measures: Convulsions are described in: *Foclivia SmPC: Section 4.4 and 4.8* *Foclivia PL: Section 2 and 4*

	Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Convulsions targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Encephalitis (*encephalomyelitis*)	
Risk minimisation measures	Routine risk minimisation measures: Neurological disorders, such as Encephalomyelitis, are described in: *Foclivia SmPC: Section 4.8* *Foclivia PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Encephalitis (encephalomyelitis) targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Vasculitis	
Risk minimisation measures	Routine risk minimisation measures: Vasculitis is described in: *Foclivia SmPC: Section 4.8* *Foclivia PL: Section 4* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Vasculitis targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Guillain-Barré Syndrome	
Risk minimisation measures	Routine risk minimisation measures: Guillain-Barré syndrome is described in: *Foclivia SmPC: Section 4.8* *Foclivia PL: Section 4* Additional risk minimisation measures: *None*

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Guillain-Barré Syndrome targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Demyelination	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Demyelination targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Bell's palsy	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Bell's Palsy targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*
Immune thrombocytopenia	
Risk minimisation measures	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Immune thrombocytopenia targeted follow-up questionnaire* Additional Pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety*

Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Pregnancy and breast-feeding are described in *Foclivia SmPC: Section 4.6* *Foclivia PL: Section 2* Additional risk minimisation measures: *None*
Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection and Additional Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Pregnancy Reporting/Outcome form* Additional pharmacovigilance activities: *Category 3 study - V87_27OB (pregnancy registry)*

II.C Post-authorisation development plan

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

As a specific post-authorisation pharmacovigilance requirement, in accordance with EMA/CHMP/VWP/457259/2014 Guidance on Influenza Vaccines (CHMP, 2014), the following studies are planned:

- The Enhanced Safety Surveillance will be performed during the pandemic period aiming rapidly collect the data within a month from the start of vaccination.
- A non-interventional study of vaccine effectiveness of pandemic influenza vaccine (Foclivia®), an analysis of vaccine effectiveness for pandemic influenza vaccination versus no vaccination.

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

It is considered that for the majority of safety concerns, routine pharmacovigilance activities alone will be sufficient. However, in the situation of a pandemic, required Category 3 Study V87_27OB study is planned to address the missing information Use in pregnancy and lactation: V87_27OB is a postmarketing, observational cohort study to evaluate the safety of

pandemic A/H5N1[3] vaccine (Foclivia®) in pregnant women (pregnancy registry). This study is planned in case of pandemic and will follow from enrolment to pregnancy outcome and in live-born infants until 3 months of age.

[3] *The strain is subject to change to be matched with the next pandemic strain*

Part VII: Annexes

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Annex 4 Specific adverse drug reaction follow-up forms

CCI Seqirus Pregnancy Reporting / Outcome Form

CCI : CSL Seqirus Foclivia RMP Follow-up Questionnaires

- Peripheral Neuropathy Including Neuritis Targeted Follow-up Questionnaire
- Febrile Convulsion / Seizure Targeted Follow-up Questionnaire
- Encephalitis, Myelitis, Acute Disseminated Encephalomyelitis Targeted Follow-up Questionnaire
- Vasculitis Targeted Follow-up Questionnaire
- Guillain-Barré Syndrome (and subtypes) and Demyelination Targeted Follow-up Questionnaire
- Bell's palsy Targeted Follow-up Questionnaire
- Immune thrombocytopenia Targeted Follow-up Questionnaire

Note: CCI : Seqirus Pregnancy Reporting / Outcome Form and CCI : CSL Seqirus Foclivia RMP Follow-up Questionnaires will be used for Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus.

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 Other supporting data (including referenced material)

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