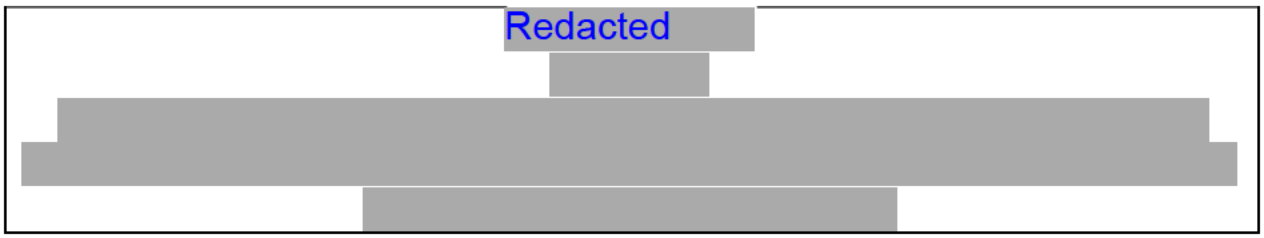
EU Risk Management Plan (EU-RMP)

For

aH5N1c

(pandemic and zoonotic H5N1 influenza vaccines, prepared in cell cultures, adjuvanted)



RMP Version number:	0.4
Data lock Point for this RMP:	07 Jan 2022
Date of final sign off:	20 Feb 2024
Rationale for submitting of updated RMP:	Not applicable
Summary of significant changes in this RMP:	Not applicable
Other RMP under Evaluation:	Not Applicable
Details of the current approved RMP:	Not Applicable
Qualified Person responsible for Pharmacovigilance (QPPV) name:	Juergen Zorn, MD
QPPV signature:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

TABLE OF CONTENT

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
CDC	Centers for Disease Control and Prevention
DIBD	Development International Birth Date
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
ECDC	European Centre for Disease Control and Prevention
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESS	Enhanced Safety Surveillance
EPSS	Enhanced Passive Safety Surveillance
EU	European Union
GBS	Guillain-Barre Syndrome
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HA	Haemagglutinin
HIV	Human Immunodeficiency Virus
ICSR	Individual Case Safety Report
INN	International non-proprietary name
MDCK	Madin-Darby Canine Kidney Cells
NA	Neuraminidase
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of Product Characteristics
QPPV	Qualified Person responsible for Pharmacovigilance
US	United States
WHO	World Health Organisation

PART I. PRODUCT OVERVIEW

Part I. 1: Product Overview

Active substance(s) (INN or common name)	Influenza virus surface antigen, inactivated, adjuvanted, prepared in cell cultures A/turkey/Turkey/1/2005 (H5N1) like strain (NIBRG 23) (Pandemic influenza vaccine aH5N1c) A/turkey/Turkey/1/2005 (H5N1) like strain (NIBRG 23) (Zoonotic influenza vaccine aH5N1c)
Pharmacotherapeutic group(s) (ATC Code)	Group: Influenza vaccine ATC Code: J07BB02
Marketing Authorisation Holder	Seqirus Netherlands B.V. Paasheuvelweg 28 1105BJ Amsterdam Netherlands
Medicinal products to which this RMP refers	Pandemic influenza vaccine aH5N1c [A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23)] Zoonotic influenza vaccine aH5N1c [A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23)]
Invented name(s) in the European Economic Area (EEA)	Incellipan Celldemic
Marketing authorisation procedure	Centralised procedure
Brief description of the product	aH5N1c pandemic and zoonotic influenza vaccines are monovalent (H5N1), inactivated, purified surface antigen vaccines, adjuvanted with MF59 prepared in cell cultures. They contain: Influenza virus surface antigens (haemagglutinin and neuraminidase) * of strain: A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23) or zoonotic 7.5 micrograms** per 0.5 ml dose **propagated in Madin Darby Canine Kidney (MDCK) cells* *** expressed in micrograms haemagglutinin* Adjuvant MF59C.1 contains: squalene 9.75 milligrams per 0.5 ml polysorbate 80 1.175 milligrams per 0.5 ml

	sorbitan trioleate 1.175 milligrams per 0.5 ml 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. The vaccine may contain trace residues of RedRedacted Redacted Haemagglutinin and neuraminidase antigens present in the vaccine induce a protective antibody response in vaccinated individuals after immunisation.
Hyperlink to the Product Information	Not applicable
Indication(s) in the EEA	Pandemic influenza vaccine aH5N1c (Incellipan) Active immunisation against influenza in an officially declared pandemic. Zoonotic influenza vaccine aH5N1c (Celldemic) Active immunisation against H5N1 subtype of Influenza A virus in adults and infants from 6 months of age and above.
Dosage in the EEA	Administer two doses (0.5 ml each), 21 days apart
Pharmaceutical form(s) and strengths	Suspension for injection
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

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

Indication

Pandemic and zoonotic influenza vaccines aH5N1c (Incellipan and Celldemic), collectively referred to as aH5N1c influenza vaccine throughout this RMP, are indicated for active immunisation against H5N1 subtype of influenza A virus in adults and infants from 6 months of age and above (Celldemic) or active immunisation against influenza in an officially declared pandemic (Incellipan).

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 haemagglutinin (HA) and neuraminidase (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). All of these zoonotic influenza type A viruses are distinct from human influenza viruses and do not easily transmit among humans (WHO, 2020).

Aquatic birds are the primary natural reservoir for most subtypes of influenza A viruses. Most avian influenza A viruses cause asymptomatic or mild infection in birds, where the range of symptoms depends on the virus properties (WHO, 2020).

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, can result in the merging of zoonotic and human influenza viruses increasing 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, 2018).

This phenomenon has been observed only with Influenza A viruses and results from the emergence of a new antigenic variant (antigenic shift) typically 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 & Choi, 2017; Webster & Govorkova, 2014; WHO, 2018). 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, 2018).

There have been four influenza pandemics since the beginning of 20th century: 1918 H1N1 which caused more than 50 million deaths; 1957 H2N2 which caused approximately 1.1 million deaths; 1968 H3N2 which caused approximately 1 million deaths and 2009 H1N1 which caused more than 18,000 deaths (WHO, 2018; CDC, 2018). 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 coronavirus 2 (SARS-CoV-2) pandemic, which started in Wuhan in Dec 2019, showed that with the current mobility, the virus has the potential to spread rapidly and cause a global pandemic within a short period of time.

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, which 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. This is because sometimes fatal bird-to-human transmission occurred, at a time when human Influenza A virus was also circulating (Peiris, 1999; De Jong et al., 2005; Fouchier, 2004; Greco et al., 2012). Currently, H5 strains continue to circulate in wild birds and domestic poultry in a number of countries and result in mammalian outbreaks and human infections and deaths (WHO, 2024). As of October 2023, the cumulative number of confirmed human cases of avian Influenza A/ (H5N1) reported to WHO were 876 cases and 458 (53%) deaths (WHO, 2023). The occurrence of an influenza pandemic before adequate preparations are in place could result in a public health emergency, 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 60

billion US dollars, representing about 2 million US dollars per person infected (Institute of Medicine, 2018). In order to assist medical and public health leaders to optimise the response to the potential threat of pandemic influenza, the US Government (CDC, 2018; Scorza, 2017), individual states in the US and countries in the EU have developed Influenza Pandemic Preparedness plans (WHO, 2018; Cox et al., 2003).

The WHO has provided detailed guidance on the content of influenza pandemic preparedness planning (WHO, 2018; Palkonyay & Ftaima, 2016; Stohr, 2003). 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, 56th World Health Assembly 2003). In particular, the need to ensure adequate supplies of pandemic vaccine must be addressed (Fedson, 2003; WHO, 2018) 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. 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 for vaccination is represented by the general population from the age of 6 months and above. The majority of zoonotic human infections with H5N1 have occurred among children and adults younger than 40 years old (CDC, 2021). 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, 2021; 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, 2018):

- Adults 65 years or older and children under 59 months 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 Immuno-deficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS), 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 (Rubin et al., 2014; Danziger-Isakov et al., 2019). 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 & 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, 2020). 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, 2020).

Four pandemic preparedness vaccines are currently authorised in the EU, which can be modified into pandemic influenza vaccines in a future pandemic (EMA, 2021):

- Foclivia (pandemic influenza vaccine (H5N1) (adjuvanted, inactivated, purified surface antigen vaccines) Seqirus)
- 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 ((H5N1) (adjuvanted, inactivated, purified surface antigen vaccines) Seqirus), no other zoonotic influenza vaccines are currently licensed in the EU.

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, 2020). In practice, antiviral drugs are not an alternative to influenza vaccination, but may be a useful adjunct in some situations. Antiviral drugs are most effective when they are administered within 48 hours of symptom onset. 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 (ECDC, 2022):

- Avoiding contact with sick people, maintaining at least one-meter distance from sick person
- 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. If isolation is impossible, the use of face masks is recommended
- Avoiding touching of one's eyes, nose or mouth
- Surface and object cleaning, given that influenza virus can survive on surfaces for prolonged periods and increase ventilation

PART II. MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Non-clinical studies were performed to support the development of aH5N1c influenza vaccines. Zoonotic aH5N1c influenza vaccine is intended for use before a pandemic to protect against the strain of influenza that experts believe could cause a future pandemic. Pandemic aH5N1c influenza vaccine 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 and the subtype or strain of influenza virus used to manufacture these vaccines may differ, the antigens included in both the zoonotic and pandemic vaccines are produced using the same manufacturing process and both vaccines contain the adjuvant MF59.

The primary pharmacological effect of an influenza vaccine is the induction of antibodies to HA (immunogenicity), which can confer protection against influenza infection. The immunogenicity and efficacy of cell-culture derived influenza antigens with MF59 adjuvant have been evaluated. The completed non-clinical programme supports the use of aH5N1c in children and adults.

Repeat-dose toxicity and reproductive and developmental effects were evaluated in rabbits in two Good Laboratory Practice (GLP) toxicology studies. There was no evidence of local or systemic toxicity following vaccine treatment, and no effects on reproductive and developmental parameters.

A reproductive and developmental toxicity study was performed to evaluate possible effects of vaccination on female New Zealand White rabbits prior to mating and during gestation (Study No. AB20852). Groups of 55 female rabbits received either the control article (saline) or aH5N1c. Each 0.5 ml dose of aH5N1c contained 7.5 micrograms HA with 0.25 ml MF59. aH5N1c was immunogenic in treated rabbits, and antibodies were transferred to foetuses and offspring. The vaccine was well-tolerated, did not cause maternal or embryofoetal toxicity, was not teratogenic, and had no effects on postnatal development. The results of this study were consistent with those observed with a similar vaccine formulation, aH1N1c.

The antigens contained in Seqirus' cell culture vaccines are produced using a Madin-Darby Canine Kidney Cells (MDCK) cell line. A series of *in vivo* studies was performed to characterise the tumorigenicity of the MDCK cell line, and the oncogenicity of process intermediates (cell lysates and purified MDCK cell Deoxyribonucleic acid (DNA)). Only intact MDCK cells were tumorigenic in immunocompromised adult (nude) mice. Cell lysates or purified MDCK cell DNA were not oncogenic in infant mice, rats and hamsters. Since intact MDCK cells are reliably excluded from the vaccine during multiple steps of the manufacturing process, and because studies with MDCK cell lysates and DNA demonstrated no oncogenicity in three species of very sensitive animal models, the theoretical safety risk was exceedingly low.

Pivotal toxicology studies performed with MF59 included the evaluation of single- and repeat-dose toxicity (including local tolerability), genotoxicity, sensitisation, and embryofoetal and developmental toxicity. MF59 was not associated with systemic toxicity and it had 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 were consistent with the effects of intramuscular injections of an immunological adjuvant. These findings were 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 was not genotoxic (Ames test) or clastogenic (mouse micronucleus), was not a dermal sensitiser (Guinea pig) and was not maternally toxic (rat and rabbit), teratogenic (rat and rabbit), or a developmental toxicant (rat).

Table Part II. 1: Key safety findings from non-clinical studies

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity findings include:	
Toxicity programme supporting aH5N1c: • 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, out of 6,983 subjects enrolled into the aH5N1c clinical programme since the Development International Birth Date (DIBD) of 08 Jan 2008; 5,977 received aH5N1c and 987 received placebo/comparator treatment. In total, 753 subjects participated in the Phase 1 trial V89P1, with 752 subjects dosed (561 subjects received aH5N1c and 191 received vaccine that did not contain the MF59 adjuvant). In the Phase 2 trials, out of the total of 3,034 enrolled subjects; 3,021 subjects were dosed with aH5N1c. In the Phase 3 trial, a total of 3,191 subjects received study treatment (aH5N1c or placebo), of whom 2,395 subjects received aH5N1c and 796 received placebo. The characteristics of the subjects exposed to aH5N1c 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 Table SIII.1, based upon actual exposure data from completed studies.

Table SIII. 1: Estimated subject exposure in completed clinical studies*

Vaccination	Number of subjects
aH5N1c influenza vaccine	5,977
Saline Placebo	796
Other comparators	191*
Total	**6,964**

**191 subjects in V89P1 clinical trial received vaccine without the MF59 adjuvant. These subjects are accounted for in the comparator group as no adjuvant was included in the vaccination. Hence, subjects are excluded from Tables SIII.2 and SIII.3.*

Cumulative exposure to aH5N1c influenza vaccine by age and gender for completed clinical trials sponsored by Seqirus is provided in Table SIII.2.

Table SIII. 2: Cumulative subject exposure from completed clinical trials by age and gender

Number of subjects			
Age Range	**Male**	**Female**	**Total**
6-35 months	111	101	212
3-17 years	233	213	446
18-64 years	1,231	1,503	2,734
≥65 years	1,126	1,459	2,585
Total	**2,701**	**3,276**	**5,977**

Cumulative exposure to aH5N1c influenza vaccine by racial/ethnic group for completed clinical trials sponsored by Seqirus is provided in the Table SIII.3.

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

Racial group	Number of subjects
American Indian/Alaskan Native	28
Asian	1,183
Black	788
Caucasian	3,918
Native Hawaiian/Pacific Islander	15
Other	45
Total	**5,977**

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

In general, the majority of immunogenicity and safety studies of aH5N1c influenza vaccine were conducted in healthy adult/elderly subjects, however one study (Study V89_11) was conducted in a special population (children aged 6 months to less than 18 years of age).

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

In the majority of the 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 has been identified as a safety concern (missing information) from the exclusion criteria in clinical studies within the development programme.

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

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

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

Ability to detect ADRs	Limitation of trial programme	Discussion of implication for target population
Which are rare	Overall, 5,977 subjects received aH5N1c 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 (≤0.1%) ADRs according to the EMA guideline CHMP/VWP/263499/2006.

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

The limitations with respect to exposure in special populations are described in the Table SIV.2

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

Type of special population	Exposure
Pregnant or nursing women	Pregnant and nursing women were not included in the clinical development programme. However, 55 subjects became pregnant in the development programme (exposed to aH5N1c, n=47). Use in pregnancy has been identified as a safety concern (missing information) from the exclusion criteria in clinical studies within the development programme.
Subjects with relevant comorbidities: • hepatic impairment • renal impairment • cardiovascular impairment	Subjects with comorbidities were not included in the aH5N1c clinical development programme. However, a clinical study (V87_25) for an egg-based vaccine which contained the same H5N1 strain and adjuvant (MF59) as included in aH5N1c, was conducted in subjects with comorbidities. A total of 294 adult and elderly subjects with chronic pulmonary disease, cardiovascular disease, peripheral vascular disease, diabetes mellitus, and/or renal impairment participated in the study. No safety concerns were identified from these populations. The study findings are relevant for aH5N1c vaccine due to same composition (both vaccines contain H5N1 antigen and MF59 adjuvant). There is no indication that the safety profile of aH5N1c influenza vaccine in this population differs from the populations characterised so far.
Immunocompromised subjects	Immunocompromised subjects were not included in the aH5N1c clinical development programme. However, study V87_26 included 295 adult and elderly subjects with immunosuppressive conditions such as HIV infection, transplant recipients and those with specific cancers and/or receiving chemotherapy, who received aH5N1 egg-based vaccine which contained the same H5N1 strain and adjuvant (MF59) as included in aH5N1c. No safety concerns have been identified from these populations. The study findings are relevant for aH5N1c vaccine due to same composition (both vaccines contain H5N1 antigen and MF59 adjuvant).

Type of special population	Exposure
	There is no indication that the safety profile of aH5N1 influenza vaccine in this population differs from the populations characterised so far.
Subjects with disease severity different from inclusion criteria in clinical trials	Not applicable to aH5N1c influenza vaccine.
Population with relevant different ethnic origin	Per Part II. Module SIII, studies included different racial/ethnic groups; however, the majority: 66% (n=3,918) of subjects identified as Caucasian and 20% (n=1,183) Asian. Although a limited number of subjects from different racial/ethnic groups were exposed to aH5N1c in clinical studies, there is no indication that the safety profile of aH5N1c 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	Not applicable for aH5N1c influenza vaccine.
Other • Children • Elderly	Per Part II. Module SIII, studies included 212 subjects aged 6-35 months and 446 subjects aged 3 to less than 18 years. No data are available in children aged less than 6 months. Per Part II. Module SIII, studies included 2,585 subjects aged ≥ 65 years. There have been no safety concerns identified from the elderly population.

Use in pregnancy has been identified as safety concerns (missing information) from populations typically underrepresented in clinical trials within the development programme.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

Pandemic aH5N1c vaccine (Audenz®) was approved in the US on 31 Jan 2020 for use in persons 6 months of age and older for active immunisation for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. aH5N1c vaccine has not been marketed in any country at the time of Data Lock Point (DLP) of this RMP and thus there has been no post-authorisation exposure.

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable. aH5N1c vaccine has not been marketed in any country at the time of DLP of 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 aH5N1c 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, including angioedema, skin reactions (e.g., 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: List of safety concerns for inclusion in the RMP

Safety Concern	Evidence for inclusion
Important potential risk: Neuritis	Although no cases were observed from clinical trials, neuritis is considered an adverse event of special interest (AESI) for pandemic influenza vaccines (CHMP, Sep 2009) and a very rare potential pharmacological class effect (CHMP, Jul 2009). 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 et al., 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Convulsions	Although no related cases (ADRs) of convulsions were observed from clinical trials, convulsions are considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009) and a rare potential pharmacological class effect (CHMP, Jul 2009). 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 young 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 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). Based on evidence from the scientific literature, and the potentially serious and severe nature of the event as described above, convulsions is considered to potentially impact the benefit-risk profile of aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.

Important potential risk: Encephalomyelitis	Although no cases were observed from clinical trials, encephalomyelitis is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009) and a very rare potential pharmacological class effect (CHMP, Jul 2009). 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 encephalomyelitis may range widely, from complete recovery to persistent disability, coma or death. A proportion of patients developing encephalomyelitis will be expected to have persistent neurological, functional, and cognitive sequelae lasting for months, years or indefinitely (Sejvar et al., 2007). 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, encephalomyelitis is considered to potentially impact the benefit-risk profile of aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Vasculitis	Although no related cases (ADRs) of vasculitis were observed from clinical trials, vasculitis is also considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009) and is a very rare potential pharmacological class effect (CHMP, Jul 2009). 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 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 et al., 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). Based on 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.

Important potential risk: Guillain-Barre Syndrome	Although no related cases (ADRs) of Guillain-Barr é syndrome (GBS) were observed from clinical trials, GBS is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009) and a very rare potential pharmacological class effect (CHMP, Jul 2009). 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.
Important potential risk: Demyelination	Although no related cases (ADRs) of demyelination were observed from clinical trials, demyelination is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009). 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, 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 aH5N1c influenza vaccine 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	Although no related cases (ADRs) of Bell's palsy were observed from clinical trials, Bell's palsy is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009). 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). Based on evidence from the scientific literature as described above, Bell's palsy is considered to potentially impact the benefit-risk profile of aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.

Important potential risk: Immune thrombocytopenia	Although no cases of immune thrombocytopenia reported for aH5N1c were observed from clinical trials, immune thrombocytopenia is considered a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009). 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). Based on evidence from the scientific literature as described above, immune thrombocytopenia is considered to potentially impact the benefit-risk profile of aH5N1c influenza vaccine and is therefore classified as an important potential risk. Refer to Section SVII.3 for further characterisation of this risk.

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. 1: 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 et al., 2010).
Evidence source(s) and strength of evidence	The strength of evidence is low, as there have been no observed cases from clinical trials. However, based on evidence from the scientific literature, neuritis is considered an AESI (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 0.45 neuritis cases per million influenza vaccinations (Vellozzi et al., 2009). Because 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk.

Characterisation of the risk	Cumulatively to DLP, no cases were observed from 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, Jul 2009). 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 et al., 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, because 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 aH5N1c influenza vaccine 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.
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 young 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 no related cases (ADRs) of convulsions were observed from aH5N1c clinical trials. However, because of evidence from scientific literature, convulsions are considered an AESI (CHMP, Sep 2009), and a rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 0.16 convulsion (febrile and afebrile) cases per million influenza vaccinations (Vellozzi et al., 2009). Based on 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 aH5N1c influenza vaccine and are therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, two cases were reported from clinical trials, both were 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 0.16 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, Jul 2009). 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 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, because 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 aH5N1c influenza vaccine 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: 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 clinical trials. However, because of evidence from the scientific literature, encephalomyelitis is considered an AESI (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), 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, encephalomyelitis is considered to

	potentially impact the benefit-risk profile of aH5N1c influenza vaccine and is therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, no cases were observed from 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). Encephalomyelitis is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009). The outcome in patients developing encephalomyelitis may range widely, from complete recovery to persistent disability, coma, or death. A proportion of patients developing encephalomyelitis will be expected to have persistent neurological, functional, and cognitive sequelae lasting for months, years or indefinitely (Sejvar et al., 2007). 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	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, encephalomyelitis is considered to potentially impact the benefit-risk profile of aH5N1c influenza vaccine 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 no related cases (ADRs) of vasculitis were observed from aH5N1c clinical trials. However, on the basis of evidence from the scientific literature, vasculitis is considered an AESI (CHMP, Sep 2009) and a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009), with a potential rate of 341.8 vasculitis cases per 100,000 person-years after influenza vaccination (Gao et al., 2013). Based on 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk.

Characterisation of the risk	Cumulatively to DLP, one not related case was observed from clinical trials. According to a surveillance study, the incidence rate of vasculitis was 341.8 per 100,000 person-years for intramuscular influenza vaccine (Gao et al., 2013). Vasculitis is generally considered a very rare potential pharmacological class effect of pandemic influenza vaccines (CHMP, Jul 2009). 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 et al., 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, because of 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 aH5N1c influenza vaccine 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-Barre 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 related cases (ADRs) observed from aH5N1c clinical trials. However, on the basis of evidence from the scientific literature, GBS is considered an AESI (CHMP, Sep 2009), and a very rare potential pharmacological class effect of pandemic influenza vaccines. (CHMP, Jul 2009), 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). Based on 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, one unrelated case was reported from 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 et al. (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 et al. (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, Jul 2009). 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, because 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 aH5N1c influenza vaccine 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 et al., 2017).
Evidence source(s) and strength of evidence	The strength of evidence is low, as no related cases (ADRs) of demyelination were observed from aH5N1c clinical trials. However, because of evidence from the scientific literature, inflammatory demyelinating disorders of the central nervous system are considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009), 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). Based on 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 aH5N1c influenza vaccine and are therefore classified as an important potential risk.
Characterisation of the risk	Cumulatively to DLP, one not related case was observed from clinical trials. 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 et al., 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 aH5N1c influenza vaccine 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 no related cases (ADRs) of Bell's palsy were observed from aH5N1c clinical trials. However, because of evidence from the scientific literature, Bell's palsy is considered an AESI for pandemic influenza vaccines (CHMP, Sep 2009), and have been reported vary rarely 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 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk.
Characteristics of the risk	Cumulatively to DLP, one unrelated case was reported from clinical trials. 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 etal., 2009). Wijnans et al. (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, 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, because 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 aH5N1c influenza vaccine 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 (ITP)	
Potential mechanisms	Aetiology is unclear, however the suggested mechanism for immune thrombocytopenia (also called idiopathic thrombocytopenic purpura) may be molecular mimicry (Perricone et al., 2014).
Evidence source(s) and strength of evidence	The strength of evidence is low, as no cases reported for aH5N1c were observed from aH5N1c 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, Jul 2009), with one publication identifying 22 ITP events from 3.1 million influenza vaccinations (Liu et al., 2014). Based on 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 aH5N1c influenza vaccine and is therefore classified as an important potential risk.
Characteristics of the risk	Cumulatively to DLP, there were no cases reported for aH5N1c 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, Jul 2009). 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 6 weeks after vaccination (Perricone et al., 2014; Liu 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, because of 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 aH5N1c influenza vaccine 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 Terms (HLT): Thrombocytopenias

SVII.3.2 Presentation of the missing information

Table SVII. 2: Missing information. Use in pregnancy

Missing information: Use in pregnancy	
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, however currently available information on aH5N1c influenza vaccine 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. An observational cohort study V89_20OB to evaluate the safety of adjuvanted pandemic influenza vaccine (aH5N1c) in pregnant women (pregnancy registry) is planned in case of pandemic.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1: Summary of safety concerns for aH5N1c

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalomyelitis Vasculitis Guillain-Barré syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy

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 (GVP) 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 (ICSRs), Periodic Safety Update Reports (PSURs), monitoring safety profiles, and safety signal detection and evaluation.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- 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 the aH5N1c influenza vaccine. 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 aH5N1c 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 will also be in place which specifically details the plans to ensure resource is prioritised and necessary technical requirements are met.
- As a specific post-authorisation pharmacovigilance requirement, in accordance with EMA/CHMP/VWP/457259/2014 Guidance on Influenza Vaccines, the Enhanced Passive Safety Surveillance (EPSS) will be performed during the pandemic period aiming to rapidly collect the data within a month from the start of vaccination.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

It is considered that for the majority of the safety concerns, routine pharmacovigilance activities alone will be sufficient. However, in the situation of a pandemic, required Category 3 study V89_20B, for the missing information *Use in pregnancy*, is planned:

V89_20OB is a postmarketing, observational cohort study to evaluate the safety of adjuvanted pandemic influenza vaccine A/H5N1c 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.

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

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.3. 1: Ongoing 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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
V89_20OB is a postmarketing observational cohort safety study of pandemic influenza A/H5N1c* vaccine in pregnant women (Planned)	To evaluate the safety of pandemic influenza vaccine in pregnant women	Use in pregnancy	Protocol to be provided once pandemic is declared. Milestones to be confirmed	To be confirmed

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

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

In the case of a pandemic, a vaccine effectiveness study will be conducted in accordance with the Guideline on Influenza vaccine (EMA/CHMP/VWP/457259/2014).

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 observational effectiveness study in children and adults* against laboratory confirmed influenza (Planned)	To perform an analysis of pandemic vaccine effectiveness against laboratory confirmed influenza for aH5N1c** versus no vaccination	Not applicable	Protocol to be provided when pandemic is declared. Milestones to be confirmed	To be confirmed

**The age population may be subject to change based on Health Authority recommendations once pandemic is declared*

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

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: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Neuritis	Neuritis is described in Section 4.8 of the SmPC and Section 4 of the Package Leaflet (PL)
Convulsions	Convulsions are described in Sections 4.4 and 4.8 of the SmPC, and Sections 2 and 4 of the PL
Encephalomyelitis	Encephalomyelitis is described in Section 4.8 of the SmPC and Section 4 of the PL
Vasculitis	Vasculitis is described in Section 4.8 of the SmPC and Section 4 of the PL
Guillain-Barré syndrome	Guillain-Barré syndrome is described in Section 4.8 of the 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	Use in pregnancy is described in Section 4.6 of the 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 aH5N1c.

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V. 2: 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: *Incellipan and Celldemic: SmPC Section 4.8* *Incellipan and Celldemic: 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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional Pharmacovigilance (PV) activities*
Convulsions	Routine risk minimisation measures: Convulsions are described in: *Incellipan and Celldemic: SmPC Sections 4.4 and 4.8* *Incellipan and Celldemic: PL Sections 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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
Encephalomyelitis	Routine risk minimisation measures: Encephalomyelitis is described in: *Incellipan and Celldemic: SmPC Section 4.8* *Incellipan and Celldemic: 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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
Vasculitis	Routine risk minimisation measures: Vasculitis is described in: *Incellipan and Celldemic: SmPC Section 4.8*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

	Incellipan and Celldemic: PL Section 4 Additional risk minimisation measures: *No additional measures*	*S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
Guillain-Barré syndrome	Routine risk minimisation measures: Guillain-Barre syndrome is described in: *Incellipan and Celldemic: SmPC Section 4.8* *Incellipan and Celldemic: 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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
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)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *No additional PV activities*
Missing information		
Use in pregnancy	Routine risk minimisation measures: Pregnancy is described in: *Incellipan and Celldemic: SmPC Section 4.6* *Incellipan and Celldemic: PL Section 2*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)*

	Additional risk minimisation measures: *No additional measures*	Additional pharmacovigilance activities: *V89_20OB (in situation of pandemic)*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR PANDEMIC AND ZOONOTIC aH5N1c INFLUENZA VACCINES (INCELLIPAN AND CELLDEMIC)

Summary of Risk Management Plan for Incellipan (Pandemic influenza vaccine aH5N1c)

This is a summary of the risk management plan (RMP) for Incellipan (Pandemic influenza vaccine aH5N1c). The RMP details important risks of Incellipan, how these risks can be minimised, and how more information will be obtained about Incellipan risks and uncertainties (missing information).

Incellipan summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Incellipan should be used.

This summary of the RMP for Incellipan 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 safety concerns or changes to the current ones will be included in updates of Incellipan RMP.

I. The medicine and what it is used for

Incellipan is indicated for active immunisation against influenza in an officially declared pandemic. Incellipan should be used in accordance with official recommendations. It contains an inactivated, surface antigen monovalent, influenza vaccine adjuvanted with MF59, prepared in cell cultures. It is to be administered as two doses of 0.5 ml by intramuscular injection, 21 days apart. For those over 12 months of age, the preferred injection site is the region of the deltoid muscle of the upper arm; for those 6 to less than 12 months of age, the preferred injection site is the anterolateral thigh. Further information about the evaluation of Incellipan benefits can be found in Incellipan

EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *(link to be provided after product authorisation).*

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

II.A List of important risks and missing information

Important risks 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 safety concerns for which there is sufficient proof of a link with the use of Incellipan. Potential risks are safety 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 Incellipan

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalomyelitis Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy

II.B Summary of Safety Concerns

Table Part VI. 2: Summary of Safety Concerns for Incellipan

Neuritis	
Risk minimisation measures	Routine risk minimisation measures: *Incellipan SmPC: Section 4.8* *Incellipan PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *None*
Convulsions	
Risk minimisation measures	Routine risk minimisation measures: *Incellipan SmPC: Sections 4.4 and 4.8* *Incellipan PL: Sections 2 and 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)*

	Additional pharmacovigilance activities: *None*
Encephalomyelitis	
Risk minimisation measures	Routine risk minimisation measures: *Incellipan SmPC: Section 4.8* *Incellipan PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *None*
Vasculitis	
Risk minimisation measures	Routine risk minimisation measures: *Incellipan SmPC: Section 4.8* *Incellipan PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: *None*
Guillain-Barré Syndrome	
Risk minimisation measures	Routine risk minimisation measures: *Incellipan SmPC: Section 4.8* *Incellipan PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *EPSS (in situation of pandemic)* Additional pharmacovigilance activities: None
Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: Pregnancy is described in:

	Incellipan SmPC: Section 4.6 *Incellipan PL: Section 2* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* Additional pharmacovigilance activities: *V89_20OB (in situation of pandemic)*

S-PSUR: simplified Periodic Safety Update Report, SmPC: Summary of Product Characteristics, PL: Package Leaflet

II.C Post-authorisation development plan

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

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).

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

A non-interventional (observational) study of vaccine effectiveness in children and adults* against laboratory confirmed influenza will be performed during the next declared pandemic as a specific obligation in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances, in accordance with the Guideline on Influenza vaccine (EMA/CHMP/VWP/457259/2014).

**The age population may be subject to change based on Health Authority recommendations once pandemic is declared*

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

It is considered that for the majority of the safety concerns, routine pharmacovigilance activities alone will be sufficient. However, in the situation of a pandemic, required Category 3 study V89_20B, for the missing information *Use in pregnancy*, is planned:

- V89_20OB is a postmarketing, observational cohort study to evaluate the safety of adjuvanted pandemic influenza vaccine A/H5N1c* 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.

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

Summary of Risk Management Plan for Celldemic (Zoonotic influenza vaccine aH5N1c)

This is a summary of the risk management plan (RMP) for Celldemic (Zoonotic influenza vaccine aH5N1c). The RMP details important risks of Celldemic, how these risks can be minimised, and how more information will be obtained about Celldemic risks and uncertainties (missing information).

Celldemic summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Celldemic should be used.

This summary of the RMP for Celldemic 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 Celldemic RMP.

I. The medicine and what it is used for

Celldemic is indicated for active immunisation against H5N1 subtype of Influenza A virus in adults and infants from 6 months of age and above. Celldemic should be used in accordance with official recommendations. It contains an inactivated, surface antigen monovalent, influenza vaccine adjuvanted with MF59, prepared in cell cultures. It is to be administered as two doses of 0.5 ml by intramuscular injection, 21 days apart. For those over 12 months of age, the preferred injection site is the region of the deltoid muscle of the upper arm; for those 6 to less than 12 months of age, the preferred injection site is the anterolateral thigh. Further information about the evaluation of Celldemic benefits can be found in Celldemic EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *(link to be provided after product authorisation).*

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

II.A List of important risks and missing information

Important risks 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 safety concerns for which there is sufficient proof of a link with the use of Celldemic. Potential risks are safety 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 Celldemic

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalomyelitis Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia

Missing information	Use in pregnancy

II.B Summary of Safety Concerns

Table Part VI. 4: Summary of Safety Concerns for Celldemic

Neuritis	
Risk minimisation measures	Routine risk minimisation measures: *Celldemic SmPC: Section 4.8* *Celldemic PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Convulsions	
Risk minimisation measures	Routine risk minimisation measures: *Celldemic SmPC: Sections 4.4 and 4.8* *Celldemic PL: Sections 2 and 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Encephalomyelitis	
Risk minimisation measures	Routine risk minimisation measures: *Celldemic SmPC: Section 4.8* *Celldemic PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Vasculitis	
Risk minimisation measures	Routine risk minimisation measures:

	Celldemic SmPC: Section 4.8 *Celldemic PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Guillain-Barré Syndrome	
Risk minimisation measures	Routine risk minimisation measures: *Celldemic SmPC: Section 4.8* *Celldemic PL: Section 4* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* 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: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: Pregnancy is described in: *Celldemic SmPC: Section 4.6* *Celldemic PL: Section 2* Additional risk minimisation measures: *No additional measures*
Pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *None* *Additional pharmacovigilance activities:* *None*

SmPC: Summary of Product Characteristics, PL: Package Leaflet

II.C Post-authorisation development plan

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

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.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable.