EU RMP	
Drug Substance	Influenza vaccine (live attenuated, nasal)
Version Number	Version 12
Succession Number	1
Data lock point	31 August 2023
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR FLUENZ TETRA, FLUENZ, FLUMIST QUADRIVALENT and FLUMIST (INFLUENZA VACCINE LIVE ATTENUATED, NASAL)

The content of this RMP has been reviewed and approved by the EU QPPV

Fluenz Tetra™ ,Fluenz™, FluMist Quadrivalent™ and FluMist™ are trademarks of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Administrative Information

Rationale for the update to RMP

Update of the RMP to version 12.0 in order to:

Adapt the document to support both the quadrivalent and the trivalent versions of the product. LAIV is used when information applies to either T/-or Q/LAIV. Where information applies specifically to one formulation this is designated as T/- or Q/LAIV as appropriate.

Summary of significant changes in this RMP

Part I

- Adjustments to describe both the quadrivalent and the trivalent versions

Part II SV

- Updated post authorization exposure data

Part II SVII

- Updated post authorization exposure data

Part III

- Other forms of routine pharmacovigilance activities
    - Removal of detail concerning ESS activity MEA/004.13, which was reported in May 2023.

Other RMP versions under evaluation	Not Applicable
Details of currently approved RMP	Version Number: 11.0 Approved with procedure: EMEA/H/C/002617/IB/0106 Date of approval: 2 March 2023

TABLE OF CONTENTS **PAGE**

LIST OF TABLES

PART VII. ANNEXES

Annex 1	EudraVigilance Interface (Not applicable)
Annex 2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme (Not applicable)
Annex 3	Protocols for proposed, on-going and completed studies in the pharmacovigilance plan (Not applicable)
Annex 4	Specific adverse drug reaction follow-up forms (Not applicable)
Annex 5	Protocols for proposed and on-going studies in RMP part IV (Not applicable)
Annex 6	Details of proposed additional risk minimisation activities (Not applicable)
Annex 7	Other supporting data (including referenced material) (Not applicable)
Annex 8	Summary of changes to the risk management plan over time

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AOM	Acute Otitis Media
att	Attenuated
ca	Cold-Adapted
CI	Confidence Interval
CNS	Central nervous system
EEA	European Economic Area
ESS	Enhanced Safety Surveillance
EU	European Union
GBS	Guillain-Barré syndrome
HA	Hemagglutinin
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
LAIV	Live attenuated influenza vaccine
MAH	Marketing Authorization Holder
MDV	Master Donor Virus
MHRA	Medicines and Healthcare Products Regulatory Agency
N/C	Narcolepsy with or without Cataplexy
OR	Odds Ratio
PCV	Pneumococcal conjugate vaccine
PSUR	Periodic Safety Update Report
PHE	Public Health England
PT	Preferred Term
Q/LAIV	Quadrivalent Live Attenuated Influenza Vaccine
SAE	Serious Adverse Event
sADRs	Suspected Adverse Drug Reactions
SmPC	Summary of Product Characteristics
SRC	Safety Report Card
T/LAIV	Trivalent Live Attenuated Influenza Vaccine
ts	Temperature-Sensitive
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Events Reporting System
VE	Vaccine Effectiveness
WHO	World Health Organization

I: PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	**Influenza vaccine (live attenuated, nasal)**
Pharmacotherapeutic group(s) (ATC Code)	Influenza vaccines, influenza live attenuated. ATC code: J07BB03
Marketing Authorisation Holder	AstraZeneca AB SE-151 85 Södertälje Sweden
Medicinal products to which this RMP refers	FLUENZ (Influenza vaccine [live attenuated, nasal]) in either a trivalent or quadrivalent version
Invented name(s) in the European Economic Area (EEA)	FLUENZ / FLUENZ TETRA
Marketing authorisation procedure	Centralized (EMA/H/C/002617/R/0162)
Brief description of the product	Chemical class: live attenuated influenza vaccine Summary of mode of action: A live attenuated influenza vaccine (Fluenz and FluMist) has been developed and exists either as a quadrivalent (Q/LAIV) or a trivalent (T/LAIV) version.
	Important information about its composition: **Q/LAIV** consists of two cold-adapted (*ca*), temperature-sensitive (*ts*), attenuated (*att*) strains of influenza virus of subtype A (ie, H1N1 and H3N2), and two *ca*, *ts*, *att* influenza strains of type B, one from each lineage (B/Yamagata and B/Victoria). **T/LAIV** consists of two cold-adapted (*ca*), temperature-sensitive (*ts*), attenuated (*att*) strains of influenza virus of subtype A (ie, H1N1 and H3N2), and one *ca, ts, att* influenza strain of type B, (B/Victoria). The *ca* reassortant strains in LAIV are produced by genetic reassortment between *wt* influenza virus and a *ca* master strain. Each reassortant strain contains two gene segments encoding the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins from the wt virus strain (A/H1N1, A/H3N2, or B) and 6 gene segments encoding internal virus proteins from the *ca, ts, att* master donor viruses (MDVs), (subtype A or type B). The resulting *ca, ts, att* strains are referred to as 6:2 reassortants. LAIV is formulated to contain $10^{7.0 \pm 0.5}$ fluorescent focus units (FFU) per dose of each of the strains of live, attenuated influenza virus reassortants that were propagated in chicken eggs. The *ca* phenotype allows the vaccine virus strains to replicate in the nasopharynx, and the *ts* and *att* phenotypes prevent replication in the lower respiratory tract.
Hyperlink to the Product Information	FLUENZ, Summary of Product Characteristics

Table I-1 Product Overview

Indication(s) in the EEA	**Current**: Prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age. **Proposed**: Not applicable
Dosage in the EEA	**Current**: For children who have not previously been vaccinated against seasonal influenza, the recommended dosage schedule is one 0.2-mL dose (administered as 0.1 mL per nostril) followed by a second 0.2-mL dose (0.1 mL per nostril) given after an interval of at least 4 weeks. For all other individuals, the recommended schedule is one 0.2-mL dose (administered as 0.1 mL per nostril) annually. **Proposed**: Not applicable
Pharmaceutical form(s) and strengths	**Current:** 0.2-mL single use nasal spray, suspension Each 0.2-mL dose of **Q/LAIV** contains $10^{7.0 \pm 0.5}$ FFU of live att influenza virus reassortants of each of the strains (A/H1N1, A/H3N2, B/Victoria and B/Yamagata) as recommended for the given influenza season. Each 0.2-mL dose of **T/LAIV** contains $10^{7.0 \pm 0.5}$ FFU of live *att* influenza virus reassortants of each of the strains (A/H1N1, A/H3N2, and B/Victoria) as recommended for the given influenza season. **Proposed**: Not applicable
Is/will the product be subject to additional monitoring in the EU?	**No**

II: PART II: SAFETY SPECIFICATION

II: 1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II: 1.1 Prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age

Incidence in the general population:

The incidence of influenza varies every year, and the variability depends on factors such as the genetic make-up of the virus, the susceptibility of the population, and regions. In addition, weather conditions (especially humidity and temperature) may influence influenza virus survival and transmission. The Global Burden of Disease (GBD) 2017 study estimated the global incidence of influenza-attributable lower respiratory tract infections (LRTIs) to be 713 per 100,000, while the rate of hospitalisations was 124 per 100,000 (Troeger et al 2019). There were variations across age groups and regions, with the highest rates of hospitalized influenza-LRTIs, respectively, in the extremes of age (resulting in a U-shape distribution) and in Eastern Europe (489 per 100,000). These rates, however, do not capture the broader spectrum of influenza illness, which include upper respiratory and asymptomatic infections.

In more recent years, the COVID-19 pandemic has altered the timing, magnitude, and duration of seasonal influenza epidemic activity, with a relatively late and low-activity season in 2021-22 (ECDC 2022). This pattern appears to be reversed in the current 2022-23 influenza season, with reported early onset and increased transmission of type B viruses, particularly among children four years of age and younger (WHO 2022).

Incidence in paediatric populations:

A systematic review and meta-analysis estimated that 110 million new episodes of influenza occurred in children aged < 5 years worldwide in 2018 (Wang et al 2020). Reported rates of influenza illness varied across studies by paediatric age groups, settings/regions, time periods, and influenza virus subtype. As noted above, rates of influenza attributed-LRTIs represent a fraction of the broad spectrum of influenza illness, and therefore, higher rates would result when accounting for non-hospitalized cases. By modelling surveillance data on all influenza-like illness (ILI) in England, Italy, the Netherlands and Spain from 2002 to 2008, the European Paediatric Influenza Analysis project calculated that between 0.3 and 9.8 % of children aged 0–14 years present to a physician with influenza in the average season (Paget et al 2010). In a systematic review of 13 randomized controlled trials (RCTs), the pooled incidence for all laboratory confirmed, symptomatic influenza in unvaccinated children < 18 years was 12.7%, and for symptomatic influenza A and B the rate was 11.2% (Somes et al 2018). The rate in children < 3 years for all symptomatic influenza was 13.5% while for children 3 to 17 years it was 11.8%. Higher incidence rates in the youngest groups of children

were observed during two seasons considered to be milder influenza epidemics, namely 2000–2001 (primarily A/H1N1) and 2001–2002 (primarily A/H3N2), with an average annual rate of influenza in Finnish children < 3 years old seen as outpatients of 17.9% (Heikkinen et al 2004).

Young children are also at increased risk of secondary household transmission. Despite the marked heterogeneity of reported secondary attack rates in household studies, evidence suggests higher susceptibility as well as infectivity among younger age groups (Tsang et al 2016). In a prospective household transmission study in France, the overall secondary attack rate of laboratory confirmed influenza A(H3N2) clinical episodes was 24.1% among 543 contacts. The risk of influenza transmission was significantly higher in preschool children (aged 0–5 years) as compared to school-age children and adults (HR 1.85, 95% CI 1.09-3.26) (Viboud et al 2004). Contacts exposed to preschool and school-age children were at higher risk compared to those exposed to infected adults (HRs 1.93 and 1.68, respectively).

Demographics of the population in the authorized indication, age, and risk factors for the disease:

Demographics are variable by country and vaccination practices differ from country to country. Children with influenza contribute to the burden in older age groups because of their high infectiousness (Tsang et al 2016). Several studies demonstrate that the burden of hospital admission and emergency department visits in younger children who are infected with influenza is considerable. Younger children are much more likely to be hospitalized as a result of influenza and its complications than their older counterparts. Many surveys have reported that influenza-associated hospitalization rates were higher in those aged <5 years than aged ≥5 years. The GBD study estimated that influenza virus accounted for 7% and 5% of all acute LRTI-cases and -hospitalizations in children under 5 years, respectively (Wang et al 2020). It was estimated that 2.2 million influenza attributed LRTI hospitalisations among children < 5 years in 2017 (Troeger et al 2019).

In adults, the estimated global mean annual influenza-associated respiratory excess mortality rates ranged from 0.1 to 6.4 per 100,000 individuals for people < 65 years, 2.9 to 44.0 per 100,000 individuals for people aged 65 to 74 years, and 17.9 to 223.5 per 100,000 for people older than 75 years. Persons > 65 years of age and persons with certain medical conditions are at greatest risk of serious illness and death from influenza. Approximately 90% of deaths related to pneumonia and influenza occur in persons ≥ 65 years of age (Thompson et al 2003).

Influenza can affect anyone; however, some conditions may put individuals at a higher risk of influenza disease, such as pregnant women, children under 5 years adults 65 years of age and older, individuals with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver, or hematologic diseases) and individuals with

immunosuppressive or immunocompromising conditions (such as HIV/AIDS, receiving chemotherapy or steroids, or malignancy) (ECDC 2008). 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. (WHO 2017).

The main existing treatment options:

There are currently three types of medications approved to treat influenza: adamantanes (amantadine and rimantadine), neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir), and a polymerase acidic endonuclease inhibitor (baloxavir). All of these are considered antiviral drugs; however, the adamantanes are no longer recommended for use due to resistance issues.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

According to the World Health Organization (WHO), classical seasonal influenza is characterized by a sudden onset of high fever, cough (usually dry), headache, muscle and joint pain, severe malaise (i.e., feeling unwell), sore throat, and runny nose (WHO 2023). The signs and symptoms of influenza are not specific as they can be caused by other respiratory viruses. Moreover, in contrast to adolescents and adults, children with influenza A and B infections often report gastro-intestinal symptoms. A common complication of influenza in children is acute otitis media (AOM). Among children 10 years or younger who had AOM, influenza virus was detected in middle ear fluid (MEF) samples of nearly 30% of cases (Yano et al 2009). The risk to develop AOM is largely dependent on age and highest in those aged less than 2 years. Also, influenza virus infection in children is known to cause croup and bronchiolitis, although less frequently than many other respiratory viruses. Irrespective of age, asthmatic children infected with influenza often suffer from exacerbations. Following influenza virus infection, bacterial invasion of the respiratory tract may cause pneumonia.

As to non-respiratory complications, neurological complications appear to be more common in severely ill children. The most common neurological complication in children is febrile convulsion, precipitated by fever of abrupt onset. Usually, febrile convulsions occur in children under 5 years of age. Other neurologic complications of influenza, such as encephalitis/encephalopathy, acute necrotizing encephalopathy, and Guillain–Barre's syndrome are far more serious and associated with long-term sequelae or death. In a French study of 181 children admitted to hospital with H1N1pdm09, 14 (7.7 %) had central nervous system (CNS) dysfunction; of the 14 children (median age, 5.1 years), eight had febrile seizures and 3 had encephalitis or encephalopathy (Frobert et al 2011). Twenty-four of the 181 children who were hospitalized, required admission to intensive care unit (ICU), including 9 (37.5%) of those with CNS complications. In another Australian study, ~10% of 506 children

who were hospitalized with H1N1pdm09 had neurological complications (median age 4.8 years (range 0.5–12.6 years)), with seizure being the most common (7.5%) and nearly a third of children required ICU admission (Khandaker et al 2012).

The incidence of Reye's syndrome decreased due to avoidance of acetylsalicylic acid in children. Other complications include influenza-associated acute myositis which is reported as a complication of both influenza A and B virus infections. Pericarditis and myocarditis are occasionally reported in children suffering from seasonal influenza. The exact pathogenetic mechanisms of non-respiratory complications are still unclear. Influenza virus may directly cause damage to infected tissues; influenza viruses have been occasionally detected in blood and CNS fluid. In addition, reports of replication of influenza viruses in tissues other than blood and CNS are rare. High-titre viral replication and an increased inflammatory response with cytokine dysregulation have been suggested in the pathogenesis of non-respiratory complications.

The number of deaths resulting from influenza are difficult to estimate. Most deaths attributed to influenza are not confirmed through virology testing, and influenza-related deaths can result from many causes, such as pneumonia and other respiratory ailments, as well as circulatory conditions (Dushoff et al 2006). Although deaths due to influenza are rare in children, the majority occur in those under 5 years of age, and nearly half of the influenza-related deaths in children of all ages are in otherwise healthy children (Bhat et al 2005). Children with pre-existing neurological and cardio-respiratory disease run the highest risk of developing severe influenza, and they also display the highest mortality rates (Fraaij and Heikkinen 2011). Globally, it was estimated that influenza virus accounted for 4% of all acute LRTI-deaths in children under 5 years, with an estimated incidence of 2 per 100,000 (Troeger et al 2019,Wang et al 2020).

In adults, influenza-related mortality is higher among the elderly than among children. The estimated global mean annual influenza-associated respiratory excess mortality rates ranged from 0.1 to 6.4 per 100,000 individuals for people < 65 years, 2.9 to 44.0 per 100,000 individuals for people aged 65 to 74 years, and 17.9 to 223.5 per 100,000 for people older than 75 years. Persons > 65 years of age and persons with certain medical conditions are at greatest risk of serious illness and death from influenza. Approximately 90% of deaths related to pneumonia and influenza occur in persons ≥ 65 years of age (Thompson et al 2003). The EU European Centre for Disease Prevention and Control (ECDC) estimated the average number of excess deaths from seasonal influenza in the EU to be approximately 38,500 deaths annually (ECDC 2010).

Important co-morbidities:

There are no known expected co-morbidities co-existing within the target population that are deemed to be clinically relevant or have an impact on the FluMist / Fluenz product.

II: 2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II: 2.1 Summary of key safety findings from non-clinical data

Toxicity

- Repeat-dose toxicity (assessment of local tolerance and single-dose toxicity included): no adverse test article-related findings identified
- Reproductive and developmental toxicity: no adverse test article-related findings identified

Safety pharmacology

- Neurotropism: Vaccine viruses were not neurotropic.

Other toxicity-related information or data as applicable

- Eye irritation: no adverse test article-related findings identified
- Environmental safety in birds and mammals: the vaccine viruses did not replicate in any bird species. In mammals, replication of the vaccine viruses was only noted in hamsters, guinea pigs, and ferrets. These species have previously been experimentally infected with human influenza virus. No novel tropism for nonhuman species was observed.

Seven Good Laboratory Practice (GLP)-compliant toxicology studies that supported the safety of LAIV were conducted, 2 with quadrivalent live attenuated influenza vaccine (Q/LAIV) and 5 with trivalent live attenuated influenza vaccine (T/LAIV). Intranasal administration was the proposed route of administration for humans; therefore, Q/LAIV and T/LAIV were administered intranasally to either rats or ferrets. The exception was studies evaluating eye irritation, where T/LAIV was instilled into the conjunctival sac of New Zealand white rabbits. The results of the toxicology studies showed no significant systemic, local, intraocular, reproductive, or developmental toxicity of LAIV.

The vaccine strains of influenza virus were not neurovirulent. In addition, the results of environmental safety studies revealed no novel tropism of the vaccine viruses for nonhuman species.

II: 3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Estimates of overall cumulative subject exposure are provided in Table II-1, based on actual exposure data from completed clinical trials.

Table II-1 Cumulative Subject Exposure from Clinical Trials

	T/LAIV[a] (Frozen/Refrigerated[b])	Q/LAIV _Total (Q/LAIV in _Accuspray[c] + Q/LAIV in _BFS[d])	Monovalent/ Bivalent _Vaccine[e]	Total (T/LAIV+Q/LAIV+Monovalent and Bivalent Vaccine)
Subjects Received				
1 Dose or More	51,942	5,605	1,705	**59,252**
2 Doses or More	25,822	1205	0	**27,027**
3 Doses or More	5,044	0	0	**5,044**
4 Doses or More	1,525	0	0	**1,525**
5 Doses or More	479	0	0	**479**
6 Doses or More	2	0	0	**2**

[a]ONLY SUBJECTS WHO RECEIVED 10^7 DOSAGE OF FROZEN T/LAIV SPRAY OR REFRIGERATED T/LAIV ARE INCLUDED. INCLUDES STUDY PM001, AL002, AR001, AV001, AV002, AV002-2, AV003, AV004, AV005, AV006 , AV007, AV008, AV009, AV010, AV012, AV014, AV015, AV017, AV018, AV019, D145-P500, D145-P501, D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504,D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.
[b]INCLUDES STUDY D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504, D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.
[c]INCLUDES STUDY MI-CP208, MI-CP185, D2560C00006, D2560C00007, D2560C00009, D2560C00012, D2560C00013, D2560C00014.
[d]INCLUDES STUDY MI-CP206.
[e]INCLUDES STUDY AV024, MI-CP154, MI-MA205, CD-VA-FluMist-1045, MI-CP113, MI-CP125 AND MI-CP134.
Source: Program (Output): /SASDATAC/cars/prod/medi3250/pooled/2017psur2/tables/table1.sas (table1.rtf)

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table II-2 and Table II-3.

Table II-2 Cumulative Subject Exposure in Clinical Studies by Age and Sex

	T/LAIV[a] (Frozen + Refrigerated[b])				Q/LAIV Total (Q/LAIV in Accuspray[c] + Q/LAIV in BFS[d])			Monovalent/Bivalent Vaccine[e]			Total (T/LAIV+Q/LAIV+Monovalent and Bivalent Vaccine)			
	Male	**Female**	**Missing**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Missing**	**Total**
Age group														
<1 years	1003	956	0	1959	0	0	0	0	0	0	1003	956	0	1959
1 - <2 years	4952	4706	0	9658	0	1	1	0	0	0	4952	4707	0	9659
2 - <18 years	14970	14555	5	29530	1241	1225	2466	0	0	0	16211	15780	5	31996
2 - <9 years	10348	10072	1	20421	756	778	1534	0	0	0	11104	10850	1	21955
9 - <18 years	4622	4483	4	9109	485	447	932	0	0	0	5107	4930	4	10041
>= 18 years	5246	5549	0	10795	1359	1779	3138	733	972	1705	7338	8300	0	15638
18 - <50 years	2583	3269	0	5852	1359	1779	3138	726	932	1658	4668	5980	0	10648
50 - <64 years	924	803	0	1727	0	0	0	7	39	46	931	842	0	1773
>=64 years	1739	1477	0	3216	0	0	0	0	1	1	1739	1478	0	3217
Total	**26171**	**25766**	**5**	**51942**	**2600**	**3005**	**5605**	**733**	**972**	**1705**	**29504**	**29743**	**5**	**59252**

[a]ONLY SUBJECTS WHO RECEIVED 10^7 DOSAGE OF FROZEN T/LAIV SPRAY OR REFRIGERATED T/LAIV ARE INCLUDED. INCLUDES STUDY PM001, AL002, AR001, AV001, AV002, AV002-2, AV003, AV004, AV005, AV006 , AV007, AV008, AV009, AV010, AV012, AV014, AV015, AV017, AV018, AV019, D145-P500, D145-P501, D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504,D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.

[b]INCLUDES STUDY D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504, D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.
[c]INCLUDES STUDY MI-CP208, MI-CP185, D2560C00006, D2560C00007, D2560C00009, D2560C00012, D2560C00013, D2560C00014.
[d]INCLUDES STUDY MI-CP206.
[e]INCLUDES STUDY AV024, MI-CP154, MI-MA205, CD-VA-FluMist-1045, MI-CP113, MI-CP125 AND MI-CP134.
Age at first dose was used for age group.
Source: Program (Output): /SASDATAC/cars/prod/medi3250/pooled/2017psur2/tables/table2.sas (table2.rtf)

Table II-3 Cumulative Subject Exposure in Clinical Studies by Racial Group

	T/LAIV[a](Frozen + Refrigerated[b])	**Q/LAIV _Total (Q/LAIV in Accuspray[c]+ Q/LAIV in BFS[d])**	**Monovalent/Bivalent _Vaccine[e]**	**Total (T/LAIV+Q/LAIV+Monovalent and Bivalent Vaccine)**
Racial Group				
American Indian or Alaska Native	121	24	8	**153**
Asian	5929	1008	15	**6952**
Black or African American	4427	1029	186	**5642**
Native Hawaiian or Other Pacific Islander	11	6	2	**19**
White	33402	3322	1038	**37762**
Other	7725	129	447	**8301**
Multiple Categories Checked	114	87	9	**210**
Unknown	213	0	0	**213**

[a]ONLY SUBJECTS WHO RECEIVED 10^7 DOSAGE OF FROZEN T/LAIV SPRAY OR REFRIGERATED T/LAIV ARE INCLUDED. INCLUDES STUDY PM001, AL002, AR001, AV001, AV002, AV002-2, AV003, AV004, AV005, AV006 , AV007, AV008, AV009, AV010, AV012, AV014, AV015, AV017, AV018, AV019, D145-P500, D145-P501, D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504,D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.
[b]INCLUDES STUDY D153-P001, D153-P002, D153-P003, D153-P004, D153-P005, D153-P500, D153-P501, D153-P502, D153-P503, D153-P504, D153-P507, D153-P510, D153-P511, D153-P513, D153-P514, D153-P515, D153-P516, D153-P518, D153-P522, D153-P526, FM026, MI-CP111, MI-CP112, MI-CP114, MI-CP123, MI-CP128, MI-CP129, MA182, DMID 98-005, DMID 99-012, VA CSP 448, CD-VA-FluMist-1114, MED-VA-FluMist-1156, D2560C00013.
[c]INCLUDES STUDY MI-CP208, MI-CP185, D2560C00006, D2560C00007, D2560C00009, D2560C00012, D2560C00013, D2560C00014.
[d]INCLUDES STUDY MI-CP206.
[e]INCLUDES STUDY AV024, MI-CP154, MI-MA205, CD-VA-FluMist-1045, MI-CP113, MI-CP125 AND MI-CP134.
Source: Program (Output): /SASDATAC/cars/prod/medi3250/pooled/2017psur2/tables/table3.sas (table3.rtf)

II: 4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II: 4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Hypersensitivity to the active substances or to any of the excipients.

Reason for exclusion:

Patients with known hypersensitivity to gelatin or to gentamicin were excluded because these individuals may have a higher risk of hypersensitivity (anaphylactic reaction).

Is it considered to be included as missing information: No

Rationale:

LAIV is contraindicated in patients with known hypersensitivity to active substance and excipients; therefore, this population is not relevant for the approved indication.

Concomitant salicylate therapy

Reason for exclusion:

Patients receiving concomitant salicylate therapy may be at a higher risk of Reye's syndrome.

Is it considered to be included as missing information: No

Rationale:

LAIV is contraindicated in patients receiving concomitant salicylate therapy; therefore, this population is not relevant for the approved indication.

Severe immunodeficiency or concurrent immunosuppressive therapy

Reason for exclusion:

Patients with severe immunodeficiency or concurrent immunosuppressive therapy may be at a higher risk for illness associated with viral replication.

Is it considered to be included as missing information: No

Rationale:

LAIV is contraindicated in immunocompromised patients; therefore, this population is not relevant for the approved indication.

Pregnant or breastfeeding women

Reason for exclusion:

There were no safety issues identified in reproductive toxicology studies; however, LAIV has not been extensively studied in this population.

Is it considered to be included as missing information: No

Rationale:

LAIV is indicated only until the age of 18 years in the EU with use mainly in young children. The anticipated use in pregnant and breast-feeding women is therefore expected to be very low. LAIV use is also not recommended in the label for this population (SmPC Section 4.6), therefore, not relevant for consideration as missing information.

Severe asthma or active wheezing

Reason for exclusion:

Patients with severe asthma or active wheezing may be at a higher risk of developing wheezing.

Is it considered to be included as missing information: No

Rationale:

Use in severe asthmatics is not anticipated because use in children and adolescents with severe asthma or active wheezing is not recommended in the SmPC section 4.4, as these individuals have not been adequately studied in clinical studies. Therefore, not relevant for consideration as missing information.

II: 4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effects, or adverse reactions which have a long latency.

II: 4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table II-4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children less than 24 months of age	11, 617 (male: 5,995; female: 5,662).
Children under the age of 6 months	181 subjects
Elderly (≥ 65 years of age)	3,217
Pregnant women	17 pregnancies reported in Q/LAIV clinical trial subjects, one of whom had not received any study vaccine.
Breast feeding women	Not included in the clinical development programme
Patient with relevant comorbidities: • Patients with severe asthma or active wheezing • Immunocompromised Vaccine Recipients • Patients with concomitant underlying chronic medical conditions (including chronic lung or cardiac disease, diabetes mellitus, or other chronic metabolic disease, hemoglobinopathy, renal, or other chronic disease)	 • 48 patients (9 to 17 years) with moderate to severe asthma (Study AV010) • 24 HIV infected children (1 to 7 years) and 243 HIV-infected children and adolescents (5 through 17 years of age) • 241 children (Study MI-CP111) with underlying medical conditions and more than 10,000 children and adolescents with underlying medical conditions in post-marketing study (MA-194).

II: 5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II: 5.1 Method used to calculate exposure

Patient exposure is based on the assumption that the number of doses distributed is approximately the number of doses used. Exposure data by vaccine recipient age and gender are not available. All exposure is intended for the same indication and route of administration.

II: 5.1.1 Exposure

Cumulative global post-marketing patient exposure for LAIV since launch to 31 August 2023, the worldwide cumulative exposure is estimated to be approximately 190 million doses.

Exposure is summarised by country in Table II-5.

Table II-5 Seasonal LAIV Exposure by Country

Country	**Exposure by Doses Distributed**
EU Total	8,242,434
Nordics (Norway, Sweden, Finland, Denmark, Iceland)	1,715,330
Germany (includes Austria)	2,792,727
Poland	464,545
Romania	57,140
France	17,660
Spain	715,636
Slovakia/Czech Republic	132,920
Hungary & Balkans	55,189
Italy	2,291,287
United Kingdom (Includes Ireland)	60,770,330
US	111,574,170
Rest of World	8,473,085
Total	**189,060,019**

Doses distributed through August 2023, excluding 2009 monovalent H1N1 vaccine
EU European Union; LAIV Live Attenuated Influenza Vaccine; US United States

II: 6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

LAIV is administered annually, is non-habit forming, is non-narcotic, and is unlikely to have any potential for abuse. There have been no reported cases of drug abuse or misuse for illegal purposes involving LAIV to date.

II: 7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II: 7.1 Identification of safety concerns in the initial RMP submission

Not applicable

II: 7.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns or reclassifications**.**

II: 7.3 Details of important identified risks, important potential risks and missing information

There are no important identified risks, important potential risks or missing information.

II: 8 SUMMARY OF THE SAFETY CONCERNS

II: 8.1 Summary of the safety concerns

There are no safety concerns for LAIV.

III: PHARMACOVIGILANCE PLAN

III: 1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for the following important risks:

Not applicable

Other forms of routine pharmacovigilance activities:

A Passive Enhanced Safety Surveillance (ESS), Post-Authorisation Measure, MEA/004.13 was run, including flu season 2022-2023, and was submitted in May 2023. After that, safety surveillance data will continue to be reported through PSURs.

III: 2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities.

III: 3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities.

IV: PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV: 1 SUMMARY OF POST AUTHORISATION EFFICACY STUDIES

There are no efficacy studies that are a specific obligation and/or condition of the MAA.

V: PART V: RISK MINIMISATION MEASURES

V: 1 ROUTINE RISK MINIMISATION MEASURES

Not applicable

V: 2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable

V: 3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable

VI: PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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

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

This summary of the RMP for LAIV 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 LAIV's RMP.

VI: 1 THE MEDICINE AND WHAT IT IS USED FOR

LAIV is authorised for prophylaxis of influenza in children and adolescents from 24 months to less than 18 years of age. It contains Influenza vaccine (live attenuated, nasal) as the active substance and it is given by nasal route of administration, one 0.2-mL dose (administered as 0.1 mL per nostril).

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002617/human_med_001713.jsp&mid=WC0b01ac058001d124

VI: 2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine *pharmacovigilance activities*.

VI: 2.1 List of important risks and missing information

Important risks of LAIV are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LAIV. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

There are no important risks or missing information for LAIV.

VI: 2.2 Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

VI: 2.3 Post-authorisation development plan

VI: 2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations for LAIV.

VI: 2.3.2 Other studies in post-authorisation development plan

There are no studies required for LAIV.

LIST OF REFERENCES

Ahmed et al 2015
Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med. 2015 ;7(294):294ra105.

Bandell et al 2022
Bandell A, Baum U, Kassianos G. P-256: Real-world effectiveness of live attenuated and inactivated influenza vaccines in children during multiple seasons: 2016–2022. Poster presented at OPTIONS for the Control of Influenza XI Meeting. 2022. Belfast, UK.

Bhat et al 2005
Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza associated deaths among children in the United States, 2003-2004. N Engl J Med. 2005 Dec 15;353(24):2559-67.

Dushoff et al 2006
Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L. Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. Am J Epidemiol. 2006 Jan 15;163(2):181-7. Epub 2005 Nov 30.

Dimachkie MM 2013
Dimachkie MM, Barohn RJ. Guillain-Barre´ Syndrome and Variants. Neurol Clin. 2013 May;31(2):491-510.

Dibben et al 2021
Dibben O, Crowe J, Cooper S, Hill L, Schewe KE, Bright H. Defining the root cause of reduced H1N1 live attenuated influenza vaccine effectiveness: low viral fitness leads to inter-strain competition. NPJ Vaccines. 2021;6(1):35-46.

Dempsey et al 2022
Dempsey R, Tamburrino G, Schewe KE, Crowe J, Nuccitelli A, Dibben O. Haemagglutinin substitutions N125D, D127E, D222G and R223Q improve replicative fitness and vaccine effectiveness of an A/H1N1pdm09 live attenuated influenza vaccine virus by enhancing α-2,6 receptor binding. PLoS Pathog. 2022;18(5):e1010585.

ECDC 2008
ECDC Guidance: Priority Risk Groups for Influenza Vaccination. August 2008. Available from: https://www.ecdc.europa.eu/en/publications-data/expert-opinion-priority-risk-groups-influenza-vaccination

ECDC 2010
European Centre for Disease Prevention and Control (ECDC). Revised Estimates of Deaths Associated with Seasonal Influenza in the US. ECDC Reviews. 2010. Available from: http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/basic_facts/pages/factsheet_professionals_seasonal_influenza.aspx.

ECDC 2022
European Centre for Disease Prevention and Control. Seasonal influenza 2021-2022. In: ECDC. Annual epidemiological report for 2021. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-2021-2022-annual-epidemiological-report (last accessed 24.02.2023)

Fraaij and Heikkinen 2011
Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. Vaccine. 2011;29(43):7524-8. doi: 10.1016/j.vaccine.2011.08.010.

Frobert et al 2011
Frobert E, Sarret C, Billaud G, Gillet Y, Escuret V, Floret D et al. Pediatric neurological complications associated with the A(H1N1)pdm09 influenza infection. J Clin Virol. 2011;52(4):307-13. doi: 10.1016/j.jcv.2011.08.018.

Hauser at al 1996
Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996;71:576-86.

Heikkinen et al 2004
Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, et al. Burden of influenza in children in the community. J Infect Dis. 2004 Oct 15;190(8):1369-73.

Khandaker et al 2012
Khandaker G, Zurynski Y, Buttery J, Marshall H, Richmond PC, Dale RC, et al. Neurologic complications of influenza A(H1N1)pdm09: surveillance in 6 pediatric hospitals. Neurology. 2012 Oct 2;79(14):1474-81.

Mallory et al 2020
Mallory RM, Nyborg A, Kalyani RN, Yuan Y, Block SL, Dubovsky F. A study to evaluate the immunogenicity and shedding of live attenuated influenza vaccine strains in children 24-<48 months of age. Vaccine. 2020;38(5):1001-8.

Paget et al 2010
Paget WJ, Balderston C, Casas I, Donker G, Edelman L, Fleming D et al. Assessing the burden of paediatric influenza in Europe: the European Paediatric Influenza Analysis (EPIA) project. Eur J Pediatr. 2010;169(8):997-1008.

Somes et al 2018
Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis. Vaccine. 2018 May 31;36(23):3199-207.

Thompson et al 2003
Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003 Jan 8;289(2):179-86.

Troeger et al 2019
Troeger CE, Blacker BF, Khalil IA, Zimsen SRM, Albertson SB, Abate D. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2019;7(1):68-9.

Tsang et al 2016
Tsang TK, Lau LLH, Cauchemez S, Cowling BJ. Household Transmission of Influenza Virus. Trends Microbiol. 2016 Feb;24(2):123-33.

UpToDate 2023
Clinical features and diagnosis of narcolepsy in adults – UpToDate. Accessed- Feb 2023.

Viboud et al 2004
Viboud C, Boëlle PY, Cauchemez S, Lavenu A, Valleron AJ, Flahault A, Carrat F. Risk factors of influenza transmission in households. Br J Gen Pract. 2004 Sep;54(506):684-9.

Wang et al 2020
Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson MA, Byass P, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. The Lancet Global Health 2020 Apr;8(4):e497-510.

WHO 2017
World Health Organization. Influenza (Seasonal) Fact Sheet. December 2017.

WHO 2022
World Health Organization. Joint statement - Influenza season epidemic kicks off early in Europe as concerns over RSV rise and COVID-19 is still a threat Fact Sheet. December 2022.

WHO 2023
World Health Organization. Influenza (Seasonal) Fact Sheet. December 2023.

Yano et al 2009
Yano H, Okitsu N, Hori T, Watanabe O, Kisu T, Hatagishi E, et al. Detection of respiratory viruses in nasopharyngeal secretions and middle ear fluid from children with acute otitis media. Acta Otolaryngol. 2009 Jan;129(1):19-24.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: riskmgtsystem-influenza-vaccine-version-12-succession 1		
Document Title:	EU Risk Management Plan for influenza vaccine live attenuated quadrivalent version 12 succession 1	
Document ID:	Doc ID-004527038	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
26-Feb-2024 12:30 UTC	Magnus Ysander	Qualified Person Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.