Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Quadrivalent live attenuated influenza vaccine

Proprietary Product Name: FluMist Quadrivalent

Sponsor: AstraZeneca Pty Ltd

November 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACIP	Advisory Committee on Immunization Practices (US)
ACIR	Australian Childhood Immunisation Register
AE	Adverse event
AF	Allantoic fluid
AIR	Australian Immunisation Register
AIVC	Australian Influenza Vaccine Committee
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
ASCOV	Advisory Committee on the Safety of Vaccines
ATAGI	Australian Technical Advisory Group on Immunisation
BD	Becton-Dickinson
BFS	Blow-fill seal
BVDV	Bovine viral diarrhoea virus
CDC	Centers for Disease Control and Prevention (US)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicines Information
CNS	Central nervous system
CPD	Certified Product Details
DHHS	Department of Health and Human Services (US)
DIR	Dealings involving Intentional Release
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FBS	Fetal bovine serum

Abbreviation	Meaning
FDA	Food and Drug Administration (US)
FFA	Fluorescent focus assay
FFU	Fluorescent focus units
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	Genetically modified
GMT	Geometric mean titre
HA	Haemagglutinin
HAI	Haemagglutination inhibition
ICH	International Conference on Harmonisation
IIV	Inactivated influenza vaccine
ITT	Intent-to-treat
LAIV	Live attenuated influenza virus
MAARI	Medically attended acute respiratory illness
MMR	Measles, Mumps and Rubella (vaccine)
MPH	Monovalent pooled harvest
NA	Neuraminidase
NAI	Neuraminidase inhibiting
NIP	National Immunisation Program
NOCD	New onset chronic disease
OGTR	Office of the Gene Technology Regulator
OMCL	Official Medicines Control Laboratories
PBAC	Pharmaceutical Benefits Advisory Committee
Ph Eur	European Pharmacopoeia
PI	Product Information
PIP	Paediatric Investigational Plan

Abbreviation	Meaning
PSUR	Post-marketing safety update report
Q/LAIV	Quadrivalent live attenuated influenza virus vaccine
QIV	Quadrivalent influenza vaccine
qRT-PCR	Reverse transcription quantitative real time polymerase chain reaction
RCT	Randomised control trial
RMP	Risk management plan
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SPF	Specific pathogen free
T/LAIV	Trivalent live attenuated influenza virus vaccine
TFF	Tangential flow filtration
TIV	Trivalent Influenza Vaccine
UK	United Kingdom
US	United States
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centres

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	12 October 2016
Date of entry onto ARTG	18 October 2016
Active ingredient(s):	Influenza virus
Product name(s):	FluMist Quadrivalent influenza virus vaccine nasal spray applicator
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
Dose form:	Nasal spray
Strength:	10000000 FFU[1]/strain/0.2 mL dose
Container:	Nasal applicator
Pack sizes:	1 x 0.5 mL and 10 x 0.5 mL nasal spray applicator(s)
Approved therapeutic use:	*FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age*
Route of administration:	Nasal
Dosage:	Please see product background information below
ARTG number:	244892

Product background

This AusPAR describes the application by the sponsor to register FluMist Quadrivalent, a quadrivalent, live attenuated influenza virus vaccine (Q/LAIV) in the form of a nasal spray for the following indication:

> *'FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.'*

FluMist Quadrivalent is an intranasally administered vaccine that contains 4 live reassortant strains of influenza virus. Each 200 µL (0.2 mL) dose of the Q/LAIV is

[1] $10^{7.0 \pm 0.5}$ FFU

formulated with $10^{7.0 \pm 0.5}$ FFU[2] (fluorescent focus units) of live attenuated influenza virus (LAIV) reassortants, propagated in specific pathogen free (SPF) eggs, for each of the four strains selected for the specific influenza season: two type A influenza strains (A/H1N1 and A/H3N2) and two type B strains (one strain from each of the B/Victoria and B/Yamagata lineages).

For children 24 months to 8 years of age who have not previously been vaccinated against seasonal influenza, the recommended dose is 0.2 mL (administered as 0.1 mL per nostril), followed by a second 0.2 mL dose (0.1 mL per nostril) after an interval of at least 4 weeks. For all other individuals, including children who have previously been vaccinated against seasonal influenza, the recommended dose is 0.2 mL (administered as 0.1 mL per nostril) each year.

The Q/LAIV, FluMist Quadrivalent was developed to replace the sponsor's seasonal trivalent live attenuated influenza virus vaccine (T/LAIV), marketed as FluMist in the United States (US) and as Fluenz in the European Union (EU). Although FluMist T/LAIV has not previously been registered in Australia, it has been in clinical use for over a decade in the US and the EU. The safety and efficacy of FluMist T/LAIV have been extensively documented.

FluMist Quadrivalent is identical to FluMist T/LAIV except that a fourth strain of influenza B is blended into the final vaccine. The two vaccines are produced by the same process; use the same attenuated master donor viruses and excipients; are blended with the same potency specification: $10^{7.0 \pm 0.5}$ FFU per strain; and are administered intranasally using the Becton Dickinson (BD) Accuspray device.

FluMist Quadrivalent was developed to address the issues of co-circulation of B strains from 2 lineages and mismatch between the single B strain lineage included in seasonal trivalent influenza vaccines and the predominantly circulating strain. Previous influenza vaccines, whether live or inactivated, contained 3 strains: A/H1N1, A/H3N2, and a single type B strain; however, B strains from two genetically and antigenically distinct lineages, B/Victoria/02/87 and B/Yamagata/16/88, have been co-circulating annually. Individuals vaccinated against a strain from one B lineage have limited protection against disease caused by B strains from the other lineage.[3] This vaccine contains, in addition to the 2 influenza A subtypes, 2 type B strains, one from each B lineage (B/Victoria/02/87 and B/Yamagata/16/88), to provide broader protection against influenza caused by type B viruses.

As FluMist Quadrivalent is intended to provide prophylaxis from seasonal circulating influenza, the specific vaccine strain composition for that year is based on the seasonal recommendations of the World Health Organization (WHO). Following registration of an influenza vaccine product, the Australian Influenza Vaccine Committee (AIVC) reviews and evaluates data relating to the strains of influenza that were circulating in Australia and the Southern Hemisphere in the preceding winter in conjunction with WHO guidelines before making recommendations about changes to the strains recommended to be included in the latest seasonal influenza vaccine.

FluMist Quadrivalent contains no preservatives or adjuvants. The reassortant influenza virus strains in this Q/LAIV are:

- cold adapted, meaning they replicate efficiently at 25°C, a temperature that is restrictive for the replication of many wild type influenza viruses;

[2] 10000000 FFU

[3] Belshe RB, Coelingh K, Ambrose CS, Woo JC, Wu X. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine.2010;28:2149-56.

- temperature sensitive, meaning they are restricted in replication at 37°C (type B strains) or 39°C (type A strains), temperatures at which many wild type influenza viruses grow efficiently); and
- attenuated, meaning they do not produce classic influenza like illness in the ferret model of human influenza infection.

The cumulative effect of these phenotypes is that replication of the attenuated vaccine viruses is restricted to the nasopharynx, where the vaccine induces both local (mucosal) and systemic (humoral and cellular) protective immunity similar to that induced after infection with wild type influenza virus.

Quadrivalent influenza vaccines

Quadrivalent influenza vaccines (QIV) are now available under the National Immunisation Program (NIP), following recommendations of the Pharmaceutical Benefits Advisory Committee (PBAC). Given the potential advantage of protection against an additional B virus, the Australian Technical Advisory Group on Immunisation (ATAGI) recommends QIV as the preferred option over trivalent influenza vaccines (TIV).[4] QIV are expected to be at least as effective as TIV, based on clinical studies in children and adults which demonstrated QIV to be at least as immunogenic as TIV (an accepted surrogate for protection against influenza) for the three influenza virus strains common to both QIV and TIV.[5]

The magnitude of the additional benefit conferred by an additional B strain will vary by year, depending on the epidemiology of the additional influenza B lineage, vaccine uptake and the level of cross-protection against the additional B lineage afforded by that year's TIV. QIV currently available under the 2016 NIP include FluQuadri Junior and Fluarix Tetra.[4,6]

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 October 2016.

At the time the TGA considered this application, similar applications for FluMist Quadrivalent had been considered in other countries as shown in Table 1, below.

The T/LAIV, FluMist has been registered overseas for more than 10 years, by the US Food and Drug Administration (FDA) since 2003 and more recently in Canada (2010) and by the European Medicines Agency (EMA) in Europe (2011, marketed as Fluenz). The licence for the T/LAIV, Fluenz/FluMist will soon be (or has already been) withdrawn and replaced by the Q/LAIV Fluenz Tetra/FluMist Quadrivalent in Europe and Canada.

Table 1. FluMist Quadrivalent international regulatory status

Country	Approval date	Comment/outcome
Canada	20 Jun 2014	Launched 2014/2015 season, approved as new license

[4] ATAGI bulletin: Australian Technical Advisory Group on Immunisation (ATAGI). 58th Meeting, 15 and 16 October 2015
[5] Australian Immunisation Handbook 10th Edition, 4.7 Influenza. (Last updated June 2015)
[6] Australian Government. Department of Health. Australian Technical Advisory Group on Immunisation (ATAGI) advice for immunisation providers regarding the administration of seasonal influenza vaccines in 2016

Country	Approval date	Comment/outcome
EU	04 Dec 2013	Approved as Fluenz Tetra, launched 2014/2015 season
USA	29 Feb 2012	Launched 2013/2014 season, approved as a supplement to the trivalent licence
Singapore	Not applicable	No application submitted
Switzerland	Not applicable	No application submitted

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

The drug substance is the monovalent pooled harvest (MPH) from each of the four influenza strains.

Manufacture

The active substance is composed of cold adapted reassortant vaccine strains produced by reverse genetics between the wildtype influenza virus and a cold adapted master donor virus (H1N1 and H3N2) and Influenza B (Yamagata/16/88 and Victoria/2/87 lineages). Master seed viruses are prepared by plasmid rescue/reverse genetics between a wildtype influenza strain and a cold-adapted master strain, generating 6:2 reassortants. These reassortants contain 6 genes from the attenuated master strain and two (haemagglutinin (HA) and neuraminidase (NA)) from the wildtype strain. A new master viral seed is generated for each new recommended influenza strain.

All strains are produced in the United Kingdom (UK), according to the same manufacturing process as the T/LAIV, FluMist licensed in the EU and US release testing of the monovalent bulks is also performed at the same site.

The drug substance production process involves inoculation of eggs with working virus seed lot, harvest of allantoic fluid (AF) from eggs, clarification and concentration of AF, centrifugation, pooling and dilution of virus concentrate, sterile filtration to a monovalent bulk drug substance. The manufacturing process generates a live, attenuated influenza bulk drug substance, this differs from the conventional influenza vaccines supplied in Australia which are typically inactivated and split. The manufacturing process does not contribute to the viral safety of the final lot in terms of its ability to clear contaminating virus. Instead raw material control and in-process/release testing are used as controls. Manufacturing process consistency was addressed in terms of biological, physical and genetic and biochemical properties.

Specifications

Lot release specifications for the LAIV monovalent bulk drug substance were detailed in the submission. Given the manufacturing process results in a live attenuated virus the testing described for the monovalent bulk in terms of sterility, viral safety and attenuation is critical to ensuring the safety of the product. The tests and specifications are in accordance with the European Pharmacopoeia (Ph. Eur.) monograph for live, nasal influenza vaccine.

The potency assay is a fluorescent focus assay (FFA). The evaluator raised the issue of the lack of interassay controls across all assays for the product lifetime. Although the assay uses internal controls, these are monovalent bulks and given the nature of the vaccine strain changes they are not useful in tracking the assay consistency over time and cannot detect assay drift due to possible changes in sensitives of the cell to the virus nor differentiate them from decay of the control. No international standard is available for this purpose.

The evaluator has recommended that the establishment of a reference be considered a condition of registration.

Assay for total protein and DNA where added to drug substance has in-process testing. These assays were previously included as characterisation tests for initial lots included in process development.

Risk of adventitious agents

There was an initial concern that Insufficient evidence has been provided to demonstrate that the risks related to the adventitious presence of infectious viral, prion and mycoplasma agents in the manufacturing of FluMist Quadrivalent had not been controlled to an acceptable level. *An application for an exemption from the testing requirements specified in the Ph. Eur. general text 2.6.16 'Tests for extraneous agents in viral vaccines for human use' was later submitted by the sponsor.* This is discussed further on in this AusPAR (see below).

Post evaluation note: The sponsor provided responses to the outstanding issues regarding the risk of adventitious agents directly to the infectious disease safety evaluator well prior to the agreed timeframe. This included an exemption application submitted directly to the infectious disease safety evaluator as part of these overall responses. The evaluator confirmed these issues had been resolved prior to approval of FluMist Quadrivalent.

Stability

The proposed shelf-life of the LAIV monovalent bulk is 24 months at ≤ -60˚C. The degradation profile was assessed over a 24 month period using 13 batches. All lots passed potency specification of 7.7log FFU/mL.

Container safety

The nasal spray applicator consists of a plunger rod and dose divider, glass barrel and a spray nozzle assembly. All components in contact with the product were assessed for compliance to the relevant standards and found to be acceptable.

All sterility, endotoxin and container safety issues have been resolved.

Drug product

Formulation(s)

The drug product is a live, attenuated blend of four strains of LAIV derived from the cold adapted, temperature sensitive, attenuated influenza strains which are thawed and combined with stabilisers and buffers. The active components in the finished drug product are list in the following table.

Table 2. Active components of Q/LAIV drug product

Components	Quantity per dose	Function
Influenza Virus, Type A, H1N1	$10^{7.0 \pm 0.5}$ FFU/dose	Immunogen
Influenza Virus, Type A, H3N2	$10^{7.0 \pm 0.5}$ FFU/dose	Immunogen
Influenza Virus, Type B (Yamagata lineage)	$10^{7.0 \pm 0.5}$ FFU/dose	Immunogen
Influenza Virus, Type B (Victoria lineage)	$10^{7.0 \pm 0.5}$ FFU/dose	Immunogen

The product complies with the Ph. Eur. monograph 2772 for final lot testing. The sponsor was requested and agreed to include a thermal stability test for the final lot in accordance with the Ph. Eur. This test was previously undertaken of initial lots in process development. As stated in the Ph. Eur. the concentration represents an approved minimum virus concentration for release of the product for each virus strain to ensure that the minimum concentration stated on the label will be present at the end of the validity period. The label concentration is consistent with the potency specification.

The final blended product is aseptically filled into a 0.5 mL single-use nasal applicator. The presence of gelatin is necessary to decrease the degradation of some strains in the formulation. Gelatin is the source of the majority of protein in the final vaccine lot. The drug product is manufactured in the US, release for supply is also conducted at this site. Quality control testing is undertaken in the UK and the US.

Stability

The storage conditions and shelf life for the drug product are unique among influenza vaccines and will require ongoing monitoring. The shelf life of the final lot of up to 18 weeks at 2 to 8°C is supported by stability studies. It is noted that the stability analysis of the product included initial storage at -20°C for up to 20 weeks prior to distribution following by storage at 2 to 8°C for the 18 week shelf life. Minor temperature deviations where shown not to affect the product potency.

Stability study results support a shelf life of up to 18 weeks at 2 to 8˚C.

Labelling, PI and CMI

With respect to quality evaluation, the Product Information (PI) and Consumer Medicines Information (CMI) are acceptable. As per other seasonal influenza vaccines, these documents will require evaluation with the next annual strain update submission. The product label does not comply with the current standards in terms of the statements required on the label. The quantity of active ingredient is not stated on the container label. An exemption for this standard will need to be submitted.

All manufacturing and labelling issues have not been resolved. Please refer to the quality summary and conclusions below.

Biopharmaceutics

Biopharmaceutical data are not required for this product.

Quality summary and conclusions

Summary

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The manufacture of the drug substance using attenuated influenza donor viruses has appropriate specifications in place in terms of genetic characterisation and identification in accordance to relevant standards. Minimal purification steps are involved in the drug substance production, in order to generate a LAIV. The drug product is sufficiently characterised and specifications are in place to ensure product consistency in terms of final bulk and final lot testing. However the in vitro potency assay should be strengthen to include a reference that will enable assay performance to be tracked long term. The final bulk is filled in to nasal spray applicators stored at -20˚C for up to 20 weeks followed by a shelf life of up to 18 weeks at 2 to 8˚C. The labelling of the drug product does not comply with the current standard, in this respect an application for exemption should be submitted to the TGA. *The sponsor, in discussion with the quality evaluator, was able to modify the label text in order to meet the current standard and therefore an exemption was not required].*

The following issues are yet to be resolved:

1. Development of a potency assay standard used to track potential assay drift. The standards currently used are strain specific and have an expiry of around 24 months so are unable to provide a long term track of the performance of the assay.

To encourage the manufacturer to investigate the development of a potency assay standard for long term use, it is proposed that this become a condition of registration.

Overall conclusion

The quality evaluator recommends that FluMist Quadrivalent 1 x 0.2 mL and 10 x 0.2 mL presentations containing 10^7 FFU/strain 0.2 mL dose via 0.5 mL nasal spray applicator should be approved after:

1. The sponsor provides an undertaking that the outstanding quality issues (summarised under 'recommendations' below) will be addressed before the agreed timeframe; and
2. Subject to the following proposed conditions of registration (see below).

Conditions and recommendations

Proposed conditions of registration

Development of a potency assay standard to track potential assay drift: The standards currently used are strain specific and have an expiry of around 24 months so are unable to provide a long term track of the performance of the assay.

The sponsor should review availability and nominate material for the development of such standard in collaboration with the TGA.

Recommendations

The following issues are yet to be resolved:

- Development of a potency assay standard used to track potential assay drift. The standards currently used are strain specific and have an expiry of around 24 months so are unable to provide a long term track of the performance of the assay.
- *As part of the sponsor's Pre ACPM response they provided the following assurance: 'The sponsor commits to evaluate in collaboration with TGA, a suitable potency assay standard or control which could be used to evaluate drift of the assay system*.'

Batch release conditions of registration for clinical Delegate

Should the product be approved, details of the specific requirements associated with batch release and testing will be forwarded to the Delegate prior to finalisation of administrative and registration activities.

III. Nonclinical findings

Introduction

The T/LAIV and the Q/LAIV are produced by a similar manufacturing process using the same attenuated master donor viruses and excipients are blended to the same potency specification. Because of similarities between the T/LAIV and the Q/LAIV, the non-clinical sections of the FluMist Quadrivalent submission are derived in large part from studies conducted previously with the trivalent FluMist formulation. The immunogenicity and safety profile of Q/LAIV were directly compared to two formulations of the currently approved trivalent vaccine, one with B strain from B/Victoria lineage and one with B strain from the B/Yamagata lineage.

The studies were in accordance with regulatory guidelines for influenza vaccines.[7]

Pharmacology

Primary pharmacology

A pilot study in ferrets, was conducted during development of the Q/LAIV demonstrated addition of a second vaccine virus, of a different type B to the T/LAIV blend had no apparent effect on the immunogenicity of the other 3 vaccine viruses. In these studies three bivalent blends consisting of the Yamagata and Victoria Lineage and equivalent amounts of monovalent B vaccine virus were inoculated intranasally into ferrets. Haemagglutination inhibition (HAI) titres in sera collected 14 days post-inoculation showed specificity to the lineage used to vaccinate the animals and no cross-reaction with antigens from the different lineages were detected.

As the Q/LAIV and T/LAIV formulation of the vaccines are near identical, the sponsors provided data from 2 separate studies that compared two formulations of the T/LAIV (with a B strain from the B/Victoria lineage and one with a B strain from the B/Yamagata lineage) with Q/LAIV to assess the immunogenicity of Q/LAIV and its efficacy against A and B vaccine strains. The immunogenicity of the vaccines were determined by HAI serum assay and indicated that the Q/LAIV elicit a robust immune response against all four vaccine strains in the ferret model with 100% seroconversion (14 days after the second

[7] EMA (2015) Draft Guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014)

dose). HAI titres generated against the A and B strains were similar for both types of vaccines (Q/LAIV and T/LAIV), indicating that the addition of a second B virus had minimal impact on the immunogenicity of the A strains. Likewise, the HAI titres generated against the B strains were similar for both groups of vaccines indicating the addition of a second B virus had minimal impact on the immunogenicity of the B strains. Combining the two B strains in the same vaccine did not result in immunological interference. Efficacy was determined by measuring inhibition of wildtype homologous virus replication in nasal wash material and lungs post challenge. Wild type virus shedding was detected at lower levels to the placebo in the nasal washes and was completely inhibited in lungs at the time points tested indicating the vaccine is highly effective in protecting the lower respiratory tract. More supportive efficacy data was also provided in the repeat dose toxicity studies (see Repeat dose toxicity section, below).

Additional pharmacology data were presented from studies in non-pregnant rats and their offspring confirmed immunogenicity of Q/LAIV in rats and their offspring and thus its suitability for evaluating toxicity of Q/LAIV. Collectively from all the pharmacology data provided by the sponsor it can be concluded that the Q/LAIV is equally immunogenic, has similar replication kinetics and confers comparable protection following challenge with wildtype influenza virus when compared to the T/LAIV vaccines that have been in use in the US for over 10 years.

There were no direct studies of the potential for animal to animal transmission, although vaccine virus shedding in ferret nasal washes was low, and replication in the lungs was negligible. A clinical study (Study D145-P500) in a child day care setting reported a low transmission rate. There were no studies in immunosuppressed or immunocompromised animals.

Safety pharmacology

A safety pharmacology study using the T/LAIV vaccine was only done for central nervous system (CNS) effects, to evaluate the possibility of neurotoxicity, neurotropism of vaccine viruses either in monovalent formulations or in combination. This is an appropriate safety concern for a live influenza vaccine that is being administered intranasally, in close proximity to neurons in the olfactory epithelium. The mouse neuro-adapted A/WSN/33 strain of influenza virus used as a positive control causes a lethal infection with prominent involvement of neurons.[8] Safety pharmacology experimental data presented, conclusively showed absence of vaccine strains in mice brain tissue consistent with lack of neural tropism and replication. A sensitive reverse transcription quantitative real time polymerase chain reaction (qRT-PCR) assay was used for virus detection in brain homogenates. Titres of vaccine viruses used in this study were lower than the human clinical dose. However virus titres tested were reasonably high and the detection method chosen was highly sensitive detecting both infectious and non-infectious virus particles and therefore was not considered to be a problem.

No tests were carried out using Q/LAIV. The sponsor states that the vaccine viruses of subtypes A and B in Q/LAIV will be generated from the master donor viruses, which confer cold adaptive, temperature sensitive, and attenuated phenotypes as those studied in this study and thus the results of this safety pharmacologic would support Q/LAIV. They have also confirmed that neurovirulence testing will be conducted on the master virus seeds of any novel live attenuated influenza viral strain, that is, if a new haemagglutination antigen of subtype A or type B of influenza virus differing from the currently circulating genetic lineages is included in the vaccine in case specific safety concerns rise. With this

[8] Aronsson F et al. Invasion and persistence of the neuroadapted influenza A/WSN/33 in the mouse olfactory system. Viral Immunol 16:415-423. 2003.

assurance, the safety pharmacology evaluated using the T/LAIV vaccine is sufficient and acceptable.

Pharmacokinetics

Typical pharmacokinetics studies including absorption, metabolism and excretion do not pertain to live vaccines.[7]

Pharmacokinetic drug interactions

Studies evaluating pharmacodynamic drug interactions with Q/LAIV were not conducted. However clinical studies to evaluate concomitant vaccination with T/LAIV and other vaccines have been conducted. These studies assessed the safety, tolerability and immunogenicity of the T/LAIV vaccine administered concurrently with measles, mumps, rubella (MMR), varicella and oral polio vaccines in young children and showed minimal interference.

Toxicity

Acute toxicity/local tolerance

Stand-alone single dose toxicity studies, acute toxicity and local tolerance for Q/LAIV and T/LAIV were not submitted. However, data for these studies were provided in the repeat-dose toxicity studies (see below).

Repeat dose toxicity

Two repeat dose toxicity studies in ferrets were submitted, the first was with Q/LAIV and the second with T/LAIV. The clinical dose of Q/LAIV was administered intranasally, using an insulin syringe, once every two weeks for a total of 3 weeks (Days 0, 14 and 28) and animals were necropsied on either Days 31 or 56. The clinical dose of T/LAIV was administered intranasally using the clinical spray device used in clinical trials, three times (Week 0, Week 4 (28 days) and Week 14 (98 days)) and animals were necropsied either on Days 105 or 106. The doses used in both these studies are approximately, 136 times the human dose or 54 times a child dose in ferrets (based on FFU/kg body weight). The volumes inoculated were 0.5 mL and 0.1 mL per nare for Q/LAIV and T/LAIV respectively. This meets the minimum volume requirement of 50 µL in small animals and since T/LAIV was administered using a spray device a higher volume of 100 µL would not be considered problematic.[9] The animals were also anesthetised before inoculation reducing any complication during administration.

In both these studies all ferrets survived till scheduled termination. There were no adverse vaccine related changes identified at the inoculation site. However histopathology of the nasal turbinates showed formation of cellular exudates in the meatus of level 1 turbinates mainly in animals that were vaccine treated. This observation was distinctly attributed to the vaccine treatment group, 3 days after administration and was not observed at a later terminal necropsy suggesting this was most likely a transient, local response to inoculations.

A total of 5 animals from both the control and test group used for Q/LAIV studies were infected with coccidiosis (unrelated to the vaccine) and required treatment during the

[9] Turner V et al. Administration of substances to laboratory animals: Routes of administration and factors to consider. Journal of Animal Association for Laboratory Animal Service 50 (5) – 600-613. 2011.

course of the experiment, however, it is unlikely to have affected the outcomes. In both these studies body weight increased through the course of the study and inoculation site gross evaluation showed normal appearance with no nasal discharge or no abnormal secretion. Body temperatures were all within the normal range of ferrets. The temperatures were observed only 24 hours after each dosing and not at any earlier time points post administration of the vaccine. Earlier time points would have been useful in determining likelihood of fever linked to rare febrile seizures during the 24 hours after a child receives a vaccine.

A 100% seroconversion was observed in studies with Q/LAIV after 2 doses (unusually 1 out of 10, Q/LAIV inoculated ferrets showed comparably low titre response to 'A/Uruguay/716/07' component of the vaccine and this could only be attributed to biological variability). HAI titres at Day 56 were ≥ 128 for A/South Dakota, ≥ 32 for A/Uruguay, ≥ 32 for B/Florida and ≥ 16 for B/Malaysia in the seroconverted ferrets.

Ferrets used for the T/LAIV vaccine studies were positive for the B/Panama vaccine strain (with high HAI titres ranging from 256 to > 1024) at time points even before the animals were vaccinated. Therefore it is not possible to confirm seroconversion of the Panama strain in the T/LAIV vaccine studies but 100% seroconversion was observed with the other two stains. The HAI titres at day 106 were ≥ 32 for A/New Caledonia and ≥ 16 for B/Victoria.

Haematology, serum chemistry, urinalysis, bone marrow smear analysis, gross pathology, histopathology reports showed no clinical indications of toxicity related to the vaccine. The formation of cellular exudate in the meatus of the nasal turbinates shown on Day 3 in the single dose response in animals treated with Q/LAIV were unequivocally related to the vaccine but in the repeat dose studies, the inflammation was observed in both the vaccine and control groups. Similarly in the T/LAIV vaccine studies, multifocal suppurative inflammation of the nasal turbinates was only predominantly seen in test animals at Day 3 and was absent in test and controls at terminal necropsy. This most likely could be attributed to a transient, local response due to inoculations 3 days prior.

In conclusion, both vaccines were generally well tolerated when administered in repeated intranasal inoculations in ferrets. The studies were in accordance with regulatory guidelines for influenza vaccines.[7]

Reproductive toxicity

The sponsor submitted two reproductive and developmental toxicological studies in rats and ferrets which were designed in compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Stages C through to E.[10] The studies evaluated the impact of Q/LAIV and T/LAIV in rats from before mating through to implantation and lactation. Recommended human clinical doses (that is, approximately 150 times the human dose and 80 times the child dose in rats, based on FFU/kg body weight) showed no evidence of impaired fertility or harm to the fetus due to the vaccines. Q/LAIV and T/LAIV administered prior to mating and during gestational period or just during gestational period showed no effects on fertility, pregnancy, parturition, lactation, or embryofetal or pre-weaning development. Vaccine antigen-specific antibodies were transferred from the rat dams to the fetuses and lactating pup. These studies showed no effects on female rat fertility and embryo fetal development with either vaccine. Embryo

[10] ICH Topic S 5 (R2): Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility. Stage C: Implantation to closure of the hard palate (adult female reproductive functions, embryonic development, major organ formation); Stage D: Closure of the hard palate to the end of pregnancy (adult female reproductive functions, fetal development and growth, organ development and growth). Birth to weaning (adult female reproductive functions, neonate adaptation to extrauterine life, pre-weaning development and growth).

fetal development testing in one species is consistent with vaccine regulatory guidelines for influenza vaccines.[11]

The developmental toxicity of T/LAIV beginning prior to implantation throughout organogenesis was evaluated in ferrets using human clinical doses which is approximately 136 times the human dose or 54 times a child dose in ferrets (based on FFU/kg body weight). No serious treatment related effects were observed.

An Australian Pregnancy category of B1 has been proposed.[12] In the light of no negative findings in the reproductive and developmental toxicity studies a category of B1 is acceptable. The US pregnancy category is B.[13] The US Centers for Disease Control and Prevention (CDC) do not recommend use of the LAIV vaccine in pregnancy. Although no adverse findings were observed in animal developmental toxicity studies, clinical advice is also sought on use in pregnancy.

Paediatric use

The Q/LAIV is proposed for use in children from the age of 2 to 18 years. No clinical toxicity studies were conducted in infant animals; however rat fetuses and lactating pups were exposed to vaccine antigen-specific antibodies in the reproductive toxicity studies with no adverse effects. These studies used the same human clinical dose and therefore data provided is adequate for recommending for safe paediatric use.

Vaccine residuals and porcine gelatine excipient

The vaccine product information contains adequate warnings regarding residual gentamicin, egg proteins and the porcine gelatine excipient.

Nonclinical summary

- The vaccine virus strains are 2:6 reassortants, with HA and NA antigens from wildtype virus, and 6 gene segments from the cold adapted (efficient replication at 25°C), temperature-sensitive (restricted replication at 37/39°C for A and B strains respectively), and attenuated master donor virus. Published data indicate that multiple gene segments are responsible for the attenuation, and the attenuated strains are genetically stable in animals and humans.
- As the Q/LAIV and T/LAIV formulation of the vaccines are nearly identical, the sponsor compared two formulations of the T/LAIV with a B strain from the B/Victoria lineage and one with a B strain from the B/Yamagata lineage with Q/LAIV to assess the immunogenicity of Q/LAIV, its efficacy against A and B Influenza virus strains in ferrets and the replication kinetics of the vaccine viruses in ferrets. The studies showed complete seroconversion in all vaccinated animals (determined by measurement of IgG antibodies in sera), developmental of a functional immune response (determined by comparing virus numbers found in lung nasal washes after

[11] FDA CBER (2006) Guidance for Industry. Considerations for reproductive toxicity studies for preventive vaccines for infectious disease indications (not adopted in Australia).
[12] TGA Pregnancy Classification B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage; Australian Therapeutic Goods Act 1989.
[13] US FDA Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling; Federal Register/Vol. 73, No. 104/29 May 2008.

administration of the first and second doses of the vaccine) and complete protection after wild type homologous challenge.

- There were no direct studies of the potential for animal to animal transmission, although vaccine virus shedding in ferret nasal washes was low, and replication in the lungs was negligible. Vaccine virus transmission was investigated clinically.
- Neurovirulence testing of vaccine virus strains in mice was negative.
- Acute/local tolerance and repeat-dose toxicity studies in ferrets administered the human dose of the Q/LAIV or the T/LAIV via the intranasal route did not reveal any significant vaccine related toxicity. Histopathology of nasal turbinates at day 3 post inoculation, showed formation of cellular exudates in the meatus of level 1 nasal turbinates. This was only transient and was not obvious at terminal necropsy.
- Reproductive and developmental toxicity studies in female rats and ferrets administered human doses of Q/LAIV or the T/LAIV showed no effects on female fertility, pregnancy, parturition, lactation, embryo foetal and pre-weaning development. All dams seroconverted and vaccine antigen-specific antibodies were detected in their fetuses and pups.
- The potential eye irritation during intranasal administration of the T/LAIV was assessed in 2 studies and no evidence of any ocular irritation was observed in either study.

Nonclinical conclusions and recommendation

- The non-clinical data provided were satisfactory.
- Published data indicate that multiple gene segments are responsible for vaccine virus attenuation, and the attenuated strains are genetically stable in animals and humans.
- Animal models (ferrets, rat and mouse), inoculation doses and route of administration used in these studies were appropriate and an acceptable package of good quality studies was submitted. Relevant toxicity studies were Good Laboratory Practice (GLP) compliant.
- The primary pharmacology studies adequately demonstrated the seroconversion of animals against the virus strains present in the vaccines tested.
- Vaccine virus shedding in ferret nasal washes was low, and replication in the lungs was negligible. There were no animal studies of vaccine virus transmission. Vaccine virus transmission was investigated clinically.
- Safety pharmacology investigated vaccine virus transmission into the CNS of mice, and this was adequate, showing no detection of vaccine influenza virus in the CNS.
- Typical pharmacokinetics studies including absorption, metabolism and excretion are not required for live vaccines and were not provided.
- Adequate acute and repeat dose toxicity studies with Q/LAIV and T/LAIV vaccines did not reveal any serious vaccine-related toxicity.
- Genotoxicity and carcinogenicity studies are not required for vaccines and were not provided.
- Adequate reproductive and developmental toxicity studies in rats and ferrets with Q/LAIV and the T/LAIV revealed no vaccine related toxicity. An Australian Pregnancy Category of B1 is acceptable.[12] Although no adverse findings were observed in animal developmental toxicity studies, clinical advice is also sought on use in pregnancy.

- Local tolerance was not investigated however, the site of vaccination with Q/LAIV was evaluated in ferrets, in repeat dose toxicity studies and only a slight transient nasal turbinate inflammation was observed on Day 3 post inoculation. This is as an expected response to the vaccine.
- Adequate eye irritation studies showed no evidence of any ocular irritation.
- There are no non-clinical objections to the vaccines registration.
- The environmental safety of the vaccine will be evaluated by the Office of the Gene Technology Regulator (OGTR). The spray device will be evaluated separately.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Influenza is a highly contagious, acute febrile illness and is the most common vaccine preventable disease in the developed world. The site of infection and viral replication in humans is the upper respiratory tract; infection usually produces a systemic disease. Influenza epidemics of variable severity occur annually worldwide in all age groups, typically during the winter months in temperate climates. These annual epidemics are thought to result in 3 million to 5 million cases of severe illness and approximately 250,000 to 500,000 deaths every year around the world.[14] In Australia, an annual average of 310,650 (95% CI: 282,300 to 338,950) encounters were estimated to occur nationally where influenza/influenza-like illness was the problem managed and an estimated excess of 94.2 hospitalisations per 100,000 persons was attributable to influenza.[15]

In humans, influenza illness is caused mainly by two types of viruses: influenza A (with multiple subtypes categorised by HA and NA surface antigens) and influenza B. Since 1977, influenza A/H1N1, A/H3N2, and B viruses have circulated globally and have been included in all licensed trivalent seasonal influenza vaccines. The strains included in influenza vaccines are selected by public health authorities based on global influenza surveillance and may change from year to year depending on which strains are predicted to circulate. Selecting matching strains for inclusion in the vaccine is a key driver of vaccine efficacy, because all vaccines have greater activity against antigenically matched strains.

The selection of B strains for inclusion in annual vaccines poses a particular problem, because two antigenically distinct lineages of influenza B viruses, B/Victoria/02/87 and B/Yamagata/16/88, have circulated since the late 1980s, and it is difficult to predict which lineage will be primarily responsible for annual epidemics caused by influenza B.[16] Some seasons include influenza B viruses of both lineages, and antibodies specific for one

[14] World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2012-2013 Northern Hemisphere influenza season.
[15] Newall A et al. Influenza-related disease: the cost to the Australian healthcare system. Vaccine. 2008 Dec 9;26(52):6818-23.
[16] Rota P et al. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990 Vol.175 No.1 pp.59-68

influenza B virus lineage cross react poorly with viruses from the other lineage.[17] Given this poor cross reactivity and the fact that co-circulation of influenza B strains from both the Victoria and Yamagata lineages is likely to continue, the inclusion of an additional B strain in an annual influenza vaccine (that is, a quadrivalent vaccine) would provide direct health benefit to individual vaccine recipients and their contacts.

Based on analyses performed by the CDC (US), complete replacement of TIVs with QIVs in all age groups in the USA from the 1999 to 2000 influenza season through the 2008 to 2009 season would have resulted in approximately 2,700,000 fewer cases of influenza and 21,000 fewer hospitalisations, and would have prevented more than 1,300 deaths.[18]

Guidance

The T/LAIV, FluMist was not registered in Australia but has been for many years in the US, Canada and Europe (marketed at Fluenz). The development plan was based on the principles outlined in the EMA Guideline on Clinical Evaluation of New Vaccines (Committee for Medicinal Products for Human Use (CHMP), 2006) and the US FDA influenza guidance documents (US Department of Health and Human Services (DHHS), May 2007 (pandemic); US DHHS, May 2007 (seasonal inactivated)). The EMA provided guidance around the clinical development of the Q/LAIV, FluMist Quadrivalent in the form of centralised Scientific Advice as well as in comments received on the Paediatric Investigational Plan (PIP) for the vaccine. Recommendations from the EMA were incorporated into the development plan. Scientific Advice was received from the EMA in relation to the immunogenicity and safety bridging strategy for Q/LAIV in December 2010 (EMA/CHMP/SAWP/784772/2010). An immunologic bridging strategy, in which the immunologic non-inferiority of Q/LAIV compared to the trivalent vaccine would be demonstrated, was endorsed by EMA CHMP, which acknowledged the difficulty of performing an efficacy study covering all 4 strains. A safety bridging strategy was also endorsed. A validated assay was developed to evaluate neuraminidase inhibiting (NAI) antibodies in children 2 to 5 years of age, and neutralising antibody responses were also evaluated in a subset of children this age using a validated assay.

Contents of the clinical dossier

The objective of the development plan was to demonstrate the comparability of the Q/LAIV FluMist Quadrivalent to the T/LAIV FluMist, a vaccine with a well-established safety and efficacy profile. The primary endpoints of the studies involved demonstrating the non-inferiority of immune responses to Q/LAIV compared to T/LAIV, while secondary endpoints included demonstration that the two vaccine formulations had similar safety profiles.

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies pertaining to FluMist Quadrivalent
- 1 supportive efficacy/safety study pertaining to FluMist Quadrivalent
- Multiple other clinical study reports pertaining to FluMist studies and data
- Literature references

[17] Belshe R et al. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine.2010;28:2149-56.
[18] Reed C et al. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine. 2012;30:1993-8.

Paediatric data

The submission included paediatric efficacy/safety data.

Good clinical practice

As far as can be determined, all studies complied with Good Clinical Practice (GCP) guidelines.

Pharmacokinetics

Not applicable for vaccine studies.

Pharmacodynamics

Not applicable for vaccine studies.

Dosage selection for the pivotal studies

Each dose contained $10^{7.0 \pm 0.5}$ FFU of each of 4 cold adapted, attenuated, temperature sensitive, 6:2 reassortant influenza strains: A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), B of Victoria lineage, and B of Yamagata lineage. The 200 mL dose was given intranasally using the BD Accuspray device. This dose and the recommendations for timing of the vaccinations are identical to the registered product FluMist with the addition of the fourth strain of influenza.

Efficacy

Studies providing efficacy data

Two clinical studies, Study MI-CP208 (paediatric population) and Study MI-CP185 (adult population) were considered pivotal for the evaluation of efficacy; one further study, Study MI-CP206 (adult population) was considered supportive.

In addition, multiple other clinical study reports pertaining to FluMist (T/LAIV formulation) studies were available.

For details of these studies see Attachment 2.

Evaluator's conclusions on efficacy

In both the pivotal paediatric and adult studies, the primary study objective was met: Q/LAIV was demonstrated to be immunologically non-inferior to FluMist T/LAIV based on the pre-specified non-inferiority margin of 1.5 for the upper bound for each of the four 95% confidence intervals (CI) for the strain specific post dose GMT HAI antibody ratios (FluMist T/LAIV divided by Q/LAIV). In addition, analyses of GMFR ratios, which account for differences in baseline HAI antibody titres, support the conclusion of the non-inferiority of Q/LAIV. Overall, secondary immunogenicity outcomes supported the conclusions of the primary analysis as did analyses of NAI antibodies and neutralising antibodies in children 2 to 5 years of age. In addition, for both studies, Q/LAIV demonstrated higher immune responses to B strains that were not contained in the FluMist T/LAIV comparator arms. With regard to immunogenicity in children and adults, Q/LAIV is comparable to FluMist T/LAIV for the 3 strains recommended for inclusion in the trivalent vaccine and superior for the additional B strain. These results fulfilled the

pre-specified non-inferiority requirement that permits the bridging of the extensive FluMist T/LAIV clinical efficacy data to Q/LAIV.

Safety

Studies providing safety data

Studies MI-CP208 and MI-CP185 were pivotal studies that assessed safety as a primary outcome. Data for general adverse events (AE), including specified and non-specified AEs were collected. AEs of particular interest included fever, runny/stuffy nose, sore throat, cough, headache, generalised muscle aches, decreased activity level (lethargy) or tiredness/weakness, and decreased appetite.

The non-pivotal efficacy study (Study MI-CP206) is considered supportive of Q/LAIV safety for AEs and serious adverse events (SAE) only; however, solicited symptoms are presented for completeness.

Patient exposure

A total of 3,779 subjects received at least one dose of Q/LAIV in the 3 studies, including 1,382 children and adolescents in Study MI-CP208 and 1,198 and 1,199 adult subjects in Studies MI-CP185 and MI-CP206, respectively. Randomisation was not equal in these studies, with ratios of 3:2 and 2:1, Q/LAIV to All FluMist (the combined FluMist safety analysis group, in which data from each FluMist vaccine group were combined), in the paediatric and adult studies, respectively. The paediatric study, by design, was weighted towards enrolment of younger children who received two doses to enable a robust assessment of the safety of repeat dosing. Of subjects dosed with Q/LAIV in Study MI-CP208, 299 subjects 9 to 17 years of age received one dose of Q/LAIV; 1,041 subjects 2 to 8 years of age received two doses of Q/LAIV as per protocol, and 42 subjects 2 to 8 years of age received only one dose of Q/LAIV either because Dose 2 was not given or because they incorrectly received FluMist T/LAIV at Dose 2. The Safety Population, defined as subjects who received any dose and had any safety follow up, was numerically and demographically similar to the Intent-to-treat (ITT) Population and therefore appropriately represents the ITT population. Subjects were excluded from the safety population only for absence of dosing or absence of safety data. Follow up rates through each period of safety assessment were very high, and lack of follow up was balanced across treatment arms. There does not appear to be any bias in safety assessment due to loss of data, and the high extent of data capture in the study supports the validity of study data. The paediatric study provided over 98% confidence to detect an AE occurring at a rate of 0.3% (1 in 330); the 2 adult studies combined provided over 99% confidence to detect an AE occurring at a rate of 0.2% (1 in 500). All studies combined provided over 99% confidence to detect an AE occurring at a rate of 0.13% (1 in 770).

The safety populations for AEs across studies are summarised in Table 3, below.

Table 3. Safety populations for adverse events by study, as dosed

Study Dose Group	Q/LAIV N	All FluMist N
MI-CP208 (all subjects post Dose 1)	1,382	923
MI-CP208 (2-dose group post Dose 1)	1,083	719
MI-CP208 (2-dose group post Dose 2)	1,041	693
MI-CP185 (1 dose)	1,198	598
MI-CP206 (1 dose)	1,198	596
Pooled safety analysis in adults (1 dose)	2,396	1,194

All FluMist = data from both the FluMist-Y arm and the FluMist-V arm (both T/LAIV) combined; Q/LAIV = quadrivalent live attenuated influenza vaccine. The safety populations included subjects who received any investigational product and for whom any follow-up safety data were recorded. Subjects in Study MI-CP206 received Q/LAIV-BFS.

Post-marketing data

There was minimal post-marketing data for Q/LAIV at the time of this submission, although Q/LAIV is now being substituted into the post-marking trials currently being conducted for FluMist T/LAIV overseas. As part of a post-marketing commitment with the US FDA, the effectiveness of Q/LAIV was to be further evaluated in Study MA-VA-MEDI3250-1116, starting with the 2013 to 2014 Northern Hemisphere influenza season. This study is discussed in Section 7.2.2. of Attachment 2. There is also an observational post-marketing safety surveillance study of Q/LAIV in children 2 years through 8 years of age. The study is designed to evaluate rates of medically attended events of interest in a minimum of 10,000 FluMist Quadrivalent recipients, compared to three non-randomised comparison groups.

Evaluator's conclusions on safety

In the safety data submitted, rates of SAEs were low, particularly in children, and were balanced between Q/LAIV and FluMist T/LAIV groups in the 2 pivotal Q/LAIV studies: 0.4% and 0.5% for the Q/LAIV and All T/LAIV FluMist groups in paediatric Study MI-CP208, respectively, and 1.0% in the Q/LAIV and All T/LAIV FluMist groups for adult Study MI-CP185. There was no pattern of specific events that suggested an imbalance between treatment groups. For the supportive Study MI-CP206, more subjects who received Q/LAIV-BFS reported one or more SAEs (1.3%) than did subjects who received FluMist T/LAIV (0.3%); however, the rate in the FluMist T/LAIV group was unexpectedly low as compared to the All FluMist T/LAIV group in Study MI-CP185, and there was no pattern that suggested an imbalance for any particular SAE between the treatment groups. When SAEs in Studies MI-CP185 and MI-CP206 were assessed together in the pooled analysis of safety in subjects 18 to 49 years of age, SAE events were balanced between study arms.

Two SAEs, both in adults, were considered to be possibly related to study dosing. The first, hypersensitivity in an adult subject who received FluMist T/LAIV in Study MI-CP185, had an onset approximately 26 hours after dosing and consisted of throat tightening, dyspnoea, chest pain, and bronchospasm. No other attributable aetiology was identified. The second SAE considered initially by the investigator to be possibly related to study dosing was an event of spontaneous abortion in a Q/LAIV-BFS recipient who, by ultrasound performed a month after dosing, was calculated to have been pregnant at dosing although her pregnancy test had been negative. The temporal association led to the assessment of a possible relationship to Q/LAIV, but there is no overall pattern to suggest a causal relationship between Q/LAIV and spontaneous abortion. In children enrolled in Study MI-CP208 and adults enrolled in Studies MI-CP185 and MI-CP206, no new onset

chronic diseases (NOCD) were considered related to study dosing, and there was no pattern of NOCDs that suggested an association with Q/LAIV dosing.

The main goal of safety assessment within the Q/LAIV development program was to demonstrate that the addition of a fourth vaccine strain maintained the safety and tolerability profile of FluMist T/LAIV. Q/LAIV study data demonstrated that Q/LAIV was safe and well tolerated in children and adults who were healthy or who had stable chronic diseases at enrolment. Solicited symptoms were generally comparable in subjects who received either Q/LAIV or FluMist T/LAIV and were consistent with those observed in previous studies of FluMist (runny nose, sneezing). The solicited symptom that was significantly more commonly observed in children who received Q/LAIV than those who received FluMist T/LAIV was fever; however, overall rates of fever were low, fevers were generally mild and of short duration with comparable high grade fever (≥ 39.5°C) rates, no febrile seizures were observed, and no impact on the overall tolerability of Q/LAIV compared to FluMist T/LAIV is expected. AEs and SAEs were also comparable in Q/LAIV and FluMist T/LAIV recipients and were consistent with those expected to occur in subjects in this age group.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Q/LAIV in the proposed usage are:

- Use of a broadened vaccine to protect against 4 strains of influenza, includes two A strains, A/H1N1 and A/H3N2, and two B strains, one each from the B/Yamagata and B/Victoria lineages.
- The additional benefits of Q/LAIV as compared to FluMist T/LAIV are derived from the protective efficacy induced by including vaccine viruses from both influenza B lineages. Illness caused by influenza B is of public health importance, particularly in children and adolescents, improving protection against B strains should provide an overall public health benefit.
- These clinical studies demonstrated that the strain specific immune responses induced by Q/LAIV to all 4 strains contained in the vaccine were non-inferior to the immune responses generated by the 2 T/LAIV formulations.
- The tolerability and safety of Q/LAIV were comparable to those of FluMist T/LAIV.
- These data form the clinical bridge that is the basis of licensure application for Q/LAIV, and they suggest that the safety and protective efficacy data generated during the clinical development of FluMist T/LAIV to be applied to the new FluMist Quadrivalent formulation.
- The efficacy of FluMist T/LAIV has been demonstrated in multiple randomised, controlled studies conducted in children. In placebo controlled studies conducted in children, protection from culture confirmed influenza like illness caused by any matched strain has ranged from 72.9% to 93.4%. In TIV controlled studies, FluMist T/LAIV demonstrated a 34.7% to 52.7% reduction in influenza compared to TIV as measured by culture confirmed illness caused by wildtype strains antigenically similar to those contained in the vaccine, and a 31.9% to 54.9% reduction compared to TIV for all strains regardless of match.
- Q/LAIV (like FluMist T/LAIV) is likely to have enhanced acceptability because of the greater ease of administration that is associated with intranasal administration by sprayer rather than an injection (currently licensed influenza vaccines in Australia).

First round assessment of risks

The risks of Q/LAIV in the proposed usage are:

- The safety of Q/LAIV was compared to FluMist T/LAIV during the clinical development program. Due to the similarities between Q/LAIV and FluMist T/LAIV, the two safety signals associated with use of FluMist T/LAIV, medically significant wheezing in children < 24 months of age and an increased risk of hospitalisation in children 6 through 11 months of age, are both presumed to apply to Q/LAIV. Hence these children have not been studied and Q/LAIV is not licensed for children < 24 months.
- Rates of solicited symptoms were generally comparable between Q/LAIV and FluMist T/LAIV. Although the rates of fever were slightly increased after the first dose of Q/LAIV in children, the fevers were generally low grade and of brief duration with comparable high grade fever (≥ 39.5°C) rates. Because the overall rates of fever observed in both treatment arms were comparable to or lower than the fever rates previously described in children of this age following FluMist T/LAIV administration, this observation does not represent a new safety risk. There were no febrile convulsions reported.
- Other adverse event rates were also similar between Q/LAIV and FluMist T/LAIV groups in both adults and children, and the specific adverse events are consistent with those seen in previous FluMist T/LAIV studies.
- There were no deaths or new onset chronic diseases related to Q/LAIV.
- Overall, there were no unexpected safety signals observed for Q/LAIV but there is a need for post-marketing surveillance, to identify any new safety issues, particularly in young children, children with respiratory disease and immunocompromised children/adolescents (who were excluded from the current studies).
- A single SAE of spontaneous abortion was thought to be possibly related to Q/LAIV due to temporal association alone. Post-marketing studies of FluMist T/LAIV have not shown an increased risk of miscarriage.
- Potential additional risks associated with the use of Q/LAIV need to be (and are currently being) evaluated in post-marketing safety studies. These are currently being conducted in the US and in the EU and through routine pharmacovigilance activities.

First round assessment of benefit-risk balance

The benefit-risk balance of Q/LAIV, given the proposed usage, is favourable.

First Round Recommendation Regarding Authorisation

The clinical evaluator recommends approval of the submission. The only caveat would be that there needs to be ongoing attention to the post-marketing pharmacovigilance studies in relation to both efficacy and safety. In particular in children, because the safety data submitted in this application for the use of Q/LAIV in children is largely reliant on the similarity to the safety data for the use of FluMist T/LAIV in children (for which there is a great deal of data). There are a number of large post-marketing studies being conducted overseas for FluMist T/LAIV. It will be very important to continue to monitor this data when these studies switch to Q/LAIV.

Clinical Questions

The clinical evaluator had no clinical questions for the sponsor.

Second Round Evaluation of clinical data submitted in response to questions

The errors of fact and omissions notifications sent by the sponsor in response to the first round clinical evaluation report have been addressed in this second round report.

No questions were raised and no new information was submitted by the sponsor.

Second Round Benefit-Risk Assessment

No second round benefit assessment was conducted as no questions were raised and no new information was submitted by the sponsor.

At the request of the Delegate prior to the Advisory Committee on Prescription Medicines (ACPM) meeting (first round) the clinical evaluator assessed the data provided with respect to one versus two doses in previously unvaccinated children (refer the report provided in Attachment 2). This was discussed by the Delegate within the Delegate's Overview (see ''VI. Overall conclusion and risk/benefit assessment/Clinical'' below), and subsequently responded upon by the sponsor within their Pre ACPM response (see ''VI. Overall conclusion and risk/benefit assessment/Response (ACPM first round)'' below.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), EU-RMP Version 5.3 (dated 9 July 2014; Data lock point 16 December 2012) and Australian-specific annex (ASA) Version 1 (dated 15 June 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 4.

Table 4. Sponsor provided summary of ongoing safety concerns

Important identified risks	Medically significant wheezing in children under the age of 24 months Hypersensitivity (including anaphylaxis)
Important potential risks	Guillan-Barre Syndrome Bell's Palsy Secondary transmission to severely immunocompromised patients Inadvertent administration to immunocompromised patients Seizures and convulsions Encephalitis

	Neutritis Vasculitis Vaccination Failure (Lack of efficacy) Narcolepsy with or without cataplexy
Important missing information	There is limited information regarding safety of the drug product in the following populations: · Children under the age of 24 months · Elderly · Pregnant/lactating women · Severe asthmatics · Immunocompromised vaccine recipients · Individuals with chronic illness

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities for important identified and potential risks and missing information. The additional activities (from the submitted EU-RMP) are summarised below in Table 5.

Table 5. Routine and additional pharmacovigilance activities from the EU-RMP

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (planned or actual)
MI-MA194: A Postmarketing Observational Evaluation of the Safety of Fluenz in Children and Adolescents with High-risk Conditions (to include Q/LAIV following approval) Observational, 3	To investigate the safety of <Product> in high risk paediatric populations.	All cause Serious Adverse Events (SAEs), lower respiratory SAEs and other Medically Attended Events (MAEs) in patients receiving LAIV.	2013-2014 Influenza Season	First annual report submitted Oct2014
MA-VA-MEDI3250-1115 Postmarketing Safety Study of Q/LAIV in Subjects 2 Through 49 Years of Age (USA) Observational 3	To compare MAEs rates in patients receiving Q/LIAV, TIV or no vaccine	MAEs in patients receiving Q/LAIV	2013-2014 Influenza Season	First annual report submitted Jul2016
MA-VA-MEDI3250-1116 A Case Control Study of the Effectiveness of Q/LAIV Versus Inactivated Influenza Vaccine and No Vaccine in Subjects 2-17 Years of Age (USA) Case-Control, 3	To evaluate the effectiveness of Q/LAIV vaccination in children 2 through 17 years of age	Potential Risk: Lack of effect	2013-2014 Influenza Season	First annual report submitted Sep2014
D2560C00008: A Postmarketing Noninterventional Cohort Study of the Safety of Live Attenuated Influenza Virus (LAIV) in Subjects 2 through 17 Years of Age (UK) Observational, 3	To evaluate the safety of the product each season	Reactogenicity events in patients receiving LAIV	Planned to start 2014-2015 influenza season	Annually, within 30 days of data being collected in at least 100 subjects in each age group

SAE= Serious Adverse Event MAE= Medically Attended Event

Risk minimisation activities

Only routine risk minimisation activities are proposed for all safety concerns in Australia.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the major points from the first round evaluation of the RMP, the sponsor's responses to major issues raised by the RMP evaluator and the evaluation of the sponsor's responses to these major issues. Administrative and minor recommendations have not been included in Table 6.

At the request of the TGA, the sponsor provided an updated ASA (Version 2 – issued February 2016), EU-RMP (Version 7.0 – issued December 2015) and Periodic Safety Update Report (PSUR – through 16 December 2015). The updated EU-RMP and PSUR included updated annual surveillance data from the 2015-2016 seasons (ie Study MA-VA-MEDI3250-1115, Study MA-VA-MEDI3250-1116 and Study MI-MA-194).

Table 6. Reconciliation of major issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. The sponsor should provide a summary of long-term safety with this product, or in the absence of this add 'long-term safety' as a missing information item.	As outlined in the initial dossier (Clinical Summary), the safety and tolerability of the LAIV were evaluated in four pivotal Phase III studies in which the vaccine was given over two successive influenza seasons (AV006 Year 1, AV006 Year 2, D153-P501, D153-P502 and D153-P504). In addition, the safety and tolerability of the vaccine administered over four successive influenza seasons was evaluated in Studies AV012 and AV017. These data, in combination with the post-marketing safety surveillance data gathered for the vaccine since its initial approval in 2003 in the US, provide assurance regarding the long-term safety of the vaccine. AV006 Year 1: Study AV006 was a Phase III, prospective, randomised, double blind, placebo controlled, multicentre, 2 year study in subjects initially 15 to 71 months of age. Year 1 of the study was conducted at 10 sites in the USA during the 1996 to 1997 influenza season. A total of 1,602 subjects were enrolled and randomised 2:1 to receive frozen FluMist (N = 1,070) or placebo (N = 532). A slight increase in post vaccination solicited events, including runny nose/nasal congestion and mild fever, was noted in FluMist recipients. Abdominal pain (2% FluMist; 0.2% placebo) was the only AE that was statistically significantly increased in FluMist subjects. Of the 5 post-vaccination SAEs reported (4 FluMist; 1 placebo), none was considered to be vaccine-related. In summary, FluMist was safe, and well tolerated during the first year of the study. AV006 Year 2: Study AV006 was a Phase III, prospective, randomised, double blind, placebo controlled, multicentre, 2-year study in subjects initially 15 to 71 months of age recruited in Year 1 (initial year of dosing) and revaccinated in Year 2. Returning subjects remained in the same treatment group, FluMist (N = 917) or placebo (N = 441), to which they had been randomised in a 2:1 ratio in the prior year. The incidence of side effects was the same for both treatment groups (58%). There were no statistically significant differences between treatment groups for any individual solicited events or for solicited events overall. Two SAEs (1 FluMist subject; 1 placebo subject) were reported during the	This is considered acceptable in the context of this application.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	42 days following revaccination: neither was considered related to vaccine. In summary, the single revaccinating dose of FluMist administered in Year 2 to subjects who received 1 or 2 doses in Year 1 was generally safe, well tolerated. Study D153-P501: Study D153-P501 was a prospective, 2-year, randomised, double blind, placebo controlled Phase III study designed to evaluate the safety and efficacy of FluMist in subjects 12 to < 36 months of age. The study was conducted during the 2000 to 2001 and 2001 to 2002 influenza seasons in South, Southeast, and East Asia. In Year 1, 3,174 subjects were randomised at a 3:2 ratio to receive 2 doses of refrigerated FluMist or placebo separated by 28-56 days. In Year 2, 2,947 subjects were randomised again at a 1:1 ratio to receive a single dose of FluMist or placebo, irrespective of their treatment assignment in Year 1. The administration of multiple doses of FluMist to subjects 12 to < 36 months of age was safe and well tolerated. Study D153-P502: Study D153-P502 was a Phase III, prospective, 2-year, randomised, double blind, placebo controlled study to evaluate the safety and efficacy of FluMist in subjects 6 to < 36 months of age who attended day care. Two safety endpoints, solicited events and adverse events, were evaluated in FluMist recipients relative to placebo recipients. The study was conducted between October 2000 and May 2002 at multiple centres throughout Belgium, UK, Spain, Israel, and Finland. Prior to the first influenza season, a total of 1,784 subjects were randomised in a 3:2 ratio to receive 2 doses in Year 1, and a single dose in Year 2 of either FluMist or placebo. In Year 2, subjects received the same treatment they had received in the first year. In both years of the study the safety and tolerability of FluMist were similar to that of placebo. Study D153-P504: this was a Phase III prospective, 2-year, randomised, double blind, placebo controlled study to evaluate the safety, immunogenicity and efficacy of FluMist in subjects 6 to < 36 months of age. The study was conducted during the 2001 and 2002 influenza seasons in South Africa, Brazil, and Argentina. In Year 1, 3,200 subjects were randomised to a primary series of either 1 or 2 doses of FluMist, or 2 doses of either excipient placebo or saline placebo. In Year 2, 2,202 subjects continued and received 1 dose of vaccine or saline placebo. In both years of the study the safety and tolerability of FluMist was similar to that of placebo.	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	Study AV012: this was a 4 year, community based, nonrandomised, open label study designed to evaluate the safety and herd immunity of frozen FluMist in subjects 18 months to 18 years of age. The primary objective of this study was to assess the total effectiveness of immunisation of preschool and school aged children with FluMist in the vaccinated subjects as compared to unvaccinated children in each control community with adjustments for potential covariates. Assessment of safety was a secondary objective and included: (a) frequency of SAEs within 42 days of vaccination; (b) occurrence of medically attended acute respiratory illness (MAARI) events in the first 14 and 42 days following vaccination compared to time periods before and after vaccination; and (c) a database search for rare and less common AEs possibly related to influenza. The study enrolled a total of 18,780 subjects over 4 years, of whom 848 were enrolled throughout the duration of the study. Subjects with intermittent wheezing (Wheezing Subset) who received FluMist had no increased risk of MAARIs, including asthma exacerbation. In addition, there was no increased risk of new-onset asthma in the 11,475 subjects without a history of wheezing. None of the 41 SAEs that occurred over 4 years were judged to be vaccine related by the investigators. In summary, this study demonstrated the safety of a single primary dose and up to 3 annual revaccination doses of FluMist in subjects 18 months to 18 years of age, as well as in subjects with a history of intermittent wheezing. In addition, FluMist was not associated with increased risk for MAARIs, including acute asthma exacerbation. Study AV017: this was a prospective, multicentre study in subjects ≥ 1 to < 10 years of age to assess the safety, tolerability, and immunogenicity of annual vaccination with FluMist. AV017 was conducted during the 1999 influenza season at 10 sites in the US and was the fourth in a sequence of consecutive annual studies of frozen FluMist. Of the prior 3 studies (AV006 Year 1, AV006 Year 2, and AV015), only participation in AV006 Year 1 was mandatory for enrolment. The populations evaluated in AV017 were first through fourth-year vaccines, previously unvaccinated subjects similar in age to the prior AV006 subjects (new similar aged cohort) who were randomised 2:1 under blinded conditions to receive a 2-dose regimen of FluMist or placebo, and previously unvaccinated siblings of prior participants of Study AV006 (Non-randomised Siblings group). A total of 1,245 subjects were	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	enrolled in Study AV017; 918 had been subjects in Year 1 of AV006, 217 were randomised in the new similar-aged cohort, and 110 were members of the non-randomised siblings group. The frequency of solicited events in subjects receiving a fourth-year revaccination was lower than that following the first dose in the initial year of vaccination (73%) as well as following Dose 1 in vaccine recipients of the new similar-aged cohort (66%). In subjects receiving FluMist across all 4 years, the frequency of any other AE decreased with each consecutive year (18.6%, 14.6%, 14.4%, and 11.8% for first through fourth years, respectively). In summary, the results of Study AV017 showed that FluMist was safe and well tolerated in subjects ≥ 1 to 10 years of age following up to 4 consecutive annual vaccinations.	
2. The sponsor should provide a summary of the post-market experience with regard to seizures.	Please refer to the most recent post-marketing safety update report (PSUR), with data through 16 December 2015, for summaries of interval and cumulative seizure reports. These reports do not affect the sponsor's overall assessment of seizures as an important potential risk. Please refer to Recommendation 8 below, for additional details.	The sponsor's response has been noted.
3. The sponsor should provide a summary of the experience with patients with variations in nasal anatomy that may affect use of this product, or in the absence of this add this issue as a missing information item.	The sponsor is not aware of any information about effects of nasal anatomic variations on safety or efficacy for FluMist Quadrivalent. However, given the relative infrequency of these variations and the fact that subjects with variations in nasal anatomy were not specifically excluded from the clinical development of the vaccine, the sponsor does not consider that this issue rises to a level where it should be classified as missing information.	The sponsor's response has been noted.
4. The sponsor should outline how the sponsor plans to measure the occurrence of off-label use for this product.	The sponsor will continue to monitor off-label use of FluMist Quadrivalent through routine pharmacovigilance.	Routine pharmacovigilance is not sufficient. The sponsor should propose a drug utilisation study that uses primary care data to analyse the extent of off-label use.
5. The sponsor should provide a summary of the	Please refer to the most recent PSUR, with data through 16 December 2015 (Plunger rod defect) for a discussion of the FluMist Quadrivalent sprayer's	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
post-market experience with device failure and its effects (for example, underdosing).	plunger rod issues. In previous seasons, device issues have included reports of sprayer barrels breaking and of water droplets appearing at the sprayer tips. Both issues have been resolved, and neither of these nor the recent plunger rod issues have had any effect on dosing. Briefly, as of 16 December 15, a total of 48 complaints impacting 73 units have been reported by customers regarding malfunctions with the plunger rod assembly backing out, displacement, or loose in sprayer barrel. While no trend for an increase was noted for the 10 pack presentation an increase was noted in the single-unit dose presentation used in Germany. There were no reports of serious or non-serious AEs associated with these product complaints. As the vaccine is administered to the nose, which is a non-sterile area of the body, there is minimal possibility for a potential signal event for a non-sterile administration of vaccine in this location. Corrective actions have been generated to address the identified potential root causes for this issue and, as outlined in the most recent PSUR, no further risk minimisation measures were deemed necessary.	
6. The sponsor should provide a summary of the post-market experience with transmission of infections agents, in particular where vaccination of a patient has led to disease in a contact.	Please refer to the most recent PSUR, with data through 16 December 2015, for discussion of interval and cumulative reports of secondary transmission to severely immunocompromised patients. None of 3 non-serious spontaneous reports of potential secondary transmission to severely immunocompromised patients described any actual adverse event. In addition, a clinical study (D145-P500) conducted to evaluate the potential for transmission of vaccine virus from FluMist recipients to unvaccinated controls identified only a single confirmed case of vaccine strain transmission; this subject experienced symptoms consistent with FluMist administration. Study D145-P500 was a randomised, double-blind, placebo controlled study in subjects ≥ 8 to < 36 months of age.[19] The primary objective was to determine the rate of transmission of virus from subjects vaccinated with FluMist to subjects vaccinated with placebo in a day care setting. Eligible subjects were in a day care contact group consisting of ≥ 4 subjects, at least 1 of whom was vaccinated with FluMist, for at least 4 hours per day over at least 3 days per week. The study was conducted in young children (who are known to shed FluMist at the	The sponsor's response has been noted.

[19] Vesikari T et al. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics. 2006 Dec;118(6):2298-312.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	highest titres) and in a day-care setting where children have frequent contact, in order to maximise the potential for potential transmission events. One hundred ninety-seven subjects were randomised at a 1:1 ratio to receive FluMist (98 subjects) or placebo (99 subjects). A 19 month old child shed vaccine virus for one day in the only confirmed case of transmission of a vaccine virus strain (type B) to a placebo vaccine recipient; no increased reactogenicity or other safety concerns were noted for this child.	
7. With regard to the requested additional risk minimisation activities, the sponsor should provide the TGA with the following details for agreement: All draft Australian education materials; A clear distribution plan for Australia; and A clear plan to measure the effectiveness of the education program as an additional risk minimisation activity.	The sponsor acknowledges this recommendation. The sponsor will liaise with the TGA to prepare materials which meet the final PI proposals as agreed with the TGA closer to launch.	The sponsor's response has been noted. It is noted that the updated version of the ASA has no reference to the additional risk minimisation activities. This is not considered acceptable. The sponsor should provide an updated ASA that contains a description of the additional activities prior to approval. A Dear Healthcare Professional Letter may be an acceptable activity.
8. In the 'Precautions' section, a statement on the known information with regard to febrile seizures should be provided.	As noted above (response to Recommendation 2), the most recent PSUR, with data through 16 December 2015 provides summaries of interval and cumulative seizure reports. Adults had no seizures in the controlled trials. Among children 2 to 17 years of age in randomised, controlled trials, the incidence of febrile seizures (through Day 180) was 0.12% in FluMist subjects versus 0.13% in placebo subjects, and in active controlled studies, 0.05% in FluMist versus 0.10% in active comparator subjects. The incidence was also balanced for shorter latency periods. These data showing lower rates of febrile seizures in recipients of FluMist than recipients of placebo or inactive influenza vaccine, together with the paucity of post-marketing reports for febrile	This is considered acceptable for RMP purposes in the context of this application pending the decision by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	seizures (5 of 63 seizure reports from all sources), strongly suggest that FluMist Quadrivalent will not be associated with an increased risk for febrile seizures. No labelling for this or other LAIV products (FluMist/Fluenz or FluMist Quadrivalent/Fluenz Tetra) contains any language about febrile seizures. The sponsor recommends not adding such language to the labelling for FluMist Quadrivalent in Australia.	
9. In the 'Contraindications' section, the PI should contain 'patients younger than 18 years of age receiving salicylate therapy' as a contraindication (as indicated in the RMP).	The EU-RMP originally submitted contained a table that was incorrectly titled and referring to 'contraindicated' patient populations. This table title has since then been corrected and provides information on patient populations that have been excluded from clinical trials. No cases of Reye's Syndrome associated with LAIV use have been reported since initial approval of the vaccine in 2003, and the risk of a LAIV recipient developing the syndrome is a theoretical one based on the association with wild-type influenza. Based on this, and on the demonstrated benefits of vaccination with LAIV, the sponsor believes it appropriate that this patient population be listed under 'Precautions' as opposed to the 'Contraindications' section of the PI.	The recommendation is based on best practice recommendations.[20] Furthermore, it is noted that the FDA label contains this as a contraindication as well. The recommendation remains and is referred to the Delegate for decision: In the contraindications section, the PI should contain 'patients younger than 18 years of age receiving salicylate therapy' as a contraindication.
10. In the 'Contraindications' section, the PI should contain 'patients with clinical immune-deficiency' (with examples) as a contraindication (as indicated in the RMP)	The EU-RMP originally submitted contained a Table that was incorrectly titled and referring to 'contraindicated' patient populations. This table title has since then been corrected, providing information on patient populations that have been excluded from clinical trials. Therefore, FluMist Quadrivalent is not contraindicated for 'patients with clinical immunodeficiency.' Subjects who were immunosuppressed, whether due to a medical condition or to drug treatment, were generally excluded from LAIV studies; however, 6 studies specifically examined the safety of the vaccine in immunocompromised subjects (Studies MI-CP114, DMID 99-012, DMID 98-005, PACTG 1057 FLU040-09 and MI-MA175; these studies did not	The sponsor's response has been noted. The presented studies have been noted. Most of the studies presented only contain mildly immunocompromised subjects, and the retrospective cohort study appears to have sample sizes too small to detect relevant signals.

[20] Grohskopf L et al., RA 2015. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunisation Practices, United States, 2015-16 Influenza Season. MMWR Morb Mortal Wkly Rep 64(30):818.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	indicate an increased safety risk in these subjects and, as a result, the sponsor does not believe that this patient population should be included in the 'Contraindications' section of the PI. Study MI-CP114 was a Phase I, randomised, double blind study in mildly to moderately immunocompromised children 5 through 17 years of age with cancer. The primary objective was to assess the safety of FluMist compared to placebo. The secondary objectives were to describe the immune response and determine the incidence and duration of viral replication following vaccination with FluMist. Overall, FluMist was well tolerated in this population, and its safety profile is comparable to that seen in the general population. In summary, administration of a single dose of FluMist in mild and moderately immunocompromised children 5 to 17 year of age with solid tumours and haematological malignancies was generally safe and well tolerated. Study DMID 99-012 was a randomised, double blind, placebo controlled, crossover study in subjects 1 to 7 years of age who had either asymptomatic or mildly symptomatic human immunodeficiency virus (HIV) disease or were not HIV-infected.[21] The primary objective was to evaluate the safety of FluMist in the HIV-infected subjects compared with subjects of similar age who were not infected with HIV. Secondary objectives included evaluating immunogenicity and vaccine virus shedding in all subjects and assessing the effects of FluMist on laboratory measures of disease status (HIV RNA levels and CD4+ T-cell counts) in the HIV-infected subjects. FluMist was generally safe and well tolerated when given to subjects 1 to 7 years of age with asymptomatic or mildly symptomatic HIV infection. FluMist induced comparable immune responses to all 3 constituent strains in HIV-infected subjects and HIV-negative subjects. Study DMID 98-005 was a prospective, randomised, double blind, placebo controlled study in subjects 18 to 50 years of age who either had asymptomatic or mildly symptomatic HIV disease (CDC class A1-2) or were not HIV infected.[22] The primary objective of this study was to evaluate the SE profile of FluMist	Given the theoretical risk of a live vaccine causing disease/adverse events in patients with clinical immunodeficiency while a safer, alternative vaccine is available, this should remain as a contraindication. The recommendation remains and is referred to the Delegate for decision: In the Contraindications section, the PI should contain 'patients with clinical immunodeficiency' (with examples). Furthermore, it is noted that the EU SmPC contains this as a contraindication as well.

[21] King J et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. Pediatr Infect Dis J. 2001 Dec;20(12):1124-31.
[22] King et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. J Infect Dis. 2000 Feb;181(2):725-8.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	compared to placebo in HIV-infected subjects. Secondary objectives were to evaluate immunogenicity and vaccine virus shedding in all subjects and to assess the effects of FluMist on laboratory measures of disease status (blood HIV RNA values and CD4+ T-cell counts) in the HIV-infected subjects. FluMist was safe and well tolerated when given to subjects with asymptomatic or mildly symptomatic HIV disease (CDC class A1 to 2). Except for runny nose/nasal congestion, the SE profile of FluMist compared to placebo was similar for the HIV-infected subjects and the HIV-negative subjects. The results suggest that inadvertent administration of FluMist to individuals with undiagnosed HIV infection would not be harmful. Study PACTG 1057, was a randomised, open label, TIV controlled study in human immunodeficiency virus (HIV)-infected subjects, ≥ 5 to < 18 years of age.[23,24,25] The primary objectives were to compare the safety and immunogenicity of FluMist with those of TIV and to determine the incidence and duration of vaccine virus shedding in HIV infected subjects vaccinated with FluMist. The safety profiles were similar between the FluMist and TIV treatment groups. FluMist had no effect on markers of HIV progression. Shedding of vaccine virus was uncommon, of short duration, and titres were 100 to 10,000 times lower than the administered dose. Study MI-MA175 was a retrospective, descriptive cohort study of children included in a large US medical insurance claims database (Thomson Reuters MarketScan with data from approximately 17 million individuals per year within the USA) conducted as part of a post-marketing commitment to evaluate the effectiveness of a risk minimisation action plan (RiskMAP) to help prevent FluMist use in populations for whom the vaccine is not intended.[26] The objectives of the study were to evaluate the rate of FluMist use in pediatric populations less than 24 months of age, 24 to 59 months of age with asthma or recurrent wheezing, and 24 to 59 months of age with immunocompromised (the majority were	

[23] Levin M et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine. 2008;26:4210–4217.
[24] Weinberg A et al. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. J Acquir Immune Defic Syndr. 2010;55:189–196.
[25] Weinberg A et al. T cell responses of HIVinfected children after administration of inactivated or live attenuated influenza vaccines. AIDS Res Hum Retroviruses. 2010;26:51–59.
[26] Tennis P, et al. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine 2011;29:4947– 4952.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	receiving corticosteroids; others were receiving chemotherapy or had congenital immune deficiency); to describe in these 3 paediatric populations who receive FluMist the type and frequency of all events and events of special interest associated with an insurance claim within 42 days of receiving FluMist in the emergency department or hospital setting. The incidence of safety events was compared between children immunised with FluMist and those immunised with TIV. FluMist use was monitored from August through February for 3 influenza vaccination seasons, starting in the 2007 to 2008 season. There were no safety signals observed in these children but sample sizes were small (138, 537, and 775 children identified in years 1, 2 and 3, respectively) as was dosing in immunocompromised children (12, 89 and 361 children, respectively). There were no safety concerns identified in the few emergency department visits or hospitalisations that occurred in these subjects. Study FLU040-09 was an investigator-initiated study to evaluate the safety of viral shedding and immune responses to FluMist in children with cancer as well as viral shedding after dosing (Carr et al, 2011).[27] Children with cancer, 2 to 21 years of age, were randomised to LAIV (N = 28) or TIV (N = 27). Both vaccines were well tolerated, and reactogenicity events were similar in both groups; all were grade 1 and 2. Rhinorrhoea reported within 10 days of vaccination was similar in both groups (36% LAIV versus 33% TIV). One SAE of pneumonia was considered possibly related to LAIV; however, the clinical impression was probable fungal pneumonia. Ten LAIV recipients shed virus; the latest viral shedding was detected 7 days after vaccination. In summary, both vaccines were well tolerated, and prolonged viral shedding after LAIV was not detected. Overall, these data demonstrated that the safety profile of FluMist in subjects with mildly to moderately compromised immune function was similar to that in healthy individuals and prolonged shedding of vaccine virus was not detected.	
11. In the 'Contraindications' section, the PI should contain 'patients with	The EU-RMP originally submitted in the submission contained a Table that was incorrectly titled and referring to 'contraindicated' patient populations. This table title has since then been corrected, providing information on patient populations that	The sponsor's response has been noted. The presented studies have been noted.

[27] Carr S et al. Safety and Immunogenicity of Live Attenuated and Inactivated Influenza Vaccines in Children With Cancer. J Infect Dis (2011) 204 (10): 1475-1482.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
severe asthma and wheezing as a contraindication (as indicated in the RMP).	have been excluded from clinical trials. Therefore, FluMist Quadrivalent is not contraindicated for 'patients with severe asthma and active wheezing.' Limited data exist regarding administration of LAIV to patients with severe asthma and active wheezing, however, the sponsor does not believe that these patients should be listed in the 'Contraindication' section of the PI as data from Study AV010 do not indicate that there is an increased safety risk in subjects with moderate to severe asthma. In addition, the results of Study D153-P515 A demonstrated that the LAIV was more efficacious than the inactivated vaccine in children with asthma. Study AV010 was a prospective, randomised, double blind, placebo controlled, multicentre study designed to assess the safety and tolerability of FluMist in subjects 9 to 17 years old who had a history of moderate to severe asthma.[28] Subjects were randomised 1:1 to receive a single dose of FluMist (N = 24) or placebo (N = 24). There was no indication that administration of FluMist reduced pulmonary function in subjects 9 to 17 years old with moderate to severe asthma, and the clinical features of asthma did not appear to worsen in subjects who received FluMist. Study D153-P515 was a Phase III prospective, randomised, open label study to evaluate the efficacy, safety, and tolerability of FluMist in subjects 6 to 17 years of age with stable, medically-treated asthma. The study was conducted in 12 European countries and Israel, before and during the 2002-2003 influenza season. A total of 2,229 subjects were randomised at a 1:1 ratio to receive a single dose of either FluMist (N = 1,114) or TIV (N = 1,115); 2,226 subjects received treatment as randomised; and 2,211 subjects (FluMist, 1,109; TIV, 1,102) were evaluable per protocol. Results demonstrated statistically superior relative efficacy of FluMist compared to TIV against community-acquired influenza illness, whether caused by matched strains (34.7% superior efficacy) or all strains regardless of match (31.9% superior efficacy). The incidence of first episode of asthma exacerbation after vaccination was similar for FluMist and TIV recipients (31.2% versus 29.6%, respectively). Rates of first episode of hospitalisation for asthma were 0.7% in both groups. In summary, FluMist demonstrated superior relative efficacy against community-acquired influenza compared to TIV,	The sample size of the double-blind study was too small to make meaningful conclusions with regard to incidence of asthma exacerbations. The other study presented by the sponsor was open-label. LAIVs have been associated with asthma exacerbations and current best-practice recommendations advise against use of LAIVs in patients with asthma[1]. For RMP purposes it is not necessary to retain this as a contraindication. However, the information should be provided in the 'Precautions' section: In the 'Precautions' section, the PI should contain a statement that patients with wheezing or asthma in the last 12 months should not be given this vaccine.

[28] Redding G et al. Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2002 Jan;21(1):44-8.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	with no associated increase in post vaccination asthma exacerbation rates in subjects 6 to 17 years of age with asthma.	
12. In the 'Contraindications' section, the PI should contain 'pregnant women and women that may be pregnant' as a contraindication.	The EU-RMP originally submitted contained a Table that was incorrectly titled and referring to 'contraindicated' patient populations. This table title has since then been corrected providing information on patient populations that have been excluded from clinical trials. Therefore, FluMist Quadrivalent is not contraindicated for 'pregnant women and women that may become pregnant.'	Current best-practice recommendations advise against use of LAIVs in pregnant women.[20] For RMP purposes it is not necessary to retain this as a contraindication. However, the information should be provided in the 'Precautions' section: In the 'Precautions' section, the PI should contain a statement that pregnant women should not be given this vaccine.
13. In the 'Contraindications' section, the PI should contain 'patients with close contacts that are immunosuppressed and require a protected environment' as a contraindication.	There is a limited amount of data in this patient population. However, as outlined above in response to Recommendation 18, the frequency and duration of vaccine virus shedding in mildly to moderately immunosuppressed patients were comparable to that seen in healthy children and adolescents and no specific safety signals were identified. There is currently information contained within the 'Precautions' section of the PI and in the CMI warning of the potential transmission to immunocompromised contacts. A recommendation is made that vaccine recipients attempt to avoid close association with severely immunocompromised individuals (for example, bone marrow transplant recipients requiring isolation) for 1 to 2 weeks following vaccination. The sponsor does not believe there is sufficient data to warrant a contraindication, and therefore recommends the information remain as currently proposed.	This is considered acceptable for RMP purposes in the context of this application pending the decision by the Delegate.
14. In the 'Interactions with other medicines' section, the PI should include a	The sponsor has evaluated concomitant administration of MMR and FluMist in two studies: Studies AV018 and D153-P522. Study AV018 was a randomised, placebo controlled,	This is considered acceptable for RMP purposes in the context of this application pending

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
statement on the immune response when concomitantly administered with the rubella vaccine.	multicentre study to evaluate the safety, tolerability, and immunogenicity of concurrent administration of FluMist with the MMR-II and varicella vaccine (Varivax) in subjects 12 to 15 months old. A total of 1251 subjects were randomised. Study AV018 demonstrated that concurrent administration of FluMist with MMR II and Varivax vaccines provided equivalent immunogenicity compared with separate administration. Study D153-P522 was a randomised, double blind, placebo controlled, multinational study in subjects 11 to < 24 months of age. The primary objective was to determine if concomitant administration of FluMist with the mumps, measles, and rubella (MMR) vaccine interfered with immune responses to measles, mumps, or rubella. A total of 1,233 subjects were randomised accordingly; 819 subjects in the FluMist plus MMR group and 414 subjects in the placebo plus MMR group. While Study D153-P522 did not meet its pre-defined non-inferiority seroconversion end point for rubella, when using an internationally accepted criterion for rubella seropositivity (10 IU/ml) the non-inferiority criterion for rubella was met. Although the EU SmPC states that there is an altered immune response for rubella (based on Study D153-P522), it also states that 'this alteration might not be of clinical relevance, with the two dose immunisation schedule of the rubella vaccine.' Because results of both studies show no clinically significant interaction, the sponsor considers that the Interactions with other medicines' section of the PI does not require any additional text included regarding interference with the immune response to the rubella component of measles, mumps, rubella vaccine.	the decision by the Delegate.
15. In the 'Dosage and Administration' section, the PI should include a statement that administration should occur by a health care practitioner in an appropriate setting with an appropriate post-vaccination observation	A statement that administration should occur by a healthcare practitioner in an appropriate setting will be considered for inclusion within relevant section(s) of the PI during the pre-ACPM response. Please note that additional instructions regarding administration setting and appropriate supervision satisfy the above request and are included with the proposed PI 'Precautions/Management of acute allergic reactions' section as follows: 'As with all vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of vaccine.'	This is considered acceptable for RMP purposes in the context of this application pending the decision by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
period.		

Summary of major recommendations

- The sponsor should propose a drug utilisation study (DUS) that uses primary care data to analyse the extent of off-label use.

  [Post RMP evaluation note: The sponsor provided a formal response to the RMP evaluation including the difficulties faced in designing feasible DUS to detect off label use. Alternative PV measures were proposed by the sponsor, and subsequently assessed by the RMP evaluator. The RMP evaluator acknowledged the difficulties in designing a DUS to detect off label use and proposed further alternative solutions. The RMP evaluator stated that the ASA should detail these with a commitment to work with the TGA to develop mutually acceptable approach o pharmacovigilance of off-label which will need to be agreed upon and implemented prior to supply. Subsequently the sponsor provided an updated ASA detailing a mutually acceptable approach to the PV of off-label use]

It is preferable for the educational materials to be available before approval. It is noted that the updated version of the ASA has no reference to the additional risk minimisation activities. This is not considered acceptable. The sponsor should provide an updated ASA that contains a description of the additional activities prior to approval.

Both the spray label and the carton should contain the age range for which FluMist Quadrivalent is approved to accommodate concerns raised by the Advisory Committee on the Safety of Vaccines (ACSOV) – see below.

Advice from the Advisory Committee on the Safety of Vaccines (ACSOV)

The RMP evaluator had the following questions for which ASCOV provided advice:

1. *Can the committee comment on the need for additional risk minimisation activities, namely educational materials to inform healthcare practitioners about the indications, contraindications and safety concerns associated with LAIVs, such as FluMist Quadrivalent?*

The committee advised that additional risk minimisation activities should be undertaken and that extra educational materials are warranted.

Prescriber education needs to address the differences between this vaccine and available inactivated influenza virus vaccines (IIV) in regard to indications, contraindications and safety profile. For example, prescribers need to be informed that severe asthma is named in the Precaution section of the proposed PI, whereas this chronic disease is not named in the Precaution section of the PIs for Quadrivalent IIVs. The committee encouraged the TGA to review educational material in this context.

The committee further commented that there are public health risks when both vaccine recipients and health practitioners refer to and understand 'influenza vaccine' as a generic term for a homogenous class, when this is not the case.

Supply under a targeted program, such as a NIP, would be a risk minimisation activity in itself for this vaccine. The UK experience has shown that use of LAIV in school-aged children has low risk, and benefit to the children and broader population.

The ACSOV supported in principle the inclusion of evidence-based Contraindications and Precautions in PIs. The committee advised that:

- the Contraindications section of the proposed PI should include patients younger than 18 years of age receiving salicylate therapy. This contraindication reflects that Reye's syndrome has been reported following the use of salicylates during wildtype influenza infection.
- the Precaution section of the proposed PI includes 'altered immunocompetence'. However, inclusion of this precaution in the PI will be insufficient to protect severely immunosuppressed people (that is, non-recipients of the vaccine) and educational material for healthcare practitioners at the introduction of the vaccine to the market and/or the NIP will need to reiterate this point. The committee agreed that secondary transmission to severely immunocompromised patients is an important potential risk, as it has not been observed to date.

The committee suggested that it would be useful to compare 'Contraindications' and 'Precautions' for the vaccine in the US, UK and Canadian markets to those proposed for Australia. The committee commented that differences in public health programs for distributing vaccines can influence whether an event (such as a recent asthma episode) is treated as a 'Contraindication' or 'Precaution'.

As the vaccine does not require injection, it is likely to be popular with patients and be sought by patients who have not previously received an influenza vaccine and by multi-age family groups with members inside and outside of the age range specified in the vaccine's indications.

Educational materials should address these situations.

The committee commented that the primary packaging could provide information on the patient groups for whom the vaccine is indicated/not indicated; as this packaging is the last point where the provider can confirm that an appropriate 'influenza vaccine' has been selected prior to administration.

2. *Can the committee comment on the need to conduct additional pharmacovigilance activities, in particular an activity designed to investigate and evaluate the likely degree of off-label use of FluMist Quadrivalent?*

The committee commented on areas of off-label use.

- Infants and young children under 24 months of age: The predominant risk of off-label use will be Wheeze in patients aged 6 to 24 months, especially infants under 12 months of age. Bergen et al observed a significantly increased relative risk of reactive airway disease in children 18 to 35 months of age administered this vaccine (relative risk 4.06; 90% CI: 1.29, 17.86).[29] Belshe et al, studied recipients of this vaccine (under another tradename) aged under 24 months, from the time of first vaccination to 42 days post last vaccination.[30] The rate of wheezing was statistically significantly higher in children receiving the T/LAIV (5.9%) compared to a trivalent IIV (3.8%). The committee noted that wheeze is not included in the relevant table of the proposed PI.
- Adults over 18 years of age: the committee noted that elderly patients had been excluded from clinical trials due to the potential lack of efficacy in this population.
- Patients with contraindications (for example patients receiving salicylate therapy, or with clinical immunodeficiency, severe asthma or wheezing; teenagers who are

[29] Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J 2004;23:138-44
[30] Belshe R et al. Live attenuated versus inactivated Influenza vaccine in infants and young children. N Engl J Med 2007;356:685-96.

pregnant or may be pregnant; patients with close contacts who are immunosuppressed and require a protected environment).

Routine AEs following immunisation surveillance will be in place. However, such passive surveillance may not detect what may be common events in groups for whom the vaccine is not indicated, for example, wheeze in children under 24 months of age or influenza-like illness in the elderly, unless of sufficient severity to require hospitalisation. Therefore, additional pharmacovigilance activities on off-label use in infants and young children under 24 months of age, and in the elderly, to capture and interpret signals of wheeze or hospitalisation would be appropriate.

The additional pharmacovigilance activities should suit supply under both NIP and in the private market.

The committee noted that annual influenza vaccination is not yet captured in the Australian Childhood Immunisation Register (ACIR) and it is unclear if the Australian Immunisation Register will record relevant demographic information at the time of each immunisation (for example if pregnant or breast-feeding). [31]

Ideally, population-based studies using data linkages from immunisation registers should be undertaken to establish the prevalence of off-label use. Until such studies can be undertaken, extraction of data from primary care prescribing software or other post market surveillance data sets would be useful, as long as the various quadrivalent vaccines are differentiated in these databases.

The committee agreed that available final or interim data from pharmacovigilance studies and post market experience mentioned in the RMP should be provided to the TGA.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- *Implement EU-RMP Version 7.0 (dated 2 December 2015, DLP 26 October 2015) and Australian-specific annex (ASA) Version TBC (date TBC) [new version needs to make reference to additional risk minimisation activities], and future updates where TGA approved, as a condition of registration.*
- *Provide and implement Additional Risk Minimisation Activities, where approved by the TGA Pharmacovigilance and Special Access Branch (PSAB) at least 3 months prior to supply, as a condition of registration.*

[If the requested drug utilisation study is not included *[see post RMP evaluation note above]* in an updated ASA, additional wording with regard to it should be inserted:

> *Conduct a drug utilisation study to assess off-label use to the satisfaction of the TGA Pharmacovigilance and Special Access Branch (PSAB), as a condition of registration.]*

[31] The Australian Childhood Immunisation Register (ACIR) is a national register administered by the Department or Human Services that records details of vaccinations given to children and young individuals under 20 years of age who live in Australia. From September 2016, the ACIR will expand to become the Australian Immunisation Register (AIR) to capture all vaccines administered throughout a person's life (birth to death), given through general practice and community clinics. This will include all vaccines funded under the NIP as well as private vaccines given through general practice.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The administrative, product usage, chemical, pharmaceutical, microbiological data for this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

All sterility, endotoxin and drug product container safety issues have been resolved.

The quality evaluator's recommendations on outstanding quality issues at the time and the subsequent sponsor's response have been covered within the Quality section above.

Nonclinical

The evaluator concluded that the non-clinical data provided were satisfactory and that there were no non-clinical objections to registration. No questions were raised in the first round report, with the exception of proposed changes to the PI, hence there was no second round non-clinical report.

Published data indicated that multiple gene segments are responsible for vaccine virus attenuation, and the attenuated strains are genetically stable in animals and humans. Adequate acute and repeat dose toxicity studies with Q/LAIV and T/LAIV vaccines did not reveal any serious vaccine-related toxicity. Adequate reproductive and developmental toxicity studies in rats and ferrets with Q/LAIV and the T/LAIV revealed no vaccine related toxicity. An Australian Pregnancy Category of B1 was deemed acceptable.[12]

The environmental safety of the vaccine was evaluated by the OGTR, with the 'Dealings involving Intentional Release' (DIR) licence granted to the sponsor for commercial supply of attenuated genetically modified (GM) influenza vaccines which covers FluMist Quadrivalent.[32]

Clinical

Clinical Pharmacology

Information in regards to clinical pharmacology was not included in the clinical evaluation, noting that conventional clinical pharmacokinetic studies are not applicable to live vaccines. The EMA's European Public Assessment Report (EPAR) states that local deposition and distribution studies have been performed in humans.[33] FluMist Quadrivalent is formulated with a refrigerated vehicle and administered intranasally with the BD Accuspray delivery device. The same vehicle and the same delivery device were tested in Study PPL-1014, a randomised, open label, 2-way crossover study in 21 adults, which was previously submitted as part of the marketing authorisation application for Fluenz (FluMist, T/LAIV formulation). Intranasal delivery of 0.2 mL refrigerated vehicle resulted in the deposition of a larger percentage of the total dose delivered in the nasal cavity, 76% on average, relative to delivery of the 0.5 mL frozen vehicle. The majority of the remaining portion of the 0.2 mL dose was deposited in the nasopharynx (8%). It was

[32] DIR 137, issued 14 January 2016.
[33] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), EMA/586629/2013. Assessment report. Fluenz Tetra. 19 September 2013

concluded that the radio-labelled vehicle was mainly deposited in the nasal cavity of human adults with little or no measurable deposition in the lower airways and lungs. This is also consistent with the relatively large droplet device of the spray material. It is expected that the Fluenz Tetra (FluMist Quadrivalent) distribution pattern would be similar, given the common delivery device.

Interactions with other medicines and vaccines

Potential drug-drug interaction studies have not been conducted with Q/LAIV.

The EMA's EPAR states that the safety and immunogenicity of Q/LAIV when administered concurrently with inactivated vaccines have not been determined.[33] US guidelines consider that FluMist T/LAIV and inactivated vaccines can be administered simultaneously.[34]

Based on studies with FluMist T/LAIV, Q/LAIV can be administered concurrently with the following live, attenuated vaccines: (MMR), varicella vaccine, and orally administered polio vaccine based on data from Studies D153-P522, AV018, and D153-P511. This information has been included in the proposed PI, although some changes to the PI are proposed.

The concurrent use of Q/LAIV or Fluenz with antiviral agents that are active against influenza A and/or B viruses has not been evaluated; however, based upon the potential for antiviral agents with activity against influenza to reduce the effectiveness of Q/LAIV, recommendations have been included in the 'Interactions' section of the PI.

Efficacy

The application for FluMist Quadrivalent (Q/LAIV) was based on a bridging strategy, designed to demonstrate immunogenicity equivalence of the Q/LAIV and T/LAIV and inferring that the safety and protective efficacy data generated during the clinical development of FluMist T/LAIV can be applied to the new Q/LAIV formulation.[33]

The safety and immunogenicity of FluMist Quadrivalent were supported by data from one pivotal paediatric (2 to 17 years of age) study (Study MI-CP208) and one pivotal adult (18 to 49 years of age) study (Study MI-CP185). An additional study in adults (Study MI-CP206) was considered to be supportive, as it was performed using a different device for vaccine administration from the licensed BD Accuspray presentation. All studies were conducted in the United States.[34]

Table 7. Overview of FluMist Quadrivalent studies

Study, Location, Year	Design	Control	Total no. of subjects randomised	Age range	Study duration
Pivotal studies					

[34] FDA Summary Basis for regulatory action. FluMist® Quadrivalent. Feb 29, 2012http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM295324.pdf

Study, Location, Year	Design	Control	Total no. of subjects randomised	Age range	Study duration
MI-CP208, USA, 2010	Randomised, double blind, multicentre, active controlled Phase III, immunogenicity	FluMist trivalent 2 formulations: either influenza B strain Yamagata (Y); or Influenza B strain Victoria(V))	2312 1385: Q/LAIV; 464: FluMist-Y; 463: FluMist-V	Children 2 to 17 years	7 to 8 months (2 dose group) 6 to 7 months (1 dose group)
MI-CP185, USA, 2009	Randomised, double blind, multicentre, active controlled, Phase IIb/III, immunogenicity	FluMist trivalent 2 formulations: either influenza B strain-Yamagata (Y); or Influenza B strain-Victoria (V)	1800 1200: Q/LAIV; 299: FluMist-Y; 301: FluMist-V	Adults, 18 to 49 years	180 days
Supportive study					
MI-CP206, USA, 2009 to 2010	Randomised, partially blind, multicentre, active controlled study	FluMist trivalent (2 formulations: either influenza B strain Yamagata (Y); or Influenza B strain Victoria (V)	1800 1202 Q/LAIV[a]; 300 FluMist-Y[b], 298: FluMist-V[b]	Adults, 18 to 49 years	180 days

a) administered via blow-fill-seal delivery system; b) administered using a BD Accuspray device

Dosage selection for the pivotal studies

The 0.2 mL dose was given intranasally, administered as 0.1 mL per nostril, using the BD Accuspray device. This dose and the recommendations for timing of the vaccinations were identical to the registered product FluMist, with the addition of the fourth strain of influenza.

Q/LAIV was supplied in the BD Accuspray device. Each 0.2 mL dose contained $10^{7.0 \pm 0.5}$ FFU of each of 4 cold adapted, attenuated, temperature sensitive, 6:2 reassortant influenza strains (A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), B of the Victoria lineage (B/Malaysia/2506/2004), and B of the Yamagata lineage (B/Florida/4/2006)).

FluMist-Yamagata (FluMist-Y) was supplied in the BD Accuspray device. Each dose contained $10^{7.0 \pm 0.5}$ FFU of each of 3 cold adapted, attenuated, temperature sensitive 6:2 reassortant influenza strains (A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), and B of the Yamagata lineage (B/Florida/4/2006)).

FluMist-Victoria (FluMist-V) was supplied in the BD Accuspray device. Each dose contained $10^{7.0 \pm 0.5}$ FFU of each of 3 cold adapted, attenuated, temperature sensitive, 6:2 reassortant influenza strains (A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), and B of the Victoria lineage (B/Malaysia/2506/2004)).

Study MI-CP208 (Children, 2 to 17 years)

This was a randomised, double-blind, multicentre, active controlled Phase III study designed to demonstrate the immunologic non-inferiority of Q/LAIV to two formulations of FluMist T/LAIV by comparing the four strain-specific serum HAI antibody GMTs post dosing.

Subjects were vaccinated with either the Q/LAIV or one of two active comparators (FluMist). They were given either one or two doses according to age and prior vaccination history.

The study was conducted by 89 investigators at 97 sites in the USA between 29 Mar 2010 and 27 Dec 2010.

Subjects were randomised in a 3:1:1 ratio to receive either:

- Q/LAIV containing two type B influenza strains (n = 1,380); or
- FluMist T/LAIV containing an influenza B strain from the Yamagata lineage (FluMist-Y) (n= 460); or
- FluMist T/LAIV containing an influenza B strain from the Victoria lineage (FluMist-V) (n = 460).

Each of the FluMist influenza B strains matched one of the two B strains contained in Q/LAIV.

Subjects received either a single dose (subjects 9 to 17 years of age) of investigational product on Day 0 or two doses (subjects 2 to 8 years of age) of investigational product on Days 0 and 28.

The primary efficacy outcome was the post dose strain-specific serum HAI antibody GMT, regardless of baseline serostatus. Immunologic non-inferiority of Q/LAIV to FluMist T/LAIV was considered to have been demonstrated if the post dose strain-specific serum HAI antibody GMTs in the Q/LAIV arm were non-inferior to those in the FluMist arms for all four strains.

The secondary immune response outcomes were:

1. The proportion of subjects who experienced post dose strain-specific HAI antibody seroresponse, by baseline serostatus (that is, seronegative, serosusceptible, and regardless of serostatus);
2. The proportion of subjects who achieved a post dose strain-specific HAI antibody titre ≥ 32, by baseline serostatus (that is, seronegative, serosusceptible, and regardless of serostatus). Seroresponse was defined as a ≥ 4-fold rise from baseline. Strain-specific baseline serostatus was defined as follows: seronegative if baseline HAI antibody titres were ≤ 4, and serosusceptible if baseline HAI antibody titres were ≤ 8.

Randomisation was stratified by age (2 to 8 years, 9 to 17 years). For subjects 2 to 8 years of age only, randomisation was also stratified by history of previous seasonal influenza vaccination. Subjects were screened for the study within 30 days prior to randomisation.

Results

Patient flow

2,277 subjects (98.5%) were dosed and followed for safety through to Day 28 post dose and 2,248 subjects (97.2%) completed the study. The most common reason for lack of study completion was loss to follow-up. Withdrawals were balanced across study arms.

Results for the primary efficacy outcome

The study met its primary objective of demonstrating the immunologic non-inferiority of Q/LAIV to two formulations of FluMist T/LAIV comparing the strain-specific GMTs post dosing, as the upper bound for each of the four 95% CIs for the GMT ratios (FluMist T/LAIV divided by Q/LAIV) was ≤ 1.5. GMT ratios and their corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.07 (95% CI 0.98, 1.16), 1.04 (95% CI 0.94, 1.14), 1.21 (95% CI 1.07, 1.37), and 1.05 (95% CI 0.93, 1.18). An analysis of geometric mean fold rise (GMFR) in HAI antibody titres, which adjusts for differences in baseline GMTs, supported the primary endpoint conclusion, as the upper bound of 95% CIs for the GMFR ratios for each of the four strains was ≤ 1.5.

Results for other outcomes

Secondary endpoints and post-hoc analyses generally supported the conclusion that the immune responses to Q/LAIV and FluMist T/LAIV were similar, however vaccine immunogenicity was statistically greater in the FluMist group than in the Q/LAIV arm for the rate of seroconversion/seroresponse to A/H1N1 in the serosusceptible subgroup and for the proportion of subjects achieving an HAI antibody titre ≥ 32 for the B/Yamagata strain in all subjects regardless of baseline serostatus, serosusceptible subjects, and seronegative subjects.

The EMA's EPAR also noted that the relevance of the non-inferiority analysis was questionable for A/H1N1 and A/H3N2 where a very low or zero response to vaccination was observed.[33] This is also illustrated in the following table from the FDA CBER statistical review analysis, included in the FDA Medical review.[35]

Table 8. Study MI-CP208. Strain specific HAI seroconversion/seroresponse rates[a] in individuals receiving Q/LAIV or comparator[b]

Strain	Q/LAIV	FluMist (V + Y)	FluMist/B/ Victoria	FluMist/B/ Yamagata
H1N1	5.4% (72/1325)	5.6% (50/885)	5.7% (25/439)	5.6% (25/446)
H3N2	3.4% (45/1325)	3.5% (31/885)	2.7% (12/439)	4.3% (19/446)
B/Victoria	35.4% (469/1325)	--	33.9% (149/439)	15.9% (71/446)
B/Yamagata	42.0% (557/1325)	--	11.9% (52/439)	43.3% (193/446)

Source: Results of CBER statistical reviewer's analysis.[35] a) If the baseline titre is < 4, the post-vac titre considered as demonstrating seroconversion was ≥ 16. If the baseline titre is ≥ 4, the post-vac titre considered as demonstrating seroconversion was ≥ 4 times the baseline titre. b) The time point at which immune response was measured was 28 to 35 days after Dose 1 for subjects 9 to 17 years of age and for subjects 2 to 8 years of age with history of prior seasonal influenza vaccination or at 28 to 35 days after Dose 2 for subjects 2 to 8 years of age with no history of prior seasonal influenza vaccination.

[35] FluMist Quadrivalent sBLA 125020/1668 Clinical Review. Feb 17 2012. Department of Health and Human services. FDA/CBER/OVRR/DVRPA.

Study MI-CP185 (Adults, 18 to 49 years)

This was a randomised, double-blind, active controlled Phase IIb/III study in adults 18 to 49 years of age, designed to demonstrate the immunologic non-inferiority of Q/LAIV to 2 formulations of FluMist T/LAIV by comparing the four strain-specific serum HAI antibody GMTs post dosing. A total of 1800 subjects were randomised by site in a 4:1:1 ratio to receive Q/LAIV, T/LAIV FluMist containing an influenza B strain from the Yamagata lineage (FluMist/B/Yamagata), or T/LAIV FluMist containing an influenza B strain from the Victoria lineage (FluMist/B/Victoria). Subjects received a single dose of Q/LAIV or FluMist T/LAIV. The study was conducted at multiple sites in the influenza off-season.

The primary objective was to demonstrate the immunologic non-inferiority of Q/LAIV to 2 formulations of FluMist T/LAIV by comparing the strain specific GMTs of HAI antibody post dosing.

Secondary objectives were:

1. To estimate the proportion of subjects who experienced strain-specific HAI seroresponse following the dose of Q/LAIV;
2. To estimate the proportion of subjects who achieved a strain-specific HAI antibody titre ≥ 32 following the dose of Q/LAIV;
3. To assess the safety and tolerability of Q/LAIV.

Study treatments were as for Study MI-CP208 (see above).

Results

Patient flow

A total of 1,800 subjects were randomised as planned; 1,798 subjects were dosed. Of the subjects randomised, 1,200 were in the Q/LAIV arm, 299 were in the FluMist/B/Yamagata arm, and 301 were in the FluMist/B/Victoria arm. The Safety Population included 1,796 subjects, the Evaluable Safety Population for solicited symptoms included 1,794 subjects, and the Immunogenicity Population included 1,770 subjects.

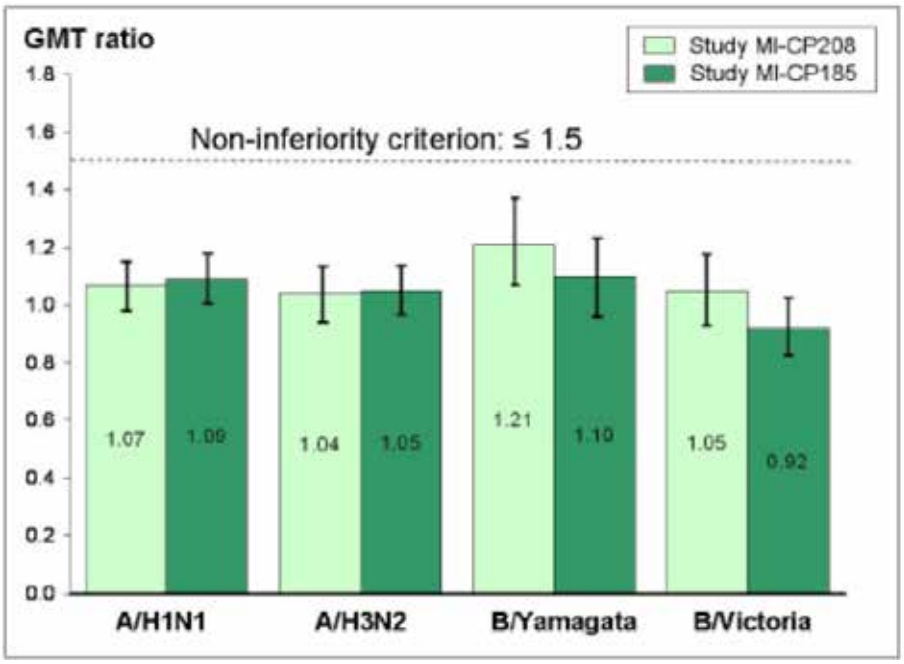
Results for the primary efficacy outcome

The study met its primary objective of demonstrating the immunologic non-inferiority of Q/LAIV to 2 formulations of FluMist in subjects 18 to 49 years of age by comparing the 4 strain-specific HAI antibody GMTs post dosing. The immune response of Q/LAIV was declared non-inferior to that of FluMist T/LAIV as the upper bound for each of the four 95% CIs for the GMT ratios.

Results for other outcomes

Study secondary endpoint data were consistent with the primary endpoint. The proportion of subjects who experienced strain-specific HAI antibody seroresponse following the dose of Q/LAIV was similar for Q/LAIV and the appropriate comparator arm in all subjects regardless of baseline status and in seropositive subjects. For subjects who were serosusceptible at baseline, seroconversion/seroresponse rates were similar between Q/LAIV and the All FluMist group for the A/H1N1 and A/H3N2 strains, but were numerically lower in the Q/LAIV arm compared to the matching FluMist arms for the B/Yamagata and B/Victoria strains; however, these differences were not statistically significant. The proportion of subjects who achieved a strain-specific HAI antibody titre ≥ 32 was similar between Q/LAIV and comparator arms.

Figure 2. Post-dose GMT ratios of HAI antibody, by strain for paediatric Study MI-CP208 and adult Study MI-CP185



CI = confidence interval; GMT = geometric mean titre; HAI = haemagglutination inhibition; Q/LAIV = quadrivalent live attenuated influenza vaccine. Note: Error bars represent 95% CIs; GMT ratios represent the GMT in the FluMist comparator group divided by the GMT in the Q/LAIV group. The non-inferiority criterion was met, because the upper bound for each of the four 95% CIs for the post dose GMT HAI antibody ratios (FluMist divided by Q/LAIV) was ≤ 1.5.

Study MI CP-206 (Adults, 18-49 years, Q/LAIV administered with blow-fill-seal delivery system)

This was a randomised, partially blind active controlled study to evaluate the immunogenicity of Q/LAIV in adults 18 to 49 years of age. The study was conducted at 18 sites in the United States between August 2009 and March 2010. It was considered supportive by the sponsor, given that a different device for vaccine administration for Q/LAIV was used, rather than the licensed BD Accuspray presentation.[33]

The primary objective was to demonstrate the immunologic non-inferiority of Q/LAIV administered intranasally through a blow-fill-seal (BFS) delivery system (Q/LAIV-BFS) to 2 T/LAIV formulations of licensed FluMist (delivered intranasally using the BD Accuspray delivery device) by comparing the strain specific GMTs post dosing.

The secondary objectives were:

1. To estimate the proportion of subjects who experienced strain specific HAI seroresponse following the dose of Q/LAIV-BFS, defined as a minimum 4-fold rise in post-vaccination HAI antibody titre, by baseline serostatus.
2. To estimate the proportion of subjects who achieved a strain-specific HAI titre ≥ 32 following the dose of Q/LAIV-BFS, by baseline serostatus.
3. To assess the safety and tolerability of Q/LAIV-BFS.
4. To determine the acceptability of the BFS dosing unit as a vaccine delivery system to vaccine recipients.

Inclusion criteria were similar to the study in adults, Study MI-CP185. Subjects were randomised in a 4:1:1 ratio to receive a single dose of Q/LAIV-BFS, trivalent FluMist

containing an influenza B strain of vaccine virus derived from the B/Yamagata lineage (FluMist/B/Yamagata), or trivalent FluMist containing an influenza B strain of vaccine virus derived from the B/Victoria lineage (FluMist/B/Victoria). On Day 0, subjects received a single dose of investigational product (Q/LAIV-BFS or comparator).

Results

Participant flow

Of the 1800 subjects randomised, 1,797 subjects received investigational product. 1,199 subjects received Q/LAIV-BFS, 300 subjects received FluMist/B/Yamagata, and 298 subjects received FluMist/B/Victoria. The ITT Population included all randomised subjects.

The Safety Population and Evaluable Safety Population for solicited symptoms included > 99% of subjects in each group. The Immunogenicity Population included 98% of subjects dosed in each group. Of the 1,800 randomised subjects, 98% were followed through Day 28 and 97% completed the study.

Primary and secondary endpoints

The study met its primary endpoint demonstrating the immunologic non-inferiority of Q/LAIV-BFS to two formulations of FluMist T/LAIV by comparing the 4 strain specific HAI antibody GMTs post dosing. The immune response of Q/LAIV-BFS was declared non-inferior to that of T/LAIV FluMist, as the upper bound for each of the four 95% CIs for the post dose GMT ratios was ≤ 1.5. Post dose GMT ratios and the corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains were 0.95 (95% CI: 0.87, 1.03), 0.93 (95% CI: 0.85, 1.00), 0.90 (95% CI: 0.79, 1.02), and 0.97 (95% CI: 0.87, 1.10), respectively.

Secondary endpoint results were consistent with the primary endpoint.

Study MA-VA-MEDI3250-1116: Case control study of the effectiveness of Q/LAIV versus inactivated influenza vaccine and no vaccine in subjects 2 to 17 years of age

This study was developed as part of a post-marketing commitment with the FDA and is ongoing. It was a case-control study of the effectiveness of Q/LAIV in subjects 2 to 17 years who were seeking care in an outpatient setting for febrile acute respiratory illness. The aim was to evaluate the effectiveness of Q/LAIV over four influenza seasons, beginning with the 2013-2014 Northern Hemisphere influenza season. The primary objective was to evaluate the effectiveness of Q/LAIV (FluMist Quadrivalent) compared to IIV or no vaccine, in community-dwelling subjects aged 2 to 17 years, against laboratory-confirmed influenza. The first patient was enrolled on 2 December 2013 and the study will be completed after 4 years (that is, after the 2016 to 2017 influenza season).

Participants were either vaccinated or not vaccinated against influenza as part of the standard clinical care they received from their healthcare providers. A total of 1,082 subjects were enrolled during the first (2013 to 2014) influenza season and these have been assessed in an interim analysis.

During the 2013-2014 influenza season Q/LAIV demonstrated high levels of effectiveness against circulating B strains (approximately 80%), but did not demonstrate effectiveness against circulating H1N1 strains. This finding appeared to be a US-specific finding as studies from Canada from the same season indicated that the vaccine was effective. The lack of effectiveness in the US for H1N1 strains in 2013 to 2014 was thought to be attributable to a unique mutation in the stalk sequence of the HA protein of the A/California/7/2009 vaccine strain not seen in any previous LAIV strains. This mutation increased the susceptibility of the strain to heat degradation at temperatures to which the vaccine was exposed as part of routine vaccine handling procedures in the US but not in

Canada and the UK. The Delegate notes the results for the 2014/2015 season indicated an overall vaccine effectiveness of 45% (95% CI: 21; 62). LAIV was highly effective against B strains as compared to no vaccine (86% (95% CI: 60; 95)) or IIV (79% (95% CI: 39; 93)); however, significant effectiveness was not demonstrated against circulating H3N2 strains (24% (95% CI: -14; 49)) which were most often highly mismatched versus the vaccine strain (in 305 out of 316 identified cases positive for A/H3N2 strains) (see also 'Issues for sponsor' below).

Efficacy studies for FluMist

It is stated that in the paediatric population, FluMist (T/LAIV) demonstrated a high degree of absolute efficacy (that is, reduction in culture-confirmed influenza cases compared to background rates) in seven placebo controlled studies, second season efficacy with revaccination in the four studies in which second season efficacy was evaluated, superior relative efficacy (that is, reduction in culture-confirmed influenza cases compared to rates among TIV-vaccinated recipients) in 3 TIV-controlled studies and, during 2 separate influenza seasons, cross protection (including cross-protection during one season that was superior to that provided by TIV) against mismatched A/H3N2 wild-type circulating strains.

These 10 studies (seven placebo controlled and three TIV-controlled) in > 26,000 paediatric subjects are discussed in Attachment 2 and results for the relative efficacy in TIV-controlled paediatric trials are summarised in Table 9, below.

Table 9. FluMist T/LAIV relative efficacy in TIV controlled paediatric trials

Study number	Region	Age range	Number of subjects in the Primary analysis population	Frozen or refrigerated FluMist	Influenza season	Relative efficacy (95% CI) Matched strains	Relative efficacy (95% CI) All strains Regardless of antigenic match
MI-CP111	USA; Europe; Asia and Oceania	6 to 59 months	7852	Refrigerated	2004 to 2005	44.5% (22.4, 60.0) fewer cases than TIV	54.9% (45.4,62.9) fewer cases than TIV
D153-P514	Europe	6 to < 72 months	2085	Refrigerated	2002 to 2003	52.7% (21.6, 72.2) fewer cases than TIV	52.4% (24.6,70.5) fewer cases than TIV
D153-P515	Europe	6 to 17 years	2211	Refrigerated	2002 to 2003	34.7% (3.9, 56.0) fewer cases than TIV	31.9% (1.1, 53.5) fewer cases than TIV

CI = confidence interval; Europe includes Western and Eastern Europe, Scandinavia, Israel and Lebanon; Asia/Oceania includes East Asia, Southeast Asia, South Asia and Australia.

Overall, the results of these studies confirmed consistent and convincing protective efficacy with FluMist T/LAIV regardless of strain match together with superior efficacy compared to TIVs in controlled studies in children.

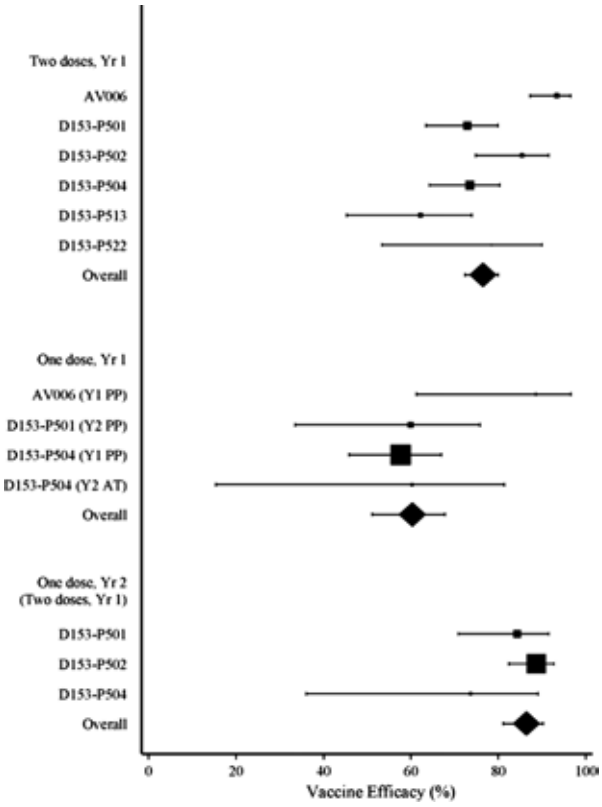
One versus two doses in previously unvaccinated children (addendum to clinical evaluation report – See Attachment 2)

At the request of the TGA, the evaluator provided an addendum to the clinical evaluation report addressing the efficacy of one versus two doses of FluMist in previously unvaccinated children. The addendum summarised the results of three studies and

provided comments on a meta-analysis of the efficacy of LAIV compared to placebo or trivalent inactivated vaccines.[36]

The evaluator concluded that there were four cohorts in these 3 studies which provided some data to assess the difference between the clinical efficacy (and immunogenicity) of 1 and 2-dose regimens of LAIV vaccine. In two of these studies, this comparison was a primary endpoint of the study (Studies AV006 and D153-504). Although not designed to assess the one versus two dose comparison, Study D153-501, a second year re-randomisation (versus the second year single booster dose or single dose placebo) and the last small cohort (in Study D153-504) due to a study error (with incorrect designation resulting in a one dose vaccination of a block of subjects) also contributed to the results. The data from the earlier, smaller study (Study AV006) was the only one to find similar clinical efficacy between the one and two-dose regimens in previously unvaccinated children. All the other data pointed to the two-dose regimen having a higher clinical efficacy. The meta-analysis also supported this finding: relative to placebo, Year 1 vaccine efficacy for two doses in vaccine-naïve young children was 77% (95% CI: 72%, 80%; $p < 0.001$) against antigenically similar strains and 72% against strains regardless of antigenic similarity. Year 1 vaccine efficacy of one dose against antigenically similar strains in vaccine-naive children was 60%.[36] A summary of results from the meta-analyses is given below in Figure 3.

Figure 3. Meta-analyses of vaccine efficacy for LAIV versus placebo (Year 1, one and two doses; Year 2, one dose) for antigenically similar subtypes



AT = As-Treated Population; LAIV = live attenuated influenza vaccine; PP = Per-Protocol Population

These findings are relevant, given the results of the UK based LAIV programme for healthy children where a single dose of LAIV was offered to all healthy children aged two to three years (and in the second year of the program, aged 2 to 4 years), together with children of primary school age (4 to 11 years) in a series of geographically discrete pilot areas. Modelling predicted that the programme would provide direct protection to the

[36] Rhorer J, et al. Vaccine 2009. 11:27(7):1101-1110

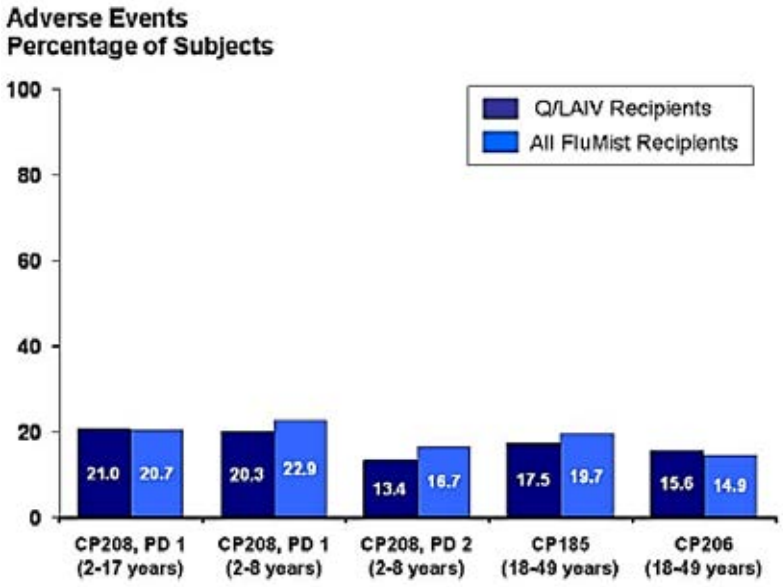
vaccinated children themselves and by reducing infection in this group, would decrease transmission of influenza in the general population and therefore provide indirect protection to groups at higher risk of severe disease (for example, the elderly and those with underlying clinical risk factors). The results of this study are described in the published report.[37]

Safety

The evaluator stated that the main goal of safety assessment within the FluMist Quadrivalent (Q/LAIV) development program was to demonstrate that the addition of a fourth vaccine strain maintained the safety and tolerability profile of FluMist T/LAIV. Q/LAIV study data demonstrated that Q/LAIV was safe and well tolerated in children and adults who were healthy or who had stable chronic diseases at enrolment. Solicited symptoms were generally comparable in subjects who received either Q/LAIV or FluMist T/LAIV and were consistent with those observed in previous studies of FluMist T/LAIV (runny nose, sneezing). The solicited symptom that was significantly more commonly observed in children who received Q/LAIV than those who received FluMist T/LAIV was fever; however, overall rates of fever were low, fevers were generally mild and of short duration with comparable high grade fever (≥ 39.5°C) rates, no febrile seizures were observed, and no impact on the overall tolerability of Q/LAIV compared to FluMist T/LAIV is expected. Adverse events and SAEs were also comparable in Q/LAIV and FluMist recipients and were consistent with those expected to occur in subjects in this age group.

Specific studies for Q/LAIV in immunocompromised populations, pre-existing lung conditions or asthma and wheezing are not yet available and hence data for these populations has been derived from studies with FluMist. The EMA EPAR concluded that the overall similarity of solicited symptoms and AEs between Q/LAIV and FluMist T/LAIV permits the understanding of the safety of FluMist from the large safety database to apply to Q/LAIV. Of note, Q/LAIV is not registered for children < 2 years, consistent with FluMist T/LAIV, due to an increased risk of wheezing and hospital admissions after receipt of FluMist T/LAIV in younger children.

Figure 4. Percentage of subjects reporting the occurrence of at least one adverse event in Q/LAIV Studies MI-CP185, MI-CP208, and MI-CP206



[37] Pebody R et al. Surveillance and outbreak report: Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Eurosurveillance. 01 Oct 2015; Vol 20:39.

Post-marketing experience

The worldwide cumulative exposure (including FluMist T/LAIV and FluMist Quadrivalent (Q/LAIV)) is estimated to be greater than 98 million doses since the first approval. The sponsor states that the safety profile is consistent with the current labelling, with no unexpected safety signals emerging.

There was minimal post-marketing data for Q/LAIV at the time of this submission, although Q/LAIV is now being substituted into the post-marking trials currently being conducted for FluMist T/LAIV overseas.

RMP evaluation and ACSOV advice

FluMist Quadrivalent was considered at the ACSOV February 2016 meeting. Key points highlighted by the committee as safety concerns specific to use of a live attenuated influenza vaccine were:

1. Medically significant wheezing in children under the age of 24 months (as an important identified risk)
2. Secondary transmission to severely immunocompromised patients and inadvertent administration to immunocompromised patients (as important potential safety risks)

Given the number of changes to influenza vaccines, including the transition from TIVs to QIVs under the NIP from 2016, it is critical that there be adequate education provided on any new influenza vaccine. Prescriber education needs to address the differences between this vaccine and available inactivated influenza vaccines with regard to indications, contraindications and safety profile.

The Delegate is of the opinion that the evidence-based Contraindications and Precautions in the PI proposed by ACSOV and the RMP evaluator should be included and that advice regarding immunocompromised patients be more specific. The comments from the sponsor have been noted and have been taken into consideration.

Outstanding major issues highlighted by the RMP evaluator to be addressed include:

- A drug utilisation study proposed by the sponsor that uses primary care data to analyse the extent of off-label use *[see post RMP evaluation note above]*
- It is preferable for the educational materials to be available before approval. It is noted that the updated version of the ASA has no reference to the additional risk minimisation activities. The sponsor should provide an updated ASA that contains a description of the additional activities prior to approval
- Both the spray label and the carton should contain the age range for which FluMist Quadrivalent is approved to accommodate concerns raised by the ACSOV.[38]

Risk-benefit analysis

Delegate's considerations (ACPM first round)

Data from a non-inferiority comparison of immune response with two different formulations of FluMist T/LAIV, each one containing one of the two B strain components

[38]This was subsequently agreed to by the sponsor and an updated label and carton were provided to, and approved by, the Delegate.

of FluMist Quadrivalent, demonstrated that the immune response to FluMist Quadrivalent met the pre-specified criteria for non-inferiority compared to that elicited by FluMist T/LAIV.[33] It was also demonstrated that the addition of a second B strain did not result in immune interference to the other strains included in the vaccine.

The non-inferiority immunogenicity studies for FluMist Quadrivalent did not address culture-confirmed infection cases but were based on serological assays as an indirect measure of efficacy, lacking an established correlate of protection. The EMA's EPAR also highlighted the uncertainties to which non-inferiority established on the basis of humoral immunity corresponds to clinical non-inferiority.[33] The efficacy of the vaccine following repeated yearly revaccinations requires further evidence.

Given that LAIV are most likely to be given by the respiratory route, immune parameters other than serum antibody responses (for example mucosal, innate and cellular immunity) are relevant and evaluation of live attenuated influenza vaccines therefore presents specific challenges. WHO guidelines state that there is no established immune correlate of protection for LAIV, although determination of neutralising haemagglutination inhibition or single-radial haemolysis antibodies is a reasonable starting point.[39]

Efficacy of FluMist Quadrivalent has therefore been inferred from data demonstrating the clinical efficacy of FluMist T/LAIV in children and in adults. Protective efficacy with FluMist T/LAIV has been consistently demonstrated regardless of strain match, together with superior efficacy compared to TIVs in controlled studies in children. Results for FluMist T/LAIV from clinical studies and a meta-analysis sponsored by the manufacturer support a two dose regimen having a higher clinical efficacy than a one dose regimen in previously unvaccinated children. The proposed recommendation in the draft PI for two doses (at least four weeks apart) to be given to this population is therefore appropriate.

As FluMist Quadrivalent does not require an injection, it is likely to be more acceptable to patients with the potential for uptake by patient groups who have not previously received an influenza vaccine and those outside the age range specified in the vaccine indications. The approved age range for FluMist Quadrivalent is different for major overseas markets, noting that the US and Canada have approved use in adults with slightly different upper age limits, while the approved age range for the EU is the same as that proposed for Australia (24 months to less than 18 years). Given the number of quadrivalent influenza vaccines being approved and adopted under the National Immunisation Program (NIP) with varying age restrictions and noting the post-marketing history available for FluMist T/LAIV in adults, the possibility of an adult indication for Australia warrants discussion.

Subject to ACPM advice and following resolution of outstanding quality, risk management plan issues and the product information, the Delegate recommends that FluMist Quadrivalent (Q/LAIV) be approved for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age. The final approved indication is to be determined post-ACPM.

Issues for the sponsor

1. Please provide an update of the overseas regulatory status.
2. With regards to the pivotal studies, one of the secondary endpoints was the proportion of subjects who achieved a post dose strain-specific HAI antibody titre ≥ 32, by baseline serostatus (that is, seronegative, serosusceptible, and regardless of serostatus). Why was a cut off-of ≥ 32 chosen for the HAI antibody titre? Was this based on previous immunogenicity experience with trivalent FluMist? Please provide further information.

[39] WHO Expert Committee on Biological Standardization. Sixtieth report. Annex 4. Recommendations to assure the quality, safety and efficacy of influenza vaccines (human, live attenuated) for intranasal administration.

3. It is noted in the application letter (2 July 2015) that the approved age range is different for major overseas markets. The approved EU age range for the trivalent vaccine and Q/LAIV is the same as that proposed for Australian (that is, 24 months to less than 18 years). The USA and Canada have approved use in adults (with different upper limits for age: 49 years for US and 59 years for Canada). Please comment on why the indication in adults is not being sought for Australia.
4. Related to point 3, above what are the sponsor's intentions with regards to studies of Q/LAIV in elderly patients?
5. Please comment on further interim analyses of efficacy and safety in the post-market Study MA-VA-MEDI3250-1116, given the unexpected 2013 to 14 season results in USA (including any relevant summaries as an attachment). The Delegate notes the results for the 2014/2015 season included in the updated RMP.
6. Please comment on the outstanding quality issues, in particular the availability of material for the development of a potency assay standard in discussion and collaboration with the TGA.

Proposed action

The Delegate has no reason to say, at this time, that the application for FluMist Quadrivalent should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The proposed age indication for children and adolescents from 24 months to less than 18 years of age, in light of variations with respect to overseas markets and in the context of other quadrivalent vaccines currently registered in Australia.
2. The adequacy of the product information with respect to contra-indications and precautions specific to live-attenuated influenza vaccines, noting the RMP evaluator's concerns with respect to immunodeficiency, Reye's syndrome, asthma and pregnancy and the overseas product information.
3. The data provided with respect to one versus two doses in previously unvaccinated children and the proposed recommendation in the product information.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor (ACPM first round)

Below the sponsor has provided comments in relation to the advice sought from the ACPM and specific issues [raised by the Delegate] for the sponsor. Please note where the advice sought and issues for the sponsor overlap, the discussion has been consolidated to reduce redundancy.

Proposed age indication

Considerable efficacy and safety data have been provided in support of the proposed paediatric population including 7 placebo controlled studies and 3 active controlled clinical studies conducted with the original trivalent presentation (FluMist, not previously registered/supplied in Australia but marketed for over 10 years overseas). As stated by the Delegate '*the results of these studies confirmed consistent and convincing protective efficacy of FluMist T/LAIV regardless of strain match together with superior efficacy compared to TIVs in controlled studies in children*.' Extrapolation of these trivalent

formulation findings to the proposed quadrivalent (Q/LAIV) formulation was primarily supported by a pivotal clinical study in paediatric patients (2 to 17 years of age) which demonstrated that the strain-specific immune responses after dosing with Q/LAIV were non-inferior to those after dosing with FluMist T/LAIV. FluMist T/LAIV has also been shown to have an acceptable safety profile, and the addition of the fourth vaccine strain to create Q/LAIV did not result in any clinically significant differences in the spectrum of safety events. As a result, the data fully supports the efficacy and safety of FluMist Quadrivalent in children and adolescents from 24 months to less than 18 years of age. Consequently, both the Delegate and clinical evaluator have recommended approval in this initially proposed patient population.

The Delegate has also commented on data in adults, noting that FluMist T/LAIV (and now also FluMist Quadrivalent) has been approved for use in adults in the US (through to 49 years, [as per the] US PI) and Canada (through to 59 years [as per the] Canadian Product Monograph) for many years. The primary evidence supporting use of the vaccine in adults was derived from 4 randomised, controlled FluMist T/LAIV efficacy/effectiveness studies which included more than 10,000 adults. These included 1 wildtype influenza experimental challenge study, 2 placebo controlled studies, and 1 TIV controlled study. The pivotal efficacy outcomes are included within the US PI ('Clinical Studies' section) and Canadian Product Monograph ('Clinical Trials' section). All of these adult FluMist T/LAIV studies were included within the data supplied for this Australian submission and were discussed to some extent within the EU submission-derived Clinical Overview and Clinical Summary. These studies demonstrated absolute efficacy in adults, efficacy against experimental challenge with wild-type influenza and effectiveness against influenza-associated febrile illnesses and related events in a year when the predominant circulating wild-type virus was mismatched to the FluMist T/LAIV vaccine strain. Extrapolation of the FluMist T/LAIV adult data to the FluMist Quadrivalent vaccine (Q/LAIV) was supported by one pivotal clinical study and one supportive study, both conducted in adults 18 to 49 years of age. These studies demonstrated that the strain specific immune responses after dosing with Q/LAIV were non-inferior to those after dosing with FluMist T/LAIV. The adult Q/LAIV studies were also included as part of the Australian submission and were discussed within the documentation. The data from these studies supported the approval of Q/LAIV in the US and Canada for the same age ranges which were previously approved for the trivalent version of the vaccine.

A considerable amount of safety and tolerability data gathered during the clinical development of FluMist T/LAIV and FluMist Quadrivalent, and during the post-marketing period, also support use of the vaccine in adults. During clinical development more than 10,000 adults were enrolled in FluMist clinical studies and more than 2,000 adults received the vaccine in Q/LAIV studies. The results of these studies indicated that both formulations of the vaccine had acceptable safety and tolerability profiles in adults. Since initial approval of the trivalent formulation in 2003 over 114 million doses of the vaccine have been distributed for use in children and adults; the safety profile of the vaccine during this period has also been consistent with that seen during development.

These data demonstrate that the live attenuated vaccine is safe and efficacious for use in adults, with efficacy in adults comparable to that seen for inactivated vaccines. However, approximately 90% of the vaccine produced by the sponsor is administered to children and adolescents for whom data exist demonstrating the superior efficacy of the vaccine compared to inactivated vaccines. The way this vaccine is being used in the countries which it is approved is one of the reasons that the sponsor decided to only apply for a paediatric indication in Australia. A further rationale for initially only seeking paediatric use was the availability of a base EU Q/LAIV submission data for an Australian submission. This submission data was prepared in line with the TGA required EU guidelines and while it did include all the adult data, the clinical summaries were prepared to support the same

indication and patient populations approved in the EU for the trivalent formulation, that is 24 months to below 18 years.

While the sponsor did not initially seek use in adults, the Australian submission did include and discuss to some extent the evidence available in support of the efficacy and safety of FluMist Quadrivalent in this older patient population. This body of evidence was considered sufficient to support approval in both the US and Canada. The sponsor commits to working with the Delegate to identify the most appropriate way forward based on the advice received from the ACPM.

One versus two doses in previously unvaccinated children

At the request of the TGA, the clinical evaluator assessed the data available on the dosing options for previously unvaccinated children of a one dose option (for all children and adolescents) or an alternative two dose option where the second dose (200 µL) is administered at least 4 weeks after the first dose. The data demonstrate slightly higher clinical efficacy with a second dose in previously unvaccinated children. This included a meta-analysis (Rhorer et al;[40] referenced by TGA, also included within the submission) which showed a Year 1 vaccine efficacy of 77% (compared to placebo) against antigenically similar strains for naïve children who received two doses of vaccine compared to 60% for naïve children who received a single dose. Thus, while meaningful clinical efficacy has been shown with a single dose in previously unvaccinated children, there appears to be benefit in administering a second dose. Consequently, the initially proposed PI included a second dose for previously unvaccinated children less than 9 years of age.

However, as noted by the Delegate, the sponsor is aware of the single dose recommendation issued by the UK national immunisation body, the Joint Committee on Vaccination and Immunisation for children not in clinical risk groups despite this not formally being stated within the approved EU SmPC. Given the challenges of implementing a national immunisation program and the meaningful clinical efficacy demonstrated with a single dose in previously unvaccinated children, a single dose vaccination regimen may be appropriate in such children. It should be noted that even in countries such as the US, where previously unvaccinated children under the age of 9 years are recommended by the national immunisation bodies to receive two doses, less than 50% of these children actually receive both doses.[41] If the ACPM considers a single dose vaccination schedule suitable for children not in high risk groups the sponsor will work with the Delegate to revise the proposed dosing recommendations for children less than 9 years of age accordingly.

Adequacy of the PI with regard to contraindications and precautions

The sponsor has accepted the Delegate's PI recommendations for immunodeficiency, Reye's syndrome and pregnancy. Please also note that the Delegate has accepted that the current PI recommendations are consistent with overseas PIs with respect to asthma/wheeze.

Issues for the sponsor

The following provides responses to the specific issues raised by the Delegate within the Issues for the sponsor section of the Delegate's Overview.

1. *Please provide an update of the overseas regulatory status*

[40] Rhorer J et al. Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. Vaccine. 2009;27:1101-1110.
[41] Pabst et al. Trends in compliance with two-dose influenza vaccine recommendations among children aged 6 months through 8 years. Vaccine. 2013 Jun 28; 31(31):3116-20.

As per the Delegate's Overview, FluMist Quadrivalent/Fluenz Tetra has been approved since 2012, 2013 and 2014 in the US, EU and Canada respectively. The only update to this overseas regulatory status is the withdrawal of the Canadian trivalent version post quadrivalent launch.

2. *With regards to the pivotal studies, one of the secondary endpoints was the proportion of subjects who achieved a post dose strain-specific HAI antibody titre ≥ 32, by baseline serostatus (that is, seronegative, serosusceptible, and regardless of serostatus). Why was a cut-off of ≥ 32 chosen for the HAI antibody titre? Was this based on previous immunogenicity experience with trivalent FluMist? Please provide further information.*

In the HAI assay used during the development of FluMist T/LAIV serum is initially diluted 1:4 in the first well of test plates; agglutination observed in the first well is reported as a titre of < 4 (imputed for statistical purposes as a value of 2) and subsequent titres increase 2-fold (that is, 4, 8, 16, 32, 64, and so on). The cut-off of 32 was chosen as the seminal trials conducted by Hobson et al. in individuals experimentally challenged with live influenza virus established that a pre-challenge serum HAI titre of 18 to 36 was associated with 50% protection from infection: a similar cut-off of 40 is used for assays that start with an initial 10-fold dilution.[42]

3. *It is noted in the application letter (2 July 2015) that the approved age range is different for major overseas markets. The approved EU age range for the trivalent vaccine (T/LAIV) and Q/LAIV is the same as that proposed for Australian (that is, 24 months to less than 18 years). The US and Canada have approved use in adults (with different upper limits for age: 49 years for US and 59 years for Canada). Please comment on why the indication in adults is not being sought for Australia.*

Refer to the proposed age indication section above.

4. *Related to point 3 [above], what are the sponsor's intentions with regards to studies of Q/LAIV in elderly patients?*

The sponsor does not have any plans to study Q/LAIV in the elderly.

5. *Please comment on further interim analyses of efficacy and safety in the post-market Study MA-VA-MEDI3250-1116, given the unexpected 2013 to 2014 season results in US (including any relevant summaries as an attachment). The Delegate notes the results for the 2014/2015 season included in the updated RMP.*

The results detailed within [the updated] RMP for Study MA-VA-MEDI3250-1116 (a 4 year US post marketing study initiated with the 2013 to 2014 influenza season) are derived from the most recent data available for this study. The final 2014 to 2015 results will be available mid-2016 and will be discussed within the next periodic benefit-risk evaluation report (PBRER) (data lock 16 June 2016), if available by then. The final report will also be included as an appendix within the relevant PBRER.

6. *Please comment on the outstanding quality issues, in particular the availability of material for the development of a potency assay standard in discussion and collaboration with the TGA.*

The sponsor's response to the outstanding quality issues has been covered within the Quality section above.

Advisory Committee Considerations (ACPM first round)

The Advisory Committee on Prescription Medicines (ACPM) agreed with the Delegate and considered FluMist Quadrivalent nasal spray 200 µL dose containing $10^{7.0 \pm 0.5}$ FFU of each

[42] Hobson D et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J. Hyg., Cambridge, 1972: 70: 767.

of the 4 influenza virus strains to have an overall positive benefit–risk profile for the proposed indication:

> *'FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.'*

In making this recommendation the ACPM was of the view that the age group proposed in the indication was appropriate and consistent with the age group in the pivotal study (Study MI-CP208).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *The proposed age indication for children and adolescents from 24 months to less than 18 years of age, in light of variations with respect to overseas markets and in the context of other quadrivalent vaccines currently registered in Australia.*

The ACPM noted that FluMist Quadrivalent was not registered in the EU for individuals 18 years of age and older. In addition, the ACPM noted that the age group studied in the pivotal study (Study MI-CP208) was 24 months to less than 18 years of age. Taking these factors into account, the ACPM advised that the proposed age group from 24 months to less than 18 years of age was the most appropriate, noting that the data submitted and evaluated focused on the 24 month to 18 years age group, with adult studies considered supportive. It was suggested that an adult indication could be considered as a separate application.

2. *The adequacy of the product information with respect to contraindications and precautions specific to live-attenuated influenza vaccines, noting the RMP evaluator's concerns with respect to immunodeficiency, Reye's syndrome, asthma and pregnancy and the overseas product information.*

The ACPM noted that the sponsor in its pre-ACPM response accepted the Delegate's PI recommendations regarding immunodeficiency, Reye's syndrome, asthma and pregnancy. The ACPM advised that the PI with respect to contraindications and precautions is now adequate. The statement with regards to use in asymptomatic HIV infection or low-dose and topical/inhaled corticosteroids could be duplicated in the precautions section.

3. *The data provided with respect to one versus two doses in previously unvaccinated children and the proposed recommendation in the product information.*

The ACPM advised that the two-dose regimen is more immunogenic and should be the dose recommended for previously unvaccinated children. The ACPM was of the view that the PI could also refer to the national guidelines.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Post-ACPM (first round) discussion

Post ACPM meeting (ACPM first round) the TGA Delegate was informed by the sponsor of interim vaccine effectiveness data from the northern hemisphere influenza season 2015-2016 for FluMist Quadrivalent. This included discussion on the recommendations from the US Advisory Committee on Immunization Practices (ACIP) against use of FluMist Quadrivalent in the upcoming 2016 to 2017 season, based on poor performance of the

vaccine against the 2009 H1N1 virus and noting the reduced effectiveness against the drifted H3N2 strain.

Subsequent to this, it was requested, in addition to post-ACPM revisions of the PI that the sponsor provides a vaccine effectiveness summary document to the TGA for consideration (see below). The sponsor also separately provided the Delegate with overseas publications and updates from third parties as soon as they were made aware of their availability (eg FDA statements, Public Health England publications, etc).

Sponsor's Vaccine effectiveness update

Overview

This [vaccine effectiveness update] summarises all currently available data regarding the effectiveness of FluMist Quadrivalent (licensed as Fluenz Tetra in the EU) during the 2015 to 2016 Northern Hemisphere influenza season. At [the time of this update], results are available from preliminary analyses of full-season data from five studies: three studies conducted in the US, one study in the UK, and one study in Finland.

Results from four of these five studies demonstrate statistically significant moderate effectiveness of FluMist Quadrivalent in children during the 2015 to 2016 influenza season, ranging from 46% to 58%. The fifth study, conducted by the US CDC did not demonstrate statistically significant effectiveness of FluMist Quadrivalent.

Influenza circulation in the US, UK and Finland

Based on national influenza surveillance data, approximately 72 to 73% of the strains that circulated during the 2015 to 2016 flu season in the US and the UK were A strains, with the remaining 27 to 28% being B strains. In both countries H1N1pdm09 strains predominated, accounting for at least 70 to 80% of the A strains. B strain circulation varied by country with B/Victoria lineage strains accounting for approximately 96% of the isolates in the UK while in the US approximately 43% of the strains were from the B/Yamagata lineage, 20% from the B/Victoria lineage and for 36% of the strains the lineage was not determined.[43] In Finland, in children 0 to 4 years of age (the most relevant population given that FluMist Quadrivalent was used in 24 to 35 month old children), 79% of strains detected were influenza A and 21% were influenza B.[44] The vast majority of A strain cases in Finland were due to H1N1 strains.

Assessing vaccine efficacy and effectiveness

Randomised controlled trials (RCT) measure the efficacy of a vaccine, which is the percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated (or comparative vaccine group) under optimal conditions.

Observational studies measure the vaccine effectiveness, or, the ability of vaccine to prevent disease in real world community conditions. There are two main types: test negative case control and cohort studies performed for seasonal influenza vaccine effectiveness. Results from observational studies can vary based on study design, outcomes measured, population studied.

Influenza viruses undergo changes in their genetic makeup which results in the need to update the vaccine composition in order to provide the best chance for protection against circulating viruses. Influenza vaccines are evaluated in annual observational effectiveness studies to estimate their effectiveness against the circulating influenza strains. For methodological reasons, effectiveness estimates are expected to be lower than efficacy estimates and are subject to bias, which are adjusted using statistical methods.

[43] UK data derived from review of weekly Public Health England influenza reports, with US data from weekly CDC influenza reports.
[44] Nohynek et al., Nordic Vaccine Meeting, April 2016.

Traditionally, the grading of evidence places RCT above the observational studies when the evidence is assessed by regulatory and policy making bodies. The licensure of FluMist (trivalent version) and FluMist Quadrivalent in the US, Canada and the EU was based on extensive data generated from RCTs, including 9 paediatric Phase III RCTs. This data is the primary evidence provided in the FluMist Quadrivalent submission currently under evaluation by the TGA.

Study designs

During the 2015 to 2016 influenza season, the US CDC conducted a test-negative vaccine effectiveness study evaluating the effectiveness of US influenza vaccines. The CDC study enrolled subjects 6 months of age through older adults; however, the data presented below are for children 2 through 17 years of age.

The sponsor study (Influenza Clinical Investigation for Children (ICICLE) study; Study MA-VA-MEDI3250- 1116) is a US four-year post-marketing commitment agreed to with the FDA upon the licensure of FluMist Quadrivalent, with the 2015 to 2016 season being the third season of the study. Additional details regarding the design of the study as well as result for the first year of the study (2013 to 2014 influenza season) were included in the FluMist Quadrivalent application and were recently published.[45] The study design was informed by FDA feedback received prior to approval of the FluMist Quadrivalent supplement;[46] and the analysis is consistent with the protocol that was submitted post approval. The study is a test-negative effectiveness study conducted in the US, similar to the test negative CDC study, and enrols children 2 through 17 years of age. An attempt was made in 2015 to 2016 to enrol children in the UK as well, but study enrolment was well below target (50 children with complete data versus target enrolment of 500) and was insufficient to yield meaningful estimates of vaccine effectiveness. As a result, only US data are presented below.

In the UK, FluMist Quadrivalent was administered as part of a national childhood immunisation program to children 2 through 4 years of age, to children in school years 1 and 2 (approximately 5 to 7 years of age) and, in pilot areas, to children through 11 years of age. The effectiveness of the vaccine was assessed by Public Health England in a test-negative effectiveness study among children 2 to 17 years of age.

In Finland, FluMist Quadrivalent was administered to children 24 to 35 months of age. A large cohort study was conducted using Finland's comprehensive databases of healthcare utilization and laboratory data to evaluate effectiveness of the vaccine. The study results were presented at the Nordic Vaccine Meeting in April 2016.

The US Department of Defense also conducted a test-negative vaccine effectiveness study during the 2015 to 2016 influenza season.[47] The study enrolled military dependents 2 through 17 years of age presenting to medical facilities with influenza-like illness. Influenza was confirmed by RT-PCR or culture and subjects' vaccination status was confirmed from electronic medical records.

Table 11 (below) provides a summary of the study designs of the above-mentioned vaccines effectiveness studies (with the exception of the Department of Defense study).

[45] Caspard H et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2-17 years of age in 2013-2014 in the United States. Vaccine. 2016;34(1):77-82.
[46] US approval for the quadrivalent was sought via a supplement to the trivalent licence not as a separate licence like other markets.
[47] additional study since the sponsor presented at the ATAGI Industry day.

Table 11. FluMist Quadrivalent/FluMist Quadrivalent effectiveness study designs for studies conducted in the US, UK and Finland

	US – CDC [1]	US - MA1116 [2]	UK PHE [3]	Finland [4]
Study design	Test-negative case control (TNCC)	Test-negative case control (TNCC)	Case control (TNCC)	Cohort study (4 national registers linked together with patient PID code)
Inclusion/ Exclusion criteria	Inclusion: ARI with cough OR fever, duration ≤7 days Exclusion: vaccination ≥ 14 days	Inclusion: ARI with fever ≥100.0°F (37.8°C), duration <5 days Exclusion: vaccination ≥ 14 days	Inclusion: ILI (individual presenting in primary care with an acute respiratory illness with physician-diagnosed fever or complaint of feverishness in ≤7 days) Exclusion: vaccination ≥ 14 days	Lab confirmed influenza (sentinel) and clinical ILI (1^{ry} care outpatient with ICD10 codes J09-J11 or ICPC2 R80 in AvoHILMO) – centralized in National Register of Primary Health Care (NRPHC)
stat analysis	1ry analysis excludes children <9yo with partial vaccination *(? In 2015)*	1ry analysis includes all children with a documented vaccination (even partial)	* Children receive only 1 dose of LAIV in NIP (risk-groups receive 2 doses)	N/A
Vaccination status	Documented in medical record or state immunization registry (or self-report)	Documented in medical record or state immunization registry (no self-report)	Standardised questionnaire completed by the GP while swabbing the patient during the consultation	National Vaccination Register (NVR) from public 1ry HC
Lab tests	Several local site laboratories / nasal and throat swabs	Central lab / nasal swabs only	Country schemes (England: RCGP or SMN) / nose and throat swabs	Collected by National Infectious Disease Register (NIDR)
Collection sites	5 sites	8 sites (4 sites in previous seasons) – 2 common with CDC	5 primary care influenza sentinel swabbing surveillance schemes	clinical microbiology laboratories from 20 HC districts

[1]Gaglani et al. J Infect Dis. (2016); [2]Caspard et al. Vaccine. 2016 Jan 2;34(1):77-82; [3]Pebody et al. Euro Surveill. 2015;20(36); [4]personal communication

Effectiveness data

The effectiveness estimates for FluMist Quadrivalent during the 2015 to 2016 season are presented in Table 10 (above), and the data for each study is discussed in the text below.

US CDC Study

The data summarised here is considered preliminary as final, end of season analyses are pending. CDC also noted limitations in the data due to the small sample size in the analyses. Final results for the 2015- 16 vaccine effectiveness study would be anticipated to be available later this year.

Including unvaccinated children, IIV recipients and FluMist Quadrivalent recipients, the CDC study effectiveness estimates were based on 2,132 subjects. The preliminary effectiveness estimates for all strains combined for FluMist Quadrivalent did not demonstrate statistically significant overall effectiveness in children 2 through 17 years of age, with a reported effectiveness estimate of 3% (estimated 95% CI: -50; 40). The preliminary effectiveness estimates for all strains combined for IIV was 63% (estimated 95% CI: 55; 75). For circulating H1N1 strains, the effectiveness of FluMist Quadrivalent was -21% (estimated 95% CI: -50; 30); IIV had a corresponding effectiveness estimate of 65% (estimated 95% CI: 50; 80). For circulating B/Yamagata strains the estimates were -4% (estimated 95% CI: -50; 55) and 64% (estimated 95% CI: 25; 85) for FluMist Quadrivalent and IIV, respectively. For circulating B/Victoria strains the estimates were 31% (estimated 95% CI: -50, 70) and 56% (estimated 95% CI: 25, 70), respectively. As noted above, these are preliminary results which may change slightly in the final analyses.

US sponsor study (ICICLE; Study MA-VA-MEDI3250-1116)

The data summarised here are preliminary. Final data from the 2015-16 season study are anticipated to be available (as an interim report) in September 2016.[48]

The US sponsor study results (as of 16 June 2016) are based on 1,012 US subjects retained in the effectiveness analysis. In the study, FluMist Quadrivalent demonstrated an overall effectiveness of 46% (95% CI: 7; 69) for all strains combined in subjects 2 through 17 years of age. The corresponding estimate for IIV was 65% (95% CI: 48; 76). For H1N1 strains, the estimate for FluMist Quadrivalent was 50% (95% CI: -2; 75) while for IIV the estimate was 71% (95% CI: 51; 82). For B strains the estimates were 47% (95% CI: -18; 76) and 56% (95% CI: 21; 75) for FluMist Quadrivalent and IIV, respectively. When examined by B lineage, point estimates for effectiveness were higher for B/Victoria strains (FluMist Quadrivalent: 69% (95% CI: -7, 91); IIV: 64% (95% CI: 20, 84)) than for the B/Yamagata strains (FluMist Quadrivalent: -9%, (95% CI: -223, 63); IIV: 45% (95% CI: -43, 79)), though the number of cases of B/Yamagata is small and confidence intervals are very broad.

UK Public Health England study

The data summarised here are provisional end of season estimates. Final estimates expected to be published later in the summer as indicated by Public Health England.

The study conducted by Public Health England enrolled 666 children total, including 112 FluMist Quadrivalent recipients. Overall effectiveness of FluMist Quadrivalent was 57.6% (95% CI: 25, 76); overall effectiveness for IIV was not reported by the PHE, likely due to the limited use of IIV in children in the UK.[49] For FluMist Quadrivalent, effectiveness for H1N1 strains was 42% (95% CI: -9, 69) with 100% (13, 100) effectiveness initially reported for the IIV. For B strains, which were predominantly from the B/Victoria lineage, the effectiveness of FluMist Quadrivalent was reported as 81% (40, 94), with IIV effectiveness of 56% (-122, 91).

Finland National Institute for Health and Welfare (THL) study

The cohort study conducted in Finland included 58,857 children 2 to 3 years of age: 46,119 unvaccinated, 8,323 FluMist Quadrivalent recipients, and 4,415 IIV recipients. Lab-confirmed influenza diagnosed during routine medical visits was reported by 321 (0.70%) unvaccinated children, 30 (0.36%) FluMist Quadrivalent recipients, and 11 (0.25%) IIV recipients. The effectiveness for all strains combined in children 24 to 35 months of age was 46.2% (95% CI: 22: 63) for FluMist Quadrivalent and 59.7% (95% CI: 27; 78) for IIV. For type A strains the estimates were 46.7% (95% CI: 20; 65) and 77.7% (95% CI: 46; 91), respectively. For B strains the estimates were 35.0% (95% CI: -56; 73) and -20.2% (95% CI: -179; 48), respectively. The effectiveness estimates presented were adjusted for prior vaccination.

US Department of Defense study

Vaccine effectiveness data for the 2015-16 season are also available from the US DoD laboratory based influenza surveillance network covering military dependents aged 2 to 17 years of age.[50] In a similar test negative design, the estimates for all strains combined were 53% (estimated 95% CI: 25, 70) for FluMist Quadrivalent and 66% (estimated 95% CI: 50, 75) for IIV. For the H1N1pdm09 strain, vaccine effectiveness estimates were 15% (estimated 95% CI: -20, 70) for FluMist Quadrivalent and 68% (estimated 95% CI: 45, 85)

[48] Note: as this is a four year study, an interim report is generated for each year of the study. It was planned to then prepare a final report summarising the data from all seasons upon completion of the four years.
[49] Public Health England (PHE) Influenza vaccine effectiveness in adults and children in primary care in the UK: provisional end-of-season results 2015-16.
[50] CDC presentation – ACIP meeting, 22 June 2016 CDC

for IIV. For B strains, the estimates were 84% (estimated 95% CI: 65, 90) for FluMist Quadrivalent and 63% (estimated 95% CI: 35, 80) for IIV.

Summary of prior year vaccine effectiveness data

Data from the 2014 to 2015 season from the US, UK and Canada indicate that both FluMist Quadrivalent and IIV showed low to no effectiveness for circulating strains that were significantly mismatched to the vaccine strains.[51,52]

Data from the 2013 to 2014 season indicted that there was an issue with the effectiveness of the H1N1 strain for FluMist Quadrivalent in the US, however, data from Canada indicated that the vaccine was effective and data from the UK also suggested that the vaccine had a positive impact on the immunization program that year.[53]

The finding of lower than expected effectiveness in the US in the 2013 to 2014 season was associated with a genetic mutation on the A/California H1N1 vaccine virus strain that affected the thermostability of the virus. A replacement strain (A/Bolivia) was identified which lacked this genetic mutation and was incorporated into the vaccine for the 2015-16 season. Data from the sponsor's 2015 to 2016 observational study, as well as from Finland and the UK, indicate that the A/Bolivia strain had improved effectiveness against influenza A (H1N1) strains compared to that previously observed in the 2013 to 2014 influenza season. However, these data also suggest that further improvements on the H1N1 component of the vaccine may be needed in order to optimise the effectiveness the vaccine. Research is underway to further understand and characterise the virus life cycle of candidate H1N1 vaccine strains.

Rest of World status

The sponsor has shared the CDC findings with Regulators in all markets where the vaccine is licensed; this includes the US FDA, the EMA, Health Canada and the Israeli Ministry of Health. These health authorities have indicated that the review and approval of the supplements and variations supporting the authorisation of the 2016-17 formulation will continue as planned.

Specifically, the US FDA has stated that: '[The] FDA continues to find that the benefits of FluMist Quadrivalent outweigh any potential risks. As such, the agency has determined that specific regulatory action is not warranted at this time. This determination is based on FDA's review of manufacturing and clinical data supporting licensure noted above, the totality of the evidence presented at the ACIP meeting, taking into account the inherent limitations of observational studies conducted to evaluate influenza vaccine effectiveness, as well as the well-known variability of influenza vaccine effectiveness across influenza seasons'.[54] The FDA has also recently approved the FluMist Quadrivalent 2016 to 2017 seasonal supplementary application.

In addition, Public Health England, after reviewing the data has noted that: '*Based on intelligence to date, there is no reason to change current recommendations regarding use of the children's nasal spray vaccine in the UK. We're delighted that the UK leads the way in offering this vaccine to children and we remain confident that the vaccines used in the Annual Flu Vaccine programme are the most effective that are currently available in protecting both those vaccinated and in reducing transmission of the flu virus in our communities*'.[55]

[51] Flannery presentation – ACIP meeting, June 22 2016; Pebody et al., Eurosurveillance 2015 and Skowronski Clin Infect Dis 2016
[52] Pebody et al., Eurosurveillance 2014
[53] Kwong et al., Vaccine 2015 and Skowronski et al., JID 2015
[54] FDA information regarding FluMist Quadrivalent Vaccine; FDA public website statement (27 June 2016)
[55] Public Health England: Child flu vaccine plays important role in annual flu programme; 23 June 2016

The sponsor will continue the dialogue with the Regulators regarding any new information on the CDC findings and our own work to identify an improved H1N1 candidate vaccine strain for future seasons.

Sponsor's interpretation

In four of five observational studies describing the effectiveness of FluMist Quadrivalent during the 2015 to 16 season, FluMist Quadrivalent provided statistically significant moderate effectiveness, ranging from 46% to 58%. This level of effectiveness is comparable to vaccine effectiveness against vaccine- similar strains estimated in observational studies during recent prior seasons (2010 through 2014) for FluMist Quadrivalent and IIV in children. The results from the two of three studies conducted in the US by the CDC, Department of Defense and the sponsor differ in their estimates of the overall effectiveness of FluMist Quadrivalent, with the sponsor's study showing statistically significant effectiveness of 44%, the Department of Defense 53%, and the CDC study showing no measurable effectiveness.

The reasons for these differing estimates are not clear. The CDC has stated the data are still being validated and reportedly may change slightly (for example, based on medical record confirmation of vaccination receipt). It is also possible that slightly different definitions of influenza illness may contribute to the findings (for example, the sponsor's enrolment criteria require subjects to have fever/feverishness and less than 5 days since symptom onset compared to fever/feverishness or cough and less than 7 days since symptom onset in the CDC study). It is also possible that differences in baseline characteristics of the subjects enrolled across the 2 studies could contribute to the results. Lastly, the small number of FluMist Quadrivalent recipients in both studies results in vaccine effectiveness estimates that are more vulnerable to random effects, as evidenced by the wide confidence intervals for the estimates.

Given the known limitations of observational research and test negative vaccine effectiveness studies specifically, failure to observe vaccine effectiveness in one study does not invalidate the findings of the other 4 studies in which statistically significant effectiveness was observed. The preponderance of the available evidence supports the effectiveness of FluMist Quadrivalent and a risk/benefit analysis conducted by the sponsor supports use of the vaccine for the upcoming 2016 to 2017 influenza season.

Request for ACPM advice (ACPM second round)

The following documents were reviewed by the Delegate in preparation for referral to ACPM for a second-round discussion.

1. The sponsor's Vaccine effectiveness update' (see above).
2. FDA statement regarding FluMist Quadrivalent.
3. Results from 2015 to 2016 Public Health England.
4. The published results of the CDC study, noting that there are more recent preliminary results from the sponsor within their vaccine effectiveness update.[56]
5. Results from the sponsored study (MA-VA-MEDI3250-1116) for which there are more recent preliminary data from the sponsor described in their vaccine effectiveness update.[57]

[56] Gaglani M et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013–2014 in the United States. J Infect Dis (2016) 213 (10): 577
[57] Caspard H et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2-17 years of age in 2013-2014 in the United States. Vaccine. 2016;34(1):77-82.

6. Results from a Finnish Cohort Study (summary data only, included in the sponsor vaccine effectiveness update).
7. Results from a US Department of Defense Study (summary data only, included in the sponsor vaccine effectiveness update).

Delegate's summary of the sponsor's Vaccine effectiveness update (submitted for ACPM advice)

The US CDC, US Department of Defense, sponsored Study US MA-VA-MEDI3250-1116and UK Public Health England studies were all test negative case-control studies, where patients with medically attended respiratory illness were enrolled and tested with sensitive and specific assays for influenza virus. The odds ratio was calculated from the rate of influenza vaccination among those with influenza, compared with those who have a negative test result. Multivariate logistic regression was used to control for potential confounders. Effectiveness was calculated as follows: (1 − odds ratio) x 100.[58]

The Finnish study was a cohort study and included 58,857 children 2 to 3 years of age: 46,119 unvaccinated, 8,323 FluMist Quadrivalent recipients, and 4,415 IIV recipients.

Study design for the included studies is summarised in Table 10 taken from sponsor response document. The summary table in the sponsor's response presents a snapshot of the effectiveness data from these studies.

Table 10. FluMist Quadrivalent/FluMist Quadrivalent effectiveness data from studies conducted in the US, UK and Finland

2015-2016 Effectiveness Data from US, UK, and Finland

	FluMist Effectiveness					IIV Effectiveness				
	CDC	MEDI	PHE[1]	THL[2]	DoD	CDC	MEDI	PHE[1]	THL[2]	DoD
All strains combined	3% (-50, 40)[3]	46% (7, 69)	58% (25, 76)	46% (22, 63)	53%[3] (25, 70)	63% (55, 75)[3]	65% (48, 76)	Not provided	60% (27, 78)	66%[3] (50, 75)
H1N1 strains	-21% (-50, 30)[3]	50% (-2, 75)	42% (-9, 69)	47%[4] (20, 65)	15%[3] (-20, 55)	65% (50, 80)[3]	71% (51, 82)	100% (13, 100)	78%[4] (46, 91)	68%[3] (40, 85)
B strains	14% (-50, 50)[3]	47% (-18, 76)	81% (40, 94)	35% (-56, 73)	84%[3] (65, 95)	65% (50, 80)[3]	56% (21, 75)	56% (-122, 91)	-20% (-179, 48)	63%[3] (35, 80)

CDC = US Centers for Disease Control and Prevention (162 FluMist subjects); **DoD** = US Department of Defense; **MEDI** = MedImmune (101 FluMist subjects); **PHE** = Public Health England (112 FluMist subjects); **THL** = National Institute for Health and Welfare, Finland (8323 individuals received FluMist)

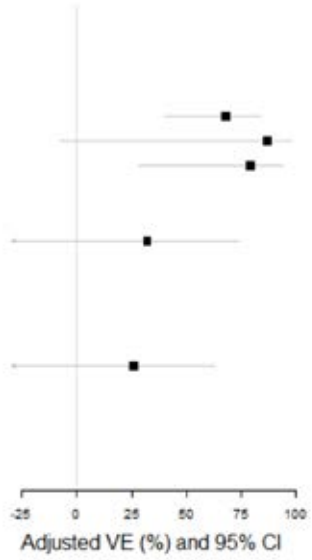
Sources: Telephone calls with CDC (May 17 and June 1); email exchange with PHE June 10; MedImmune data June 14 2016; THL presentation April 28-29 2016
[1] Confidential personal communication, June 11, 2016. [2] Cohort study; design differs from CDC, PHE and MedImmune studies. [3] Confidence intervals estimated from figures [4] Estimates for all A strains; A/H1N1 viruses were the predominant circulating A strains

The following figure (Figure 5, from Gaglani et al.) describes the 2013 to 2014 results of the CDC study, with a breakdown of cases stratified by vaccination history.**Error! Bookmark not efined.**

[58] Pavia A. Influenza Vaccine Effectiveness: Mysteries, Enigmas, and a Few Clues. J Infect Dis (2016) 213 (10): 1521-1522.

Figure 5. Results from the CDC study (2013 to 2014), stratified by vaccination history

pH1N1 Vaccination History 2013-14 and 2012-13	Total N	Influenza Cases N (%)	VE %
Current season IIV			
Current and prior season IIV	244	15 (6)	68
Current season IIV and prior season LAIV	22	1 (5)	87
Current season IIV only	53	3 (6)	76
Current season LAIV			
Current and prior season LAIV	42	7 (17)	32
Current season LAIV and prior season IIV	36	6 (17)	NR
Current season LAIV only	8	2 (25)	NR
Prior season only			
Prior season IIV	89	14 (16)	26
Prior season LAIV	16	2 (13)	NR
Unvaccinated			
Unvaccinated both seasons	278	63 (23)	Reference



It is noted that the number of children in the CDC study who received Q/LAIV in both seasons was small (n = 42), with confidence intervals wide and overlapping.

The FDA concluded that both US studies (the CDC study and the sponsor's study) showed lower effectiveness of FluMist Quadrivalent compared to IIV, and neither US study showed statistically significant effectiveness of FluMist Quadrivalent against influenza A (H1N1). However, three of the studies (the sponsor's US study, the UK. study, and the Finland study) showed statistically significant effectiveness of FluMist Quadrivalent against all influenza strains combined, ranging from 46% to 58% effectiveness. This level of overall effectiveness was deemed comparable to vaccine effectiveness against vaccine-similar strains obtained from observational studies in children for both FluMist and inactivated influenza vaccines in prior seasons. 'In contrast, CDC's US study did not show statistically significant effectiveness of FluMist Quadrivalent for all influenza strains combined. Reasons for discordant results among the studies, particularly between the two US studies, were not clear but may include limitations inherent in observational study designs' (FDA statement).

In the 2013 to 2014 influenza season, when lower than expected effectiveness of FluMist Quadrivalent was first observed, possible problems with thermostability of the Influenza A (H1N1) vaccine strain led to a manufacturing change that was implemented in time for the 2015 to 2016 influenza season. A replacement strain (A/Bolivia) was incorporated into the vaccine for the 2015 to 16 season. Available data from observational studies of influenza vaccine effectiveness for the 2015 to 2016 influenza season suggest that this change led to improved FluMist Quadrivalent effectiveness against Influenza A (H1N1) compared to that previously observed in the 2013 to 2014 influenza season. 'However, these data also suggest that factors other than thermostability may be contributing to the lower than expected effectiveness of FluMist Quadrivalent observed in recent years' (FDA statement).

Other health authorities have indicated that the review and approval of the supplements and variations supporting the authorisation of the 2016 to 2017 formulation will continue as planned.

Request for ACPM advice (ACPM second-round)

The committee is requested to provide advice on the following specific issues:

1. Do the data influence the previous recommendation to register this product?
2. In the event of registration, could ACPM advise on the suggested wording for the PI, based on the preliminary effectiveness data provided by the sponsor?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations (ACPM second round)

The Advisory Committee on Prescription Medicines (ACPM) agreed with the Delegate and considered FluMist Quadrivalent nasal spray 200 µL dose containing $10^{7.0 \pm 0.5}$ FFU of each of the 4 influenza virus strains to have an overall positive benefit–risk profile for the proposed indication:

> *'FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.'*

In making this recommendation the ACPM assessed the preliminary vaccine effectiveness data recently submitted by the sponsor together with published effectiveness studies from Finland and the UK and advised that the risk benefit balance was sufficient to support registration of this product.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Do the data influence the previous recommendation to register this product?*

The ACPM assessed the vaccine effectiveness data recently submitted for consideration by the TGA Delegate. Although the lack of vaccine effectiveness in several studies was of concern, it was noted that they were based on relatively small observational studies and there was heterogeneity in vaccine effectiveness estimates from different countries and studies. Descriptions of seasons of vaccine failure in some but not all geographic regions where quadrivalent LAIV was available remains important but does not alter the risk benefit assessment on which the recommendation for registration was made. The committee advised there were no changes to the position expressed at the ACPM Meeting 310 (June 2016) to support product registration.

2. *In the event of registration, could ACPM advise on the suggested wording for the PI, based on the preliminary effectiveness data provided by the sponsor?*

The ACPM suggested the following statement to be included in the PI in regards to the preliminary effectiveness data:

'Observational studies that have estimated vaccine effectiveness have generally confirmed a protective effect of LAIV, although there does appear to be variation in estimated vaccine effectiveness. The reasons for vaccine failure are not yet known and are the subject of ongoing studies'. It is also recommended that tabulated effectiveness outcomes be included in the PI where possible and when published data are available.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product. This would include vaccine effectiveness monitoring as part of the risk management plan with annual vaccine effectiveness updates to be provided to the TGA.

Post-ACPM note:

The sponsor had concerns regarding the two requested ACPM PI amendments, as follows:

- *Observational studies statement: The sponsor was concerned about the term 'vaccine failure' within the proposed observational studies PI text. As discussed above in the Delegate's comments sections and Sponsor responses, the preliminary data for the 2015/2016 Northern Hemisphere influenza season vaccine effectiveness studies have generally confirmed a protective effect (ie vaccine effectiveness) with only a single study (the CDC study) suggesting low to no overall effectiveness.*

The Delegate acknowledged this concern and the final PI wording was modified (refer Attachment 1 for final PI wording).

- *Inclusion of the effectiveness outcomes within the PI: The observational studies are small season specific (currently Northern hemisphere only) studies conducted by independent public health bodies and the Sponsor, with final outcomes not available until approximately 6 months post season. The vaccine effectiveness data rapidly become out of date. Inclusion of 2015-2016 data now within the PI would result in out-of-date information at the time of launch. Given that there is no process to quickly update this type of information within a PI, it would always be a few seasons out of date and thus limited benefit to the prescriber.*

The Delegate acknowledged that these would be difficult to include within the PI and the specific season vaccine effectiveness outcomes were subsequently not included within the approved PI.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of FluMist Quadrivalent influenza virus vaccine nasal spray applicator, live attenuated containing 10000000 FFU/strain/0.2 mL dose for nasal administration, indicated for:

> *'FluMist Quadrivalent is indicated for the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.'*

Specific conditions of registration applying to these goods

Supply of Flumist Quadrivalent (Q/LAIV) is not permitted until such time that sponsor provides evidence to satisfy the TGA that the following conditions are met:

- *Implementation of the FluMist Quadrivalent influenza virus vaccine nasal spray Risk Management Plan (RMP)*: EU-RMP version 7.0 (dated 2 December, data lock point 26 October 2015) with Australian Specific Annex version 3.0 (dated 4 October 2016) and any future updates as agreed with the TGA. This includes a commitment to report on annual vaccine effectiveness studies.
- *Batch release testing by the TGA*: It is a condition of registration that all independent batches of Flumist Quadrivalent (Q/LAIV) imported into Australia are not released into the Australian market for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.
- *Potency FFA assay development*: The requested samples and reagents should be provided to facilitate assay development at least 12 months prior to the receipt of any consignments of the vaccine.
- *Development of an assay control for the FFA*: During the evaluation phase, the sponsor was asked to develop a FFA assay control in collaboration with the TGA. The Sponsor should submit a work plan, review availability and nominate material for the

development of such a standard in collaboration with the TGA at least 12 months prior to the supply of the vaccine in Australia.

Attachment 1. Product Information

The PI for FluMist Quadrivalent approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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https://www.tga.gov.au