Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Quadrivalent live attenuated influenza vaccine

Proprietary Product Name: FluMist Quadrivalent

Sponsor: Astra Zeneca Pty Ltd

First Round: 10 October 2015

Second Round: 10 March 2016

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Copyright
© Commonwealth of Australia 2017
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

List of common abbreviations 5

1. Introduction 7

2. Clinical rationale 7

3. Contents of the clinical dossier 8

3.1. Scope of the clinical dossier 8

3.2. Paediatric data 8

3.3. Good clinical practice 8

4. Pharmacokinetics 9

5. Pharmacodynamics 9

6. Dosage selection for the pivotal studies 9

7. Clinical efficacy 9

7.1. Pivotal efficacy studies for use of Q/LAIV 9

7.2. Other efficacy studies 24

7.3. Analyses performed across trials 26

7.4. Evaluator's conclusions on clinical efficacy 30

8. Clinical safety 31

8.1. Studies providing evaluable safety data 31

8.2. Patient exposure 31

8.3. Adverse events 33

8.4. Deaths and other serious adverse events 37

8.5. Laboratory tests 37

8.6. Post-marketing experience 38

8.7. Evaluator's overall conclusions on clinical safety 42

9. First round benefit-risk assessment 43

9.1. First round assessment of benefits 43

9.2. First round assessment of risks 43

9.3. First round assessment of benefit-risk balance 44

10. First round recommendation regarding authorisation 44

11. Clinical questions 44

12. Second round evaluation 44

13. Second round benefit-risk assessment 44

14. References 45

15. Addendum to the clinical evaluation report 45

15.1. Clinical question for this addendum 45

15.2. Contents of the clinical dossier ____ 45
15.3. Clinical efficacy ____ 46
15.4. Conclusions about available clinical data ____ 53
15.5. References for the clinical addendum ____ 54

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
att	Attenuated
BD	Becton Dickinson
BFS	Blow-fill-seal
ca	Cold adapted
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract research organization
CSR	Clinical study report
EMA	European Medicines Agency
EU	European Union
FFU	Fluorescent focus units
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HAI	Haemagglutination inhibition
HIV	Human immunodeficiency virus
ILI	Influenza-like illness
ITT	Intent to Treat
MDV	Master donor virus
MAA	Marketing Authorisation Application
MN	Microneutralisation
MSW	Medically significant wheezing
NA	Neuraminidase
NAI	Neuraminidase inhibiting

Abbreviation	Meaning
NOCD	New onset chronic disease
PIP	Paediatric Investigational Plan
Q/LAIV	Quadrivalent Live Attenuated Influenza Vaccine (FluMist Quadrivalent)
SAE	Serious adverse event
SE	Solicited (reactogenicity) events
SPC	Summary of Product Characteristics
TIV	Trivalent inactivated vaccine
ts	Temperature sensitive
US CDC	Centers for Disease Control and Prevention of the United States of America
US DHHS	United States Department of Health and Human Services
US FDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization
wt	Wild-type

1. Introduction

This is a submission to register a new chemical entity, FluMist Quadrivalent, quadrivalent live attenuated influenza vaccine (Q/LAIV) nasal spray for the prevention of influenza.

This is a live vaccine for the prevention of seasonal influenza.

The proposed indication is the prevention of influenza in children and adolescents from 24 months to less than 18 years of age.

The submission proposes registration of the following dosage forms and strengths: each 200 µL dose of Q/LAIV is formulated with 6.5 to 7.5 log10 FFU (fluorescent focus units) of live attenuated influenza virus reassortants, propagated in specific pathogen free (SPF) eggs, for each of the four strains selected for the specific influenza season: 2 Type A influenza strains (A/H1N1 and A/H3N2) and 2 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 200 µL (administered as 100 µL per nostril), followed by a second 200 µL dose (100 µL 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 200 µL (administered as 100 µL per nostril) each year.

2. 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.[1] 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.[2]

In humans, influenza illness is caused mainly by two types of viruses: influenza A (with multiple subtypes categorised by haemagglutinin (HA) and neuraminidase (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

[1] World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2012 2013 northern hemisphere influenza season.
[2] Newall A et al. Influenza-related disease: the cost to the Australian healthcare system. Vaccine. 2008 Dec 9;26(52):6818-23.

lineage will be primarily responsible for annual epidemics caused by influenza B.[3] Some seasons include influenza B viruses of both lineages, and antibodies specific for one influenza B virus lineage cross react poorly with viruses from the other lineage.[4] 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 Centers for Disease Control and Prevention (CDC), complete replacement of trivalent influenza vaccines with quadrivalent vaccines in all age groups in the United States of America (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.[5]

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The objective of the development plan was to demonstrate the comparability of Q/LAIV to 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 FluMist, 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
- An Introduction, Clinical and non-clinical Overview. Summary of Clinical and non-clinical Efficacy, Summary of Clinical Safety, and literature references.

3.2. Paediatric data

The submission included paediatric efficacy/safety data.

3.3. Good clinical practice

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

[3] 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
[4] 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.
[5] 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.

4. Pharmacokinetics

Not applicable for vaccine studies.

5. Pharmacodynamics

Not applicable.

6. Dosage selection for the pivotal studies

Each dose contained $10^{7.0 \pm 0.5}$ FFU of each of 4 cold adapted (ca), attenuated (att), temperature sensitive (ts), 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 Becton Dickinson (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.

7. Clinical efficacy

7.1. Pivotal efficacy studies for use of Q/LAIV

7.1.1. Study MI-CP208

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 by comparing the 4 strain-specific serum HAI antibody GMTs post dosing.

7.1.1.1. Study design, objectives, locations and dates

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. Study design is shown in Table 1, below. Subjects 9 to 17 years of age (one dose group) were to receive one dose of investigational product on Day 0. Blood for the assessment of immune response was to be obtained on Day 0 prior to dosing and at 28 to 35 days after dosing. Subjects/legal representatives were given temperature logs to record a daily temperature during Days 0 to 14 post dosing. Three telephone contacts were to occur after study vaccination, that is at 3 to 5 days, 7 to 10 days, and 14 to 18 days post dose to monitor for safety. Additional telephone contacts were to occur approximately monthly (± 10 days) starting at approximately 2 months post dose (Day 60 ± 10 days) until the final phone contact at the end of the study (180 to 187 days post dose). Subjects 2 to 8 years of age (two dose group) were to receive two doses of investigational product. Dose 1 was to be given on Day 0, and Dose 2 was to be given 28 to 35 days later. The immunogenicity time point was at 28 to 35 days after Dose 1 for subjects with a history of prior seasonal influenza vaccination or 28 to 35 days after Dose 2 for subjects with no history of prior seasonal influenza vaccination. Safety logs/calls were identical after Dose 2 and continued until the final phone contact at the end of the study (180 to 187 days after the final dose). The duration of subject participation, including screening, was approximately 7 to 8 months for subjects who received two doses of investigational product and approximately 6 to 7 months for subjects who received one dose.

Table 1. Summary of the design of Q/LAIV clinical studies

Study Number (Year Conducted)	Age Range	Total Number of Subjects[a]	Q/LAIV Delivery System	Design	Primary Efficacy Objective
Pivotal Studies					
MI-CP208 (2010)	2 to 17 Years	2,312 (3:1:1)	Becton Dickinson Accuspray device (spray, 0.1 mL per nostril)	Randomized, double-blind, immunogenicity study of Q/LAIV compared to FluMist-V and FluMist-Y	Noninferior immunogenicity of each of 4 strains in Q/LAIV to corresponding strains in FluMist-V and FluMist-Y
MI-CP185 (2009)	18 to 49 Years	1,800 (4:1:1)	Becton Dickinson Accuspray device (spray, 0.1 mL per nostril)	Randomized, double-blind, immunogenicity study of Q/LAIV compared to FluMist-V and FluMist-Y	Noninferior immunogenicity of each of 4 strains in Q/LAIV to corresponding strains in FluMist-V and FluMist-Y
Supportive Study					
MI-CP206 (2009-10)	18 to 49 Years	1,800 (4:1:1)	Blow-fill-seal delivery system (liquid stream, 0.2 mL into a single nostril)	Randomized, partially blind immunogenicity study of Q/LAIV-BFS compared to FluMist-V and FluMist-Y	Noninferior immunogenicity of each of 4 strains in Q/LAIV-BFS to corresponding strains in FluMist-V and FluMist-Y

BFS = blow-fill-seal; FluMist-Y = FluMist containing a B strain from the Yamagata lineage; FluMist-V = FluMist containing a B strain from the Victoria lineage; Q/LAIV = quadrivalent live attenuated influenza vaccine a: Ratio of Q/LAIV:FluMist-Y:FluMist-V.

Immunogenicity

Serum HAI antibody titres to strains antigenically matched to those contained in Q/LAIV (the same strains were contained in the two FluMist comparator vaccines) were examined. Two serum samples were obtained: on Day 0 prior to receipt of investigational product, and post dosing at the immunogenicity sample time point. The immunogenicity time point was 28 to 35 days after Dose 1 for all subjects aged 9 to 17 years of age and subjects 2 to 8 years of age with a history of prior seasonal influenza vaccination, or 28 to 35 days after Dose 2 for subjects 2 to 8 years of age with no history of prior seasonal influenza vaccination. At outline is available in Table 2, below.

Table 2. Study MI-CP208, outline of dosing, safety, and immunogenicity sample schedules

Dosing Group and Age Group	Vaccination History at Enrollment	Dosage Schedule in MI-CP208	Primary Safety Period(s)	Immunogenicity Sample Time Point
Two-dose group: children 2 to 8 years of age	Not previously vaccinated with seasonal influenza vaccine	2 doses (28 to 35 days apart)	28 days post Dose 1 and post Dose 2	28 to 35 days post Dose 2
Two-dose group: children 2 to 8 years of age	Previously vaccinated with seasonal influenza vaccine	2 doses (28 to 35 days apart)	28 days post Dose 1 and post Dose 2	28 to 35 days post Dose 1
One-dose group: children and adolescents (9 to 17 years)	Any	1 dose	28 days post Dose 1	28 to 35 days post Dose 1

Two formal analyses were planned for the study. The interim clinical study report contained an interim analysis that provided the final immunogenicity and 28 days post last dose safety assessments. All company staff were unblinded after this analysis was completed; however, study investigators and other site staff, study subjects, and research personnel directly associated with the conduct of this study remained blinded to the treatment assignment for individual subjects until the completion of the study. The final study report includes the previously reported final immunogenicity data and updated safety data to provide final safety data collected through 180 days post last dose.

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

In all studies included in this submission:

- Strain specific baseline serostatus was defined as serosusceptible if HAI antibody titres were < 8 and seropositive if > 8.
- Seroresponse was defined as a > 4 fold rise from baseline. Serosusceptible was defined as baseline strain specific HAI antibody titre of ≤ 8; a value of two was assigned for an HAI antibody titre reported as < 4.

7.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were male and female children 2 to 17 years of age, specific inclusion and exclusion criteria are shown below in Table 3.

Table 3. Study MI-CP208, inclusion and exclusion criteria

Inclusion criteria
· Male or female; · Age 2 through 17 years at the time of randomisation; · Written informed consent · Females of childbearing potential, unless surgically sterile (that is, bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), had sterile male partner, were pre-menarchal, or practiced abstinence, were required to use an effective method of avoiding pregnancy (including oral, transdermal, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide, or used of a condom with spermicide by the sexual partner) for 30 days prior to the first dose of investigational product and were to agree to continue using such precautions for 60 days after the final dose of investigational product. · A subject who was considered by the investigator to be at risk of pregnancy had to have a negative urine pregnancy test at screening and, if screening and Day 0 did not occur on the same day, on the day of vaccination prior to randomisation. · Able to complete follow up period of 180 days post last dose of vaccine as required by protocol; · Subject/legal representative was available by telephone; · Childs legal representative was able to understand and comply with the requirements of the protocol, as judged by the investigator.

Exclusion criteria
Subjects who met any of the following criteria were not eligible for entry into the study: · Acute illness or evidence of significant active infection at randomisation; · Fever ≥ 100.4°F (38.0°C) at randomisation; · History of asthma, or in children < 5 years of age, history of recurrent wheezing; · Any drug therapy from 15 days prior to randomisation or expected drug therapy through 28 days post last dose with the exception of the following classes/types of medications, which

Exclusion criteria
were allowed: contraceptives; topical corticosteroids, calcineurin inhibitors, or antifungals for uncomplicated dermatitis; chronic medications that were not initiated and/or did not have a dosage change within 90 days prior; · Current or expected receipt of immunosuppressive medications within a 28-day window around any dose, including an immunosuppressive dose of corticosteroids, which was defined as ≥ 20 mg/day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days (intranasal, intra-articular, and topical corticosteroids were permitted); · Receipt of immunoglobulin or blood products within 90 days before randomisation; · Receipt of any investigational drug therapy within 28 days prior to Dose 1 or planned receipt of any investigational drug therapy through 90 days after final dosing of investigational product · Receipt of any non-study vaccine within 28 days prior to randomisation or planned receipt of non-study vaccine through 28 days after final dosing; · Receipt of any non-study seasonal influenza vaccine within 90 days of Dose 1 or planned receipt of non-study seasonal influenza vaccine prior to 35 days post last dose of product; · Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV); · History of allergic disease or reactions likely to be exacerbated by any component of the investigational product including allergy to eggs, egg proteins, gentamicin, or gelatin or serious, life threatening, or severe reactions to previous influenza vaccinations; · Use of aspirin or salicylate containing medications within 28 days prior to randomisation or expected receipt through 28 days after final vaccination; · History of Guillain-Barré syndrome; · Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir, and zanamivir) within 28 days prior to first dose of investigational product or anticipated use of such agents within 28 days after last scheduled vaccination; · Known or suspected mitochondrial encephalomyopathy; · Pregnant or lactating female; · History of alcohol or drug abuse that, in the opinion of the investigator, would have affected the subject's safety or compliance with study; · Any condition that, in the opinion of the investigator, might have compromised the safety of the subject in the study or would interfere with evaluation of the safety or immunogenicity of the investigational products; · Subject, legal representative, or immediate family member of subject who was an employee of the clinical study site or who was otherwise involved with the conduct of the study; · A history of epilepsy, seizure, or an evolving neurological condition except that a single febrile seizure that occurred 3 or more years prior to enrolment would not have disqualified a subject.

7.1.1.3. Study treatments

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

· Q/LAIV (quadrivalent live, attenuated influenza vaccine containing two type B influenza strains) (N = 1,380); or

- trivalent FluMist containing an influenza B strain from the Yamagata lineage (FluMist-Y) (N = 460); or
- trivalent FluMist 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.

7.1.1.4. Efficacy variables and outcomes

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 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 4 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); and
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.

7.1.1.5. Randomisation and blinding methods

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. Eligible subjects were randomised in a 3:1:1 ratio to receive Q/LAIV, trivalent FluMist containing an influenza B strain from the Yamagata lineage (FluMist-Y), or trivalent FluMist containing an influenza B strain from the Victoria lineage (FluMist-V). An interactive voice response system (IVRS) system was used at screening (all subjects screened), at randomisation/assignment of Dose 1 (all eligible subjects), and assignment of Dose 2 (for randomised subjects age 2 to 8 years of age).

The IVRS that was used to assign the SID number to each subject at screening was used again for randomising each eligible subject to a treatment arm. The randomisation incorporated a block design and stratification by age (2 to 8 years, 9 to 17 years). For subjects 2 to 8 years of age only, randomisation was also stratified by previous seasonal influenza vaccination history.

7.1.1.6. Analysis populations

The Intent-to-Treat (ITT) Population included all randomised subjects. The As-Treated Population was defined as all subjects who received any investigational product. Treatment arm for this population was assigned according to the actual treatment received at Dose 1. The Safety Population included all subjects who received any investigational product and had safety data available. Treatment arm for safety analysis was assigned according to the actual treatment received at Dose 1.

Consistent with the protocol, 504 subjects 9 to 17 years of age were enrolled to receive a single dose of investigational product, and 1,808 subjects 2 to 8 years of age were enrolled to receive 2 doses of investigational product. Safety follow up was robust: the Safety Population and the evaluable subjects for post Dose 1 solicited symptoms each included 503 subjects 9 to 17 years of age, and 1,802 subjects and 1,794 subjects 2 to 8 years of age, respectively. For Dose 2 in subjects 2 to 8 years of age, the Safety Population included 1,734 subjects, and the number of

evaluable subjects for solicited symptoms analysis was 1,731. The evaluable Immunogenicity Population was slightly smaller: 500 subjects 9 to 17 years of age and 1,710 subjects 2 to 8 years of age.

7.1.1.7. Sample size

A total of 2,300 subjects were planned for this study. A total of 2,312 subjects were randomised; 2,305 received at least one dose of investigational product. Of the subjects randomised, 1,385 were in the Q/LAIV arm, 464 were in the FluMist-Y arm, and 463 were in the FluMist-V arm.

7.1.1.8. Statistical methods

In relation to the primary endpoint, the post dose serum HAI antibody GMTs for the A/H1N1 and A/H3N2 strains in Q/LAIV were compared to those in the combined FluMist-Y and FluMist-V arms, and the post dose serum HAI antibody GMTs for the B strains of the Yamagata and the Victoria lineage in Q/LAIV were compared to those in the FluMist-Y arm and FluMist-V arm, respectively. The non-inferior immune response was assessed by evaluating the upper bound of the two sided 95% confidence interval (CIs) for the strain specific HAI antibody GMT ratios (FluMist divided by Q/LAIV) to the non-inferiority margin of 1.5. If the upper bound of the 95% CIs were found to be ≤ 1.5 for all 4 strains, the immunologic non-inferiority of Q/LAIV compared to FluMist would be declared. No multiplicity adjustment was planned for the primary endpoint. Each of the 4 strain specific non-inferiority comparisons carried a one sided 2.5% type one error rate; therefore, the overall type one error rate associated with simultaneous coverage by all 4 CIs would necessarily be no more than 2.5%. For the secondary endpoints, the two sided 95% exact CIs for each of the proportions presented were constructed to provide population estimates. Test based asymptotic two sided 95% CIs were constructed for the proportion differences (Q/LAIV minus comparator) using the standardised (score) statistic under the assumption that the standardised statistic was asymptotically normally distributed.

7.1.1.9. Participant flow

Subject disposition is summarised by treatment arm in Table 4, below.

Table 4. Study MI-CP208 subject disposition; all subjects, ITT population

Disposition/Status	Q/LAIV	All FluMist [a]	FluMist-Y	FluMist-V	Total
Number of subjects randomized, N	1,385	927	464	463	2,312
Number of subjects dosed, n (%)	1,380 (99.6)	925 (99.8)	463 (99.8)	462 (99.8)	2,305 (99.7)
Number of subjects who received Dose 1 and were followed through 28 days post Dose 1, n (%)	1,362 (98.3)	915 (98.7)	458 (98.7)	457 (98.7)	2,277 (98.5)
Number of subjects who received Dose 1 and were not followed through 28 days post Dose 1, n (%)	18 (1.3)	10 (1.1)	5 (1.1)	5 (1.1)	28 (1.2)
Number of subjects who did not receive Dose 1, n (%)	5 (0.4)	2 (0.2)	1 (0.2)	1 (0.2)	7 (0.3)
Number of subjects who completed the study, n (%) [b]	1,350 (97.5)	898 (96.9)	448 (96.6)	450 (97.2)	2,248 (97.2)
Reasons Subjects Did Not Complete Study, n (%)					
Lost to follow- up	23 (1.7)	18 (1.9)	11 (2.4)	7 (1.5)	41 (1.8)
Withdrawal of consent due to adverse event	1 (0.1)	1 (0.1)	0	1 (0.2)	2 (0.1)
Withdrawal of consent due to solicited symptom	0	0	0	0	0
Withdrawal of consent for other reason	9 (0.6)	9 (1.0)	5 (1.1)	4 (0.9)	18 (0.8)
Death	0	0	0	0	0
Other	2 (0.1)	1 (0.1)	0	1 (0.2)	3 (0.1)

a All FluMist group refers to data from both the FluMist-Y arm and FluMist-V arm combined.
b Completion = follow-up for 180 days post last dose.

Seven of the 2,312 subjects randomised did not receive any dose of investigational product: one subject had received a non-study vaccine in the 28 days prior to Dose 1 in violation of Exclusion Criterion 8; one subject was randomised after randomisation had closed, one subject was wheezing in violation of Exclusion Criterion 3; and 4 subjects were not dosed due to subject/guardian decision. A total of 2,277 subjects (98.5%) were dosed and followed for safety through Day 28 post Dose. A total of 2,248 subjects (97.2%) completed the study. The most common reason for lack of study completion was 'lost to follow up'. Withdrawals were balanced across study arms. Two subjects were withdrawn by the parent/legal guardian due to an AE. A total of 1,727 two dose subjects (95.5%) received Dose 2 (see Table 5, below) and were followed for safety through Day 28 post Dose 2. For the two-dose group, sixty-three subjects did not receive Dose 2: 12 subjects failed to meet ongoing eligibility criteria, 34 subjects were unable to be scheduled for dosing within dosing window, 12 subjects were not dosed in accordance with subject/guardian decision, and 2 subjects were withdrawn from dosing by the parent (but not the investigator).

Table 5. Study MI-CP208 investigational product exposure at Dose 2, ITT Population

Category	Q/LAIV n (%) (N = 1,085)	All FluMist n (%) (N = 723)	FluMist-Y n (%) (N = 361)	FluMist-V n (%) (N = 362)	Total n (%) (N = 1,808)
Subjects who received investigational product	1,045 (96.3)	700 (06.8)	351 (97.2)	349 (96.4)	1,745 (96.5)
Received entire dose	1,045 (96.3)	699 (96.7)	350 (97.0)	349 (96.4)	1,744 (96.5)
Received at least half of dose	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.1)
Received less than half of dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who did not receive investigational product	40 (3.7)	23 (3.2)	10 (2.8)	13 (3.6)	63 (3.5)
Failure to meet ongoing eligibility	6 (0.6)	6 (0.8)	2 (0.6)	4 (1.1)	12 (0.7)
Participant/guardian decision	6 (0.6)	6 (0.8)	3 (0.8)	3 (0.8)	12 (0.7)
Adverse event	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.3)	2 (0.1)
Solicited symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unable to schedule within dosing window	24 (2.2)	10 (1.4)	5 (1.4)	5 (1.4)	34 (1.9)
Other	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)

7.1.1.10. Major protocol violations/deviations

The majority of protocol violations were either parent/legal guardian failure to collect complete solicited symptom data or missing/out of window follow-up telephone contacts or change in medication change after enrolment (which became an exclusion criteria). The number and type of deviations reported would not be expected to have an effect on the overall safety or immunogenicity conclusions of the study.

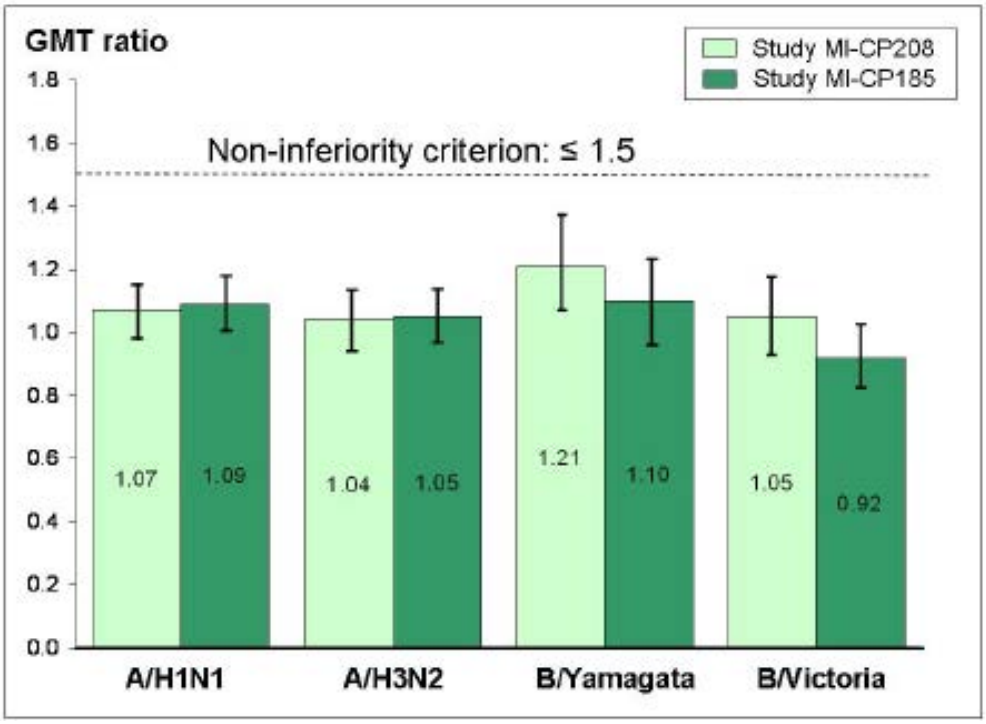
7.1.1.11. Baseline data

Study populations were well balanced according to baseline demographic factors, and the ITT Population was well represented by the Safety and Immunogenicity Populations. Follow-up was similar between study arms, and loss to follow-up was minimal.

7.1.1.12. Results for the primary efficacy outcome

For the primary endpoint of non-inferior immune response, 1,327 subjects in the Q/LAIV arm and 883 subjects in the All FluMist group (446 in the FluMist-Y arm and 437 in the FluMist-V arm) contributed data. The study met its primary objective of demonstrating the immunologic non-inferiority of Q/LAIV to two formulations of FluMist comparing the strain-specific GMTs post dosing, because the upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by Q/LAIV) was ≤ 1.5. Geometric mean titre (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) as shown in Figure 1, below.

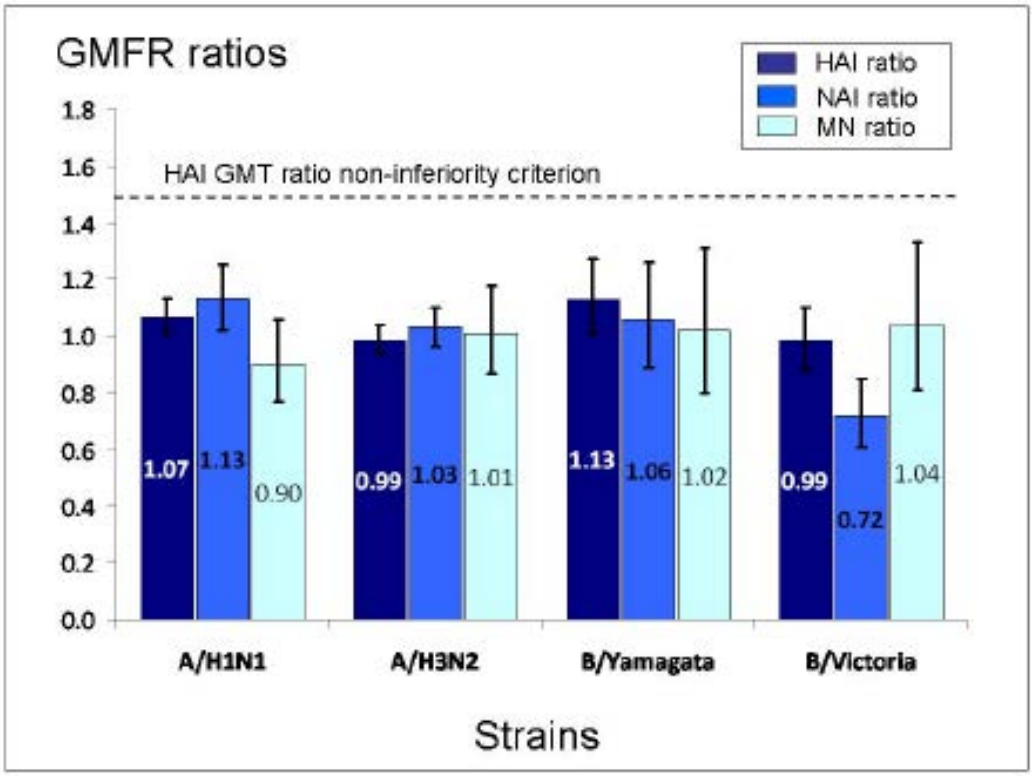
Figure 1. Post dose GMT ratios of HAI antibody, by strain for paediatric Study MI-CP208 and adult Study MI-CP185



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.

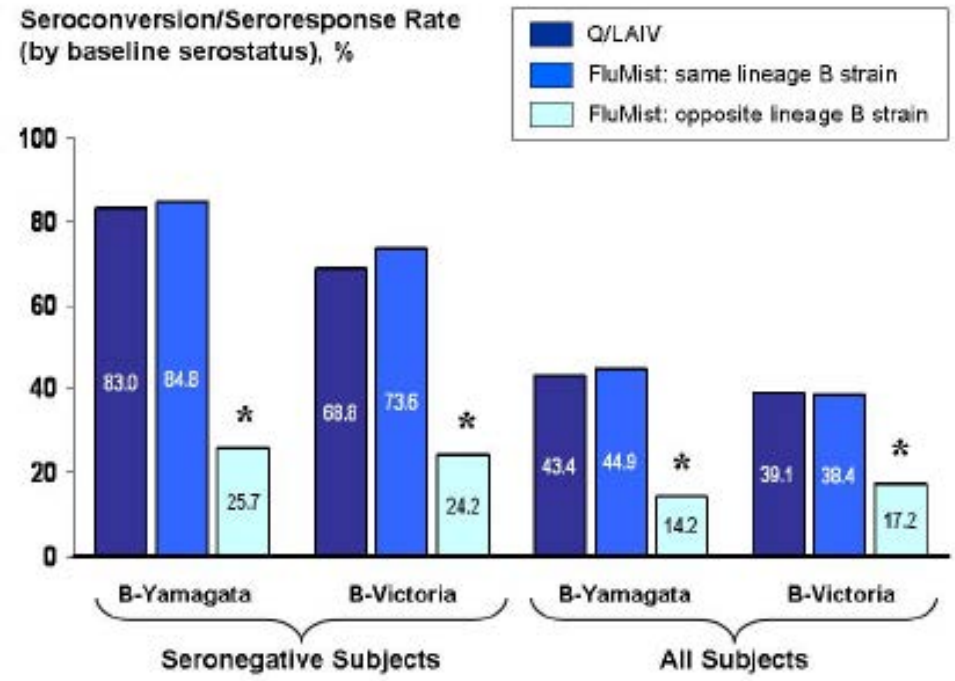
An analysis of geometric mean fold rise (GMFR) in HAI antibody titres, which adjusts for differences in baseline GMTs, supported the primary endpoint conclusion, as the upper bound of 95% CIs for the GMFR ratios for each of the four strains was ≤ 1.5: GMFRs and their corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.07 (95% CI 1.01, 1.13), 0.99 (95% CI 0.94, 1.04), 1.13 (95% CI 1.01, 1.27), and 0.99 (95% CI 0.88, 1.10) as shown in Figure 2, below. The opposite lineage comparisons in all subjects and seronegative subjects are shown in Figure 3.

Figure 2. Study MI-CP208 post-vaccination GMFR ratios, by assay type



GMFR = geometric mean fold ratio; GMT = geometric mean titre; HAI = haemagglutination inhibition; MN = microneutralisation; NAI = neuraminidase inhibition

Figure 3. Opposite lineage comparisons of post dose seroconversion/seroresponse rates (greater than or equal to 4-fold rise in HAI antibody titre from Baseline) by baseline serostatus, Immunogenicity Population (Study MI-CP208)



* denotes statistically significant; HAI = haemagglutination inhibition; Q/LAIV = quadrivalent live attenuated influenza vaccine

7.1.1.13. Results for other efficacy outcomes

For the secondary endpoint of strain-specific seroresponse post immunogenicity dose, the seroconversion/seroresponse rates for all four stains were similar for Q/LAIV and comparator arm in all subjects regardless of baseline serostatus (rate differences Q/LAIV minus comparator < 2.0 percentage points).

For subjects who were serosusceptible at baseline, the seroconversion/seroresponse rates were similar between Q/LAIV and the All FluMist group (rate differences < 1.0 percentage point) for the A/H3N2 strain, but for the A/H1N1, B/Yamagata, and B/Victoria strains, the seroconversion/seroresponse rates were higher in the All FluMist group or matching FluMist arm compared to the Q/LAIV arm, with rate differences (Q/LAIV minus comparator) of -4.9 (95% CI -9.7, -0.4) percentage points, -2.2 (95% CI -8.2, 4.7) percentage points, and -3.5 (95% CI -10.7, 4.3) percentage points, respectively. For subjects who were seronegative at baseline, the point estimates for seroconversion/seroresponse rates by study group were within 2 percentage points, except for the A/H1N1 and B/Victoria strains, where the rate difference was -5.1 (95% CI -10.6, 0.2) percentage points for A/H1N1 and -4.8 (95% CI -12.4, 3.6) percentage points for B/Victoria.

In all subjects regardless of baseline serostatus, the percentage of subjects with a post immunogenicity dose HAI antibody titre ≥ 32 was similar (within 1 percentage point) for the Q/LAIV arm and the comparator arm, with the exception of the B/Yamagata strain, for which the rate difference was statistically significant (-5.1 percentage points; 95% CI, -9.2, -0.6, with 76.5% and 81.6% of subjects in the Q/LAIV and FluMist arms, respectively, achieving a titre ≥ 32). In both seronegative and serosusceptible subjects, the percentage of subjects achieving an HAI antibody titre ≥ 32 was similar (within 1.1 percentage points) for A/H1N1 and A/H3N2 strains. For B/Victoria strains, the percentage of seronegative subjects achieving an HAI antibody titre ≥ 32 was higher in the FluMist-V arm (42.8%) than in the Q/LAIV arm (37%) (rate difference of -5.8 percentage points, 95% CI -14.7, 2.8). For serosusceptible subjects, the rate difference was -2.9 percentage points (95% CI -10.9, 5.1). For B/Yamagata strains, the percentage of seronegative subjects achieving an HAI antibody titre ≥ 32 was statistically significantly higher in the FluMist-Y arm (70.9%) than in the Q/LAIV arm (60.9%), for a rate difference of -10.0 percentage points (95% CI -17.9, -1.6). For serosusceptible subjects, the rate difference was lower but still statistically significant (-8.4 percentage points, 95% CI -15.7, -0.5).

Post Hoc Analyses of Neuraminidase Inhibiting Antibody Responses

At the request of the Paediatric Committee of the European Medicines Agency (EMA-001051-PIP01-10, Day-90 Summary Report), additional post hoc analyses were performed in the subset of subjects 2 to 5 years of age in Study MI-CP208 for whom serum samples were available; post immunogenicity dose samples were available for approximately 90% of the 1,007 subjects 2 to 5 years of age who were enrolled in the study. Geometric mean titre ratios and their corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.16 (95% CI 1.01, 1.35), 1.00 (95% CI 0.89, 1.12), 1.03 (95% CI 0.86, 1.22), and 0.82 (95% CI 0.70, 0.96). While there were no predefined non-inferiority criteria for the NAI analyses, all of the GMT ratios were close to 1.0 and none of the upper bounds of the 95% CIs for the ratios exceeded 1.5 (the criteria used to determine non-inferiority for the HAI analyses). To account for differences in NAI antibody titres at baseline, the GMFR ratios were also examined (Figure 2). The GMFR ratio data were similar to the GMT ratio data.

Post hoc analyses of neutralising antibody responses

Post hoc analyses were also performed to evaluate post dose neutralising antibody titres in a subset of subjects 2 to 5 years of age. Geometric mean titre ratios and their corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 0.86 (95% CI 0.66, 1.11), 0.93 (95% CI 0.69, 1.26), 1.28 (95% CI 1.00, 1.62), and 1.16 (95% CI 0.89, 1.51). While there were no predefined non-inferiority criteria for the neutralising antibody analyses, all of the GMT ratios were close to 1.0. The upper bounds of the 95% CIs for the GMT ratios

exceeded 1.5 (the criteria used to determine non-inferiority for the HAI analyses) for both of the B strains; however, this is likely attributable to baseline titre differences between the Q/LAIV and FluMist treatment groups resulting from the post randomisation selection of a smaller number of subjects. To account for these differences in MN antibody titres at baseline, the GMFR ratios were examined. The GMFR ratios and their corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 0.90 (95% CI 0.77, 1.06), 1.01 (95% CI 0.87, 1.18), 1.02 (95% CI 0.80, 1.31), and 1.04 (95% CI 0.81, 1.33) (see Figure 2, above).

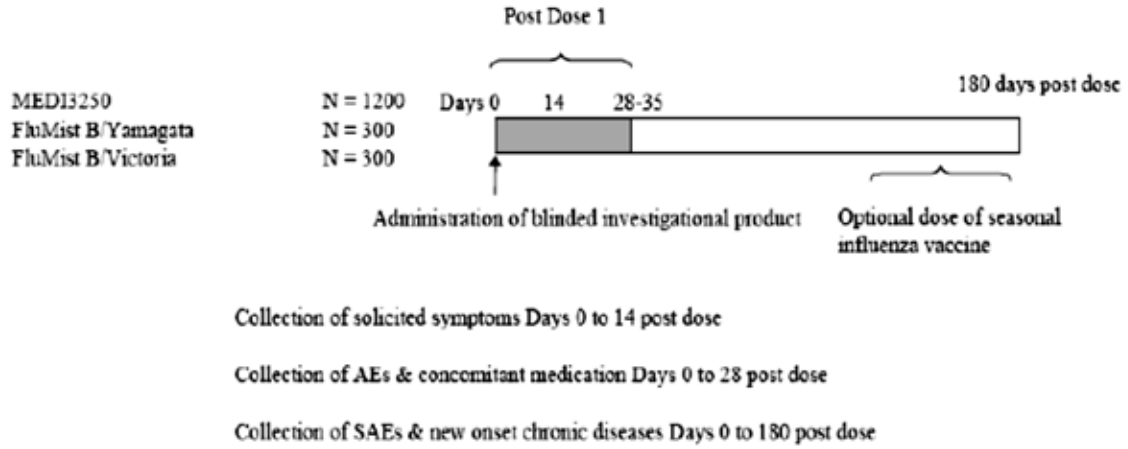
In general, secondary endpoints support the conclusion that the immune responses to Q/LAIV and FluMist were similar, except that vaccine immunogenicity was statistically greater in the FluMist group than in the Q/LAIV arm for the rate of seroconversion/seroresponse to A/H1N1 in the serosusceptible subgroup 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.

7.1.2. Study MI-CP185

7.1.2.1. Study design, objectives, locations and dates

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 by comparing the 4 strain-specific serum HAI antibody GMTs post dosing. A total of 1,800 subjects were randomised by site at a 4:1:1 ratio to receive a single dose of either Q/LAIV or 1 of 2 formulations of FluMist, each containing a B strain that matched 1 of the 2 B strains in the Q/LAIV vaccine (a B strain of the Yamagata lineage in FluMist/B/Yamagata and a B strain of the Victoria lineage in FluMist/B/Victoria). It was conducted at 18 sites in the USA between 23 Mar 2009 and 9 Oct 2009. Subjects were randomised by site in a 4:1:1 fashion to receive either Q/LAIV, trivalent FluMist containing an influenza B strain from the Yamagata lineage (FluMist/B/Yamagata), or trivalent FluMist containing an influenza B strain from the Victoria lineage (FluMist/B/Victoria). Subjects received a single dose of Q/LAIV or FluMist. The study was conducted at multiple sites in the influenza off-season. The total duration of a subject's participation in the study was 180 days following the single dose of investigational product; a screening period of up to 30 days was permitted. Design and flow for the study is shown in Figure 4, below.

Figure 4. Design and flow of Study MI-CP185



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

The secondary objectives of this study 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.

7.1.2.2. Inclusion and exclusion criteria

Subjects were male and female adults 18 to 49 years of age who were able to consent and did not have any exclusion criteria (see Table 6, below).

Table 6. Exclusion criteria for Study MI–CP185

Exclusion Criteria
· Acute illness or evidence of significant active infection at randomisation · Fever ≥ 100.4°F (38°C) at randomisation · History of asthma · Any drug therapy from 15 days prior to randomisation or expected drug therapy through 30 days post dose with the exception of contraceptives or chronic medications that were well tolerated and were not initiated and/or did not have a dosage change within 90 days of randomisation. · Previous medical history or evidence of an intercurrent illness that may have compromised the safety of the subject in the study · Current or expected receipt of immunosuppressive medications (inhaled and topical corticosteroids were permitted) including corticosteroids (≥ 20 mg/day of prednisone equivalent given daily or on alternate days for ≥ 14 days) within a 30-day window around dose of investigational product. Note: topical corticosteroids for uncomplicated dermatitis may have been used throughout the study according to the judgment of the investigator; topical calcineurin inhibitors may have been used. · Receipt of immunoglobulin or blood products within 90 days before randomisation in the study or expected receipt during study participation · Receipt of any investigational drug therapy or standard vaccine within 30 days before the dose of investigational product in this study through 30 days after the dose of investigational product (use of licensed agents for indications not listed in the package insert was permitted) · Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV) · History of allergic disease or reactions likely to be exacerbated by any component of the investigational product including allergy to eggs, egg proteins, gentamicin, or gelatin; or serious, life threatening, or severe reactions to previous influenza vaccinations · History of Guillain-Barré syndrome · Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir and zanamivir) within 30 days prior to dose of investigational product or anticipated use within 30 days after vaccination · Known or suspected mitochondrial encephalomyopathy · Lactating woman · History of alcohol or drug abuse that, in the opinion of the investigator, would have affected the subject's safety or compliance with study

Exclusion Criteria
· Any condition that, in the opinion of the investigator, would have interfered with evaluation of the investigational product or interpretation of subject safety or study results · Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals

7.1.2.3. Study treatments

One dose of the vaccine, either Q/LAIV or comparator, either FluMist/B/Yamagata (FluMist containing A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), or FluMist/B/Victoria (FluMist containing A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), and B/Victoria (B/Malaysia/2506/2004). These were administered via intranasal spray with Becton Dickinson (BD) Accuspray device on Day 0. A total volume of 0.2 mL was administered intranasally (approximately 0.1 mL into each nostril). Each dose contained 107.0 ± 0.5 FFU of each of 4 cold-adapted (ca), temperature-sensitive (ts), attenuated (att*)*, 6:2 reassortant influenza strains: A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguay/716/2007), B/Victoria (B/Malaysia/2506/2004), and B/Yamagata (B/Florida/4/2006).

7.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome was the post dose strain-specific serum HAI antibody GMTs in all 4 strains, regardless of baseline serostatus. Immunologic non-inferiority of Q/LAIV to FluMist would be demonstrated if the post dose strain-specific serum HAI antibody GMT in the Q/LAIV arm was non-inferior to that in the FluMist arm for all 4 strains.

Secondary efficacy outcomes were:

· The proportion of subjects within each treatment arm who experienced strain-specific seroresponse post dose by baseline serostatus (serosusceptible, seropositive, and regardless of serostatus);

· The proportion of subjects within each treatment arm who achieved a strain specific HAI titre ≥ 32 post dose by baseline serostatus (serosusceptible, seropositive, and regardless of serostatus).

7.1.2.5. Randomisation and blinding methods

This was a double blind study with electronic randomisation by block method as in Study MI-CP208. Q/LAIV, FluMist/B/Yamagata, and FluMist/B/Victoria were identically labelled and indistinguishable in appearance; therefore, subjects and study site personnel, including the investigators, study nurses, coordinators, and investigator's or site's designated investigational product manager, were blinded to treatment assignment.

7.1.2.6. Analysis populations

The ITT Population included all randomised subjects. The Immunogenicity Population included subjects who received a full dose of investigational product and had post-dose HAI measurement. In addition, protocol deviations were reviewed by the study team before unblinding. Subjects identified with deviations judged to have the potential to interfere with the generation or interpretation of an immune response were excluded from the Immunogenicity Population prior to unblinding. Subjects were to be included in the treatment arm corresponding to the treatment received even if it was different from the randomised treatment. The Safety Population included subjects who received any investigational product and for whom any follow-up safety data were recorded.

7.1.2.7. Sample size

A total of 1,800 subjects randomised 4:1:1 to Q/LAIV, FluMist/B/Yamagata, and FluMist/B/Victoria provided > 97% power to rule out a > 1.5-fold difference in the post dose serum HAI GMT ratios for each of the 4 strain-specific tests regardless of baseline serostatus. 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.

7.1.2.8. Statistical methods

The post dose serum HAI antibody GMTs for the A/H1N1 and A/H3N2 strains were compared to those in the combined FluMist-Y and FluMist-V arms, and the post dose serum HAI antibody GMTs for the B strains of Yamagata and Victoria lineage were compared to those in the FluMist-Y arm and FluMist-V arm, respectively. The non-inferior immune response was assessed by evaluating the upper bound of the 2-sided 95% confidence intervals (CIs) for the strain-specific HAI antibody GMT ratios (FluMist divided by Q/LAIV) to the non-inferiority margin of 1.5. If the upper bound of the CIs was ≤ 1.5 for all 4 strains, the immunologic non-inferiority of Q/LAIV compared to FluMist would be declared. Each of the 4 strain-specific non-inferiority comparisons carried a 1 sided 2.5% type 1 error rate; therefore the overall type 1 error rate associated with simultaneous coverage by all 4 CIs would necessarily be no more than 2.5%.

For the secondary outcomes, seroresponse was defined as a ≥ 4-fold rise in HAI titre from baseline. Subjects with a strain-specific baseline HAI titre of ≤ 8 were considered to be serosusceptible to that strain; subjects with a baseline HAI titre > 8 were considered to be seropositive for that strain. Ninety-five percent 2-sided exact CIs for each of the proportions presented were constructed to provide population estimates.

7.1.2.9. Participant flow

A total of 1,800 subjects were randomised into the study. Two of the 1,800 subjects randomised were not dosed: 1 withdrew consent prior to dosing, and 1 was found to be pregnant prior to dosing. The subject who withdrew prior to dosing was the only withdrawal prior to Day 28. A total of 1,777 subjects (98.7%) were dosed and followed for safety through Day 28. A total of 1,731 (96.2%) subjects completed the study. Of the 69 subjects who did not complete the study, 64 (3.6%) were lost to follow-up, 4 (0.2%) withdrew consent, and 1 (0.1%) withdrew for other reasons. The reasons for not completing the study were evenly distributed across treatment arms. No subject withdrew from the study due to an AE.

7.1.2.10. Major protocol violations/deviations

Significant protocol deviations related to eligibility for enrolment, inclusion in the immunogenicity cohort, dosing of vaccine, and data collection are described below. No subject received the wrong treatment, and all treated subjects received a full dose of investigational product. A total of 1,770 subjects were included in the Immunogenicity Population. Thirty subjects were excluded from the Immunogenicity Population because they did not receive the vaccine, did not have post-dose HAI measurements (28 subjects, including the 2 subjects who did not receive investigational product), or were treated with antiviral medications with activity against influenza because of laboratory confirmed influenza illness.

7.1.2.11. Baseline data

Baseline demographics were similar and well balanced among the treatment arms. The mean age of subjects was 32.7 years, and it was similar across treatment arms. The majority of subjects were white (76.3% Q/LAIV; 76.3% All FluMist) and not Hispanic or Latino (78.0%

Q/LAIV; 75.8% All FluMist). Demographic information was similar for the Safety and Immunogenicity Populations compared to the ITT Population.

7.1.2.12. 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 as the upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by Q/LAIV) was ≤ 1.5 (See Figure 1, above). The comparators for the GMT ratios for the primary endpoint were subjects in the All FluMist group (combined data for both FluMist arms) for A/H1N1 and A/H3N2 strains and subjects who received FluMist with a matching B strain for the B/Yamagata and B/Victoria strains. Post dose GMT ratios and the corresponding 95% CIs for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.09 (95% CI 1.01, 1.18), 1.05 (95% CI 0.96, 1.14), 1.10 (95% CI 0.97, 1.25) and 0.92 (95% CI 0.82, 1.03). Because baseline GMTs differed among study arms, a post hoc geometric mean fold rise (GMFR) analysis was performed; GMFR ratios were similar to GMT ratios, upper bounds of the 95% CIs for all 4 strains being < 1.5.

7.1.2.13. Results for other efficacy 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.

7.2. Other efficacy studies

7.2.1. Study MI CP-206

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. The primary objective of this study 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 trivalent formulations of licensed FluMist (delivered intranasally using the Becton Dickinson (BD) Accuspray delivery device) by comparing the strain-specific GMTs post dosing.

The secondary objectives of this study 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.

Subjects who met enrolment criteria (inclusion and exclusion criteria similar to Study MI-CP185) 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). Subjects were given memory aid worksheets to record solicited symptoms during the first 14 days post dosing.

A total of 1,800 subjects were randomised as planned; 1,797 subjects received investigational product. Of the 1,800 subjects, 1202, 300, and 298 subjects were randomised to the Q/LAIV-BFS, FluMist/B/Yamagata, and FluMist/B/Victoria groups, respectively; 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 included 1,198 subjects in the Q/LAIV-BFS group and 298 subjects each in the FluMist/B/Yamagata and FluMist/B/Victoria groups. The Evaluable Safety Population for solicited symptoms included 1,196, 298, and 297 subjects in the Q/LAIVBFS, FluMist/B/Yamagata, and FluMist/B/Victoria groups, respectively. The Immunogenicity Population included 1,176, 294, and 292 subjects in the Q/LAIV-BFS, FluMist/B/Yamagata, and FluMist/B/Victoria groups, respectively.

Similar to the pivotal studies, two formal analyses were planned for the study. The Day 28 analysis included the immunologic and safety data collected through 28 days post dose. To ensure the blinding of each subject's treatment assignment throughout the study, the Day 28 unblinded analyses were performed by a limited number of personnel who were not directly involved in the conduct of the study. Study site personnel and subjects randomised to receive FluMist remained blinded to which of the two FluMist comparators they received until the completion of the study Of the 1,800 randomised subjects, 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 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. Demographic data of the Intent-to-Treat Population was well balanced among the treatment groups. Demographic information was similar for the Safety and Immunogenicity Populations compared to the ITT Population.

7.2.1.1. Results

This study met its primary endpoint demonstrating the immunologic non-inferiority of Q/LAIV-BFS to two formulations of FluMist 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 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 data were consistent with the primary endpoint. For all subjects, regardless of baseline serostatus, the post dose seroconversion/seroresponse rates as measured by a ≥ 4-fold rise in HAI antibody titre from baseline were low (≤ 10%) but similar in the Q/LAIV-BFS group and in the All FluMist group. Similar results were observed for serosusceptible subjects for the type A strains (H1N1 and H3N2); seroconversion rates in serosusceptible subjects to the B strains were higher (36.0% and 20.8% in the Q/LAIV-BFS group for the B/Yamagata and B/Victoria strains, respectively, and 35.3% and 26.0% for the FluMist B/Yamagata and the FluMist/B/Victoria strains in the FluMist groups, respectively). In all subjects, regardless of baseline serostatus, the percentage of subjects achieving a post dose HAI antibody titre ≥ 32 was similar between the Q/LAIV-BFS and All FluMist groups (approximately 23% to 26% for the A/H1N1 and A/H3N2 strains, 75% to 79% for the B/Yamagata strain, and 53% to 56% for the B/Victoria strain). For baseline serosusceptible subjects, the percentage of subjects achieving a post dose HAI antibody titre ≥ 32 was low (< 3% for the A strains and < 22% for the B strains) in both the Q/LAIV-BFS and the All FluMist groups, which mimicked the results of the seroconversion rates.

7.2.2. Study MA-VA-MEDI3250-1116

This study was developed as part of a post-marketing commitment with the US FDA and is ongoing. The aim is to evaluate the effectiveness of Q/LAIV over 4 influenza seasons, beginning with the 2013 to 2014 Northern Hemisphere influenza season. The primary objective of the study is to evaluate the effectiveness of Q/LAIV (FluMist Quadrivalent) compared to inactivated influenza vaccine (IIV) or no vaccine, in community-dwelling subjects 2 through 17 years of age, against laboratory-confirmed influenza. This is a case-control study of the effectiveness of Q/LAIV in subjects 2 to 17 years of age who are seeking care in an outpatient setting for febrile acute respiratory illness. The first patient was enrolled on 02 December 2013 and the study will be completed after 4 years (that is, after the 2016 to 2017 influenza season). No investigational product is administered in this study and participants are either vaccinated or not vaccinated against influenza as part of the standard clinical care they receive 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 to 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 appears to be a US specific finding as studies from Canada from the same season indicate that the vaccine was effective.[6,7] The lack of effectiveness in the US for H1N1 strains in 2013 to 2014 is 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. Modifications to the strain selection process and to US vaccine distributor practices have been implemented to ensure that future Q/LAIV strains demonstrate the same levels of efficacy and effectiveness as previous LAIV strains. For the 2015 to 2016 Northern Hemisphere influenza season the A/California/7/2009 vaccine strain in the vaccine is being replaced by the A/Bolivia/559/2013 strain which does not have the stalk mutation. Future strains will be screened to have heat tolerance profiles similar to previous LAIV strains with demonstrated effectiveness. In addition, US distributor vaccine handling procedures are being modified to eliminate any significant heat exposures that may occur when vaccine is transferred between refrigerated storage areas. No new safety issues were identified.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

The data presented in this submission uses FluMist (the previously registered trivalent influenza vaccine, otherwise identical in composition and presentation) as its comparator. In relation to the non-inferiority strategy used, the efficacy data for FluMist efficacy is summarised here.

There were eight different trivalent vaccine blends used in 14 clinical studies which demonstrated the protective benefit of FluMist over 7 different Northern Hemisphere seasons and 2 Southern Hemisphere seasons from 1995 to 2005. These include 10 studies (7 placebo controlled and 3 TIV controlled) of vaccine efficacy in > 26,000 paediatric subjects (see Table 7, below), 3 studies (1 placebo controlled and 2 TIV controlled) of vaccine efficacy in > 6,000 adults, and 1 placebo controlled study of clinical effectiveness in > 4,000 adults. The primary endpoint in the efficacy studies was the incidence of culture-confirmed influenza in subjects

[6] Skowronski D et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness, 2013-14 season. J Infect Dis. 2015 Mar 17. pii: jiv177.
[7] Kwong J et al. Randomized evaluation of live attenuated versus inactivated influenza vaccines in schools (RELATIVES) pilot study: preliminary results from the household surveillance sub-study. Abstract from the Canadian Immunization Conference, December 2014.

with clinical influenza illness caused by strains that were antigenically matched to the vaccine (results are summarised in Table 8 and 9, below).

Table 7. FluMist efficacy in placebo controlled paediatric studies

Study Number	Region[a]	Age[b] Range	Number of Subjects in the Primary Analysis Population	Frozen or Refrigerated FluMist	Influenza Season	Efficacy (95% CI) Matched Strains	Efficacy (95% CI) All Strains Regardless of Antigenic Match
D153-P501	Asia/Oceania	12 to < 36 M	2,764	Refrigerated	2000-2001	72.9% (62.8, 80.5)	70.1% (60.9, 77.3)
					2001-2002	84.3% (70.1, 92.4)[c]	64.2% (44.2, 77.3)[c]
D153-P502	Europe	6 to < 36 M	1,616	Refrigerated	2000-2001	85.4% (74.3, 92.2)	85.9% (76.3, 92.0)
					2001-2002	88.7% (82.0, 93.2)[c]	85.8% (78.6, 90.9)[c]
D153-P504	Africa, Latin America	6 to < 36 M	1,886	Refrigerated	2001	73.5% (63.6, 81.0)	72.0% (61.9, 79.8)
					2002	73.6% (33.3, 91.2)[c]	46.6% (14.9, 67.2)[c]
D153-P513	Asia/Oceania	6 to < 36 M	2,107	Refrigerated	2002	62.2% (43.6, 75.2)[d]	48.6% (28.8, 63.3)[d]
D153-P522	Europe, Asia/Oceania, Latin America	11 to 24 M	1,150	Refrigerated	2002-2003	78.4% (50.9, 91.3)	63.8% (36.2, 79.8)
AV006 Yr1	USA	15 to 71 M	1,259	Frozen	1996-1997	93.4% (87.5, 96.5)[e]	Not applicable
AV006 Yr2	USA	27 to 83 M	1,358[f]	Frozen	1997-1998	100% (63.1, 100)[c]	87.1% (77.7, 92.6)[c]

[a] For purposes of study grouping, Europe includes Western and Eastern Europe, Scandinavia, Israel, and Lebanon; and Asia/Oceania includes East Asia, Southeast Asia, South Asia, and Australia; [b] age range as described in the protocol for the study, M = months; [c] rates shown are for second-season revaccination; [d] efficacy for subjects in the 107 FFU group; [e] results for subjects in the 2-dose group (primary endpoint); [f] all subjects in Study AV006 Year 2 were included in Study AV006 Year 1.

Table 8. FluMist strain-specific efficacy against antigenically matched strains

Study Number	Efficacy (95% CI) A/H1N1	Efficacy (95% CI) A/H3N2	Efficacy (95%CI) B
D153-P501 Year 1	80.9% (69.4, 88.5)	90.0% (71.4, 97.5)	44.3% (6.2, 67.2)
D153-P502 Year 1	91.8% (80.8, 97.1)	100% (-2,627, 100.0)[a]	72.6% (38.6, 88.9)
D153-P504 Year 1	NC	72.7% (60.7, 81.5)	81.4% (64.2, 91.2)
D153-P513	100% (-3,733.1, 100.0)[a]	64.0% (45.7, 76.6)	NC
D153-P522	100% (-168.0, 100.0)[a]	68.5% (-9.0, 91.9)	81.7% (38.2, 95.8)
AV006 Year 1	NC	96.0% (89.4, 98.5)	90.5% (78.0, 95.9)

CI = confidence interval; NC = not computable due to 0 cases of culture-confirmed illnesses caused by the specific strain in the placebo group (Studies D153-P504 and D153-P513) or 0 cases of culture-confirmed influenza caused by the specific strain in both treatment groups (Study AV006 Year 1).

Table 9. FluMist relative efficacy in TIV controlled paediatric trials

Study Number	Region[a]	Age[b] 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/Oceania	6 to 59 M	7,852	Refrigerated	2004-2005	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 M	2,085	Refrigerated	2002-2003	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 Y	2,211	Refrigerated	2002-2003	34.7% (3.9, 56.0) fewer cases than TIV	31.9% (1.1, 53.5) fewer cases than TIV

CI = confidence interval. [a] For purposes of study grouping, Europe includes Western and Eastern Europe, Scandinavia, Israel, and Lebanon; and Asia/Oceania includes East Asia, Southeast Asia, South Asia, and Australia; [b] M = months; Y = years. Age range as described in the protocol for the study.

An important secondary endpoint of many of these studies was efficacy against all strains regardless of antigenic match. Among the placebo controlled studies in paediatric subjects, 4 studies of 2 year duration each were designed to also assess the efficacy of second-season revaccination. It is from these studies that the HAI seroconversion/seroresponse data was gained.

The placebo controlled studies comprising > 13,000 paediatric subjects were conducted during 7 influenza seasons from 1996 through 2003 in Europe, Latin America, Africa, Asia/Oceania, and the USA. In these studies, FluMist protection against laboratory-confirmed influenza illness was demonstrated in a broad age range of children. In these studies, FluMist demonstrated high rates of efficacy against culture-confirmed influenza illness due to matched strains and against influenza illness due to all strains regardless of antigenic match compared to placebo.

Between 1995 and 2003, 4 randomised, controlled FluMist efficacy/effectiveness studies were conducted in more than 10,000 adults. These included 1 wildtype influenza experimental challenge study, 2 placebo controlled studies, and one TIV controlled study. FluMist demonstrated absolute efficacy in older adults. In these studies, FluMist demonstrated efficacy against experimental challenge with wild-type influenza. FluMist demonstrated effectiveness against influenza-associated febrile illnesses and related events in a year when the predominant circulating wild-type virus was mismatched to the FluMist vaccine strain. The main original Flumist studies are summarised briefly below.

7.3.1. Study AV006

This was a Phase III, randomised, double blind, placebo controlled, trial to assess the safety, immunogenicity and efficacy of influenza virus vaccine, trivalent, types A and B, live, cold-adapted (CAIV-T) in healthy children. The clinical endpoint of this efficacy study (divided into year 1 and year 2) was culture-confirmed influenza in children aged 15 to 71 months of age. Immunogenicity was also assessed in a sub-set (209 of 1602 participants).

Overall results of this study revealed that among children who received two doses of the influenza virus vaccine, trivalent, types A and B, live cold adapted (FluMist), the vaccine efficacy was 93.4% (95% CI: 87.5, 96.5) in preventing culture-confirmed influenza illness. Two doses of vaccine were also highly efficacious against individual strains, H3N2 (96.0%) and B (90.5%). Among children who were enrolled to receive one dose of FluMist, the vaccine efficacy was 88.8% (95% CI: 64.5, 96.5) in preventing culture-confirmed influenza illness. One dose of vaccine was also highly efficacious against individual strains, H3N2 (86.9%) and B (91.3%). The vaccine efficacy was 95.0% (95% CI: 90.0, 97.5) in preventing febrile illness and was 97.5% (95% CI: 85.5, 99.6) in preventing otitis media among influenza cases. The vaccine significantly reduced febrile illness and associated antibiotic use by 31 %, and febrile otitis media and associated antibiotic use by 35% in all randomised children during the influenza season.

In relation to the immunogenicity subgroup, among the baseline seronegative placebo recipients, very few participants seroconverted. Following Dose Two, there was one seroconverter for HIN1 and B and two for H3N2. The FluMist recipients had the following seroconversion rates after Dose One: HIN1, 16%; H3N2, 92%; and B, 88%. An additional 55% to 75% (33 of 60 for HIN1; 3 of 4 for H3N2; 6 of 8 for B) converted after Dose Two and the strain specific percent of baseline seronegatives who were seropositive after Dose Two were: HIN1, 61%; H3N2, 96%; and B, 96%. In relation to seroresponders, among placebo recipients, only one strain-specific four-fold rise occurred following Dose One and only seven occurred following Dose Two. The pattern of four-fold rises for all FluMist recipients was similar to the pattern for seronegative participants. The proportion of participants seroconverting to H3N2 (52%) and B (62%) was similar while the rate for HIN1 were significantly lower than for the other two strains (19%), with the 95% confidence interval below the intervals for H3N2 and B. Following Dose Two, the proportion of participants seroconverting for HIN1 (39%) was higher than for H3N2 (11%) and B (22%).

7.3.2. Study AV011

This study was an open label study in which all subjects received a single challenge dose of CAIV-M A/H1N1 vaccine approximately 5 to 8 months after receipt of FluMist (CAIV-T) or placebo as part of the Year Two AV006 study. Children who had completed both years of AV006 were recruited for this study. The protective effect of the vaccine against H1N1 had not been assessed in AV006, as the virus was not circulating. The endpoint of this trial was efficacy against shedding of vaccine strain following challenge with a monovalent vaccine strain A/Shenzhen (H1N1) in a subset of Year 1 and 2 AV006 participants. This study found that the mean duration of shedding in the first 4 days post-vaccination was significantly reduced in the prior FluMist group compared to the prior placebo group (respectively 0.06 + 0.3 versus 0.3 + 0.7, p = 0.0001). The percent of prior FluMist recipients with HAI titres > 1:8 (considered to be seropositive) prior to vaccination with the monovalent CAIV-M vaccine was 68% (96/141) compared to 33% (25/75) of prior placebo recipients, p < 0.0001.

7.3.3. Study AV009

This was a prospective, randomised, double blind, placebo-controlled, trial to assess the safety, tolerability, and effectiveness of influenza virus vaccine, trivalent, types A and B, live, cold-adapted (CAIV-T) in healthy working adults to reduce influenza-like illness, absenteeism from work and health care costs during influenza outbreaks. The clinical endpoint in this study was prevention of acute febrile illness during influenza outbreak periods in adults ages 18-65. FluMist significantly and consistently reduced days of missed work during illnesses, for example, a 13.1% reduction during AFI (p = 0.065).

7.3.4. Study AV003

This was a Phase III double blind, placebo controlled challenge study to assess the efficacy of cold-adapted influenza virus vaccine, live trivalent (CAIV-T, FluMist) in healthy adults. Study AV003 was performed to assess the efficacy of FluMist and of the trivalent inactivated influenza vaccine (TIV) in protecting subjects from laboratory diagnosed influenza disease following a challenge with a wild-type influenza virus. The primary endpoint was protective efficacy following FluMist or inactivated influenza vaccine in healthy serosusceptible adults against intranasal challenge with wild-type influenza. This was done by assessing laboratory documented influenza illness measured by symptoms of influenza accompanied by a fourfold rise in HAI titre or by viral shedding. 7% (2/29) of the FluMist group and 45% (14/31) of the placebo group had cases of laboratory-documented influenza illness, for an estimated percent protective efficacy of FluMist compared to placebo of 85%; this difference was highly statistically significant (p = 0.001; Mantel-Haenszel test stratified by strain). The study was not designed to have a large enough sample size to produce precise estimates of the strain specific protective efficacy. Although the estimated efficacy for each of the three strains was very high (80% for the H1N1 strain, 78% for the H3N2 strain, and 100% for the B strain), the estimates

were based on small numbers (FluMist versus placebo, H1N1: 1/10 versus 6/12; H3N2: 1/9 versus 4/8; B: 0/10 versus 4/11) and these strain-specific rates for FluMist did not differ significantly from the rates for placebo.

The following two studies were submitted in support of consistency of manufacturing for Flumist and used immunogenicity as a measure of this.

7.3.5. Study AV007

This was a prospective, randomised, double blind, placebo-controlled trial to assess the safety, tolerability, and immunogenicity of three manufacturing lots of influenza virus vaccine, trivalent types A and B, cold adapted (CAIV-T). This was a lot consistency trial, including comparison with 3 efficacy lots using immunogenicity as measure of consistency. It was performed in healthy children, ages 12 to 36 months (500 children). For each of the three strains, the three consistency lots showed very similar immunogenicity. The lots also showed similar rates of fourfold rises in HAI antibody titre and similar distributions of HAI titre levels after the second vaccination. A very high proportion of participants had at least a fourfold rise in serum HAI titre. For seronegative participants, over 99% of the consistency lot group seroconverted to H3N2 and B. The rates for the H1N1 strain were lower; about 85% of the seronegative consistency lots subgroup seroconverted. The data from a subgroup of participants tested against both the Texas and Shenzhen subtypes of H1N1 suggest that the subtype-specific immune response is more vigorous for the subtype to which the participant was vaccinated than to the subtype to which the participant was not vaccinated. Statistically, both the proportion experiencing a fourfold rise and the geometric mean titre ratios support a stronger immune response to the subtype in the vaccine actually administered than to the other subtype ($p < 0.001$, McNemar's test and $p = 0.0001$, paired t-test). The data from a subgroup of participants measured after Dose 1 indicate that for H3N2, vaccination with one dose of FluMist gives immune responses similar to vaccination with 2 doses, but that a 2nd dose of FluMist increases the serum HAI GMT for H1N1 in the consistency lots ($p = 0.0001$) and efficacy vaccine ($p = 0.015$) and for B in the consistency lots ($p = 0.0001$). In addition, a second dose increases the proportion with a fourfold rise in titre for the H1N1 strain ($p = 0.0003$).

7.3.6. Study AV014

This was a prospective, randomised, double blind trial to compare the safety, tolerability and immunogenicity Flumist blended and filled at 2 different facilities. It used immunogenicity as measure of consistency and was performed in healthy children, ages 12 to 42 months (225 children). The seroconversion rate between the two groups was within 20% (pre-specified criteria) for all 3 strains. The seroconversion rates in baseline seronegative participants for both treatment groups were high (100% for H3N2 and B).

When the development plan for registration of Q/LAIV was formulated, the HAI antibody GMT ratios were selected as the primary endpoint for the studies based on regulatory guidance documents in the USA that provide specific criteria regarding how the immunogenicity of influenza vaccines should be compared (US DHHS, May 2007 (pandemic); US DHHS, May 2007 (seasonal inactivated)). In addition, HAI antibody GMT ratios also were previously used to bridge the frozen and refrigerated formulations of FluMist as well as for bridging to a new manufacturing site for FluMist. The suitability of using a non-inferiority margin of 1.5 for the GMT ratio is reinforced by the fact that both the frozen and refrigerated formulations of FluMist, which were shown to generate comparable immune responses using this criterion, have both demonstrated high levels of efficacy.

7.4. Evaluator's conclusions on clinical 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 based on the pre-specified non-inferiority margin of 1.5 for the upper bound for each of the four 95% CIs for the strain

specific post dose GMT HAI antibody ratios (FluMist 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 comparator arms. With regard to immunogenicity in children and adults, Q/LAIV is comparable to trivalent FluMist 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 clinical efficacy data to Q/LAIV.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

General adverse events (AEs) were assessed by telephone contact and subject review. Subjects/guardians also were given log book diaries to fill out for both specified and non-specified AEs.

AEs of particular interest, including fever, runny/stuffy nose, sore throat, cough, headache, generalised muscle aches, decreased activity level (lethargy) or tiredness/weakness, and decreased appetite, were assessed by recording daily in a diary during Days 0 to 14 after any dose and were not graded for severity or assessed for relationship to investigational product.

8.1.2. Pivotal studies that assessed safety as a secondary outcome

Studies MI-CP208 and MI-CP185 were pivotal studies that assessed safety as a primary outcome. These studies are described above in Section 7.1.

8.1.3. Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy study provided safety data, as follows: Study MI-CP206, in which Q/LAIV was administered as a liquid stream to a single nostril using a BFS delivery system rather than as a nasal spray is considered supportive of Q/LAIV safety for AEs and serious adverse events (SAE) only; however, solicited symptoms are presented for completeness.

8.1.4. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2. 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 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 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).

Table 10. 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 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.

To examine a larger safety database for the occurrence of rare events in adults, a pooled analysis of safety in Studies MI-CP185 and MI-CP206 was created for the AE and SAE data. Because Q/LAIV development is based on a clinical bridging strategy, the safety of Q/LAIV was compared to that of FluMist in all studies of Q/LAIV. There was no placebo control group to estimate the background rate of safety events. Within Q/LAIV studies, the most relevant assessment is the rate difference between subjects who received Q/LAIV and those who received FluMist. Table 11 summarises all solicited event and AEs with Table 12 summarising the SAEs from the pooled data from the paediatric FluMist studies (used as comparator for this submission). Based on review of all SAEs for temporal relationship and biological plausibility, no rare event (for example, Guillain-Barré, facial palsy, encephalitis) was considered likely to have been causally associated with FluMist dosing.

Table 11. Summary of solicited events and adverse events from Days 0 to 10 post dosing in paediatric studies of FluMist

Study Type Event	Year 1				Year 2 (Second-Season Revaccination)	
	Post Dose 1		Post Dose 2		Post Dose	
	FluMist	Comparator	FluMist	Comparator	FluMist	Comparator
Placebo Controlled Studies						
At least one solicited event	5,581/ 7,146 (78.1%)	3,165/ 4,367 (72.5%)	3,827/ 5,678 (67.4%)	2,537/ 3,890 (65.2%)	1,793/ 2,557 (70.1%)	955/ 1,347 (70.9%)
Runny/stuffy nose	4,809/ 7,133 (67.4%)	2,551/ 4,363 (58.5%)	3,199/ 5,674 (56.4%)	2,048/ 3,887 (52.7%)	1,499/ 2,555 (58.7%)	781/ 1,345 (58.1%)
Fever ≥ 38°C[a]	1,053/ 7,113 (14.8%)	552/ 4,342 (12.7%)	667/ 5,623 (11.9%)	469/ 3,866 (12.1%)	274/ 2,552 (10.7%)	151/ 1,337 (11.3%)
At least one adverse event	2,518/ 7,266 (34.7%)	1,396/ 4,443 (31.4%)	1,656/ 5,734 (28.9%)	1,129/ 3,939 (28.7%)	716/ 2,568 (27.9%)	374/ 1,356 (27.6%)
TIV Controlled Studies						
At least one solicited event	4,070/ 5,626 (72.3%)	3,674/ 5,584 (65.8%)	1,891/ 3,325 (56.9%)	1,767/ 3,314 (53.3%)	N/A	N/A
Runny/stuffy nose	3,330/ 5,617 (59.3%)	2,622/ 5,573 (47.0%)	1,463/ 3,322 (44.0%)	1,286/ 3,309 (38.9%)	N/A	N/A
Fever ≥ 38°C[a]	608/ 5,569 (10.9%)	548/ 5,529 (9.9%)	347/ 3,244 (10.7%)	347/ 3,229 (10.7%)	N/A	N/A
At least one adverse event	1,269/ 5,702 (22.3%)	1,095/ 5,677 (19.3%)	608/ 3,399 (17.9%)	558/ 3,401 (16.4%)	N/A	N/A

N/A = not applicable; there were no TIV controlled studies in Year 2.

Table 12. Summary of SAEs from Days 0 to 42 post last dose in paediatric studies of FluMist

Study Type Event	Year 1		Year 2 (Second-Season Revaccination)	
	FluMist	Comparator	FluMist	Comparator
Placebo Controlled Studies				
At least one SAE	148/ 15,514 (0.95%)	91/ 8,500 (1.07%)	17/ 3,485 (0.49%)	12/ 1,797 (0.67%)
TIV Controlled Studies				
At least one SAE	57/ 5,800 (0.98%)	66/ 5,773 (1.14%)	N/A	N/A

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

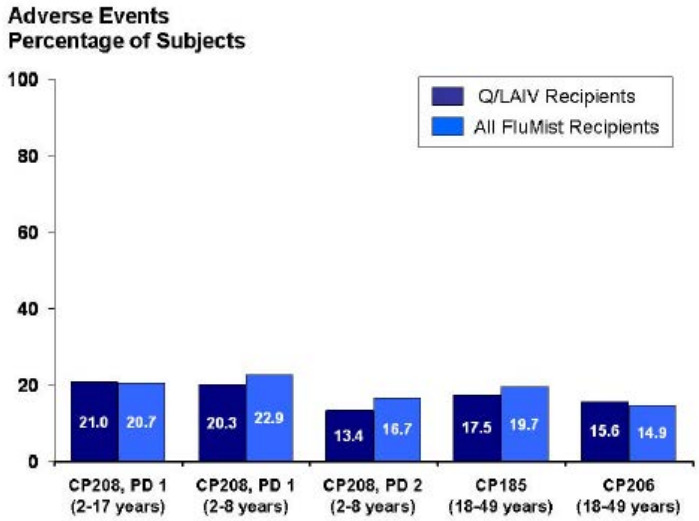
8.3.1.1. Pivotal studies

Safety endpoints were:

1. solicited symptoms experienced from administration of investigational product through 14 days post vaccination by dose number (as appropriate);
2. AEs experienced from administration of investigational product through 28 days post vaccination by dose number (as appropriate);
3. SAEs experienced from administration of investigational product through 28 days post vaccination by dose number (as appropriate);
4. treatment emergent SAEs and NOCDs experienced through 180 days post last dose.

Percentages of subjects experiencing at least one AE in the 3 Q/LAIV studies are summarised in Figure 5 (below) and were similar between the Q/LAIV and FluMist groups.

Figure 5. Percentage of subjects reporting the occurrence of at least one adverse event in Q/LAIV Studies MI-CP185, MICP208, and MI-CP206



Study MI-CP208

For all subjects post Dose 1, similar proportions of subjects in the Q/LAIV arm (21.0%) and the All FluMist Group (20.7%) reported the occurrence of ≥ 1 AE during Days 0 to 28 post Dose 1. The preferred term AE with the largest rate difference was pyrexia (1.0 percentage point). The most common AEs by frequency in the Q/LAIV arm were vomiting (2.6%), cough (2.0%), pyrexia (1.7%), diarrhoea (1.6%), rhinorrhoea (1.6%), and sneezing (1.2%). Post Dose 1 in the two-dose group, more subjects in the All FluMist group (22.9%) reported the occurrence of ≥ 1 AE during Days 0 to 28 than did subjects in the Q/LAIV arm (20.3%). In children and adolescents enrolled in Study MI-CP208, events with a rate difference (Q/LAIV minus FluMist) of ≥ 0.5 percentage points were pyrexia, headache, oropharyngeal pain, epistaxis, abdominal pain, and nausea. Although the rate difference for vomiting was < 0.5 percentage points, it was the most frequently reported AE in both the Q/LAIV arm (2.6%) and the All FluMist group (2.2%). New onset chronic diseases (NOCD) were reported by 1.4% (19/1,382) of subjects in the Q/LAIV arm and 0.8% (7/923) of subjects in the All FluMist group. None of the NOCDs were assessed by the investigator as being related to investigational product.

Study MI-CP185

Unsolicited AEs reported by subjects in all study arms were similar in type and incidence. The AE with the largest rate difference (Q/LAIV > All FluMist) was sneezing, with a rate difference of 0.7 percentage points; sneezing was also the most common AE by frequency (1.5%) in the Q/LAIV arm. The most common AE in subjects who received a FluMist vaccine was rhinorrhoea (1.5%). The most commonly reported preferred term AEs considered to be related to investigational product were sneezing (0.9%) in the Q/LAIV arm and rhinorrhoea (0.7%) in the All FluMist arm. For the adult Study MI-CP185, events with a rate difference (Q/LAIV arm minus All FluMist group) of ≥ 0.5 percentage points were sinusitis, oropharyngeal pain, and sneezing. Sneezing was the most frequently reported preferred term AE in subjects who received Q/LAIV (1.5%, compared to 0.8% of FluMist subjects), and it was the event reported with the highest rate difference (0.7 percentage point).

8.3.1.2. Other studies

Study MI-CP206

The safety of Q/LAIV-BFS was comparable to that observed for the two FluMist comparators. AEs were also reported with similar frequencies among subjects in the Q/LAIV-BFS group and those in the All FluMist group, with overall frequencies of 15.6% of subjects in the Q/LAIV-BFS group and 14.9% of subjects in the All FluMist group. The AEs occurring more frequently in the

Q/LAIV-BFS group for which the rate differences were highest were headache (rate difference, 0.8 percentage point), cough (rate difference, 0.7 percentage point) and back pain (rate difference, 0.6 percentage point). There was no preferred term AE with a rate difference of ≥ 1.0 percentage point (that is, in at least 1.0% more subjects in the Q/LAIV-BFS group than in the All FluMist group) or ≤ -1.0 percentage point (that is, in at least 1.0% more subjects in the All FluMist group than in the Q/LAIV-BFS group). The percentage of subjects with reported NOCDs was low and similar between treatment groups (0.5% in both the Q/LAIV-BFS and All FluMist groups).

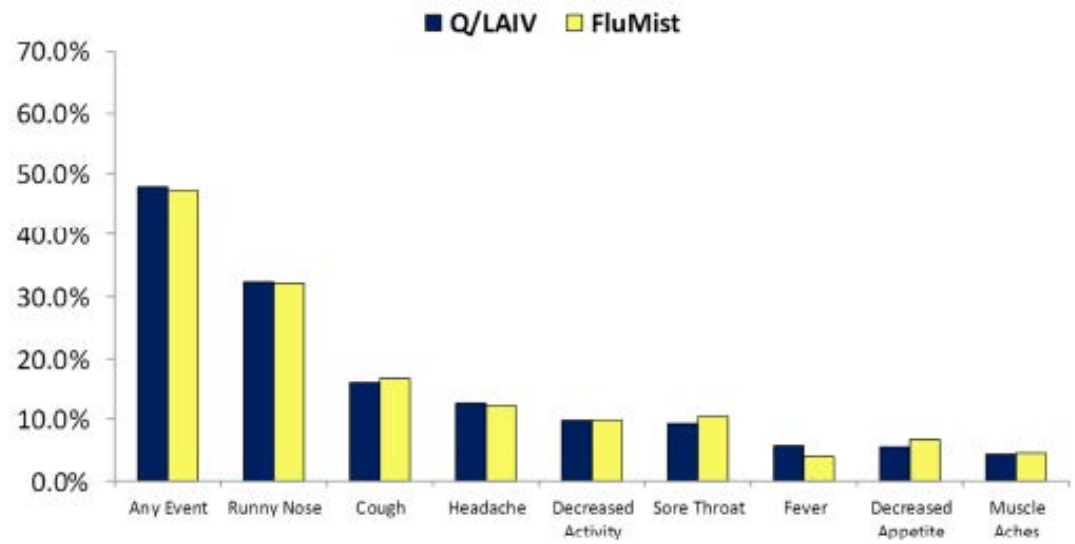
8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

Study MI-CP208

For all subjects post Dose 1, a total of 659/1,377 (47.9%) subjects in the Q/LAIV arm reported at least one solicited symptom, while 436/920 (47.4%) subjects in the All FluMist group reported at least one solicited symptom. Fever ≥ 100.4°F (38.0°C) was reported by more Q/LAIV subjects (5.7%) than All FluMist subjects (3.9%); fever ≥ 101.3°F (38.5°C) was reported by 3.3% of Q/LAIV subjects and 2.3% of subjects in the All FluMist group. No other solicited symptom occurred with a rate difference of ≥ 1.0 or ≤ -1.0 percentage point (see Figure 6, below). For the two-dose group post Dose 1 (a subset of all subjects post Dose 1), a total of 519/1,078 (48.1%) subjects in the Q/LAIV arm reported at least one solicited symptom, while 340/716 (47.5%) subjects in the All FluMist group reported at least one solicited symptom. Fever ≥ 100.4°F (38.0°C) was reported by more Q/LAIV subjects (6.6%) than All FluMist subjects (4.2%); fever ≥ 101.3°F (38.5°C) was reported by 4.0% of Q/LAIV subjects and 2.2% of subjects in the All FluMist group. The only solicited symptom that occurred with a rate difference of > 1.0 percentage point (Q/LAIV minus FluMist) was runny/stuffy nose (2.1 percentage points).

Figure 6. Proportion of subjects reporting solicited symptoms during days 0 to 14 post Dose 1, evaluable Safety Population for solicited symptoms (All Subjects), paediatric Q/LAIV Study MI-CP208



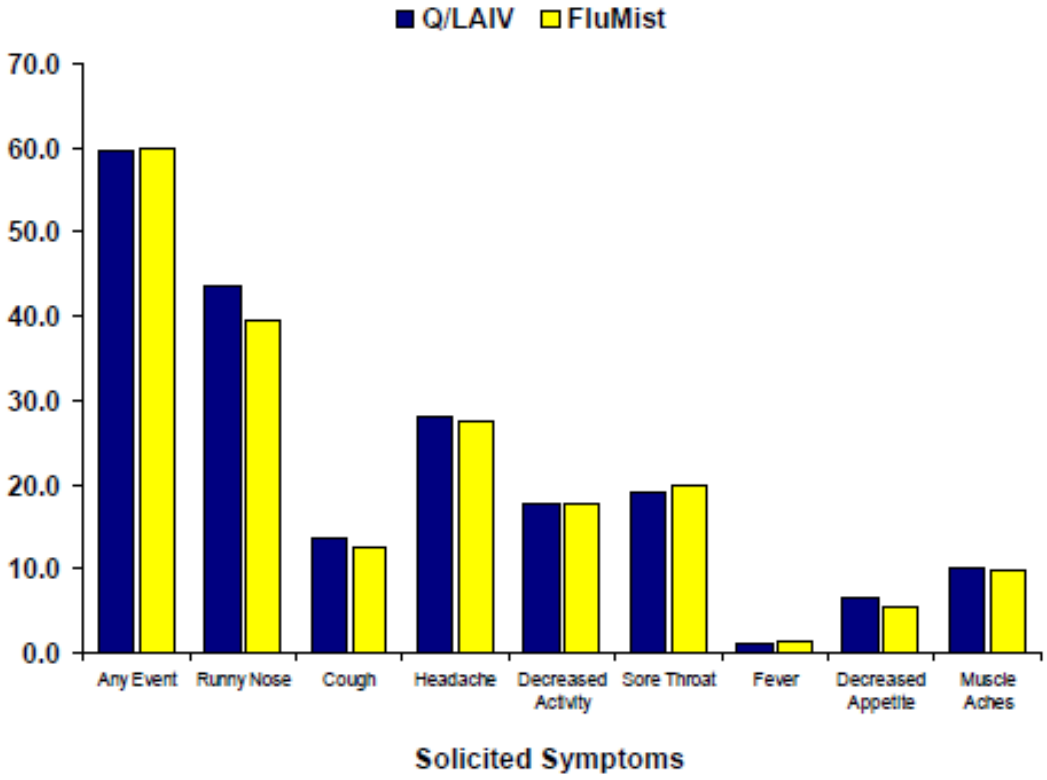
Overall, solicited symptoms and AEs were generally reported by similar proportions of subjects in the Q/LAIV and FluMist treatment arms, as was expected given the similarity between the two products. Fever was more commonly reported by Q/LAIV recipients than by FluMist recipients, but the overall rates of fever reported in either study arm were low. Fewer subjects in either study group reported solicited symptoms after Dose 2 than after Dose 1. AEs reported by subjects in all study arms were similar in type and incidence; pyrexia was the AE most

commonly reported in a relatively larger proportion of Q/LAIV than FluMist subjects. There was no pattern of SAEs or NOCDs that suggested an imbalance between treatment groups.

Study MI-CP185

Solicited symptoms were generally reported in similar proportions of subjects in the Q/LAIV and FluMist treatment arms, as was expected given the similarity between the 2 products (see Figure 7, below). The most commonly reported solicited symptom was runny/stuffy nose, which was reported by more Q/LAIV subjects (43.6%) than All FluMist subjects (39.5%). It was also the solicited symptom with the largest rate difference (Q/LAIV rate minus All FluMist rate; 4.1 percentage points). Fever was uncommon in all study arms.

Figure 7. Proportion of subjects reporting solicited symptoms during days 0 to 14 post dose, evaluable Safety Population for solicited symptoms, Study MI-CP185



8.3.2.2. Other studies

Study MI-CP206

The frequency of any solicited symptom was similar between subjects in the Q/LAIV-BFS group and the All FluMist group (50.6% Q/LAIV-BFS versus 54.3% All FluMist). The percentage of subjects reporting at least one solicited symptom were similar in the Q/LAIV-BFS group as compared to the All FluMist group (50.6% Q/LAIV-BFS versus 54.3% All FluMist), which represents combined data from both FluMist groups. The largest rate difference (-6.4%) was observed for runny/stuffy nose, which was reported at a higher rate in the All FluMist group (37.6%) compared to the Q/LAIV-BFS group (31.3%). A rate difference of -2.6% was also observed for generalised muscle aches in the All FluMist group (11.1%) compared to the Q/LAIV-BFS group (8.4%). Rate differences ≥ 1% for which the Q/LAIV-BFS group was higher than the All FluMist group included 2.3 percentage points for sore throat (17.3% Q/LAIV-BFS versus 15.0% All FluMist) and 1.7 percentage points for cough (9.6% Q/LAIV-BFS versus 7.9% All FluMist). The percentage of subjects reporting a fever ≥ 101.3°F was 0.7% in the Q/LAIV-BFS group and the All FluMist group.

8.4. Deaths and other serious adverse events

8.4.1. Pivotal studies

8.4.1.1. Study MI-CP208

No deaths and no SAEs considered to be related to investigational product were reported in study subjects. No SAEs occurred within 28 days of Dose 1. Within 28 days of Dose 2, 3 subjects reported 4 SAEs (appendicitis, salmonella gastroenteritis with dehydration, and major depression). During Days 0 to 180 after dosing, 0.4% (6/1,382) of subjects who received Q/LAIV reported 7 SAEs and 0.5% (5/923) of subjects who received FluMist reported 9 SAEs. All SAEs were considered by the investigator to be not related to investigational product.

8.4.1.2. Study MI-CP185

There were no deaths and no SAEs considered to be related to investigational product that occurred in subjects in the Q/LAIV arm. There was one SAE of hypersensitivity (allergic reaction with bronchospasm) considered to be related to investigational product. Of the other events, none considered to be related to investigational product, were diverticulitis, fibula fracture, tibia fracture, and asthma. The subject with the SAE of asthma had a significant history of asthma that was not revealed prior to enrolment.

8.4.2. Other studies

8.4.2.1. Study MI-CP206

A slightly higher percentage of subjects experienced SAEs in the Q/LAIV-BFS group (1.3%) as compared to the All FluMist group (0.3). This included 4 subjects who did not meet the eligibility criteria based on their prior medical history of asthma, medical noncompliance, non-Hodgkin's lymphoma, and hospitalisation within 1 year of randomisation. Two of these SAEs resulted in fatal outcomes that were considered unrelated to investigational product (one cholecystitis and sepsis, the other was pneumonia and renal failure). Additionally, one subject was pregnant at the time of enrolment, but due to a false negative pregnancy test at the time of randomisation, received treatment. This subject experienced a miscarriage, which was assessed by the investigator as possibly related to investigational product. Review of this case by the Independent Safety Monitoring Committee (ISMC) resulted in the unanimous decision that this event was unrelated to investigational product.

8.4.3. Discontinuation due to adverse events

Nil.

8.5. Laboratory tests

Not applicable.

8.5.1. Liver function

Not applicable.

8.5.2. Kidney function

Not applicable.

8.5.3. Other clinical chemistry

Not applicable.

8.5.4. Haematology

Not applicable.

8.6. Post-marketing experience

There is currently 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 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 more in Section 7.2. 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.

8.6.1. Safety in special populations

There are not yet any specific studies for Q/LAIV in populations of immunocompromised individuals, pre-existing lung conditions or asthma and wheezing. These issues/populations have been extensively studied as part of the registration process for FluMist and results are summarised below.

Table 13. Special patient groups evaluated in FluMist studies

Study Number	Total Number of Subjects Entered	Age Range	Special Patient Group
MI-CP111	8,475 (n = 483 with underlying medical conditions)	6 to 59 M	**Underlying medical conditions**: chronic lung or cardiac disease, diabetes mellitus or other chronic metabolic disease, hemoglobinopathy, renal, or other chronic disease
AV008	200	≥ 65 Y	**Underlying medical conditions**: chronic pulmonary, cardiac, or metabolic disease, renal dysfunction, or hemoglobinopathy
AV010	48	9 to 17 Y	**Respiratory illness**: moderate to severe asthma
D153-P514	2,187	6 to <72 M	**Respiratory illness**: history of recurrent respiratory tract infections
D153-P515	2,229	6 to 17 Y	**Respiratory illness**: stable, medically treated asthma
VA CSP 448	2,215	≥ 50 Y	**Respiratory illness**: chronic obstructive pulmonary disease
DMID 98-005	111 (n = 57 HIV-infected)	18 to 50 Y	**Immunocompromised**: HIV-infected with asymptomatic or mildly symptomatic disease
DMID 99-012	49 (n = 24 HIV-infected)	1 to 7 Y	**Immunocompromised**: HIV-infected with asymptomatic or mildly symptomatic disease
PACTG 1057	243	5 to 17 Y	**Immunocompromised**: receiving stable HAART for HIV disease, with plasma HIV RNA < 60,000 copies/ml
MI-CP114	20	5 to 17 Y	**Immunocompromised**: solid tumors in remission or hematologic malignancies treated with maintenance therapy

8.6.1.1. Asthma and wheezing – medically significant wheezing (MSW)

Multiple prospective studies were conducted on FluMist to evaluate the risk of asthma and wheezing in at-risk populations. These studies enrolled approximately 2,200 children and adolescents with a medical history of asthma (Studies AV010 and D153-P515);[8,9] approximately 2,200 children with recurrent respiratory tract infections (45% of whom had a history of medically documented wheezing and 23% of whom had medically diagnosed asthma) (Study D153-P514[12]);[10] and approximately 2,200 adults with chronic obstructive pulmonary disease (Study VA CSP 448).[11] These studies indicated that FluMist was safe and well tolerated and did not induce post vaccination asthma or wheezing or clinically significant changes in pulmonary function in these high risk populations.

In contrast to the studies in adults and children with underlying respiratory disease, 2 other studies (Studies AV019 and MI-CP111) that mainly enrolled healthy children indicated a small but measurable asthma/wheezing risk. Study AV019 was a Phase III placebo controlled safety study conducted in approximately 9,700 children 1 to 17 years of age.[12] In pre-specified analyses, asthma/reactive airways disease within 42 days after vaccination occurred in a higher proportion of children 18 to 35 months of age who received FluMist (2.2%) than those who received placebo (0.54%). In post hoc analyses, a statistically significantly increased risk could not be ruled out in children up to 59 months of age. Among children 12 to 59 months of age, the rates of asthma/reactive airways disease were 0.69% for FluMist recipients versus 0.20% for placebo recipients. There was no increased risk found in children 5 years of age and older; indeed, rates of asthma/reactive airways disease were significantly decreased in some analyses of older children who received FluMist versus placebo.[13] Based on these findings, the sponsor conducted a pivotal study to prospectively evaluate both safety and efficacy of FluMist and TIV in children 6 to 59 months of age (MI-CP111).[14] A total of 8,475 children 6 to 59 months of age were randomised to receive either TIV or FluMist, using a double blind design. Administration of FluMist resulted in a 44.5% greater reduction in influenza illness due to matched strains compared to TIV, and a 55% greater reduction in illness due to all strains regardless of antigenic match. The incidence of wheezing was similar between the FluMist and TIV groups after Dose 1 of vaccine until 42 days post dosing. But in analyses of MSW during Days 0 to 42 after each dose, a significant increase for FluMist recipients was detected after Dose 1 in the group of subjects who were not previously vaccinated (2.3% FluMist versus 1.5% TIV). In pre-specified analyses, the subgroup that most contributed to the increase was subjects < 24 months of age (MSW rates of 3.2% FluMist versus 2.0% TIV). None of the analyses after each dose for subjects ≥ 24 months of age showed statistically significant differences between FluMist and TIV. In subjects ≥ 24 months of age, rates of MSW from Day 0 to 42 days post last dose were 2.1% in the FluMist arm versus 2.5% in the TIV arm. Analyses failed to demonstrate a baseline factor other than age < 24 months that contributed to an increase in post vaccination wheezing, including gender, country of residence, and prior history of wheezing or asthma.

[8] Redding G et al., Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2002;21:44-8.
[9] Fleming DM et al., Health benefits, risks, and cost-effectiveness of influenza vaccination in children. Pediatr Infect Dis J. 2008;27:S154-8.
[10] Ashkenazi S et al., Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006 Oct;25(10):870-9.
[11] Gorse G et al., Immunity to influenza in older adults with chronic obstructive pulmonary disease. J Infect Dis. 2004;190(1):11-9.
[12] Bergen R 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.
[13] 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
[14] Belshe R et al., Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356:685-96.

8.6.1.2. FluMist safety in individuals with concomitant underlying chronic medical conditions

Two clinical studies evaluated the safety of FluMist in individuals with concomitant underlying medical conditions: Study MI-CP111 (described above) in the paediatric population and Study AV008 in the adult population. Study AV008 demonstrated that FluMist was safe in high-risk subjects when administered concurrently with an intramuscular injection of TIV. Among the 8,475 children enrolled in Study MI-CP111, 483 (5.7%) had an underlying medical condition (including chronic lung or cardiac disease, diabetes mellitus or other chronic metabolic disease, haemoglobinopathy, renal, or other chronic disease). A total of 241 of these children were randomised to receive FluMist and 242 to receive TIV. In post hoc analyses of these 483 children with an underlying medical condition, the safety and efficacy profile of FluMist compared to TIV was similar to that observed in the general study population. Despite the relatively small size of the subset, a statistically significantly higher relative efficacy was demonstrated for FluMist versus TIV against culture confirmed modified CDC-ILI associated with antigenically mismatched A/H3N2 strains: attack rates of 0.9% for FluMist and 4.1% for TIV, with 85% fewer cases of influenza illness for FluMist (relative efficacy 85.3% (95% CI: 6.9, 99.3). Thus, among children with high risk medical conditions in this study, there was no evidence that the safety profile of FluMist was altered, and relative efficacy compared to TIV was similar to that seen in the overall study population.

8.6.1.3. FluMist safety in individuals with respiratory illness

Four clinical studies including > 4,400 paediatric subjects 6 months to 18 years of age and > 2,200 adults examined the effects of FluMist in subjects with a history of respiratory illness (see Table 13, above). Overall, these studies demonstrated that vaccination with FluMist was efficacious, provided protection against influenza illness that was superior to that of TIV, and was not associated with increased rates of post-vaccination asthma exacerbation, respiratory tract infection, wheezing, exacerbation of COPD, or hospitalisation for respiratory illness.

Study AV010 was a randomised, double blind, placebo controlled study conducted in 48 children and adolescents 9 to 17 years of age with moderate to severe asthma (reversibly impaired forced expiratory volume over 1 second at Baseline). Efficacy and immunogenicity were not assessed. Results showed that there were no significant differences between treatment groups post vaccination in asthma stability using multiple measures of pulmonary function (for example, forced expiratory volume over 1 second, forced vital capacity, peak expiratory flow rate) and measures of clinical asthma status (for example, daily symptom scores, night time awakening scores, change in daily albuterol use, occurrence of at least 1 asthma exacerbation). The overall occurrence of SEs and AEs was similar between the 2 groups during Days 0 to 10 post dose.

Study D153-P514 was a randomised, open label, TIV controlled study conducted in 2,187 children 6 to < 72 months of age who had a medical history of recurrent respiratory tract infections (45% had a history of medically documented wheezing and 23% had medically diagnosed asthma). Subjects were randomised to receive 2 doses of either FluMist or TIV. Following both vaccine doses, runny nose/nasal congestion and rhinitis were statistically significantly more frequent in FluMist subjects. There were no statistically significant differences between the FluMist and TIV groups after either Dose 1 or Dose 2 of vaccine in the incidence of wheezing during Days 0 to 10 or during Days 11 to 41. Statistically significant superior efficacy was observed for FluMist relative to TIV; efficacy for FluMist was 53% greater relative to that of TIV for matched strains, and 52% greater relative to that of TIV for all strains regardless of antigenic match**.**

Study D153-P515 was a randomised, open label, TIV controlled study conducted in 2,229 children and adolescents 6 to 17 years of age who had stable, medically treated asthma. Subjects were randomised to receive a single dose of FluMist or TIV. The incidence of asthma exacerbation post vaccination was similar for both treatment groups (31% FluMist, 30% TIV),

and rates of hospitalisation for asthma were 0.7% in both groups. FluMist was well tolerated and demonstrated a safety profile comparable to that of TIV with regard to incidence of SEs and other AEs. Statistically significant superior efficacy was observed for FluMist relative to TIV; efficacy was 35% for FluMist greater relative to that of TIV for matched strains, and 32% relative efficacy compared to that of TIV for all strains regardless of antigenic match.

Study VA CSP 448 evaluated the efficacy, immunogenicity, and safety of FluMist in 2,215 subjects ≥ 50 years of age with clinically stable COPD[13]. The results of this study showed that adding FluMist vaccination to TIV vaccination in older adults with stable COPD was generally well tolerated and did not alter the stability of COPD.

In summary, data from 4 clinical studies in subjects with underlying asthma, COPD, or recurrent respiratory tract infections indicated that FluMist had an acceptable safety and tolerability profile in individuals with a history of respiratory illness.

8.6.1.4. FluMist safety in immunocompromised individuals

Three clinical studies involving > 400 subjects 1 to 50 years of age examined the effects of FluMist in subjects with HIV infection, and 1 study evaluated the effects of FluMist in 20 children 5 to 17 years of age with solid tumours or haematologic malignancies (see Table 13 above). Overall, these studies demonstrated that the safety profile of FluMist in subjects with mildly to moderately compromised immune function was similar to that in healthy individuals.

Study DMID 98-005 was conducted in subjects 18 to 50 years of age who were either HIV infected with asymptomatic or mildly symptomatic disease (N = 57) or who were not infected with HIV (N = 54).[15] Subjects were randomised to receive a single dose of either FluMist or placebo. Efficacy was not evaluated in this study. The overall rates of SEs and other AEs were similar between HIV infected and non-infected subjects in each treatment group. FluMist recipients had higher rates of runny nose/nasal congestion than placebo recipients. In HIV infected subjects, neither HIV RNA nor CD4 assessments differed significantly between FluMist and placebo recipients at 1, 3, or 6 months after dosing.

Study DMID 99-012 was conducted in children 1 to 7 years of age who were either HIV infected with asymptomatic or mildly symptomatic disease (N = 24) or who were not infected with HIV (N = 25; King et al, 2001). Subjects were randomised to receive FluMist or placebo as Dose 1, followed approximately 28 days later by cross-over to the other treatment as Dose 2. Approximately 28 days after Dose 2, all subjects received open label FluMist as Dose 3. Efficacy was not evaluated in this study. Fever > 38.0°C (100.4°F) occurred in 4% of HIV infected subjects and 12% of non-HIV infected subjects after FluMist administration; these rates were not statistically different. Other SEs and AEs were no more common in HIV infected subjects than in non-HIV infected subjects. FluMist vaccination of HIV infected subjects did not result in significant changes in CD4 counts or HIV viral load. Vaccine virus shedding was documented in 13% of HIV-infected and 28% of non-HIV infected FluMist recipients. Prolonged shedding did not occur.

Study PACTG 1057 was conducted in children 5 to 17 years of age who were receiving stable highly active antiretroviral therapy for HIV disease and had plasma HIV RNA < 60,000 copies/mL. Subjects were randomised to receive a single dose of FluMist (N = 122) or TIV (N = 121). Efficacy was not evaluated in this study. Nasopharyngeal symptoms (discharge, congestion, and sore throat) were more frequent among FluMist than TIV subjects, but rates of other AEs, including pulmonary signs and symptoms, were similar between the 2 treatment groups. No significant changes in plasma HIV RNA or CD4 counts were observed in either FluMist or TIV subjects at 4 and 28 weeks after vaccination. Prolonged shedding of FluMist

[15] 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.

vaccine virus did not occur; none of 128 specimens obtained after Day 15 was positive for influenza virus.

Study MI-CP114 was a randomised, double blind, placebo controlled study in children 5 to 17 years of age who had solid tumours in remission or hematologic malignancies treated with maintenance chemotherapy. A total of 20 subjects were enrolled and treated at 4 sites in the USA, including 10 subjects in the FluMist group and 10 subjects in the placebo group. All of the subjects completed the study. There were no deaths, related SAEs, or severe or life threatening AEs in the FluMist group. In the FluMist group, all AEs were mild or moderate and no AE was reported by more than 1 subject. Reactogenicity events were balanced in both groups with the exception of runny nose/nasal congestion which, as expected, occurred more frequently in the FluMist group (77.8% versus 20.0%). A small numerical imbalance in vomiting was detected (FluMist, 3/9 versus placebo, 1/10) and should be interpreted cautiously due to the small sample size. Importantly, only 1 mild fever (≥ 100 to ≤ 101°F oral) was reported in FluMist recipients.

Overall, FluMist was well tolerated in this population, and its safety profile was comparable to that seen in the general population In summary, data from 4 clinical studies indicated that FluMist had an acceptable safety and tolerability profile in subjects with mildly to moderately compromised immune function.

8.7. Evaluator's overall conclusions on clinical safety

In the safety data submitted, rates of SAEs were low, particularly in children, and were balanced between Q/LAIV and FluMist groups in the 2 pivotal Q/LAIV studies: 0.4% and 0.5% for the Q/LAIV and All FluMist groups in paediatric Study MI-CP208, respectively, and 1.0% in the Q/LAIV and All 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 (0.3%); however, the rate in the FluMist group was unexpectedly low as compared to the All FluMist 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 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 NOCDs 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. 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 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 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 is expected. AEs 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.

9. First round benefit-risk assessment

9.1. 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 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 trivalent formulations.
- The tolerability and safety of Q/LAIV were comparable to those of FluMist.
- 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 to be applied to the new quadrivalent formulation.
- The efficacy of FluMist, has been demonstrated in multiple randomised, controlled studies conducted in children. In placebo controlled studies conducted in children, protection from culture confirmed ILI caused by any matched strain has ranged from 72.9% to 93.4%. In TIV controlled studies, FluMist 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) 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).

9.2. First round assessment of risks

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

- The safety of Q/LAIV was compared to FluMist during the clinical development program. Due to the similarities between Q/LAIV and FluMist, the two safety signals associated with use of FluMist, 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. 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 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 groups in both adults and children, and the specific adverse events are consistent with those seen in previous FluMist 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 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 USA and in the EU and through routine pharmacovigilance activities.

9.3. First round assessment of benefit-risk balance

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

10. 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 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. It will be very important to continue to monitor this data when these studies switch to Q/LAIV.

11. Clinical questions

Not applicable.

12. Second round evaluation

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

13. 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.

14. References

World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2012-2013 northern hemisphere influenza season.

Newall A et al. Influenza-related disease: the cost to the Australian healthcare system. Vaccine. 2008 Dec 9;26(52):6818-23.

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

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.

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.

Belshe R et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007; 356:685-96.

Fleming DM, Elliot AJ. Health benefits, risks, and cost-effectiveness of influenza vaccination in children. Pediatr Infect Dis J. 2008;27:S154-8.

Skowronski D et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness, 2013-14 season. J Infect Dis. 2015 Mar 17. pii: jiv177

Kwong J et al. Randomized evaluation of live attenuated vs. inactivated influenza vaccines in schools (RELATIVES) pilot study: preliminary results from the household surveillance sub-study. Abstract from the Canadian Immunization Conference, December 2014.

Cotter C et al. A single amino acid in the stalk region of the H1N1pdm influenza virus HA protein affects viral fusion, stability and infectivity. PLoS Pathog. 2014 Jan;10(1)

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

Fleming D et al. Health benefits, risks, and cost-effectiveness of influenza vaccination in children. Pediatr Infect Dis J. 2008;27:S154-8.

Ashkenazi S et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006 Oct;25(10):870-9.

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.

Gorse G et al. Immunity to influenza in older adults with chronic obstructive pulmonary disease. J Infect Dis. 2004;190(1):11-9.

Bergen R 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.

15. Addendum to the clinical evaluation report

This is an addendum to assess efficacy of one versus two doses of FluMist in previously unvaccinated children. The data being examined relates to FluMist (LAIV) rather than FluMist Quadrivalent.

15.1. Clinical question for this addendum

As the practical implications of a 2-dose annual vaccination regimen in children are quite onerous, the purpose of this addendum is to examine available data regarding the efficacy of one versus two doses of the vaccine, in terms of efficacy.

15.2. Contents of the clinical dossier

Although 2 doses of influenza vaccine are recommended for previously unvaccinated children, three studies also compared 1 dose of LAIV with placebo in previously unvaccinated young children.

In 2 studies (Studies AV006 and D153-P504), children received 1 dose (versus placebo) per-protocol in Year 1.

Another study that re-randomised subjects in its second year, vaccinated some subjects for the first time in Year 2 with 1 dose (Study D153-P501).

Additionally, in the second year of Study D153-P504, a cohort that received placebo in Year 1 received 1 dose of LAIV in Year 2 because of an error in vaccine assignment.

A meta-analysis of these studies, including these four subsets of data is also discussed.[16]

15.3. Clinical efficacy

15.3.1. Studies examining one-dose efficacy versus two-doses

15.3.1.1. Study AV006

This was a prospective, multicentre, double blind, placebo controlled trial of a live attenuated, cold adapted, trivalent influenza virus vaccine in children 15 to 71 months old.[17] Subjects in the 1-dose cohort were enrolled and vaccinated from September 30, 1996, through December 5, 1996. Two hundred eighty-eight healthy children were assigned to receive 1 dose of vaccine (189) or placebo (99) given by intranasal spray, and 1314 were assigned to receive 2 doses (881 vaccine and 433 placebo) approximately 60 days apart. The strains included in the vaccine were antigenically equivalent to those in the inactivated influenza virus vaccine in use at the time. The subjects were monitored with viral cultures for influenza during the subsequent influenza season. A case of influenza was defined as an illness associated with the isolation of wildtype influenza virus from respiratory secretions.

The primary objective in Year 1 was to demonstrate that subjects receiving a 2-dose primary vaccination regimen of FluMist were protected from culture-confirmed influenza illness caused by antigenically matched strains. Estimating the efficacy of a 1-dose primary vaccination regimen of FluMist against culture-confirmed influenza illness caused by antigenically matched strains was a secondary efficacy objective of the study. A case of influenza was defined as any illness detected by active surveillance (as described above) that was associated with a positive culture for wild-type influenza virus. Two hundred three subjects participated in a sub-study of immunogenicity to characterize strain-specific antibody responses to the vaccine.

Results

Vaccine significantly reduced the occurrence of culture-confirmed influenza in the study population. Results are shown in Table 14, below.

Among the 1070 children who received vaccine, 14 had culture-confirmed influenza, and among the 532 children who received placebo, 95 had 1 or more influenza infections. Among the vaccinated children, none had influenza A (H3N2) followed by influenza B, but among the controls, 6 children had 2 distinct culture-positive episodes of influenza, for a total of 101 illnesses among 95 controls. The vaccine was effective when given in either 1 or 2 doses, and it also prevented infection with the 2 viral subtypes causing disease during this epidemic season, influenza A (H3N2) and influenza B.

[16] Rhorer J et al. Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomised clinical trials. Vaccine. 2009 Feb 11;27(7):1101-10.
[17] Belshe R et al. The efficacy of live attenuated, cold adapted, trivalent, intranasal influenza virus vaccine in children. N Engl J Med 1998;338(20):1405–12.

Table 14. Efficacy of one or two doses of live attenuated, cold-adapted influenza virus vaccine for the prevention of culture-confirmed influenza

Influenza Type	Subjects Assigned to One Dose			Subjects Assigned to Two Doses Who Received Two Doses†			All Study Subjects‡		
	Cases of Influenza		Efficacy (95% CI)	Cases of Influenza		Efficacy (95% CI)	Cases of Influenza		Efficacy (95% CI)
	Vaccine Group (N = 189)	Placebo Group (N = 99)		Vaccine Group (N = 849)	Placebo Group (N = 410)§		Vaccine Group (N = 1070)	Placebo Group (N = 532)§	
A(H3N2)	2	8	87 (47–97)	4	49	96 (90–99)	7	64	95 (88–97)
B	1	6	91 (46–99)	6	31	91 (78–96)	7	37	91 (79–96)
Any type	3	14	89 (65–96)	10	74	94 (88–97)	14	95	93 (88–96)

Notes: CI denotes confidence interval. † This analysis excluded 55 subjects who were not per protocol. ‡ The efficacy calculation includes all children assigned to receive 1 dose, all children assigned to receive 2 doses who received 2 doses, and all other children assigned to 2 doses who had wild-type influenza before the second dose or for some reason did not receive the second dose. Among the children who did not receive the second dose there was 1 additional case of influenza in the vaccine recipients and seven additional cases in the placebo recipients. § 6 children had 2 illnesses with influenza A(H3N2) and influenza B isolated, and all six were in the 2-dose cohort. These children are counted once in the calculation of any type of influenza.

The overall vaccine efficacy was 93% (95% CI: 88, 96%) against culture confirmed influenza. Both the 1-dose regimen (89% efficacy) and the 2-dose regimen (94% efficacy) were efficacious, and the vaccine was efficacious against both strains of influenza circulating in 1996 to 1997, A(H3N2) and B. Among children who were initially seronegative, antibody titres increased by a factor of four in 61 to 96%, depending on the influenza strain (highest for B and A (H3N2), lowest for A (H1N1). There was however no correlation between immunogenicity (lower in the younger age groups) and clinical efficacy (which was equivalent for all age groups).

In this study, there was not a statistical difference between the 1 and 2 dose regimens and the CI for the efficacy of the 1 dose group was very broad which probably relates to the small size of this group (189 subjects) The cohorts were relatively small and the efficacy for both groups was higher than in subsequent studies. This study was undertaken 20 years ago and most of the breakthrough influenza in the 1996 to 1997 season was A (H3N2).

15.3.1.2. Study D153-P501

This prospective, randomised, double blind, placebo controlled, multicentre, crossover trial was conducted during 2 consecutive years at 16 sites in 8 regions (China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, and Thailand) between 30 September 2000 and 31 May 2003.[18]

This study was designed to evaluate the efficacy and safety of cold-adapted influenza vaccine, trivalent (LAIV) against culture-confirmed influenza in healthy children 12 to < 36 months of age during 2 consecutive influenza seasons at multiple sites in Asia.

In Year 1, 3174 children aged 12 to < 36 months were randomised to receive 2 doses of LAIV (n = 1900) or placebo (n = 1274) intranasally ≥ 28 days apart. In Year 2, 2947 subjects were re-randomised to receive 1 dose of LAIV or placebo (so 596 subjects that received placebo in the first year of the study were included in the Per-Protocol Population to be vaccinated with a single dose of LAIV in the second year of the study (PP, N = 503).

Surveillance for ILI was based on weekly telephone contacts, clinic visits, or home visits, beginning on the eleventh day after receipt of the first dose of study treatment and continued

[18] Tam J et al. Efficacy and safety of a live attenuated, cold adapted influenza vaccine, trivalent against culture confirmed influenza in young children in Asia. Pediatr Infect Dis J 2007;26(7 (July)):619–28.

for 2 years until the end of the study. A nasal swab sample was obtained if subjects exhibited any predefined symptoms considered associated with an influenza-like illness.

The primary efficacy endpoint was the first episode of culture-confirmed influenza illness caused by a subtype antigenically similar to that in the vaccine after receipt of the second dose of study vaccine or placebo during Year 1 in the PP population. Secondary efficacy end points included the first episode of culture-confirmed influenza illness caused by any influenza virus subtype after receipt of the second dose of study vaccine or placebo during Year 1 and the first episode of culture-confirmed influenza caused by subtypes antigenically similar to vaccine components after completion of a primary series in Year 1 and a single dose in Year 2.

Results

Per-protocol vaccine efficacy against culture-confirmed influenza in Year 1 is summarised in Table 15, below. The incidence of influenza caused by strains antigenically similar to vaccine was 3.4% and 12.5% in the LAIV and placebo groups, respectively. Overall efficacy of LAIV against influenza viruses antigenically similar to those in the vaccine was 72.9% (95% CI: 62.8, 80.5%). Statistically significant vaccine efficacy was observed against all 3 circulating viruses antigenically similar to the vaccine, influenza A/H1N1 (80.9%) and AH3N2 (90.0%), and B (44.3%). Overall, vaccine efficacy against any influenza strain was 70.1% (95% CI: 60.9, 77.3%).

Table 15. Efficacy of LAIV against culture confirmed influenza in Year 1

Influenza Subtype	Treatment Group				Efficacy, % (95% CI)
	CAIV-T		Placebo		
	No. Subjects in Population	No. (%) With Culture-Confirmed Influenza	No. Subjects in Population	No. (%) With Culture-Confirmed Influenza	
Subtypes antigenically similar to the vaccine					
Per-protocol population					
Any antigenically similar strain	1653	56 (3.4)	1111	139 (12.5)	72.9 (62.8–80.5)
A/H1N1	1653	23 (1.4)	1111	81 (7.3)	80.9 (69.4–88.5)
A/H3N2	1653	4 (0.2)	1111	27 (2.4)	90.0 (71.4–97.5)
B	1653	29 (1.8)	1111	35 (3.2)	44.3 (6.2–67.2)
Intent-to-treat population					
Any antigenically similar strain	1900	70 (3.7)	1274	157 (12.3)	70.1 (60.1–77.8)
Any subtypes					
Per-protocol population					
Any strain	1653	81 (4.9)	1111	182 (16.4)	70.1 (60.9–77.3)
A/H1N1	1653	23 (1.4)	1111	82 (7.4)	81.1 (69.8–88.7)
A/H3N2	1653	14 (0.8)	1111	60 (5.4)	84.3 (71.6–91.9)
B	1653	44 (2.7)	1111	52 (4.7)	43.1 (13.4–62.8)
Intent-to-treat population					
Any strain	1900	98 (5.2)	1274	204 (16.0)	67.8 (58.8–74.9)

In Year 2 (see Table 16, below) revaccination with LAIV demonstrated significant efficacy against antigenically similar (84.3%; 95% CI: 70.1, 92.4%) and any (64.2%; 95% CI: 44.2, 77.3%) influenza strains.

Table 16. Efficacy of LAIV against culture-confirmed influenza in Year 2: comparison of treatment groups (Per-Protocol Efficacy Population)

Treatment Comparison* (Year 1 Treatment/Year 2 Treatment)	Antigenically Similar Strain		Any Strain	
	Influenza Cases/ Comparison Populations	Efficacy, % (95% CI)	Influenza Cases/ Comparison Populations	Efficacy, % (95% CI)
CAIV-T/CAIV-T vs. placebo/placebo	12/771 vs. 49/494	84.3 (70.1–92.4)	33/771 vs. 59/494	64.2 (44.2–77.3)
CAIV-T/placebo vs. placebo/placebo	33/759 vs. 49/494	56.2 (30.5–72.7)	70/759 vs. 59/494	44.8 (18.2–62.9)
CAIV-T/CAIV-T vs. CAIV-T/placebo	12/771 vs. 33/759	64.2 (28.9–83.2)	33/771 vs. 50/759	35.0 (−2.9–59.5)
CAIV-T/CAIV-T vs. placebo/CAIV-T	12/771 vs. 20/503	60.9 (15.9–82.6)	33/771 vs. 26/503	17.2 (−44.2–52.0)
placebo/CAIV-T vs. placebo/placebo	20/503 vs. 49/494	59.9 (31.3–77.4)	26/503 vs. 59/494	56.7 (30.3–73.8)

*Subjects randomised to LAIV in Year 1 received 2 doses of LAIV in Year 1. Subjects re-randomised to LAIV in Year 2 received a single dose of LAIV. LAIV indicates cold-adapted influenza vaccine, trivalent; CI, confidence interval.

A single dose of LAIV in Year 2 (placebo/LAIV) was superior to no vaccination at all (placebo/placebo) with an efficacy of 59.9% (95% CI: 31.3, 77.4%) against antigenically similar strains.

For the purpose of this review, the most relevant comparison (although data was collected in different years, but within the same study) is the efficacy of the 2-dose regimen in the first year (72.9% for similar strains) versus the 1-dose regimen in the second year (59.9% for similar strains). This study was not designed to directly compare these 2 groups and the difference of the relative efficacy between the single and 2-dose group was not assessed, nor the impact of the second year revaccination on these 2 groups. Both groups were significantly better than placebo. In the immunogenicity cohort, both groups were significantly higher in terms of seroconversion rates and fold-increases in geometric mean titres than placebo and there was no significant difference between them in this respect. Once again, although not directly designed for this comparison, the 2-dose regimen was more efficacious than the single-dose regimen.

15.3.1.3. Study D153-P504

This was a placebo controlled, multicentre study conducted during the 2001 and 2002 influenza seasons at 35 sites in South Africa, Brazil, and Argentina.[19] Subjects were children 6 to 36 months of age who were in good health. Subjects were randomised to 1 of 4 regimens in Year 1: 2 doses LAIV, 1 dose LAIV, excipient placebo, or saline placebo. In Year 2, LAIV recipients were to receive 1 dose of LAIV and placebo recipients were to receive saline placebo. Because of an unintended treatment allocation error in Year 2, 1 block of subjects who were randomised to LAIV received saline placebo and 1 block who were randomised to placebo received LAIV (346 subjects) and inadvertently another single dose group was produced (although the size of the per protocol group was reduced by this error).

Surveillance for ILI was based on regular telephone contacts, clinic visits, or home visits, with weekly contacts through the end of the surveillance period. If there was a suggestive history/examination, nasal swab samples were obtained within 4 days after onset of illness. Nasal swab specimens were cultured and typed for influenza using standard techniques. Specific strains were identified by standard haemagglutination inhibition assays. Blood samples for assessment of serum antibody titres to each of the vaccine virus strains were collected each year in a subset of subjects before each dose and 7 days after the final dose.

The primary efficacy endpoint was the first episode of culture-confirmed influenza illness caused by community-acquired subtypes antigenically similar (same type, subtype, and serotype) to those contained in the vaccine during Year 1. Secondary efficacy endpoints included the first episode of culture-confirmed influenza caused by community-acquired subtypes antigenically similar to those in the vaccine during Year 2; the first episode of culture confirmed influenza caused by any community-acquired subtypes during Years 1 and 2; and the first and all episodes of AOM, including any AOM, AOM associated with culture-confirmed influenza virus antigenically similar to a vaccine strain, and AOM associated with fever.

Results

There were 3200 children enrolled and randomised. Base-line characteristics were similar across treatment groups. A total of 2821 subjects (88.2%) completed Year 1 without major protocol violations and constituted the Year 1 per-protocol population and 2202 subjects continued in Year 2. Because of the unintended treatment allocation error in season 2, the overall Year 2 per-protocol population included 1364 children (42.6%). The placebo-placebo/LAIV group was assessed as an 'as treated' group.

Study D153-P504 met its primary objective demonstrating efficacy compared with placebo of both 1 and 2 doses of FluMist during the first season against influenza illness caused by any

[19] Bracco H et al. Efficacy and safety of one and two doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J 2009;28: 365–371.

matched strain. During Year 1, the LAIV–LAIV and LAIV–placebo regimens showed efficacy of LAIV against influenza strains antigenically similar to those in the vaccine of 73.5% (95% CI: 63.6, 81.0) and 57.7% (95% CI: 44.7, 67.9), respectively (see Table 17, below). In Year 1, the majority of influenza cases were caused by strains antigenically similar to the vaccine strains, and consequently, the efficacies against any community acquired subtypes were similar to that against similar strains: 72.0% (95% CI: 61.9, 79.8) and 56.3% (95% CI:43.1, 66.7) for the LAIV/LAIV and LAIV/placebo groups, respectively.

Table 17. Efficacy of live attenuated influenza vaccine against culture-confirmed influenza (Per-Protocol Population)

Year/Influenza Strain	Treatment Group*		
	LL/L		LP_s/L
	Efficacy vs. PP/P % (95% CI)	Relative Efficacy vs. LP_s/L % (95% CI)	Efficacy vs. PP/P % (95% CI)
Year 1, n†	944		935
Antigenically similar to those in vaccine‡			
Any strain	73.5 (63.6–81.0)	37.3 (9.5–56.9)	57.7 (44.7–67.9)
A/H1	NC	NC	NC
A/H3	72.7 (60.7–81.5)	34.0 (−1.3 – 57.4)	58.7 (43.4–70.2)
B	81.4 (64.2–91.2)	50.5 (−6.6 – 78.3)	62.4 (37.8–78.1)
Any subtype			
Any strain	72.0 (61.9–79.8)	36.0 (8.5–55.6)	56.3 (43.1–66.7)
A/H1	NC	NC	NC
A/H3	72.0 (59.8–80.9)	34.5 (0.2–57.5)	57.2 (41.6–69.0)
B	78.7 (60.9–89.3)	46.3 (−9.6 – 74.9)	60.4 (35.5–76.4)
Year 2, n†	338		684
Antigenically similar to those in vaccine§			
Any strain	73.6 (33.3–91.2)	24.1 (−104.2 – 75.7)	65.2 (31.2–82.8)
A/H1	94.0 (62.0–99.9)	77.5 (−62.3 – 99.5)	73.5 (37.2–89.6)
A/H3	49.4 (−253.0 – 95.4)	−304.7 (−23,778.2 – 78.9)	87.5 (−26.3 – 99.7)
B	−102.4 (−2137.1 – 71.0)	−34.9 (−468.9 – 72.0)	−50.0 (−1419.7 – 73.2)
Any subtype			
Any strain	46.6 (14.9–67.2)	0.5 (−57.7 – 38.5)	46.4 (21.1–63.5)
A/H1	94.0 (62.0–99.9)	79.8 (−42.3 – 99.5)	70.6 (32.0–88.0)
A/H3	49.4 (−253.0 – 95.4)	−304.7 (−23,778.2 – 78.9)	87.5 (−26.3 – 99.7)
B	24.1 (−28.5 – 55.7)	−13.8 (−86.1 – 31.7)	33.3 (−5.7 – 57.6)

Vaccination regimen shown as Year 1 dose 1 dose 2/Year 2 dose. † Number of patients in the population. ‡ The following strains isolated in this study were considered antigenically similar to those in the Year 1 vaccine: A/New Caledonia/20/99-like (A/H1N1), A/Panama/2007/99-like (A/H3N2), /Yamanashi/166/98-like, and B/Victoria/504/00-like. § The following strains isolated in this study were considered antigenically similar to those in the Year 2 vaccine: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Victoria/504/00-like. L indicates live attenuated influenza vaccine; NC, not computable; Pany placebo; PS, saline placebo.

Relative efficacy for subjects randomised to LAIV–LAIV was significantly higher than that of the LAIV–placebo group (37.3%; 95% CI: 9.5, 56.9; see Table 17, above). The efficacy of 2 doses was statistically superior to 1 dose, with a relative efficacy for 2 doses versus 1 dose of 37.3%.

In the Year 2 per-protocol population, the LAIV–LAIV/LAIV and LAIV–placebo/LAIV regimens showed significant efficacy against any strain of influenza virus antigenically similar to those in the vaccine: 73.6% (95% CI: 33.3, 91.2) and 65.2% (95% CI: 31.2, 82.8) for the LAIV–LAIV and LAIV–placebo groups, respectively. There was no statistically significant difference in efficacy between the LAIV–LAIV/LAIV group and the LAIV–placebo/LAIV group.

Table 18. Efficacy of live attenuated influenza vaccine against acute otitis media (Per-Protocol Efficacy Population)

Year/Illness	Treatment Group*	
	LL/L Efficacy vs. PP/P % (95% CI)†	LP_S/L Efficacy vs. PP/P % (95% CI)†
Year 1, n‡	944	934
AOM		
First episode	20.9 (1.7–36.4)	20.5 (1.3–36.1)
All episodes	19.3 (−0.4 – 35.1)	15.2 (−5.4 – 31.7)
Febrile AOM		
First episode	31.5 (8.0 – 49.2)	19.4 (−7.0 – 39.4)
All episodes	34.5 (12.7–50.9)	20.1 (−5.4 – 39.4)
Influenza-associated AOM§		
First episode	73.2 (50.9 – 86.3)	69.0 (44.8 – 83.5)
All episodes	73.5 (52.4 – 85.3)	69.6 (46.9 – 82.6)
Year 2, n‡	338	682
AOM		
First episode	3.3 (−38.2 – 32.5)	26.7 (−1.6 – 46.8)
All episodes	−0.1 (−41.9 – 29.4)	31.0 (5.4 – 49.7)
Febrile AOM	22.3 (−25.1 – 52.2)	33.5 (−1.2 – 56.0)
First episode		
All episodes	9.6 (−44.0 – 43.3)	33.5 (1.2–55.3)
Influenza-associated AOM§		
First episode	59.5 (−147.2 – 96.1)	90.0 (10.4–99.8)
All episodes	59.8 (−106.7 – 92.2)	90.1 (15.0–98.8)

*Vaccination regimen shown as Year 1 dose 1 dose 2/Year 2 dose. † For all episodes, the estimate and CIs were computed from the Andersen-Gill model with treatment as the only effect. For first episodes, the estimate and CIs were computed from the proportions of cases by the exact conditional binomial, as for influenza. ‡ Number of patients in the calculation. §Influenza-associated AOM due to strains antigenically similar to those in the vaccine. L indicates live attenuated influenza vaccine; P, any placebo; PS, saline placebo; AOM, acute otitis media.

The LAIV–LAIV regimen in Year 1 was significantly effective in preventing against the first episode of AOM, the first and all episodes of febrile AOM, and the first and all episodes of influenza-associated AOM caused by strains antigenically similar to those in the vaccine (see Table 18, above). The LAIV–placebo regimen was also significantly effective against the first episode of AOM and the first and all episodes of AOM associated with influenza strains antigenically similar to those in the vaccine. The relative efficacies for the 2 versus 1 dose regimens (all influenza associated AOM) are 73.5 versus 69.6% respectively (no statistically significant difference. The rates of any LRI in Year 1 were similar among the 3 randomised treatment groups (LAIV–LAIV, LAIV–placebo, and placebo–placebo), that is, 20.4% (n 193), 18.8% (n 176), and 19.0% (n 179), respectively. The Year 1 immunogenicity cohort consisted of 406 subjects of whom 334 (82%) were evaluable (LAIV–LAIV/LAIV, n = 113; LAIV-placebo/LAIV, n = 112; placebo–placebo/placebo, n = 109). In the evaluable immunogenicity population, seroconversion rates (p = 0.003), GMTs, geometric mean fold rises (GMFRs), and ratios of GMFRs in Year 1 were higher among LAIV–LAIV and LAIV–placebo recipients than placebo recipients (Seroconversion rates and GMFRs after 2 doses of LAIV were significantly higher than after 1 dose (LAIV–LAIV versus LAIV–placebo, p = 0.037 for seroconversion rates; p = 0.001 for GMFRs).

The treatment error group (PP/L) was assessed as an 'as-treated' group. The unintended Year 2 treatment error permitted additional analyses. Vaccine protection against viruses antigenically similar to those in the vaccine, predominantly A/H1N1 strains, persisted through a second season (without revaccination), with an efficacy of 57.0% (95% CI: 6.1, 81.7). This efficacy result is very similar to the Year 1, single dose vaccination group.

This was a good study apart from the allocation error (which resulted in an additional analysis group but reduced the size of the PP group). One dose of LAIV provided clinically significant protection against influenza in young children previously unvaccinated against influenza but this was less than in the 2 dose group. Results between the PP and the 'as treated' group for single dose vaccination were similar.

15.3.2. Meta Analyses of efficacy of LAIV in previously unvaccinated children

This meta-analysis assessed 9 randomised clinical trials (see Table 19, below) including approximately 25,000 children aged 6 to 71 months and 2000 children aged 6 to 17 years, have evaluated the efficacy of live attenuated influenza vaccine (LAIV) against culture confirmed influenza as compared to placebo or trivalent inactivated vaccine (TIV).[19] They conducted meta analyses, based on Mantel–Haenszel relative risks from fixed effect models, to provide an estimate of vaccine efficacy. Most of the data related to the 2 dose regimen, but the 3 studies discussed above were included in the meta-analysis and the difference between 1 and 2 dose initial regimen was assessed using the available data from these studies.

Table 19. Studies comparing LAIV with placebo included in meta-analyses

Study period	Population studied countries	Age range (months)	Treatment group (doses, n)[a]	n[b]	Vaccine strains	Circulating strains
AV006[20,21] Year 1: August 1996 to April 1997	Healthy children, influenza vaccine-naive (year 1) United States	≥15 to ≤71	LAIV (2), placebo (2)	881, 433	Year 1: A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like	Year 1: A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
Year 2: September 1997 to May 1998			LAIV (1), placebo (1)	189, 99	Year 2: A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (Nanchang-like) (H3N2), B/Harbin/7/94-like	Year 2: A/Sydney/5/97 (H3N2), A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
DIS3-P501[18] Year 1: September 2000 to October 2001	Healthy children, influenza vaccine-naive (year 1) China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, Thailand	≥12 to <36	LAIV (2), placebo (2)	1900, 1274	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/Ulawai/15/01-like (H1N1), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/22/01-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c]
Year 2: November 2001 to October 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Brisbane/32/02-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Shizuoka/15/01-like, B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c], B/Yamanshi/166/98-like
DIS3-P502[17] Year 1: October 2000 to May 2001	Healthy children attending day care, influenza vaccine-naive (year 1) Belgium, Finland, Israel, Spain, United Kingdom	≥6 to <36	LAIV (2), placebo (2)	1059, 725	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Sichuan/379/99-like
Year 2: December 2001 to May 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Victoria/504/00-like
DIS3-P504[18] Year 1: April 2001 to November 2001	Healthy children, influenza vaccine-naive (year 1) South Africa, Brazil, Argentina	≥6 to <36	LAIV (2), placebo (1 or 2)[d]	1064, 1060	Year 1: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Victoria/504/00-like[c], B/Yamanashi/166/98-like[c]
Year 2: March 2002 to November 2002			LAIV (1), placebo (1 or 2)[d]	1067, 1069	Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/Moscow/10/99-like (H3N2), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Shenzhen/654/99-like, B/Sichuan/379/99-like, B/Victoria/504/00-like[c], B/Yamanashi/166/98-like[c]

MMR=mumps, measles, and rubella vaccine; a) all studies used the refrigerated formulation of LAIV except AV006 which used the frozen formulation; b) sample size is the number of subjects randomised in the first year of study; c) same strain circulating both study years; d) the placebo groups for 1 and two doses are combined for the meta-analysis; the same placebo subjects are used in the comparisons with both the 1 and two dose LAIV groups.

Table 20. Vaccine efficacy for two doses versus placebo, overall and for subjects < 3 years (antigenically similar subtypes)

Study	Age range (months)	LAIV[a]		Placebo[a]		Vaccine efficacy[b]	Approximate 95% CI (%)	Heterogeneity (Q)	Vaccine effect (MH)
		n/N	(%)	n/N	(%)				
All strains									
AV006	≥15 to <71	10/849	1.2	73/410	17.8	93	87, 97		
D153-P501	≥12 to <36	56/1653	3.4	139/1111	12.5	73	63, 80		
D153-P502	≥6 to <36	15/951	1.6	72/665	10.8	85	75, 92		
D153-P504	≥6 to <36	50/944	5.3	188/942	20.0	74	64, 80		
D153-P513	≥6 to <36	35/525	6.7	91/516	17.6	62	45, 74		
D153-P522	≥11 to <24	9/765	1.2	21/385	5.5	78	53, 90		
Total		175/5687	3.1	584/4029	14.5	77	72, 80	χ^2 = 25 (5 d.f.), p < 0.001	χ^2 = 377 (1 d.f.), p < 0.001
All strains, age <36 months		165/4838	3.4	511/3619	14.1	74	69, 78	χ^2 = 8 (4 d.f.), p = 0.078	χ^2 = 280 (1 d.f.), p < 0.001

d.f. = degrees of freedom; LAIV = live attenuated influenza vaccine; MH= Mantel–Haenszel; a) culture confirmed influenza cases; b) Vaccine efficacy estimates are based on subjects who received both scheduled doses of vaccine (per protocol). Vaccine efficacy is based on observed cases (individual studies) or from fixed effects models (total, combined studies).

The combined efficacy of all these studies in previously unvaccinated children for 2 doses of LAIV compared with placebo after a single influenza season in the per protocol population, the estimated vaccine efficacy was 77% (p < 0.001, shown in Table 20 above) against culture confirmed influenza for antigenically similar subtypes for all strains. Across all studies in this meta-analysis, the percentage of children developing influenza ranged between 1% and 7% (LAIV recipients) and 6% and 20% (placebo recipients). For subtypes regardless of antigenic similarity, the estimated vaccine efficacy was 72% (p < 0.001) and the percentages of children developing influenza were similar, ranging between 1% and 11% in LAIV recipients and 8% and 21% in placebo recipients. For the ITT population, the efficacy of 2 doses of LAIV compared with placebo on culture confirmed influenza for antigenically similar subtypes and subtypes regardless of antigenic similarity were 75% (p < 0.001, Table 17, above) and 72% (p < 0.001).

15.3.3. Efficacy of one dose of LAIV in previously unvaccinated children

In this meta-analysis, three of the studies (those detailed above) also compared 1 dose of LAIV with placebo in previously unvaccinated young children. In 2 studies (Studies AV006 and 154), children received 1 dose per-protocol in Year 1. Another study that rerandomised subjects for Year 2 vaccinated some subjects for the first time in Year 2 with 1 dose (Study 151). Lastly, in the second year of Study 154, a cohort that received placebo in Year 1 received 1 dose of LAIV in Year 2 because of an error in vaccine assignment. Rhorer et al. combined the 'as treated' (AT) results from the Year 2 cohort with the results for the per-protocol Year 1 cohort from this study.

A meta-analysis of these four subsets of data yielded an estimated combined efficacy of approximately 60% (p < 0.001) for antigenically similar strains based on 6% of LAIV children and 15% of placebo children developing influenza. For subtypes regardless of similarity, the combined efficacy is slightly less (59%, p < 0.001) with 7% (LAIV) and 17% (placebo) of children developing influenza. They also evaluated the impact of including and excluding the AT data. Including the additional data in the meta-analysis does not substantially change the estimated efficacy. For the ITT population, the meta-analyses suggested a combined efficacy estimate of 58% for antigenically similar subtypes and 56% for subtypes regardless of similarity (compared to 77% and 72% for the 2-dose regimen).

15.4. Conclusions about available clinical data

There are four cohorts in these 3 studies which provide some data to assess the difference between the clinical efficacy (and immunogenicity) of 1 and 2 dose regimens of LAIV vaccine. In 2 of these studies, this comparison was a primary endpoint of the study (Studies AV006 and D153-504). In Study D153-501, a second year re-randomisation (versus the second year single

booster dose or single dose placebo) and the last small cohort (also in Study D153-504) was due to a study error (with incorrect designation resulting in a 1 dose vaccination of a block of subjects). The data from the earlier, smaller study (Study AV006) was the only study to find similar clinical efficacy between the 1 and 2 dose regimens in previously unvaccinated children, all the other data points to the 2 dose regimen having a higher clinical efficacy. The meta-analysis also supports this finding. Overall, the efficacy of a single dose is probably around 60% versus 72% for 2 doses in previously unvaccinated children.

In the 2 year studies, after a second year booster, there was no difference in response, between 1 or 2 dose primary series in the first year according in both Studies D153-501 and D153-504.

A Cochrane review examining all childhood influenza vaccines was unable to draw conclusions about 1 versus 2 dose regimens, particularly in relation to durability of clinical protection.

The errors of fact and omissions report sent by the sponsor on 14 April 2016 in response to this Clinical Addendum have been addressed in this version.

15.5. References for the clinical addendum

Rhorer J et al. Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomised clinical trials. Vaccine. 2009 Feb 11;27(7):1101-10.

Belshe R et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. N Engl J Med 1998;338(20):1405–12.

Tam J et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J 2007;26(7 (July)):619–28.

Bracco H et al. Efficacy and safety of one and two doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J 2009;28: 365–371.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au