PASS Information

Title:	**A Postmarketing Safety Study of Q/LAIV in Subjects 2 Through 49 Years of Age**
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Date of Last Version:	24 April 2013
EU PAS Register Number:	Study not registered
Active Substance:	A live attenuated influenza vaccine containing four virus strains: A/H3N2, A/H1N1, B/Yamagata, and B/Victoria Pharmacotherapeutic group: Influenza vaccines, influenza live attenuated; ATC Code: J07BB03
Medicinal Product:	FluMist Quadrivalent
Product Reference:	NCT (not yet available)
Procedure Number:	NA
Marketing Authorisation Holder(s):	MedImmune, LLC, a wholly owned subsidiary of AstraZeneca
Joint PASS:	No
Research Question and Objectives:	The primary objective of this study is to assess the safety of Q/LAIV vaccination including assessments of medically attended events (MAEs) and hospitalizations in children and adults 2 through 49 years of age relative to controls (within-cohort, matched unvaccinated, and matched inactivated influenza vaccine recipients).
Country(ies) of Study:	United States of America

Author: Herve Caspard, MD
Senior Director, Medical and Scientific Affairs, MedImmune
Phone: 301-398-1922; Fax: 301-398-9922

Marketing Authorization Holder

Provide the name and address of the marketing authorization holder.

Marketing Authorization Holder(s):	MedImmune, LLC, a wholly owned subsidiary of AstraZeneca One MedImmune Way Gaithersburg, Maryland, 20878, USA
Marketing Authorization Holder Contact Person:	Herve Caspard, MD Senior Director, Medical and Scientific Affairs, MedImmune Phone: 301-398-1922; Fax: 301-398-9922

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2 List of Abbreviations

Abbreviation or Specialized Term	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
att	Attenuated
BLA	Biologics License Application
ca	cold-adapted
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CSR	clinical study report
FFU	fluorescent focus units
FluMist-V	trivalent FluMist containing an influenza B strain from the Victoria lineage
FluMist-Y	trivalent FluMist containing an influenza B strain from the Yamagata lineage
GCP	Good Clinical Practice
GMT	geometric mean titer
HAI	hemagglutination inhibition
HMO	health maintenance organization
HR	hazard ratio
KITS	Kaiser Immunization Tracking System
KP	Kaiser Permanente
MAE	medically attended event
NCKP	Northern California Kaiser Permanente
QIIV	quadrivalent inactivated influenza vaccine
Q/LAIV	quadrivalent live attenuated influenza vaccine (FluMist® Quadrivalent)
PSUR	periodic safety update report
RR	relative risk
SAE	serious adverse event
TIV	trivalent inactivated vaccine
T/LAIV	trivalent live attenuated influenza vaccine
ts	temperature-sensitive
US FDA	United States Food and Drug Administration

Abbreviation or Specialized Term	Definition
USA	United States of America
wt	wild-type
US FDA	United States Food and Drug Administration

3 Responsible Parties

Herve Caspard, MD
Senior Director, Medical and Scientific Affairs
MedImmune, LLC
One MedImmune Way
Gaithersburg MD 20878

Phone: 301-398-1922

Roger Baxter, MD
Co-director, Vaccine Study Center
1 Kaiser Center Plaza, 16B
Oakland, CA 94612

Phone: 510-267-7529

4 Abstract

TITLE

A Postmarketing Cohort Study of the Safety of Q/LAIV in Subjects 2 Through 49 Years of Age

Version 1.0; 24 April 2013

Herve Caspard, MD; Senior Director, Medical and Scientific Affairs, MedImmune

RATIONALE AND BACKGROUND

Influenza is a highly contagious, acute febrile illness of global importance and is the most common vaccine-preventable disease in the developed world. In humans, influenza illness is caused by 2 types of viruses: influenza A, with multiple subtypes categorized by hemagglutinin and neuraminidase surface antigens, and influenza B, which circulates as 2 major antigenic lineages. Subtypes A/H3N2 and A/H1N1 are the 2 influenza A subtypes that have circulated and caused human disease since 1977 (Kilbourne, 2006). 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 (WHO, 2005).

While the majority of influenza disease is commonly attributed to influenza A strains, type B strains of influenza are responsible for significant morbidity (Thompson et al, 2004). In recent years, marketed influenza vaccines have been trivalent and included the 2 influenza A strains but only one influenza B strain. The selection of B strains for inclusion in annual vaccines poses a particular problem because 2 antigenically distinct lineages of influenza B viruses, B/Victoria/02/87-like and B/Yamagata/16/88-like, have circulated globally since 1985. Beginning with the 2001-2002 season, influenza B viruses from both lineages have co circulated each season in the United States of America (USA), increasing the difficulty of accurately predicting the correct lineage to include in the seasonal vaccine. In 6 of the 11 influenza seasons from 2001-2002 through 2011-2012, the predominant circulating influenza B lineage was different from that contained in the vaccine (www.cdc.gov/flu; Belshe et al, 2010). Individuals vaccinated with one lineage do not appear to be substantially protected against disease caused by the other lineage (FDA, 2007), and antibody responses to the lineage not contained in the vaccine are significantly reduced in all age groups and appear to be minimal in children (FDA, 2007). As a result, quadrivalent influenza vaccines containing 2 influenza A strains and 2 influenza B strains, one from each lineage, have been developed.

Vaccination is the primary method for preventing illness and severe complications related to influenza. Prevention of the spread of influenza by vaccination of children is an important part of influenza control. In 2008, the Advisory Committee on Immunization Practices (ACIP) included all children up to the age of 18 years in its recommendation for annual vaccination (CDC, 2008). Beginning with the 2010-2011 influenza season, ACIP revised the recommendations of annual influenza vaccination to include all eligible individuals 6 months of age or older (CDC, 2010).

FluMist® Quadrivalent, an intranasal, quadrivalent live attenuated influenza vaccine (Q/LAIV), was approved by the United States Food and Drug Administration (US FDA) on 29Feb2012 in individuals 2 to 49 years of age for the prevention of influenza caused by the 2 type A (A/H1N1 and A/H3N2) and 2 type B influenza viruses contained in the vaccine. The approval was predicated on conducting an observational postmarketing safety surveillance study in children 2 years through 8 years of age. The current study implements this postmarketing commitment between MedImmune and the US FDA. In addition, MedImmune has expanded the study to document the safety profile of Q/LAIV in vaccine recipients between 9 years and 49 years of age. It is anticipated that the study will be conducted in a single season with vaccination of approximately 80,000 individuals, including approximately 10,000 to 30,000 individuals in each of the following 4 age groups: 2 to 4, 5 to 8, 9 to 17, and 18 to 49 years.

RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to assess the safety of Q/LAIV vaccination in children and adults 2 through

49 years of age within 180 days after vaccination: incidence rates of adverse events of interest during periods at risk after Q/LAIV vaccination will be compared to incidence rates during reference periods later in the follow-up (within-cohort analysis) and to incidence rates in controls (matched unvaccinated subjects and matched inactivated influenza vaccine [IIV] recipients).

STUDY DESIGN

In this postmarketing, nonrandomized, observational cohort study, children and adults will be immunized with Q/LAIV as part of routine clinical practice at Kaiser Permanente Northern California (NCKP) sites. Using existing data on healthcare utilization, rates of medically attended events (MAEs) of interest will be evaluated in all eligible Q/LAIV recipients who are vaccinated in the Kaiser Permanente (KP) Northern California Health Care Plan during the 2013-2014 influenza season. Enrollment must include a minimum of 10,000 children 2 through 8 years of age; based on previous utilization of FluMist at NCKP, enrollment is expected to include approximately 80,000 children and adults 2 to 49 years of age.

Similar to previous postmarketing safety studies conducted with FluMist (Studies FM025 and MI-MA162), this study will be conducted using data collected by the KP Vaccine Study Center.

Incidence rates of MAEs and hospitalizations during periods at risk after Q/LAIV vaccination will be compared versus incidence rates during reference periods later in the follow-up (within-cohort analysis) and versus rates in 2 nonrandomized control groups: matched unvaccinated controls and matched concurrent inactivated influenza vaccine (IIV) recipient controls identified from the KP healthcare database. Trivalent inactivated vaccine (TIV) recipients will serve as controls along with quadrivalent inactivated influenza vaccine (QIIV) recipients if a QIIV is approved and administered during the study period.

POPULATION

Individuals vaccinated with Q/LAIV and controls will be identified for inclusion in this study via the Kaiser Immunization Tracking System (KITS) database. Immunizations of KP members are recorded in this database as part of routine care. Because each recipient has a unique medical record number assigned once enrolled in the KP Health Care Plan and because administration records of all vaccinees are entered in the KITS database, the study population can be assembled from the KITS system on an ongoing basis. The lot number of administered vaccine is entered in the KITS immunization database for each vaccinee.

Subjects must meet *all* of the following criteria:

1) Age 2 through 49 years (prior to 50th birthday) at the time of vaccination (or index date for unvaccinated controls)

2) Membership in the KP Health Care Plan for at least 12 months prior to vaccination/index date

3) Continuous enrollment in the KP Health Care Plan through 6 months following vaccination/index date.

There are no exclusion criteria. Subjects with any high-risk underlying medical condition as defined by ICD-9-CM codes or successor (Annex 3) will be analyzed separately.

VARIABLES

Vaccine safety will be assessed using diagnoses recorded in the KP utilization databases as a result of emergency, hospital, and outpatient clinic visits. Adverse events (AEs) will be collected via extraction of records from the KP utilization databases from 0 through 180 days post vaccination. Time periods when the subject is considered at risk after vaccination will depend upon the nature of the AE. The adverse events of interest and the time periods when the subject is considered at risk after vaccination are presented in the table below.

Table Summary of Planned Analyses

Event of Interest	Period at Risk After Vaccination	Reference Period
Hypersensitivity MAEs [a] Seizures/convulsions MAEs [a]	0-3 days [c]	7-9 days[d]
Lower respiratory MAEs Wheezing MAEs Guillain-Barré syndrome MAEs [a] Bell's palsy MAEs [a] Encephalitis MAEs [a] Neuritis MAEs [a] Vasculitis MAEs [a] Any hospitalization Respiratory hospitalization[b]	1-42 days [c] (1-14 days and 15-42 days)	43-84 days
Narcolepsy/cataplexy MAEs[a]	1-180 days [c]	NA

MAE = medically attended event; NA = not applicable

[a] Narratives of each case will be included in the final clinical study report.

[b] A respiratory hospitalization will be defined by the ICD-9-CM codes sets for lower respiratory MAEs and wheezing MAEs.

[c] It is not possible to detect from clinical databases whether an event occurring on the day of vaccination began prior to or after administration of vaccine, although events of hypersensitivity or seizures/convulsions may occur just subsequent to vaccination but are unlikely to be recorded on the same day prior to vaccination. As a result, the period at risk after vaccination for events of hypersensitivity and seizures/convulsions begins on the day of vaccination (Day 0), and the period at risk after vaccination for all other events of interest begins 1 day after vaccination (Day 1).

[d] The reference period for the period at risk for 0 to 3 days was defined from 7 to 9 days to take into account cyclical variations that may occur during the same days of the week.

An MAE is defined as a coded medical diagnosis made by a health care provider and associated with a medical encounter (ie, visit to a medical clinic or emergency department, or a hospital admission). One or more MAEs could be assigned for a single encounter.

For MAEs of Guillain-Barre syndrome, Bell's palsy, encephalitis, neuritis, vasculitis, and narcolepsy/cataplexy, events will only be counted if the subject does not have a prior record of the event in the 12 months prior to vaccination (or index date for unvaccinated controls).

In addition, listings of any hospitalization within 180 days, any deaths throughout the entire study period, and exposed pregnancies throughout the entire study period will be provided.

A hospitalization is any medical event that results in inpatient hospitalization of any duration. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting. Hospitalization for elective surgery related to a pre-existing condition that did not increase in

severity or frequency following initiation of the study need not be considered a hospitalization. If anything untoward is reported during an elective procedure, that occurrence will be captured as an MAE or hospitalization according to the usual criteria.

For analyses of any hospitalization and respiratory hospitalizations (see preceding table entitled Summary of Planned Analyses), only the primary discharge diagnosis will be analyzed.

DATA SOURCES

Study data are derived directly from NCKP clinical and institutional databases, which are not research databases. Rather they make up the electronic medical record documenting vaccine administration, medical utilization, participant demographics, and HMO membership for all NCKP members. These clinical databases are maintained by Kaiser Permanente Information Technology (IT). This information is tracked with an automated audit trail (eg, adds, deletes, updates to study records). This information is stored on a secure SQL server that is administered, secured, backed up, and maintained by Division of Research IT personnel.

STUDY SIZE

Enrollment of at least 10,000 children 2 through 8 years of age is planned. A sample size of 10,000 children will provide approximately 90% power to observe a statistically significant increase in relative risk (RR) of 1.5 for an event that occurs in 1 in 100 subjects in the comparison group. The study will also be able to rule out with 95% probability the occurrence of an event at a rate of 0.03% (1 in 3,333 subjects) assuming that incidence of the event follows a Poisson distribution. Enrollment is expected to be completed in the 2013-2014 influenza season but the study will be continued for additional seasons, if needed, until enrollment of 10,000 Q/LAIV recipients 2 through 8 years of age is completed to fulfill the postmarketing commitment to the US FDA.

However, because the study is expanded to adolescents and adults up to 49 years of age, it is expected that a total of approximately 80,000 individuals will be enrolled (including approximately 10,000 to 30,000 individuals in each of the following 4 age groups: 2 to 4 years, 5 to 8 years, 9 to 17 years, and 18 to 49 years of age) in the influenza season 2013-2014. Enrollment of 20,000 children per age group will provide approximately 90% power to observe a statistically significant increase in RR of 1.5 for an event that occurs in 1 in 200 subjects in the comparison group. A sample size of 20,000 will also be able to rule out with 95% probability the occurrence of an event with an incidence rate of 0.015% (1 in 6,666 subjects).

MILESTONES

Milestone	Date
Start of data collection	Fall 2013 (post launch of Q/LAIV in USA)
End of data collection	Upon completion of full enrollment but no later than 30 June 2018
Study progress report	Included in United States Biologics Licensing Application (BLA) Postmarketing Annual Reports (data cut-off 30 September) Included in biannual periodic safety update reports (PSURs; data cut-offs 16 June / 16 December)
Registration in the EU PAS register	No later than August 2013
Final report of study results	No later than 30 June 2019

5 Amendments and Updates

Table 5-1 Amendments

Number	Date	Section of Protocol	Amendment or Update	Reason
None				

6 Milestones

Study milestones are presented in Table 6-1.

Table 6-1 Milestones

Milestone	Date
Start of data collection	Fall 2013 (post launch of Q/LAIV in USA)
End of data collection	Upon completion of full enrollment but no later than 30 June 2018
Study progress report	Included in United States Biologics Licensing Application (BLA) Postmarketing Annual Reports (data cut-off 30 September) Included in biannual periodic safety update reports (PSURs; data cut-offs 16 June / 16 December)
Registration in the EU PAS register	No later than August 2013
Final report of study results	No later than 30 June 2019

7 Rationale and Background

Q/LAIV is an intranasally administered vaccine for the active immunization of individuals against influenza disease. The 2 type A (A/H1N1 and A/H3N2) and 2 type B (B-Victoria and B-Yamagata) strains contained in the vaccine are attenuated (*att*), cold-adapted (*ca*), and temperature-sensitive (*ts*) reassortant strains of influenza virus and are produced by the same manufacturing process as trivalent FluMist®. Each reassortant vaccine strain contains 2 gene segments encoding the hemagglutinin and neuraminidase surface glycoproteins from the wild-type (*wt*) virus strain, and 6 gene segments encoding internal virus proteins from the *ca*, *ts*, *att* master donor virus (type A, A/Ann Arbor/6/60 [H2N2] and type B, B/Ann Arbor/1/66). The subtype A and type B master donor viruses from which the reassortant vaccine strains are derived were adapted to grow in primary chick kidney cells at 25°C by sequential passage

at progressively lower temperatures. During the process of cold adaptation, each virus acquired mutations that conferred the *ca*, *ts*, and *att* phenotypes that distinguish these viruses from *wt* influenza viruses (Jin et al, 2003; Hoffmann et al, 2005; Murphy and Coelingh, 2002). The potency of each individual strain is $10^{7.0 \pm 0.5}$ fluorescent focus units (FFU) per dose. In addition, Q/LAIV has an additional specification to ensure that it does not exceed the total virus content currently allowed in the licensed trivalent FluMist formulation which is calculated to be 10^8 FFU/0.2 mL dose based on the maximum potency allowed for each individual strain.

The safety and efficacy of Q/LAIV have been evaluated in 2 studies, one in adult subjects 18 to 49 years of age (MI-CP185) and one in pediatric subjects 2 to 17 years of age (MI CP208). The study populations for both studies included adults and children who were healthy or had stable chronic conditions and thus appropriately represent the population in which Q/LAIV is indicated. Subjects were randomized in either a 3:1:1 or 4:1:1 ratio to receive Q/LAIV or trivalent FluMist containing the same 2 strains of influenza subtypes A/H1N1 and A/H3N2 as in Q/LAIV and one strain of influenza type B from either the Victoria (FluMist V) or the Yamagata (FluMist Y) lineage.

A total of 2,580 subjects received at least one dose of Q/LAIV, including 1,198 adult subjects from Study MI-CP185 and 1,382 children and adolescents from Study MI-CP208. In adults and children, solicited symptoms occurred at similar rates in Q/LAIV and trivalent live attenuated influenza vaccine (T/LAIV; FluMist) recipients. In both, the most common solicited symptom was runny/stuffy nose. In adults, runny/stuffy nose was reported by 4.1% more Q/LAIV than T/LAIV recipients; no other solicited symptom occurred with a rate difference of > 1.1%. In children 2 through 8 years of age, fever ≥ 38°C (100.4°F) was more commonly reported among Q/LAIV recipients (5.1%) compared with the T/LAIV recipients (3.1%); fevers ≥ 39.5°C (103.1°F) were infrequent (< 0.5%). Overall, Q/LAIV was well tolerated, and its safety profile is consistent with that demonstrated during the clinical development and postmarketing evaluation period of trivalent FluMist (Baxter et al, 19Apr2012; Baxter et al, 26Apr2012).

In both the adult and pediatric studies, Q/LAIV was demonstrated to be immunologically noninferior to trivalent FluMist because the upper bound for each of the four 95% confidence intervals (CIs) for the post-dose geometric mean titer (GMT) hemagglutination inhibition (HAI) antibody ratios (FluMist divided by Q/LAIV) was ≤ 1.5. Overall, secondary immunogenicity outcomes (rate of seroconversion/seroresponse and the proportion of

subjects with post-vaccination HAI antibody titers ≥ 32) supported the conclusions of the primary analysis. Q/LAIV generated greater immune responses to the additional B strain relative to FluMist that did not contain the B strain. 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.

Q/LAIV was approved by the US FDA on 29Feb2012 for individuals 2 to 49 years of age, and it will be marketed in the USA beginning in the 2013-2014 influenza season. The approval was predicated on conducting an observational postmarketing safety surveillance study in children 2 through 8 years of age. The current study implements this postmarketing commitment between MedImmune and the US FDA, and provides an expanded safety profile of Q/LAIV in the indicated populations by including vaccine recipients between 9 and 49 years of age

The design of this observational postmarketing safety surveillance study is consistent with current vaccine safety monitoring practices (Andrews, 2002; Yih et al, 2011)and the conduct of previous post-authorization safety studies of FluMist in subjects 5 to 49 years of age (Study FM025 [Baxter et al, 19Apr2012; Baxter et al, 26Apr2012] and in subjects 24 to 59 months of age (Study MI-MA162 [Toback et al, 2013]) required by the US FDA. In those studies, the incidence of medically attended events (MAEs) following FluMist receipt was compared between 2 time intervals following vaccination as well as versus matched unvaccinated controls and matched inactivated influenza vaccine (IIV) recipient controls. The results of these studies demonstrated no significant adverse outcomes following receipt of FluMist among eligible individuals.

8 Research Question and Objectives

The objective of this study is to assess the safety of Q/LAIV vaccination in children and adults 2 through 49 years of age within 180 days after vaccination: incidence rates of adverse events of interest during periods at risk after Q/LAIV vaccination will be compared to incidence rates during reference periods later in the follow-up (within-cohort analysis) and to incidence rates in controls (matched unvaccinated subjects and matched IIV recipients).

Since there are no identified safety concerns with Q/LAIV, this postmarketing safety assessment is hypothesis generating.

9 Research Methods

9.1 Study Design

Similar to previous postmarketing safety studies conducted with FluMist (Studies FM025 and MI-MA162), this study will be conducted using data collected by the Kaiser Permanente (KP) Vaccine Study Center. In this nonrandomized, observational cohort study, children and adults will be immunized with Q/LAIV as part of routine clinical practice at Northern California Kaiser Permanente (NCKP) sites. Using existing data on healthcare utilization, rates of medically attended events (MAEs) of interest will be evaluated in all eligible Q/LAIV recipients who are vaccinated in the KP Northern California Health Care Plan during the 2013-2014 influenza season. Before the study is completed enrollment must include a minimum of 10,000 children 2 through 8 years of age; based on previous utilization of FluMist at NCKP, enrollment is expected to include approximately 80,000 children and adults 2 to 49 years of age.

Incidence rates of medically attended events (MAEs) and hospitalizations during periods of risk after Q/LAIV vaccination will be compared versus incidence rates during reference periods later in the follow-up (within-cohort analysis) and versus rates in 2 nonrandomized control groups: matched unvaccinated controls and matched concurrent IIV recipient controls identified from the KP healthcare database. Trivalent inactivated vaccine (TIV) recipients will serve as controls along with quadrivalent inactivated influenza vaccine (QIIV) recipients, if a QIIV is approved and administered during the study period.

As observed in previous studies, it is anticipated that children and adults vaccinated with Q/LAIV will differ from those vaccinated with IIV or those unvaccinated in multiple underlying characteristics, such as health-seeking behavior, health status, and various demographic and socioeconomic factors. Within-cohort, risk-interval analysis control helps to control for many of these differences (Farrington et al, 1996; Yih et al, 2011; Andrews, 2002). To help reduce confounding due to differences between Q/LAIV recipients and unvaccinated and IIV controls, controls will be matched to Q/LAIV recipients as discussed below. However, even after matching for these factors, it is likely that other differences between Q/LAIV recipients and IIV control groups will remain and may generate biases in the observed rates of MAEs following vaccination.

The nonrandomized comparison groups will include:

1) Inactivated influenza vaccine recipient controls who received the current IIV formulation (trivalent or quadrivalent) but not Q/LAIV for the season at a Kaiser health maintenance organization (HMO) during the same month that the reference Q/LAIV recipient was vaccinated will be identified and matched based on age (year) and medical center relative to concurrent reference Q/LAIV recipients, using frequency matching. For children 2 to 4 years of age, matching by age will be based on calendar quarter of birth rather than year. Factors such as gender and prior health care utilization level will be included as covariates in the proposed Cox proportional hazards model.

2) Unvaccinated controls who did not receive any influenza vaccine for the season will be identified and matched based on age (year) and medical center relative to concurrent reference Q/LAIV recipients using frequency matching. For children 2 to 4 years of age, matching by age will be based on calendar quarter of birth rather than year. Factors such as gender and prior health care utilization level will be included as covariates in the proposed Cox proportional hazards model. Unvaccinated controls will be followed from the date of vaccination of the reference Q/LAIV recipient (the index date).

Health care utilization levels will be defined as “high” (≥ 2 visits to a Kaiser HMO within the 6 months prior to the date of vaccination of the reference Q/LAIV vaccinee) or "low" (≤ 1 visit).

The study is expected to begin in the fall of 2013 following the launch of Q/LAIV and to be completed in a single influenza season. However, if fewer than 10,000 Q/LAIV recipients 2 through 8 years of age are identified following the 2013-2014 influenza season, the study will be continued for additional seasons until enrollment of 10,000 Q/LAIV recipients is completed. A detailed description of safety follow-up is described in Section 11. Data will be collected on subjects for 180 days following vaccination (or the index date for unvaccinated controls).

9.2 Setting

9.2.1 Subject Participation and Identification

Individuals vaccinated with Q/LAIV and controls will be identified for inclusion in this study via the Kaiser Immunization Tracking System (KITS) database. Immunizations of KP

members are recorded in this database as part of routine care. Because each recipient has a unique medical record number assigned once enrolled in the KP Health Care Plan and because administration records of all vaccinees are entered in the KITS database, the study population can be assembled from the KITS system on an ongoing basis.

The lot number of administered vaccine is entered in the KITS immunization database for each vaccinee.

9.2.2 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Age 2 through 49 years (prior to 50th birthday) at the time of vaccination (or index date for unvaccinated controls)
2) Membership in the KP Health Care Plan for at least 12 months prior to vaccination/index date
3) Continuous enrollment in the KP Health Care Plan through 6 months following vaccination/index date.

There are no exclusion criteria. Subjects with any high-risk underlying medical condition as defined by ICD-9-CM codes or successor (Annex 3) will be analyzed separately.

9.3 Variables

Vaccine safety will be assessed using diagnoses recorded in the KP utilization databases as a result of emergency, hospital, and outpatient clinic visits. Adverse events (AEs) will be collected via extraction of records from the KP utilization databases from 0 through 180 days post vaccination. Time periods when the subject is considered at risk after vaccination will depend upon the nature of the AE. The adverse events of interest and the time periods when the subject is considered at risk after vaccination are presented in Table 9.3-1.

Table 9.3-1 Summary of Planned Analyses

Event of Interest	Period at Risk After Vaccination	Reference Period
Hypersensitivity MAEs [a] Seizures/convulsions MAEs [a]	0-3 days [c]	7-9 days[d]
Lower respiratory MAEs Wheezing MAEs Guillain-Barré syndrome MAEs [a] Bell's palsy MAEs [a] Encephalitis MAEs [a] Neuritis MAEs [a] Vasculitis MAEs [a] Any hospitalization Respiratory hospitalization[b]	1-42 days [c] (1-14 days and 15-42 days)	43-84 days
Narcolepsy/cataplexy MAEs[a]	1-180 days [c]	NA

MAE = medically attended event; NA = not applicable

[a] Narratives of each case will be included in the final clinical study report.

[b] A respiratory hospitalization will be defined by the ICD-9-CM codes sets for lower respiratory MAEs and wheezing MAEs.

[c] It is not possible to detect from clinical databases whether an event occurring on the day of vaccination began prior to or after administration of vaccine, although events of hypersensitivity or seizures/convulsions may occur just subsequent to vaccination but are unlikely to be recorded on the same day prior to vaccination. As a result, the period at risk after vaccination for events of hypersensitivity and seizures/convulsions begins on the day of vaccination (Day 0), and the period at risk after vaccination for all other events of interest begins 1 day after vaccination (Day 1).

[d] The reference period for the period at risk for 0 to 3 days was defined from 7 to 9 days to take into account cyclical variations that may occur during the same days of the week.

An MAE is defined as a coded medical diagnosis made by a health care provider and associated with a medical encounter (ie, visit to a medical clinic or emergency department, or a hospital admission). One or more MAEs could be assigned for a single encounter.

For MAEs of Guillain-Barre syndrome, Bell's palsy, encephalitis, neuritis, vasculitis, and narcolepsy/cataplexy, events will only be counted if the subject does not have a prior record of the event in the 12 months prior to vaccination (or index date for unvaccinated controls).

In addition, listings of any hospitalization within 180 days, any deaths throughout the entire study period, and exposed pregnancies throughout the entire study period will be provided.

A hospitalization is any medical event that results in inpatient hospitalization of any duration. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting. Hospitalization for elective surgery related to a pre-existing condition that did not increase in severity or frequency following initiation of the study need not be considered a hospitalization. If anything untoward is reported during an elective procedure, that occurrence will be captured as an MAE or hospitalization according to the usual criteria.

For analyses of any hospitalization and respiratory hospitalizations (see Table 9.3-1), only the primary discharge diagnosis will be analyzed.

9.4 Data Sources

Study data are derived directly from NCKP clinical and institutional databases, which are not research databases. Rather they make up the electronic medical record documenting vaccine administration, medical utilization, participant demographics, and HMO membership for all NCKP members.

9.5 Study Size

Since there are no identified safety concerns with Q/LAIV, this post-marketing safety assessment is hypothesis generating and will include multiple statistical comparisons.

Enrollment of at least 10,000 children 2 through 8 years of age is planned. A sample size of 10,000 children will provide approximately 90% power to observe a statistically significant increase in relative risk (RR) of 1.5 for an event that occurs in 1 in 100 subjects in the comparison group. The study will also be able to rule out with 95% probability the occurrence of an event at a rate of 0.03% (1 in 3,333 subjects) assuming that incidence of the event follows a Poisson distribution. Enrollment is expected to be completed in the 2013-2014 influenza season but the study will be continued for additional seasons, if needed, until enrollment of 10,000 Q/LAIV recipients 2 through 8 years of age is completed to fulfill the postmarketing commitment to the FDA.

However, because the study is expanded to adolescents and adults up to 49 years of age, it is expected that a total of approximately 80,000 individuals will be enrolled (including approximately 10,000 to 30,000 individuals in each of the following 4 age groups: 2 to 4 years, 5 to 8 years, 9 to 17 years, and 18 to 49 years of age) during the 2013-2014 influenza season. Enrollment of 20,000 children per age group will provide approximately 90% power to observe a statistically significant increase in relative risk (RR) of 1.5 for an event that occurs in 1 in 200 subjects in the comparison group. A sample size of 20,000 will also be able to rule out with 95% probability the occurrence of an event with an incidence rate of 0.015% (1 in 6,666 subjects).

9.6 Data Management

NCKP clinical databases are maintained by Kaiser Permanente Information Technology (IT). This information is tracked with an automated audit trail (eg, adds, deletes, updates to study records). This information is stored on a secure SQL server that is administered, secured, backed up, and maintained by Division of Research IT personnel.

9.7 Data Analysis

9.7.1 Analysis Populations

The populations to be assessed are all Q/LAIV recipients and the nonrandomized control groups (unvaccinated subjects, and IIV recipients) as described in Section 9.1.

Analyses will also be performed by age group (2 to 4 years, 5 to 8 years, 9 to 17 years, 18 to 49 years) and setting (clinic, hospital, emergency department).

Q/LAIV recipients with medical conditions that are a warning/precaution against the use of Q/LAIV (see Package Insert; Annex 4) will be analyzed separately. Subjects will be identified as having these conditions by using the International Classification of Diseases Clinical Modification (ICD-9-CM or successor) diagnosis codes as outlined by Daley et al, 2004 (see Annex 3).

9.7.2 Endpoints

The adverse events of interest and the time periods when the subject is considered at risk after vaccination are presented in Table 9.3-1.

9.7.3 Planned Analyses

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. The age, gender, medical center, and prior year health care utilization level of the Q/LAIV and control groups will be summarized for descriptive purposes. Race information is not available in the Kaiser HMO databases.

Rates of events will be presented per 1,000 person-years. All statistical tests will be 2-sided and performed at the significance level of 0.05. Due to the exploratory nature of the study and the lack of formal hypothesis testing, multiple CIs will be constructed in the primary analysis without multiplicity adjustment. Due to the large number of unadjusted CIs to be evaluated, it is expected by chance alone that a number of CIs will not include one and suggest higher or lower event rates in the Q/LAIV group. Therefore, further statistical and medical assessments may be performed for events with observed increases that are statistically significant and/or medically important.

Incidence rates of adverse events of interest during periods at risk after Q/LAIV vaccination will be compared to incidence rates during reference periods later in the follow-up as presented in Table 9.3-1 (within-cohort analysis) and to incidence rates in controls (matched unvaccinated subjects and matched IIV recipients).

Incidence rates will be reported as subjects with an event per 1,000 person-years. If a subject has more than one event in the analysis window, the subject will be counted only once for the analysis. Relative risks (RR) and corresponding 95% CIs will be constructed for each event for safety comparisons with control groups. Crude RR and adjusted hazard ratio (HR) and corresponding 95% CIs for each event will be derived:

- Crude RR and exact 95% CI will be calculated without adjustment of any covariate.
- Adjusted HR and corresponding 95% CI will be obtained using Cox proportional hazards model with calendar time data input adjusting for seasonal changes in

background rates and other confounders. This multivariable analysis is detailed in Section 9.7.4.

Statistical significance will be declared based on the multiple variable analysis using the Cox model. However, if the 95% CI of adjusted HR or p-value cannot be estimated, the exact method without adjustment of covariates will be used. A statistically significantly increased risk associated with Q/LAIV vaccination will be declared if the lower bound of the HR 95% CI is > 1.00. Likewise, a statistically significantly decreased risk associated with Q/LAIV vaccination will be declared if the upper bound of the HR 95% CI is < 1.00. Statistical significance will be evaluated before rounding. The corresponding p-values also will be provided. If any control group has zero events, the corresponding RR will not be estimable due to a zero value of the denominator. If the p-value is available, statistical significance will be declared according to the p-value at the 95% significance level.

9.7.4 Multivariable Analysis

One of the primary challenges with performing safety assessment in this setting is that the background rates of many outcomes, such as respiratory events, change over time during the period of vaccination and follow-up. These changes in background rates are due to factors such as patterns in circulation of a variety of respiratory viruses and changes in exposure due to behavior influences such as the school year and holidays.

Controlling for seasonal changes in background rates that are dependent upon calendar time is important to minimize the potential seasonal bias and ensure that the effect of Q/LAIV on the rate of these events from a safety perspective, if any, can be accurately estimated.

The counting-process style of input for the Cox proportional hazards model can accomplish this by allowing the use of calendar time as the structure for defining the observation intervals (Andersen and Gill, 1982). Rows of observations for each subject will be generally structured as:

pid, caldtst, caldtsp, event

where *pid* is the subject identifier, *caldtst* is the calendar date of the beginning of the observation period, *caldtsp* is the calendar date of the end of the observation period, *event* is 1 if an event occurred at the end of the observation period, and 0 if an event did not occur, indicating censoring.

For example:

101, 11Oct2013, 22Nov2013, 0

102, 15Oct2013, 02Nov2013, 1

indicates that participant 101 was under observation from October 11 through November 22 and did not experience an event and was censored on November 22. Participant 102 was under observation from October 15 and experienced an event on November 02. Although not shown in this example, the values of main effects and covariates would also be included in each row.

This method controls for the effect of seasonal and other calendar time differences on background event rates because, when each component of the Cox partial likelihood is calculated at each event, the risk set includes only subjects who were under observation during the same calendar time period.

This style of input facilitates the use of calendar time and time-dependent covariates as the time structure of the model. The RR for the main effect (or a covariate) will be estimated by e^{β}, where β is the regression coefficient for the specific effect or covariate of interest. Ninety-five percent CIs for the RR will be calculated using a normal approximation, with the variance derived from the appropriate diagonal element of the estimated covariance matrix.

9.7.4.1 Within-cohort Analyses

Within-cohort analyses will be conducted among Q/LAIV recipients to see if the incidence of safety outcomes is higher within an immediate post-vaccination "risk" period (eg, 0 to 3, 1 to 14, 15 to 42, and 1 to 42 days post vaccination) compared to later "reference" periods, ie, 7 to 9 days post vaccination for the risk period of 0 to 3 days, 43 to 84 days post vaccination for the risk periods of 1 to 14, 15 to 42, and 1 to 42 days.

This will be accomplished in the Cox models by evaluating the main effect of "period," defined as a time-dependent variable using the counting-process style of data input. Covariates, stratification factors, and the calendar time structure will be incorporated to control for the effects of age, gender, level of health care utilization, and seasonal difference in background event rates. The main effect variable of "period" will compare post-vaccination "risk" periods to "reference" periods occurring after the risk period.

For each study subject, the beginning of each reference period will follow the end of the risk period.

For example:

riskperiod03: 1 = risk (Days 0 through 3)

0 = reference (Days 7 through 9)

riskperiod142: 1 = risk (Days 1 through 42)

0 = reference (Days 43 through 84)

If specific results from the primary analyses identify a statistically significant increased risk associated with Q/LAIV administration, additional models with main effects structured to compare the "risk" periods to "reference" periods occurring prior to vaccination may be constructed. To reduce the potential bias associated with the "healthy patient effect," the reference period prior to vaccination would exclude the week immediately prior to vaccination.

9.7.4.2 Analyses Versus Matched Controls

Analyses will be conducted to see if the incidence of safety outcomes is higher among Q/LAIV recipients compared to matched controls (unvaccinated or IIV) within post-vaccination "risk" periods (eg, 0 to 3 days, 1 to 42 days, and 1 to 180 days post vaccination).

This will be accomplished in the Cox models by evaluating the main effect of "treatment group." Covariates, stratification factors, and the calendar time structure will be incorporated to control for the effects of age, gender, level of health care utilization, and seasonal difference in background event rates.

The main effect variable "treatment group" will be coded as follows:

Treatment (for unvaccinated control analysis): 1 = Q/LAIV, 0 = unvaccinated

Treatment (for IIV control analysis): 1 = Q/LAIV, 0 = IIV

9.8 Quality Control

See Section 9.4.

9.9 Limitations of the Research Methods

This study presents several limitations that are associated with its general design, the data sources, and the study size and power.

Because this study is observational and the decision to vaccinate against influenza is not controlled, the measure of the association between incidence rate of adverse events and vaccination status is exposed to several potential biases, in particular, to an indication bias: subjects who received Q/LAIV may differ from subjects vaccinated with IIV or unvaccinated subjects and present a different risk of adverse events. In order to control for this bias, incidence rates of adverse events of interest during periods at risk after Q/LAIV vaccination will be compared to incidence rates during reference periods later in the follow-up (within-cohort analysis). Additionally, subjects in the two control groups, ie, unvaccinated controls and IIV recipient controls, will be matched with subjects in the Q/LAIV group by age and medical center. Unvaccinated controls will be followed from the date of vaccination of the reference Q/LAIV recipient (ie, the index date). Other potential confounders such as gender and prior health care utilization level will be included as covariates in the proposed Cox proportional hazards model. A complementary analysis will be conducted after exclusion of subjects with high-risk underlying medical conditions.

All the study data are extracted from NCKP clinical and institutional databases; study data can be tracked via an automated audit trail. Databases are thoroughly validated within the Kaiser Permanente system, and are utilized for patient care and management, operational quality assurance, billing, and as a secondary use for research efforts. However, only medically attended events are documented and can be identified according to an ICD-9 diagnosis code, and only a limited number of critical adverse events can be validated against medical chart specifically for this study. Of note, the same limitations apply to adverse events documented during different periods of time, ie, at-risk periods as well as reference periods, and for different subjects, ie, Q/LAIV recipients and matched controls. Therefore, limitations regarding the validity of the data may impact the crude incidence rate estimates of adverse events but should not generate systematic biases of the association between incidence rates and vaccination status.

Finally, the documented population will be large and should include at least 10,000 children 2 through 8 years of age. However, the population will not be large enough to discard any association between vaccination status and very rare adverse events. For instance, a sample size of 10,000 children cannot rule out with 95% probability the occurrence of an event at a rate of less than 0.03% (1 in 3,333 subjects), assuming that the incidence of the event follows a Poisson distribution. A sample size of 20,000 cannot rule out with 95% probability the occurrence of an event with an incidence rate of less than 0.015% (1 in 6,666 subjects).

9.10 Other Aspects

Not applicable.

10 Protection of Human Subjects

10.1 Regulatory Considerations

The study will be conducted in accordance with the US Code of Federal Regulations governing Institutional Review Boards (21 CFR 56) and Obligations of Clinical Investigators (21 CFR 312). This study is an observational database study and will be conducted using records without any personal identifiers and without direct patient involvement.

Privately identifiable information will not be released without written permission of the patient, except as necessary for monitoring by the US FDA or the sponsor of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996).

10.2 Institutional Review Board

Any documents that the Institutional Review Board (IRB) may need to fulfill its responsibilities, such as protocol amendments or other information from the sponsor, will be submitted to the IRB. The written unconditional approval of the study protocol by the IRB will be in the possession of the investigator and the sponsor before the study is initiated. Protocol modifications or changes may not be initiated without prior written IRB approval.

10.3 Informed Consent

All participants in this study will be vaccinated in the course of obtaining routine medical care. Because this study presents no risk of harm to subjects and involves no procedures for which written consent is normally required outside the research setting, obtaining informed consent specifically for this study will not be required, in accordance with 21 CFR 56.109(c)(1).

11 Management and Reporting of Adverse Events/Adverse Reactions

11.1 Reporting of Serious Adverse Events

11.1.1 Definition of Serious Adverse Event for Reporting Purposes

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening

  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting

- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

11.1.2 Notifying the Sponsor of Possibly-related Serious Adverse Events

Occurrences of medical diagnoses are collected in the KP utilization databases independently of this observational study and are not assessed for possible causal association on an individual subject-event basis. However, if at any time during the study an investigator or qualified designee becomes aware of an SAE that is considered to be possibly causally related to Q/LAIV, the event must be reported to MedImmune Patient Safety, to comply with regulatory reporting requirements.

Within 24 hours, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: +1 301 398 4205

When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

11.1.3 Reporting of Pregnancies

Pregnancies will be identified using pregnancy test results and additional information about first prenatal visit, births, stillbirths or spontaneous abortion diagnoses. Available information on outcomes for the mother and child (including any premature terminations) after Q/LAIV administration to known pregnant female subjects will be described in a separate listing at the conclusion of the study.

12 Plans for Disseminating and Communicating Study Results

Annual progress reports related to this study will be provided to the regulatory authority in the US BLA Postmarketing Annual Reports which have an annual data cut-off date of 30 September, with submission date within 60 days. In addition, study progress will be summarized in the biannual periodic safety update reports (PSURs), which have data cut-off dates of 16 June and 16 December, with submission dates within 70 days.

Following completion of the study, which may require only one season, the final clinical study report (CSR) will be submitted within 12 months. As committed to the US FDA, the study will be completed no later than 30 June 2018, and the final CSR will be submitted no later than 30 June 2019.

13 References

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Annex 1 List of Stand-alone Documents

Number	Document Reference Number	Date	Title
None			

Annex 2 ENCePP Checklist for Study Protocols (applicable to EU submission only)

Annex 3 International Classification of Diseases Clinical Modification (ICD-9-CM) Codes (High-risk, Selected)

Disease Categories	ICD-9-CM Codes
Pulmonary	
Asthma and reactive airways disease	493.0–493.9, 519.1
Cystic fibrosis	277.0
Bronchopulmonary dysplasia	770.7
Bronchiectasis	494.0–494.1
Congenital lung anomalies	748.4–748.6
Chronic respiratory disease or failure	518.83–518.84, 519.9
Postinflammatory pulmonary fibrosis	515
Cardiovascular	
Congenital heart disease	745.0–747.4
Chronic pulmonary heart disease	416.0–416.9
Valvular or endocardial disease	424.0–424.3
Rheumatic heart disease	391.0–391.9, 392.0, 393–398.99
Cardiomyopathy	425.0–425.4, 429.1, 429.3
Heart failure	428.0–428.9
Renal	
Nephrotic syndrome	581.0–581.9
Chronic glomerulonephritis	582.0–582.9, 583.0–583.9
Chronic renal failure	585–586
Congenital renal anomalies	753.0–753.1
Hematologic	
Thalassemia	282.4
Sickle cell anemia	282.6
Other hemoglobinopathies	282.7
Aplastic anemia	284.0–284.9
White blood cell disorders	288.0–288.2

Annex 3 International Classification of Diseases Clinical Modification (ICD-9-CM) Codes (High-risk, Selected)

Disease Categories	ICD-9-CM Codes
Immunosuppressive disorders or therapies	
Hereditary immunodeficiency	279.0–279.9
HIV infection	042, V08
Malignancy	140.0–160.0, 160.2–208.9, 235.0–239.9
Systemic lupus erythematosus	710.0
Organ or bone marrow transplantation	V42.0–V42.9
Radiation or chemotherapy	V58.0–V58.1
Asplenia	759.0
Metabolic	
Diabetes	250.0–250.9
Amino acid disorders	270.0, 270.2–270.9
Carbohydrate disorders	271.0–271.1, 271.4–271.9
Lipid disorders	272.1–272.3, 272.5–272.9
Other metabolic disorders	277.1–277.3, 277.5–277.6, 277.8–277.9
Diseases associated with aspirin therapy	
Kawasaki disease	446.1
Rheumatoid arthritis	714.0–714.9
Other conditions	
Cerebral palsy	343.0–343.9
Muscular dystrophy	359.0–359.3
Down syndrome	758.0
Multiple HRCs	> 1 of the above ICD-9-CM codes

HIV = human immunodeficiency virus; HRC = high-risk condition; ICD-9-CM = International Classification of Diseases Clinical Modification.
Source: Daley et al, 2004.

Annex 4 FluMist Quadrivalent® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLUMIST® QUADRIVALENT safely and effectively. See full prescribing information for FluMist® Quadrivalent.

FluMist® Quadrivalent (Influenza Vaccine Live, Intranasal)
Intranasal Spray
20XX-20XX Formula
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1) 2/2012

INDICATIONS AND USAGE

FluMist Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1, 11)
FluMist Quadrivalent is approved for use in persons 2 through 49 years of age. (1)

DOSAGE AND ADMINISTRATION

For intranasal administration by a healthcare provider. (2)

Age Group	Vaccination Status	Dosage Schedule
Children (2-8 years)	Not previously vaccinated with influenza vaccine	2 doses (0.2 mL† each, at least 1 month apart) (2.1)
Children (2-8 years)	Previously vaccinated with influenza vaccine	1 dose (0.2 mL†) (2.1)
Children, adolescents, and adults (9-49 years)	Not applicable	1 dose (0.2 mL†) (2.1)

†Administer as 0.1 mL per nostril.

DOSAGE FORMS AND STRENGTHS

Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer. (3)

CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of FluMist Quadrivalent, including egg protein, gentamicin, gelatin, and arginine, or after a previous dose of any influenza vaccine. (4.1)
- Concomitant aspirin therapy in children and adolescents. (4.2)

WARNINGS AND PRECAUTIONS

- In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal). (5.1)
- Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following the administration of FluMist Quadrivalent. (5.2)
- If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist Quadrivalent should be based on careful consideration of the potential benefits and risks. (5.3)
- FluMist Quadrivalent has not been studied in immunocompromised persons. (5.4)

ADVERSE REACTIONS

The most common solicited adverse reactions (≥ 10% in vaccine recipients and at least 5% greater than in placebo recipients) reported after FluMist were runny nose or nasal congestion (ages 2 years through 49 years), fever over 100°F (children ages 2 years through 6 years), and sore throat (adults ages 18 years through 49 years). Among children and adolescents 2 through 17 years of age who received FluMist Quadrivalent, 32% reported runny nose or nasal congestion (32%) and 7% reported fever over 100°F. Among adults 18 through 49 years of age who received FluMist Quadrivalent, 44% reported runny nose or nasal congestion and 19% reported sore throat. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or VAERS at 1-800-822-7967 or *http://vaers.hhs.gov*.

DRUG INTERACTIONS

- Antiviral drugs that are active against influenza A and/or B may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after, receipt of the vaccine. (7.2)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FluMist Quadrivalent have not been established in pregnant women, nursing mothers, geriatric adults, or children less than 2 years of age. (8.1, 8.3, 8.4, 8.5)
- In clinical trials, in children 6 through 23 months of age, FluMist was associated with an increased risk of hospitalization and wheezing. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 2/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FluMist® Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine [see *Description (11)*].
FluMist Quadrivalent is approved for use in persons 2 through 49 years of age.

2 DOSAGE AND ADMINISTRATION

FOR INTRANASAL ADMINISTRATION BY A HEALTHCARE PROVIDER.

2.1 Dosing Information

Administer FluMist Quadrivalent according to the following schedule:

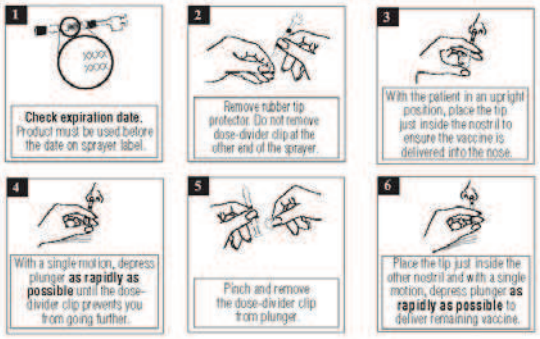
Age Group	Vaccination Status	Dosage Schedule
Children age 2 years through 8 years	Not previously vaccinated with influenza vaccine	2 doses (0.2 mL† each, at least 1 month apart)
Children age 2 years through 8 years	Previously vaccinated with influenza vaccine	1 dose (0.2 mL†)
Children, adolescents, and adults age 9 through 49 years	Not applicable	1 dose (0.2 mL†)

†Administer as 0.1 mL per nostril.

2.2 Administration Instructions

Each sprayer contains a single dose (0.2 mL) of FluMist Quadrivalent; administer approximately one half of the contents of the single-dose intranasal sprayer into each nostril (each sprayer contains 0.2 mL of vaccine). Refer to Figure 1 for step-by-step administration instructions. Following administration, dispose of the sprayer according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

Figure 1



Note: Active inhalation (i.e., sniffing) is not required by the patient during vaccine administration.

3 DOSAGE FORMS AND STRENGTHS

Each 0.2 mL dose is a suspension supplied in a single-dose pre-filled intranasal sprayer.

4 CONTRAINDICATIONS

4.1 Severe Allergic Reactions

Do not administer FluMist Quadrivalent to persons who have had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description (11)*] including egg protein, gentamicin, gelatin, and arginine, or after a previous dose of any influenza vaccine.

4.2 Concomitant Aspirin Therapy and Reye's Syndrome in Children and Adolescents
Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza infection [See *Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risks of Hospitalization and Wheezing in Children Younger than 24 Months of Age
In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal) [see *Adverse Reactions (6.1)*]. This observation with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see *Description (11)*].

5.2 Asthma, Recurrent Wheezing, and Active Wheezing
Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist Quadrivalent. FluMist Quadrivalent has not been studied in persons with severe asthma or active wheezing.

5.3 Guillain-Barré Syndrome
The 1976 swine influenza vaccine (inactivated) was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, based on data for inactivated influenza vaccines, it is probably slightly more than 1 additional case per 1 million persons vaccinated [1]. If GBS has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist Quadrivalent should be based on careful consideration of the potential benefits and potential risks.

5.4 Altered Immunocompetence
FluMist Quadrivalent has not been studied in immunocompromised persons. The effectiveness of FluMist has not been studied in immunocompromised persons. Data on safety and shedding of vaccine virus after administration of FluMist in immunocompromised persons are limited to 174 persons with HIV infection and 19 mild to moderately immunocompromised children and adolescents with cancer [see *Clinical Pharmacology (12.2)*].

5.5 Medical Conditions Predisposing to Influenza Complications
The safety of FluMist Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established.

5.6 Management of Acute Allergic Reactions
Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine [see *Contraindications (4.1)*].

5.7 Limitations of Vaccine Effectiveness
FluMist Quadrivalent may not protect all individuals receiving the vaccine.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.
This safety experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see *Description (11)*]. A total of 9537 children and adolescents 1 through 17 years of age and 3041 adults 18 through 64 years of age received FluMist in randomized, placebo-controlled Studies D153-P501, AV006, D153-P526, AV019, and AV009 [3 used Allantoic Fluid containing Sucrose-Phosphate-Glutamate (AF-SPG) placebo, and 2 used saline placebo] described below. In addition, 4179 children 6 through 59 months of age received FluMist in Study MI-CP111, a randomized, active-controlled trial. Among pediatric FluMist recipients 6 months through 17 years of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019, and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), while in D153-P501, 99% of subjects were Asian.
A total of 1382 children and adolescents 2 through 17 years of age and 1198 adults 18 through 49 years of age received FluMist Quadrivalent in randomized, active-controlled Studies MI-CP208 and MI-CP185. Among pediatric FluMist Quadrivalent recipients 2 through 17 years of age, 51% were female; in the study of adults, 55% were female. In Studies MI-CP208 and MI-CP185, subjects were White (73%), Asian (1%), Black or African-American (19%), and Other (7%); overall, 22% were Hispanic or Latino.

FluMist in Children and Adolescents
The safety of FluMist was evaluated in an AF-SPG placebo-controlled study (AV019) conducted in a Health Maintenance Organization (HMO) in children 1 through 17 years of age (FluMist = 6473, placebo = 3216). An increase in asthma events, captured by review of diagnostic codes, was observed in children younger than 5 years of age who received FluMist compared to those who received placebo (Relative Risk 3.53, 90% CI: 1.1, 15.7).
In Study MI-CP111, children 6 through 59 months of age were randomized to receive FluMist or inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia was prospectively monitored from randomization through 42 days post last vaccination. Hospitalization due to all causes was prospectively monitored from randomization through 180 days post last vaccination. Increases in wheezing and hospitalization (for any cause) were observed in children 6 months through 23 months of age who received FluMist compared to those who received inactivated Influenza Virus Vaccine, as shown in Table 1.

Table 1: Percentages of Children with Hospitalizations and Wheezing from Study MI-CP111[a]

Adverse Reaction	Age Group	FluMist (n/N)	Active Control[b] (n/N)
Hospitalizations[c]	6-23 months	4.2 % (84/1992)	3.2 % (63/1975)
	24-59 months	2.1 % (46/2187)	2.5 % (56/2198)
Wheezing[d]	6-23 months	5.9 % (117/1992)	3.8 % (75/1975)
	24-59 months	2.1 % (47/2187)	2.5 % (56/2198)

[a] NCT00128167; see www.clinicaltrials.gov
[b] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[c] Hospitalization due to any cause from randomization through 180 days post last vaccination.
[d] Wheezing requiring bronchodilator therapy or accompanied by respiratory distress or hypoxia evaluated from randomization through 42 days post last vaccination.

Most hospitalizations observed were due to gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. In post-hoc analysis, rates of hospitalization in children 6 through 11 months of age were 6.1% (42/684) in FluMist recipients and 2.6% (18/683) in inactivated Influenza Virus Vaccine recipients.

Table 2 shows pooled solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo post Dose 1 for Studies D153-P501 and AV006, and solicited adverse reactions post Dose 1 for Study MI-CP111. Solicited adverse reactions were those about which parents/guardians were specifically queried after receipt of FluMist, placebo, or control vaccine. In these studies, solicited reactions were documented for 10 days post vaccination. Solicited reactions following the second dose of FluMist were similar to those following the first dose and were generally observed at a lower frequency.

Table 2: Summary of Solicited Adverse Reactions Observed Within 10 Days after Dose 1 for FluMist and Either Placebo or Active Control Recipients in Children 2 through 6 Years of Age

	Studies D153-P501[a] & AV006		Study MI-CP111[b]	
	FluMist N = 876-1759[e]	Placebo[c] N = 424-1034[e]	FluMist N = 2170[e]	Active Control[d] N = 2165[e]
Event	%	%	%	%
Runny Nose/ Nasal Congestion	58	50	51	42
Decreased Appetite	21	17	13	12
Irritability	21	19	12	11
Decreased Activity (Lethargy)	14	11	7	6
Sore Throat	11	9	5	6
Headache	9	7	3	3
Muscle Aches	6	3	2	2
Chills	4	3	2	2
Fever				
> 100°F Oral	16	11	13	11
> 100 - ≤ 101°F Oral	9	6	6	4
> 101 - ≤ 102°F Oral	4	3	4	3

[a] NCT00122244; see www.clinicaltrials.gov
[b] NCT00128167; see www.clinicaltrials.gov
[c] Study D153-P501 used saline placebo; Study AV006 used AF-SPG placebo.
[d] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[e] Number of evaluable subjects (those who returned diary cards) for each reaction. Range reflects differences in data collection between the 2 pooled studies.

In clinical studies D153-P501 and AV006, unsolicited adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were abdominal pain (2% FluMist vs. 0% placebo) and otitis media (3% FluMist vs. 1% placebo). An additional adverse reaction identified in the active-controlled trial MI-CP111 occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to active control was sneezing (2% FluMist vs. 1% active control).
In a separate saline placebo-controlled trial (D153-P526) in a subset of older children and adolescents 9 through 17 years of age who received one dose of FluMist, the solicited adverse reactions as well as unsolicited adverse reactions reported were generally consistent with observations from the trials in Table 2. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.
In Study AV018, in which FluMist was concomitantly administered with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) to children 12 through 15 months of age, adverse reactions were similar to those seen in other clinical trials of FluMist.

FluMist Quadrivalent in Children and Adolescents
In the randomized, active-controlled Study MI-CP208 that compared FluMist Quadrivalent and FluMist in children and adolescents 2 through 17 years of age, the rates of solicited adverse reactions reported were similar between subjects who received FluMist Quadrivalent and FluMist. Table 3 includes solicited adverse reactions post Dose 1 from Study MI-CP208 that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist clinical studies (see *Table 2*). In this study, solicited adverse reactions were documented for 14 days post vaccination. Solicited adverse reactions post Dose 2 were observed at a lower frequency compared to those post Dose 1 for FluMist Quadrivalent and were similar between subjects who received FluMist Quadrivalent and FluMist.

Table 3: Summary of Solicited Adverse Reactions[a] Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208[b] in Children and Adolescents 2 through 17 Years of Age

	FluMist Quadrivalent N = 1341-1377[d]	FluMist[c] N = 901-920[d]
Event	%	%
Runny Nose/Nasal Congestion	32	32
Headache	13	12
Decreased Activity (Lethargy)	10	10
Sore Throat	9	10
Decreased Appetite	6	7
Muscle Aches	4	5
Fever		
> 100°F by any route	7	5
> 100 - ≤ 101°F by any route	3	2
> 101 - ≤ 102°F by any route	2	2

[a] Solicited adverse reactions that occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist trials (see *Table 2*).
[b] NCT01091246; see www.clinicaltrials.gov
[c] Represents pooled data from the two FluMist study arms. [see *Clinical Studies (14.2)*]
[d] Number of evaluable subjects for each event.

In Study MI-CP208, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

FluMist in Adults
In adults 18 through 49 years of age in Study AV009, solicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to AF-SPG placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weakness (26% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14% FluMist vs. 11% placebo), and chills (9% FluMist vs. 6% placebo).

In Study AV009, unsolicited adverse reactions occurring in at least 1% of FluMist recipients and at a higher rate (≥ 1% rate difference after rounding) compared to placebo were nasal congestion (9% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

FluMist Quadrivalent in Adults

In the randomized, active-controlled Study MI-CP185 that compared FluMist Quadrivalent and FluMist in adults 18 through 49 years of age, the rates of solicited adverse reactions reported were generally similar between subjects who received FluMist Quadrivalent and FluMist. Table 4 presents solicited adverse reactions that either occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.

Table 4: Summary of Solicited Adverse Reactions[a] Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP185[b] in Adults 18 through 49 Years of Age

	FluMist Quadrivalent N = 1197[d]	FluMist[c] N = 597[d]
Event	%	%
Runny Nose/Nasal Congestion	44	40
Headache	28	27
Sore Throat	19	20
Decreased Activity (Lethargy)	18	18
Cough	14	13
Muscle Aches	10	10
Decreased Appetite	6	5

[a] Solicited adverse reactions that occurred at a higher rate (≥ 1% rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in Study AV009.
[b] NCT00860067; see www.clinicaltrials.gov
[c] Represents pooled data from the two FluMist study arms. [see *Clinical Studies (14.4)*]
[d] Number of evaluable subjects for each event.

In Study MI-CP185, no unsolicited adverse reactions occurred at a higher rate (1% or greater) in FluMist Quadrivalent recipients compared to FluMist recipients.

6.2 Postmarketing Experience

The following events have been spontaneously reported during post approval use of FluMist. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac disorders: Pericarditis

Congenital, familial, and genetic disorders: Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome)

Gastrointestinal disorders: Nausea, vomiting, diarrhea

Immune system disorders: Hypersensitivity reactions (including anaphylactic reaction, facial edema, and urticaria)

Nervous system disorders: Guillain-Barré syndrome, Bell's Palsy, meningitis, eosinophilic meningitis, vaccine-associated encephalitis

Respiratory, thoracic, and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

7 DRUG INTERACTIONS

7.1 Aspirin Therapy

Do not administer FluMist Quadrivalent to children and adolescents through 17 years of age who are receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza [see *Contraindications (4.2)*]. Avoid aspirin-containing therapy in these age groups during the first 4 weeks after vaccination with FluMist Quadrivalent unless clearly needed.

7.2 Antiviral Agents Against Influenza A and/or B

Antiviral drugs that are active against influenza A and/or B viruses may reduce the effectiveness of FluMist Quadrivalent if administered within 48 hours before, or within 2 weeks after vaccination. The concurrent use of FluMist Quadrivalent with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. If antiviral agents and FluMist Quadrivalent are administered concomitantly, revaccination should be considered when appropriate.

7.3 Concomitant Administration with Inactivated Vaccines

The safety and immunogenicity of FluMist Quadrivalent when administered concomitantly with inactivated vaccines have not been determined. Studies of FluMist and FluMist Quadrivalent excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment.

7.4 Concomitant Administration with Other Live Vaccines

Concomitant administration of FluMist Quadrivalent with Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.) or the Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) has not been studied. Concomitant administration of FluMist with MMR and the varicella vaccine was studied in children 12 through 15 months of age [see *Clinical Studies (14.5)*]. Concomitant administration of FluMist with the MMR and the varicella vaccine in children older than 15 months of age has not been studied.

7.5 Intranasal Products

There are no data regarding co-administration of FluMist Quadrivalent with other intranasal preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

A developmental and reproductive toxicity study has been performed in female rats administered FluMist Quadrivalent either three times (during the period of organogenesis) or six times (prior to gestation and during the period of organogenesis), 200 microliter/rat/occasion (approximately 150 human dose equivalents), by intranasal instillation and has revealed no evidence of impaired fertility or harm to the fetus due to FluMist Quadrivalent. There are however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response FluMist Quadrivalent should be administered during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether FluMist Quadrivalent is excreted in human milk. Because some viruses are excreted in human milk, caution should be exercised when FluMist Quadrivalent is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of FluMist Quadrivalent in children 24 months of age and older is based on data from FluMist clinical studies and a comparison of post-vaccination antibody titers between persons who received FluMist Quadrivalent and those who received FluMist [see *Clinical Studies (14.1, 14.2)*]. FluMist Quadrivalent is not approved for use in children younger than 24 months of age because use of FluMist in children 6 through 23 months has been associated with increased risks of hospitalization and wheezing in clinical trials [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

8.5 Geriatric Use

FluMist Quadrivalent is not approved for use in persons 65 years of age and older because in a clinical study (AV009), effectiveness of FluMist to prevent febrile illness was not demonstrated in adults 50 through 64 years of age [see *Clinical Studies (14.3)*]. In this study, solicited events among individuals 50 through 64 years of age were similar in type and frequency to those reported in younger adults. In a clinical study of FluMist in persons 65 years of age and older, subjects with underlying high-risk medical conditions (N = 200) were studied for safety. Compared to controls, FluMist recipients had a higher rate of sore throat.

11 DESCRIPTION

FluMist Quadrivalent (Influenza Vaccine Live, Intranasal) is a live quadrivalent vaccine for administration by intranasal spray. FluMist Quadrivalent contains four vaccine virus strains: an A/H1N1 strain, an A/H3N2 strain and two B strains. FluMist Quadrivalent contains B strains from both the B/Yamagata/16/88 and the B/Victoria/2/87 lineages. FluMist Quadrivalent is manufactured according to the same process as FluMist.

The influenza virus strains in FluMist Quadrivalent are (a) *cold-adapted* (*ca*) (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive* (*ts*) (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) *attenuated* (*att*) (i.e., they do not produce classic influenza-like illness in the ferret model of human influenza infection).

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) using FluMist [see *Clinical Pharmacology (12.2)*]. For each of the four reassortant strains in FluMist Quadrivalent, the six internal gene segments responsible for *ca*, *ts*, and *att* phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant wild-type influenza viruses. Thus, the four viruses contained in FluMist Quadrivalent maintain the replication characteristics and phenotypic properties of the MDV and express the HA and NA of wild-type viruses. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the *ts* and *att* phenotypes. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the *ts* and *att* properties; five genetic loci in three gene segments control the *ca* property.

Each of the reassortant strains in FluMist Quadrivalent express the HA and NA of wild- type viruses that are related to strains expected to circulate during the 20XX-20XX influenza season. Three of the viruses (A/H1N1, A/H3N2 and one B strain) have been recommended by the United States Public Health Service (USPHS) for inclusion in the annual trivalent and quadrivalent influenza vaccine formulations. An additional B strain has been recommended by the USPHS for inclusion in the quadrivalent influenza vaccine formulation.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to allow vaccine virus replication. The allantoic fluid of these eggs is harvested, pooled, and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. The viral harvests are then sterile filtered to produce the monovalent bulks. Each lot is tested for *ca*, *ts*, and *att* phenotypes and is also tested extensively by *in vitro* and *in vivo* methods to detect adventitious agents. Monovalent bulks from the four strains are subsequently blended and diluted as required to attain the desired potency with stabilizing buffers to produce the quadrivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated FluMist Quadrivalent sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains $10^{6.5-7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the four strains: A/XXX/XX/XXXX (H1N1), A/XXX/XX/XXXX (H3N2), B/XXX/XX/XXXX (B/Yamagata/16/88 lineage), and B/XXX/XX/XXXX (B/Victoria/2/87 lineage). Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, and 0.96 mg/dose monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin (< 0.24 mcg/dose), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 0.37 mcg/dose). FluMist Quadrivalent contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. FluMist Quadrivalent is a colorless to pale yellow suspension and is clear to slightly cloudy.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FluMist Quadrivalent vaccine are not fully understood; serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role.

FluMist and FluMist Quadrivalent contain live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients (shedding) [see *Pharmacodynamics (12.2)*].

12.2 Pharmacodynamics

Shedding Studies

Shedding of vaccine viruses within 28 days of vaccination with FluMist was evaluated in (1) multi-center study MI-CP129 which enrolled healthy individuals 6 through 59 months of age (N = 200); and (2) multi-center study FM026 which enrolled healthy individuals 5 through 49 years of age (N = 344). In each study, nasal secretions were obtained daily for the first 7 days and every other day through either Day 25 and on Day 28 or through Day 28. In study MI-CP129, individuals with a positive shedding sample at Day 25 or Day 28 were to have additional shedding samples collected every 7 days until culture negative on 2 consecutive samples. Results of these studies are presented in Table 5.

Table 5: Characterization of Shedding with FluMist in Specified Age Groups by Frequency, Amount, and Duration (Study MI-CP129[a] and Study FM026[b])

Age	Number of Subjects	% Shedding[c]	Peak Titer ($TCID_{50}$/mL)[d]	% Shedding After Day 11	Day of Last Positive Culture
6-23 months[e]	99	89	$< 5 \log_{10}$	7.0	Day 23[f]
24-59 months	100	69	$< 5 \log_{10}$	1.0	Day 25[g]
5-8 years	102	50	$< 5 \log_{10}$	2.9	Day 23[h]
9-17 years	126	29	$< 4 \log_{10}$	1.6	Day 28[h]
18-49 years	115	20	$< 3 \log_{10}$	0.9	Day 17[h]

[a] NCT00344305; see www.clinicaltrials.gov
[b] NCT00192140; see www.clinicaltrials.gov
[c] Proportion of subjects with detectable virus at any time point during the 28 days.
[d] Peak titer at any time point during the 28 days among samples positive for a single vaccine virus.
[e] FluMist and FluMist Quadrivalent are not approved for use in children younger than 24 months of age [see *Adverse Reactions (6.1)*].
[f] A single subject who shed previously on Days 1-3; $TCID_{50}$/mL was less than $1.5 \log_{10}$ on Day 23.
[g] A single subject who did not shed previously; $TCID_{50}$/mL was less than $1.5 \log_{10}$.
[h] A single subject who did not shed previously; $TCID_{50}$/mL was less than $1.0 \log_{10}$.

The highest proportion of subjects in each group shed one or more vaccine strains on Days 2-3 post vaccination. After Day 11 among individuals 2 through 49 years of age (n = 443), virus titers did not exceed $1.5 \log_{10}$ $TCID_{50}$/mL.

Studies in Immunocompromised Individuals

Safety and shedding of vaccine virus following FluMist administration were evaluated in 28 HIV-infected adults [median CD4 cell count of 541 cells/mm^3] and 27 HIV-negative adults 18 through 58 years of age. No serious adverse events were reported during the one-month follow-up period. Vaccine strain (type B) virus was detected in 1 of 28 HIV-infected subjects on Day 5 only, and in none of the HIV-negative FluMist recipients.

Safety and shedding of vaccine virus following FluMist administration were also evaluated in children in a randomized (1:1), cross-over, double-blind, AF-SPG placebo-controlled trial in 24 HIV-infected children [median CD4 cell count of 1013 cells/mm^3] and 25 HIV-negative children 1 through 7 years of age, and in a randomized (1:1), open-label, inactivated influenza vaccine-controlled trial in 243 HIV-infected children and adolescents 5 through 17 years of age receiving stable anti-retroviral therapy. Frequency and duration of vaccine virus shedding in HIV-infected individuals were comparable to that seen in healthy individuals. No adverse effects on HIV viral load or CD4 counts were identified following FluMist administration. In the 5 through 17 year old age group, one inactivated influenza vaccine recipient and one FluMist recipient experienced pneumonia within 28 days of vaccination (days 17 and 13, respectively). The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in HIV-infected individuals has not been evaluated.

Twenty mild to moderately immunocompromised children and adolescents 5 through 17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks prior to enrollment) were randomized 1:1 to receive FluMist or AF-SPG placebo. Frequency and duration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in immunocompromised individuals has not been evaluated.

Transmission Study

A prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children younger than 3 years of age to assess the transmission of vaccine viruses from a vaccinated individual to a non-vaccinated individual. A total of 197 children 8 through 36 months of age were randomized to receive one dose of FluMist (N = 98) or AF-SPG placebo (N = 99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (A/H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type A (A/H1N1) and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 1-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted (*ca*) and temperature-sensitive (*ts*) phenotypes were preserved in 135 tested of 250 strains isolated at the local laboratory. Ten influenza isolates (9 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One placebo subject had mild symptomatic Type B virus infection confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This Type B isolate retained the *ca*, *ts*, and *att* phenotypes of the vaccine strain and had the same genetic sequence when compared to a Type B virus cultured from a vaccine recipient within the same playgroup. Four of the influenza Type A isolates were confirmed as wild-type A/Panama (H3N2). The remaining isolates could not be further characterized.

Assuming a single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist vaccinee in this daycare setting was 0.58% (95% CI: 0, 1.7) based on the Reed-Frost model. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6) using the Reed-Frost model.

12.3 Pharmacokinetics

Biodistribution

A biodistribution study of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentages of the delivered doses detected were as follows: nasal cavity 89.7%, stomach 2.6%, brain 2.4%, and lung 0.4%. The clinical significance of these findings is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FluMist Quadrivalent has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

14 CLINICAL STUDIES

The effectiveness of FluMist Quadrivalent is based on data demonstrating the clinical efficacy of FluMist in children and the effectiveness of FluMist in adults, and a comparison of post vaccination geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibodies between individuals receiving FluMist and FluMist Quadrivalent. The clinical experience with FluMist is relevant to FluMist Quadrivalent because both vaccines are manufactured using the same process and have overlapping compositions [see *Description (11)*].

14.1 Efficacy Studies of FluMist in Children and Adolescents

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy of FluMist compared to an intramuscularly administered, inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc. (active control) in children 6 months to less than 5 years of age during the 2004-2005 influenza season. A total number of 3916 children without severe asthma, without use of bronchodilator or steroids, and without wheezing within the prior 6 weeks were randomized to FluMist and 3936 were randomized to active control. Children who previously received any influenza vaccine received a single dose of study vaccine, while those who never previously received an influenza vaccination (or had an unknown history of influenza vaccination) received two doses. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (CDC-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature ≥ 100°F oral or equivalent) with cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 6 for a description of the results by strain and antigenic similarity.

Table 6: Comparative Efficacy Against Culture-Confirmed Modified CDC-ILI[a] Caused by Wild-Type Strains (Study MI-CP111)[b,c]

	FluMist			Active Control[d]			% Reduction in Rate for FluMist[e]	95% CI
	N	# of Cases	Rate (cases/N)	N	# of Cases	Rate (cases/N)		
Matched Strains								
All strains	3916	53	1.4%	3936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	—	—
B	3916	50	1.3%	3936	67	1.7%	27.3%	-4.8, 49.9
Mismatched Strains								
All strains	3916	102	2.6%	3936	245	6.2%	58.2%	47.4, 67.0
A/H1N1	3916	0	0.0%	3936	0	0.0%	—	—
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	66	1.7%	3936	71	1.8%	6.3%	-31.6, 33.3
Regardless of Match								
All strains	3916	153	3.9%	3936	338	8.6%	54.9%	45.4, 62.9
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	16.1%	-7.7, 34.7

ATP Population.

[a] Modified CDC-ILI was defined as fever (temperature ≥ 100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.
[b] In children 6 months through 5 years of age
[c] NCT00128167; see www.clinicaltrials.gov
[d] Inactivated Influenza Virus Vaccine manufactured by Sanofi Pasteur Inc., administered intramuscularly.
[e] Reduction in rate was adjusted for country, age, prior influenza vaccination status, and wheezing history status.

A randomized, double-blind, saline placebo-controlled trial (D153-P501) was performed to evaluate the efficacy of FluMist in children 12 through 35 months of age without high-risk medical conditions against culture-confirmed influenza illness. This study was performed in Asia over two successive seasons (2000-2001 and 2001-2002). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza. Respiratory illness that prompted an influenza culture was defined as at least one of the following: fever (≥ 100.4°F rectal or ≥ 99.5°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. A total of 3174 children were randomized 3:2 (vaccine:placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 7 for a description of the results.

During the second year of Study D153-P501, for children who received two doses in Year 1 and one dose in Year 2, FluMist demonstrated 84.3% (95% CI: 70.1, 92.4) efficacy against culture-confirmed influenza illness due to antigenically matched wild-type influenza.

Study AV006 was a second multi-center, randomized, double-blind, AF-SPG placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons (1996-1997 and 1997-1998). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in children who received two doses of vaccine in the first year and a single revaccination dose in the second year. Respiratory illness that prompted an influenza culture was defined as at least one of the following: fever (≥ 101°F rectal or oral; or ≥ 100.4°F axillary), wheezing, shortness of breath, pulmonary congestion, pneumonia, or otitis media; or two of the following: runny nose/nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. During the first year of the study, 1602 children 15 through 71 months of age were randomized 2:1 (vaccine:placebo). See Table 7 for a description of the results.

Table 7: Efficacy[a] of FluMist vs. Placebo Against Culture-Confirmed Influenza Illness Due to Antigenically Matched Wild-Type Strains (Studies D153-P501[b] & AV006[c], Year 1)

	D153-P501[d]			AV006[e]		
	FluMist n[f] (%)	Placebo n[f] (%)	% Efficacy (95% CI)	FluMist n[f] (%)	Placebo n[f] (%)	% Efficacy (95% CI)
	N[g] = 1653	N[g] = 1111		N[g] = 849	N[g] = 410	
Any strain	56 (3.4%)	139 (12.5%)	72.9%[h] (62.8, 80.5)	10 (1%)	73 (18%)	93.4% (87.5, 96.5)
A/H1N1	23 (1.4%)	81 (7.3%)	80.9% (69.4, 88.5)[i]	0	0	—
A/H3N2	4 (0.2%)	27 (2.4%)	90.0% (71.4, 97.5)	4 (0.5%)	48 (12%)	96.0% (89.4, 98.5)
B	29 (1.8%)	35 (3.2%)	44.3% (6.2, 67.2)	6 (0.7%)	31 (7%)	90.5% (78.0, 95.9)

[a] D153-P501 and AV006 data are for subjects who received two doses of study vaccine.
[b] In children 12 through 35 months of age
[c] In children 15 through 71 months of age
[d] NCT00192244; see www.clinicaltrials.gov
[e] NCT00192179; see www.clinicaltrials.gov
[f] Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.
[g] Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis.
[h] For D153-P501, influenza circulated through 12 months following vaccination.
[i] Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, children remained in the same treatment group as in Year 1 and received a single dose of FluMist or placebo. During the second year, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine, A/Wuhan/359/95; FluMist demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

14.2 Immune Response Study of FluMist Quadrivalent in Children and Adolescents

A multicenter, randomized, double-blind, active-controlled, non-inferiority study (MI-CP208) was performed to assess the immunogenicity of FluMist Quadrivalent compared to FluMist (active control) in children and adolescents 2 through 17 years of age. A total of 2312 subjects were randomized by site at a 3:1:1 ratio to receive either FluMist Quadrivalent or one of two formulations of comparator vaccine FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage or a B strain of the Victoria lineage).

Children 2 through 8 years of age received 2 doses of vaccine approximately 30 days apart; children 9 years of age and older received 1 dose. For children 2 through 8 years of age with a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and at 28 days after the first dose. For children 2 through 8 years of age without a history of influenza vaccination, immunogenicity assessments were performed prior to vaccination and 28 days after the second dose. For children 9 years of age and older, immunogenicity assessments were performed prior to vaccination and at 28 days post vaccination.

Immunogenicity was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.3 Effectiveness Study of FluMist in Adults

AV009 was a U.S. multi-center, randomized, double-blind, AF-SPG placebo-controlled trial to evaluate effectiveness of FluMist in adults 18 through 64 years of age without high-risk medical conditions over the 1997-1998 influenza season. Participants were randomized 2:1 (vaccine: placebo). Cultures for influenza virus were not obtained from subjects in the trial, thus efficacy against culture-confirmed influenza was not assessed. The A/Wuhan/359/95 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/05/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was the reduction in the proportion of participants with one or more episodes of any febrile illness, and prospective secondary endpoints were severe febrile illness and febrile upper respiratory illness. Effectiveness for any of the three endpoints was not demonstrated in a subgroup of adults 50 through 64 years of age. Primary and secondary effectiveness endpoints from the age group 18 through 49 years are presented in Table 8. Effectiveness was not demonstrated for the primary endpoint in adults 18 through 49 years of age.

Table 8: Effectiveness of FluMist to Prevent Febrile Illness in Adults 18 through 49 Years of Age During the 7-Week Site-Specific Outbreak Period (Study AV009)

Endpoint	FluMist N=2411[a] n (%)	Placebo N=1226[a] n (%)	Percent Reduction	(95% CI)
Participants with one or more events of:[b]				
Primary Endpoint:				
Any febrile illness	331 (13.73)	189 (15.42)	**10.9**	(-5.1, 24.4)
Secondary Endpoints:				
Severe febrile illness	250 (10.37)	158 (12.89)	**19.5**	(3.0, 33.2)
Febrile upper respiratory illness	213 (8.83)	142 (11.58)	**23.7**	(6.7, 37.5)

[a] Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).
[b] The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Effectiveness was shown in a post-hoc analysis using an endpoint of CDC-ILI in the age group 18 through 49 years of age.

14.4 Immune Response Study of FluMist Quadrivalent in Adults

A multicenter, randomized, double-blind, active-controlled, and non-inferiority study (MI-CP185) was performed to assess the safety and immunogenicity of FluMist Quadrivalent compared to those of FluMist (active control) in adults 18 through 49 years of age. A total of 1800 subjects were randomized by site at a 4:1:1 ratio to receive either 1 dose of FluMist Quadrivalent or 1 dose of one of two formulations of comparator vaccine, FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage and a B strain of the Victoria lineage).

Immunogenicity in study MI-CP185 was evaluated by comparing the 4 strain-specific serum hemagglutination inhibition (HAI) antibody geometric mean titers (GMTs) post dosing and provided evidence that the addition of the second B strain did not result in immune interference to other strains included in the vaccine.

14.5 Concomitantly Administered Live Virus Vaccines

In Study AV018, concomitant administration of FluMist, MMR (manufactured by Merck & Co., Inc.) and Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.) was studied in 1245 subjects 12 through 15 months of age. Subjects were randomized in a 1:1:1 ratio to MMR, Varicella vaccine and AF-SPG placebo (group 1); MMR, Varicella vaccine and FluMist (group 2); or FluMist alone (group 3). Immune responses to MMR and Varicella vaccines were evaluated 6 weeks post-vaccination while the immune responses to FluMist were evaluated 4 weeks after the second dose. No evidence of interference with immune response to measles, mumps, rubella, varicella and FluMist vaccines was observed.

15 REFERENCES

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992 – 1993 and 1993 – 1994 influenza vaccines. N Engl J Med 1998;339(25):1797-802.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FluMist Quadrivalent is supplied in a package of 10 pre-filled, single-dose (0.2 mL) intranasal sprayers. The single-use intranasal sprayer contains no natural rubber latex.
NDC 66019-300-10

16.2 Storage and Handling

The cold chain [2-8°C (35-46°F)] must be maintained when transporting FluMist Quadrivalent.

FLUMIST QUADRIVALENT SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT AND UNTIL USE. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.
DO NOT FREEZE.

Once FluMist Quadrivalent has been administered or has expired, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Information for Patients and Their Caregivers).

Vaccine recipients or their parents/guardians should be informed by the healthcare provider of the potential benefits and risks of FluMist Quadrivalent and the need for two doses at least 1 month apart in children 2 through 8 years of age who have not previously received influenza vaccine. The healthcare provider should provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization.

17.1 Asthma and Recurrent Wheezing

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children younger than 5 years of age, also ask if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group. The vaccinee or their parent/guardian should be informed that there may be an increased risk of wheezing associated with FluMist Quadrivalent in persons younger than 5 years of age with recurrent wheezing and persons of any age with asthma [see *Warnings and Precautions (5.2)*].

17.2 Vaccination with a Live Virus Vaccine

Vaccine recipients or their parents/guardians should be informed by the healthcare provider that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

The vaccine recipient or their parent/guardian should be instructed to report adverse reactions to their healthcare provider.

Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878
1-877-633-4411

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