A Phase 4 Double-blind Study to Evaluate the Shedding and Immunogenicity of Trivalent and Quadrivalent Formulations of FluMist in Children 24 to < 48 Months of Age

Sponsor Protocol Number: D2560C00013

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Investigational Product: Quadrivalent live attenuated influenza vaccine (Q/LAIV)

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca
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Medical Monitor: [redacted]

Contract Research Organization: [redacted]

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PROTOCOL SYNOPSIS

TITLE

A Phase 4 Double-blind Study to Evaluate the Shedding and Immunogenicity of Trivalent and Quadrivalent Formulations of FluMist in Children 24 to < 48 Months of Age

HYPOTHESES

No formal hypotheses will be tested in this study; detailed descriptive statistics will be provided for all endpoints. This includes descriptions of shedding characteristics, immune responses, and safety. Potential relationships among these measures will be explored.

OBJECTIVES

Primary objective:

To describe the level of serum hemagglutination inhibition (HAI) antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains.

Secondary objectives:

1. To describe the proportion of individuals who shed vaccine viruses
2. To describe the duration of shedding of vaccine viruses
3. To quantify the titer of shed vaccine viruses
4. To describe the level of serum neutralizing antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains
5. To describe the level of mucosal antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains.
6. To describe the safety and tolerability of trivalent and quadrivalent formulations of FluMist.

Exploratory objectives:

1. To further characterize the serum and mucosal immune responses following vaccination
2. To compare results of shedding analyses using culture-based methods and quantitative real-time polymerase chain reaction (qRT-PCR).

STUDY ENDPOINTS

Primary endpoints:

- The proportion of subjects with strain-specific HAI seroconversion rates (≥ 4-fold increase) from baseline through Days 28 and 56 by treatment group.

Secondary endpoints:

- The proportion of subjects who shed vaccine by formulation, strain, dose number, and baseline serostatus (by qRT-PCR)
- The number of days of shedding by formulation, strain, dose number, and baseline serostatus (by qRT-PCR)
- Viral titer by day, strain, dose number and baseline serostatus (by qRT-PCR)
- The proportion of subjects with strain-specific neutralizing antibody seroconversion rates (≥ 4-fold increase) from baseline through Days 28 and 56, by baseline serostatus
- The proportion of subjects with strain-specific nasal immunoglobulin A (IgA) increase (≥ 2-fold increase) from baseline through Days 28 and 56
- The proportion of subjects with any strain-specific antibody response defined as a ≥ 4-fold increase in HAI antibodies or a ≥ 4-fold increase neutralizing antibodies or ≥ 2-fold increase in IgA antibodies
- The proportion of subjects with solicited symptoms experienced from administration of investigational product through 14 days post last vaccination
- The proportion of subjects with treatment-emergent adverse events (AEs) experienced from administration of investigational product through 28 days post last vaccination

- The proportion of subjects with treatment-emergent serious adverse events (SAEs) experienced from administration of investigational product through 28 days post last vaccination.

Exploratory endpoints:

- Endpoints to be determined based on specific assays to characterize immune responses
- The proportion of subjects who shed vaccine by formulation, strain, dose number, and baseline serostatus (by culture-based methods)
- The number of days of shedding by formulation, strain, dose number, and baseline serostatus (by culture-based methods)
- Viral titer by day, strain, dose number, and baseline serostatus (by culture-based methods).

STUDY DESIGN

This randomized, double-blind, multi-center study will enroll approximately 200 children 24 to < 48 months of age, at screening. Subjects will be randomized (~65 subjects per group) at 1:1:1 ratio to receive two doses of either 1) a quadrivalent formulation of FluMist®. Strains included in the vaccine will be based on the World Health Organization (WHO) and Vaccines and Related Biological Products Advisory Committee (VRBPAC) 2017-2018 Northern Hemisphere recommendations and will include a replacement H1N1 strain (A/Slovenia/2903/2015) and A/New Caledonia/7/2014(H3N2), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage); 2) a second quadrivalent formulation of FluMist. Strains included in the vaccine will be based on the 2015-2016 licensed formulation of FluMist: A/Bolivia/559/2013 (H1N1), A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage); or 3) a trivalent formulation of FluMist. Strains included in the vaccine will be based on the strains recommended by the WHO and VRBPAC for the 2015-2016 season: A/Bolivia/559/2013 (H1N1), A/Switzerland/9715293/2013 (H3N2), and B/Phuket/3073/2013 (B/Yamagata-lineage).

Subjects will be screened for the study within 75 days prior to randomization. Randomization will be stratified according to whether the subject ever received prior influenza vaccination (Yes/No). It is intended that approximately 50% of randomized subjects will not have been previously vaccinated. All subjects will receive an initial dose of investigational product at the site on Study Day 1. Subjects will receive a second dose on Study Day 28.

Nasal samples for evaluation of shedding will be obtained from each subject on Days 2, 3, 4, 5, and 7 after Dose 1 and on Days 2, 4 and 6 after Dose 2. Blood and nasal samples for the assessment of immune responses will be obtained on Day 1 prior to dosing, on Day 28 (prior to dosing) and on Day 56.

Safety evaluation will consist of the collection of solicited symptoms during the 14-day period after each dose, and AEs, SAEs, and concomitant medication use through the 28-day period post each dose. On Days 1 and 28, subjects' legal representatives will be given a temperature log to record daily temperature during the 14 days post dosing. Four telephone contacts for safety follow-up will occur between Days 15-16, Days 21-23, Days 42-44 and 48-50.

The study will be conducted during the influenza "off-season" in the US. It is anticipated that enrollment will start around the beginning of June 2017. The duration of subject participation is approximately 3 to 4 months. After completion of the study all subjects will be offered and strongly encouraged to receive one or two doses (depending on their vaccination history) of an inactivated influenza vaccine approved for use in the US for the 2017-2018 influenza season.

TARGET SUBJECT POPULATION

Male and female children 24 months to < 48 months of age, at screening.

TREATMENT GROUPS AND REGIMENS

Subjects will be randomly assigned in a 1:1:1 ratio to receive a single dose on Study Days 1 and 28 of either FluMist Quadrivalent 2017-2018 formulation (approximately 65 subjects), FluMist Quadrivalent 2015-2016 formulation (approximately 65 subjects), or FluMist trivalent 2015-2016 formulation (approximately 65 subjects) by intranasal spray.

STATISTICAL METHODS

Sample size:

HAI Immunogenicity:

It is expected that for each analysis of immunogenicity, 90% of subjects will be evaluable. The resulting sample size of ~60 evaluable subjects per arm would produce a 95% confidence interval (CI) within 14 percentage points of the observed proportion of subjects seroconverting. An estimate of 40% for the proportion of subjects seroconverting was used for the purposes of CI calculations.

Assuming that the seroconversion rate in the A/Bolivia H1N1 strain (2015-2016 formulation) ranged from 10% to 40%, based on 25% of the rate difference, the sample size of 60 evaluable subjects per arm would result in approximately 80% power to detect a statistically significant difference in the seroconversion rate comparing the A/Bolivia H1N1 strain (2015-2016 formulation) to the replacement H1N1 strain selected for the 2017-2018 vaccine formulation (A/Slovenia/2903/2015). The table below summarizes the study power based on various assumptions.

Power Calculations

Percentage of Subjects with Immune Response		Absolute Difference (%)	N Per Group	Power (%)
A/Bolivia Strain	A/Slovenia Strain			
10	25	15	60	58
	30	20	60	78
	35	25	60	91
	40	30	60	97
	50	40	60	99
20	35	15	60	45
	40	20	60	67
	45	25	60	84
	50	30	60	94
30	30	45	60	39
	50	20	60	61
	55	25	60	79
	60	30	60	92
40	55	15	60	37
	60	20	60	59
	65	25	60	79
	70	30	60	92

Shedding:

It is expected that for each analysis of shedding, 90% of subjects will be evaluable. The resulting sample size of ~60 evaluable subjects per arm would produce a 95% CI within 15 percentage points of the observed proportion of subjects who shed. An estimate of 50% for the proportion of subjects shedding influenza vaccine virus was used for the purposes of sample size calculations, as this value was statistically conservative (ie, had the highest variability).

Statistical analyses:

Primary endpoint analysis:

The primary endpoint is the strain-specific HAI antibody seroconversion rates, defined as at least 4-fold increase from baseline through Day 28 and Day 56. The proportion of subjects who had seroconversion will be summarized at Days 28 and 56 visits by strain and treatment. Its corresponding 95% exact CI will be provided.

The difference in proportion between the A/Bolivia H1N1 strain (2015-2016) and the replacement H1N1 strain

selected for the 2017-2018 vaccine formulation will be tested by Cochran–Mantel–Haenszel (CMH) test adjusting for the prior flu vaccination status. If the number of subjects in any stratum is too small, Fisher's exact test will be used without adjusting for the prior flu vaccination status. If it is evident that the proportion is confounded with some of other demographic and baseline disease characteristic variables, the confounding variables will be adjusted.

Secondary endpoint analyses:

Geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) of HAI antibody, neutralizing antibody, and nasal IgA will be summarized by strain and treatment at Days 28 and 56 visits. Corresponding 95% CI will be calculated assuming log normal distribution.

Using the results of the qRT-PCR method, the proportion of subjects who shed vaccine will be summarized by treatment, strain, and dose number based on the same method as for the primary analysis. The number of days of shedding will be summarized descriptively by treatment, strain, dose number, and baseline serostatus. The viral titer will be calculated by day, strain, dose number, and baseline serostatus.

The strain-specific neutralizing antibody seroconversion rates (≥ 4-fold increase from baseline), and strain-specific nasal IgA increase (≥ 2-fold increase from baseline) at Days 28 and 56 visits will be summarized descriptively using the same method as for the primary endpoint.

Exploratory endpoint analyses:

Analyses of immune response will be conducted based on newly identified specific assays to characterize immune response.

Using the results of culture-based methods, the proportion of subjects who shed vaccine, the number of days of shedding, and the viral titer will be summarized using the same methods as described for secondary endpoint analyses.

Subgroup analyses:

Subgroup analysis by baseline serostatus and prior vaccination status will be conducted for primary and secondary endpoints.

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
att	attenuated
BD	Becton Dickinson (Accuspray™)
ca	cold adapted
CDC	Centers for Disease Control and Prevention
CI	confidence interval
eCRF	electronic case report form
EDC	electronic data capture
FFU	fluorescent focus unit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAI	hemagglutination inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
qRT-PCR	quantitative real-time polymerase chain reaction
SAE	serious adverse event
SID	subject identification
TIV	trivalent inactivated vaccine
ts	temperature sensitive
US FDA	United States Food and Drug Administration
USA	United States of America
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 INTRODUCTION

1.1 Disease Background

Influenza is a highly contagious, acute febrile illness of global importance. It is the most common vaccine-preventable disease in the developed world. In humans, influenza illness is caused mainly 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 (Yamagata and Victoria). A/H3N2 and A/H1N1 are the 2 influenza A subtypes that have circulated and caused human disease since 1977 (Kilbourne, 2006).

Uncomplicated influenza illness in healthy individuals is generally a self-limited febrile respiratory disease of 3 to 7 days' duration, sometimes with persistence of cough and malaise for several weeks. Influenza illness is characterized by the abrupt onset of signs and symptoms such as fever, myalgia, headache, malaise, chills, nonproductive cough, anorexia, sore throat, and rhinitis. Children may also have otitis media, croup, nausea, and vomiting. Complications of influenza include primary influenza viral pneumonia; exacerbation of underlying medical conditions such as cardiac or pulmonary disease, including asthma or chronic obstructive pulmonary disease; and secondary bacterial infections such as pneumonia, sinusitis, or otitis. Young children can have febrile seizures or symptoms mimicking bacterial sepsis with high fevers. Rarely, influenza virus infection has been associated with encephalopathy, transverse myelitis, myositis, rhabdomyolysis, myocarditis, pericarditis, and, in children, Reye syndrome (Fiore et al, 2007; Ramet et al, 2007).

1.2 FluMist Quadrivalent (MEDI3250) Background

FluMist® Quadrivalent is an intranasally administered influenza vaccine that was developed as a successor to the trivalent seasonal vaccine, FluMist (also referred to as trivalent live attenuated influenza vaccine [T/LAIV]). Refer to the current package insert for additional details (Appendix 10.4).

The active agents of FluMist Quadrivalent consist of 2 cold adapted (*ca*), temperature-sensitive (*ts*), attenuated (*att*) reassortant influenza strains of type A (ie, A/H1N1 and A/H3N2), 1 *ca/ts/att* reassortant influenza strain of type B-Victoria, and 1 *ca/ts/att* reassortant influenza strain of type B-Yamagata. The types A and B master donor viruses (MDVs), from which the reassortant 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 unique biological phenotypes of cold adaptation, temperature sensitivity, and attenuation, which distinguish these viruses from wild-type influenza viruses.

While the commercial formulation of FluMist Quadrivalent can be stored at 2°C to 8°C, the vaccine to be used in this study will require storage in a freezer.

1.3 Summary of Nonclinical Experience

A number of nonclinical studies of FluMist have been conducted in ferrets, as the ferret has been proven to be a good model for studying influenza.

Primary pharmacodynamic studies in ferrets have been conducted to evaluate the replication and immunogenicity of live attenuated influenza vaccine strains. Results of replication, immunogenicity, and challenge studies in ferrets demonstrated that vaccination with trivalent FluMist protected animals following challenge with wild-type virus; vaccine-induced immunity in these animals substantially decreased replication of the wild-type virus in the lungs as well as the upper airways. Studies with FluMist Quadrivalent demonstrated that it was equally immunogenic, had similar replication kinetics, and conferred equally efficient protection following challenge with wild-type viruses.

A single- and repeat-dose toxicology study was conducted in ferrets to investigate the potential adverse effects of trivalent FluMist given 1 or 3 times to ferrets over a 15-week period. The regimen consisted of up to 3 human doses of trivalent FluMist administered intranasally at Weeks 0, 4, and 14. This dosing regimen is in compliance with International Council for Harmonisation (ICH) Guideline M3, which recommends a toxicity study duration of 3 months with a product dosing duration of up to 1 month. No clinical indications of toxicity were manifest during the course of the study from any of the parameters evaluated. No test material-related toxicity was identified in the major organs examined histopathologically, except for increased incidence of acute, multifocal, suppurative inflammation of the nasal turbinates, and lymph node hyperplasia in animals at interim necropsy. These findings were most likely due to inoculation 3 days prior to necropsy and the antigenic responses of the animals to the inoculum. Overall, in this study and a similar repeat-dose study conducted with FluMist Quadrivalent in ferrets, the vaccine was well tolerated.

Studies with trivalent FluMist were conducted to evaluate reproductive and developmental toxicology in 2 different animal models (rat and ferret). Results of the study conducted with rats indicated that exposure to trivalent FluMist once prior to mating and once during

pregnancy did not produce any maternal toxicity or affect the reproductive capacity of the dam. These exposures did not produce embryo-fetal toxicity in near-term fetuses or pups evaluated for 21 days postpartum. Results of a similar study in which quadrivalent FluMist was administered 3 times prior to mating and again 3 times during gestation showed no safety concerns.

The study in ferrets involved intranasal administration of trivalent FluMist to pregnant ferrets at 4 different time points during gestation. No vaccine treatment-related effects were observed with respect to maternal mortality, clinical observations, or body weight during gestation, nor were there any treatment-related effects observed in fetal parameters or in maternal macroscopic pathology that could be attributed to the intranasal instillation of trivalent FluMist.

The potential for ocular toxicity resulting from the inadvertent instillation of trivalent FluMist into the eye was evaluated in 2 ocular toxicity studies in rabbits using a standard Draize test. Neither study elicited results consistent with ocular toxicity.

The results of the nonclinical studies performed with trivalent FluMist and FluMist Quadrivalent collectively demonstrate that the vaccine has a favorable safety and tolerability profile.

1.4 Summary of Clinical Experience

In over 60 clinical studies, more than 120,000 subjects from 6 weeks to > 90 years of age have been administered MedImmune's egg-produced vaccine, FluMist. These studies were designed to evaluate the safety, efficacy, and immunogenicity of the vaccine among various study populations, including > 90,000 children and adolescents 6 weeks to 17 years of age and > 30,000 adults 18 to > 90 years of age. In these studies, FluMist was found to be generally safe and well tolerated. In healthy adults 18 through 64 years of age, FluMist recipients reported higher rates of runny nose (44%) and sore throat (26%) than placebo recipients (27% and 17%, respectively), with a median event duration of 1 day regardless of treatment received. Other symptoms, including cough, headache, chills, muscle aches, and tiredness/weakness occurred less often and at similar rates between the treatment groups. Low-grade fever (temperature > 100ºF) occurred at a similarly low rate for FluMist and placebo recipients (1.3% and 1.5%, respectively).

The clinical development of FluMist Quadrivalent included 2 pivotal, double-blind studies conducted in the USA, one in children and adolescents 2 to 17 years of age (MI-CP208;

2,312 subjects) and one in adults 18 through 49 years of age (MI-CP185; 1,800 subjects), both of which demonstrated that the immune responses generated by FluMist Quadrivalent were noninferior to the immune responses generated by FluMist and the safety and tolerability profiles of the 2 vaccines were similar in both populations.

In addition to the clinical study experience, over 200,000 doses of FluMist have been administered in post-marketing studies, and more than [redacted] doses of FluMist have been distributed commercially worldwide from initial licensure in 2003. FluMist was initially approved for use in healthy individuals 5 to 49 years of age; however, the age indication was expanded to include children 24 to 59 months of age prior to the 2007-2008 influenza season. For this study population, there are no risks anticipated other than those described in the Package Insert (Appendix 4).

The 2016-2017 FluMist Quadrivalent Package Insert (Appendix 9.4) provides the most current safety data and product use information.

1.5 Rationale for Conducting the Study

In light of concerns regarding the low effectiveness of FluMist Quadrivalent against influenza A(H1N1)pdm09 strains in the United States during the 2013–2014 and 2015–2016 influenza seasons, the US Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation on June 22, 2016 that FluMist Quadrivalent should not be used in the US for the 2016-2017 influenza season (Grohskopf et al, 2016). The vaccine remains licensed for use by the US FDA as the agency considers that "the benefits of FluMist Quadrivalent outweigh any potential risks." (US FDA, 2016). This study is being conducted to describe the immunogenicity, safety, and viral shedding of a new A/H1N1 strain (A/Slovenia/2903/2015) that will be incorporated into the FluMist Quadrivalent for the 2017-2018 influenza season to the immunogenicity, safety, and viral shedding of the previous A/H1N1 strain (A/Bolivia/559/2013) that was included in the vaccine in the 2015-2016 and 2016-2017 influenza seasons. The results from this study will be included as part of a larger submission of data to the ACIP as they consider whether to re-issue a recommendation for use of FluMist Quadrivalent in the US.

1.6 Benefit-Risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Considerations relating to benefits:

In placebo-controlled studies with greater than 13,000 pediatric subjects conducted during 7 influenza seasons from 1996 through 2003 in Europe, Latin America, Africa, Asia/Oceania, and the US, trivalent FluMist protection against laboratory-confirmed influenza illness was demonstrated in a broad age range of children. In these placebo controlled studies, trivalent FluMist consistently demonstrated high rates of efficacy against culture-confirmed influenza caused by wild-type virus strains antigenically matched to those in the vaccine (ranging from 62.2% to 100%) and also against all strains regardless of antigenic match. In 3 trivalent inactivated vaccine (TIV)-controlled studies involving > 12,000 children, the vaccine consistently demonstrated statistically significant superior efficacy relative to TIV against culture-confirmed influenza illness caused by wild-type virus strains antigenically matched to those in the vaccine as well as against illness caused by all strains regardless of antigenic match. Compared to TIV, trivalent FluMist reduced the number of cases of culture-confirmed influenza illness by 35% to 53% for illness due to matched strains and by 32% to 55% for illness due to all strains regardless of antigenic match.

Since incorporation of 2009 H1N1pdm09 strains into the vaccine, however, the effectiveness of the vaccine against this influenza subtype has been less clear. While the vaccine has demonstrated effectiveness against H3N2 and B strains, effectiveness against H1N1 strains has varied by country and by influenza season. Based on a study from the Centers for Disease Control and Prevention (CDC), the vaccine appeared effective against H1N1 when given as a monovalent vaccine in 2009-2010. However, based on a retrospective evaluation of the CDC data for 2010-2011 season, the trivalent vaccine did not appear to have been effective against H1N1 strains in the US. For the 2013-2014 season, the quadrivalent vaccine was not effective for H1N1 strains in the US in studies performed by both the CDC and MedImmune, but the trivalent formulation does appear to have been effective in Canada, based on both a test-negative study and a cluster-randomized trial. Based on the findings from both 2010-2011 and 2013-2014 seasons, MedImmune replaced the H1N1 component of the vaccine (A/California/07/2009) with a more heat stable strain (A/Bolivia/559/2013). Replacement of the A/California strain may have improved the effectiveness of the vaccine, however, the effectiveness of the vaccine against A/H1N1pdm09 strains was still lower than expected during the 2015-2016 influenza season, and MedImmune plans to replace this strain with a new H1N1 strain (A/Slovenia/2903/2015) for the 2017-2018 season.

Study participants will be offered and encouraged to take an optional dose of a licensed inactivated influenza vaccine at the end of the study in order to maximize the likelihood that they are protected against influenza.

Considerations relating to risks:

There are two important identified risks for FluMist, wheezing in children under the age of 2 years and hypersensitivity (including anaphylaxis). Data from clinical studies found vaccine recipients < 24 months of age in both TIV and trivalent FluMist study treatment groups had higher rates of medically significant wheezing than vaccine recipients ≥ 24 months of age. In one study, FluMist recipients < 24 months of age had increased rates of medically significant wheezing compared to TIV recipients. For vaccine recipients ≥ 24 months of age, no statistically significant increases were observed between treatment groups in medically significant wheezing, with the point estimates generally being higher for TIV compared to trivalent FluMist. FluMist is not indicated for children under the age of 2 years. Hypersensitivity reactions can occur with all vaccines and typically occur in genetically predisposed individuals. The likelihood of a hypersensitivity reaction to FluMist may be decreased by not giving the product to patients with known allergies to components of the product. In addition to the important potential risks, the most common clinical trial solicited adverse reactions (≥ 10% in FluMist recipients and at least 5% greater than in placebo recipients) 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).

1.7 Research Hypotheses

No formal hypotheses will be tested in this study; detailed descriptive statistics will be provided for all endpoints. This includes descriptions of shedding characteristics, immune responses, and safety. Potential relationships among these measures will be explored.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To describe the level of serum hemagglutination inhibition (HAI) antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains

2.1.2 Secondary Objectives

1. To describe the proportion of individuals who shed vaccine viruses
2. To describe the duration of shedding of vaccine viruses
3. To quantify the titer of shed vaccine viruses
4. To describe the level of serum neutralizing antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains
5. To describe the level of mucosal antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains
6. To describe the safety and tolerability of trivalent and quadrivalent formulations of FluMist

2.1.3 Exploratory Objectives

1. To further characterize the serum and mucosal immune responses following vaccination
2. To compare results of shedding analyses using culture-based methods and quantitative real-time polymerase chain reaction (qRT-PCR)

2.2 Study Endpoints

2.2.1 Primary Endpoint

The proportion of subjects with strain-specific HAI seroconversion rates (≥ 4-fold increase) from baseline through Days 28 and 56 by treatment group.

2.2.2 Secondary Endpoints

1. The proportion of subjects who shed vaccine by formulation, strain, dose number, and baseline serostatus (by quantitative real-time polymerase chain reaction [qRT-PCR])
2. The number of days of shedding by formulation, strain, dose number, and baseline serostatus (by qRT-PCR)
3. Viral titer by day, strain, dose number, and baseline serostatus (by qRT-PCR)
4. The proportion of subjects with strain-specific neutralizing antibody seroconversion rates (≥ 4-fold increase) from baseline through Days 28 and 56, by baseline serostatus
5. The proportion of subjects with strain-specific nasal Immunoglobulin A (IgA) increase (≥ 2-fold increase) from baseline through Days 28 and 56
6. The proportion of subjects with any strain-specific antibody response defined as a ≥ 4-fold increase in HAI antibodies or a ≥ 4-fold increase neutralizing antibodies or ≥ 2-fold increase in IgA antibodies
7. The proportion of subjects with solicited symptoms experienced from administration of investigational product through 14 days post last vaccination

8. The proportion of subjects with treatment-emergent adverse events (AEs) experienced from administration of investigational product through 28 days post last vaccination
9. The proportion of subjects with treatment-emergent serious adverse events (SAEs) experienced from administration of investigational product through 28 days post last vaccination.

2.2.3 Exploratory Endpoints

1. Endpoints to be determined based on specific assays to characterize immune responses
2. The proportion of subjects who shed vaccine by formulation, strain, dose number, and baseline serostatus (by culture-based methods)
3. The number of days of shedding by formulation, strain, dose number, and baseline serostatus (by culture-based methods)
4. Viral titer by day, strain, dose number, and baseline serostatus (by culture-based methods).

3 STUDY DESIGN

3.1 Description of the Study

This randomized, double-blind, multi-center study will enroll approximately 200 children 24 to < 48 months of age, at screening. Subjects will be randomized (~65 subjects per group) at 1:1:1 ratio to receive two doses of either 1) a quadrivalent formulation of FluMist. Strains included in the vaccine will be based on the WHO and VRBPAC 2017-2018 Northern Hemisphere recommendations and will include a replacement H1N1 strain (A/Slovenia/2903/2015) and A/New Caledonia/71/2014 (H3N2), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage); 2) a second quadrivalent formulation of FluMist. Strains included in the vaccine will be based on the 2015-2016 licensed formulation of FluMist: A/Bolivia/559/2013 (H1N1), A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage); or 3) a trivalent formulation of FluMist. Strains included in the trivalent vaccine will be based on the strains recommended by the WHO and VRBPAC for the 2015-2016 season: A/Bolivia/559/2013 (H1N1), A/Switzerland/9715293/2013 (H3N2), and B/Phuket/3073/2013 (B/Yamagata-lineage).

Subjects will be screened for the study within 75 days prior to randomization. Randomization will be stratified according to whether the subject ever received prior influenza vaccination (Yes/No). It is intended that approximately 50% of randomized subjects will not have been previously vaccinated. All subjects will receive an initial dose of investigational product at the site on Study Day 1. Subjects will receive a second dose on Study Day 28.

Nasal samples for evaluation of shedding will be obtained from each subject on Days 2, 3, 4, 5, and 7 after Dose 1 and on Days 2, 4, and 6 after Dose 2. Blood and nasal samples for the assessment of immune responses will be obtained on Day 1 prior to dosing, on Day 28 (prior to dosing) and on Day 56.

Safety evaluation will consist of the collection of solicited symptoms during the 14-day period after each dose, and AEs, SAEs, and concomitant medication use through the 28-day period post each dose. On Days 1 and 28, subjects' legal representatives will be given a temperature log to record daily temperature during the 14 days post dosing. Four telephone contacts for safety follow-up will occur between Days 15-16, Days 21-23, Days 42-44 and Days 48-50.

The study will be conducted during the influenza "off-season" in the US. It is anticipated that enrollment will start around the beginning of June 2017. The duration of subject participation is approximately 3 to 4 months. After completion of the study all subjects will be offered and strongly encouraged to receive one or two doses (depending on their vaccination history) of an inactivated influenza vaccine approved for use in the US for the 2017-2018 influenza season.

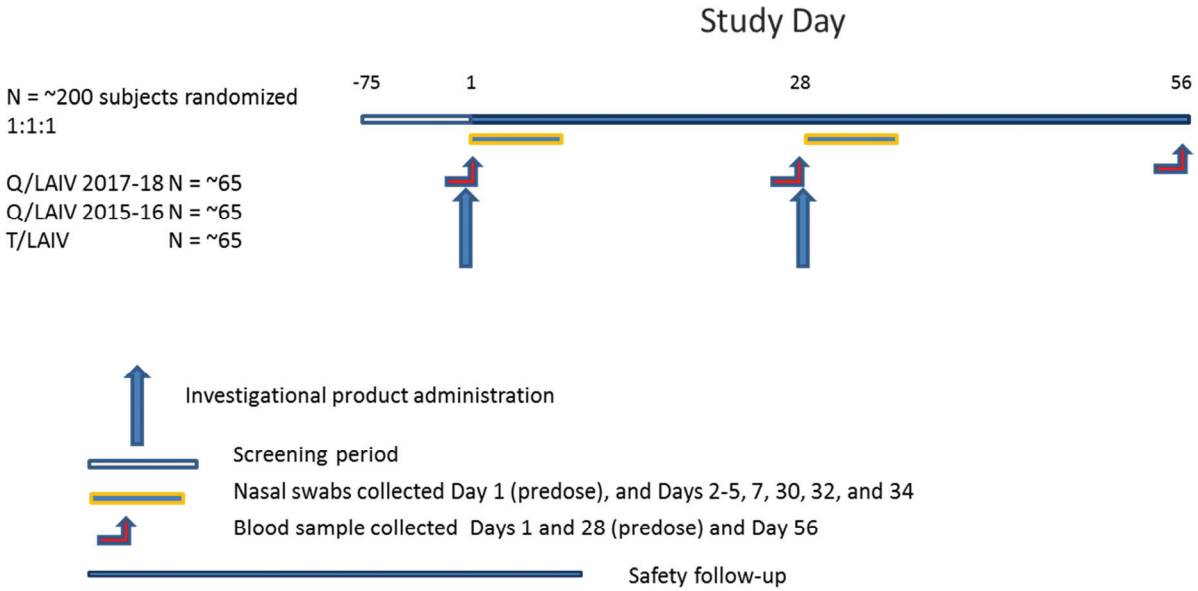

Figure 3.1-1 Study Flow Diagram

Q/LAIV = quadrivalent live attenuated influenza vaccine; T/LAIV = trivalent live attenuated influenza vaccine

The endpoints to be measured in this study are described in Section 2.2.

3.1.1 Treatment Regimen

Subjects will be randomly assigned in a 1:1:1 ratio to receive a single dose on Study Days 1 and 28 of either FluMist Quadrivalent 2017-2018 formulation (approximately 65 subjects), FluMist Quadrivalent 2015-2016 formulation (approximately 65 subjects), or FluMist trivalent 2015-2016 formulation (approximately 65 subjects) by intranasal spray.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

Subjects enrolled in the study will receive two 0.2-mL doses of vaccine (0.1 mL per nostril) with the second dose administered approximately 4 weeks after the first dose. Each 0.2-mL dose will contain $10^{7\pm0.5}$ fluorescent focus units (FFU) of each vaccine strain. The dose volume and dose level are based on the United States Food and drug Administration (US FDA) approved indication for FluMist Quadrivalent. In order to fully characterize the immunogenicity and shedding of the vaccine strains, all subjects will receive two doses.

3.2.2 Rationale for Study Population

The study population of young children was selected as this age group has been shown to have the highest level of immune responses to live attenuated influenza vaccines (Coelingh et al, 2015) and to shed vaccine viruses at high titers (Mallory et al, 2011). As a result, this population will allow for comparisons of the immunogenicity and viral shedding of the new A/H1N1 strain (A/Slovenia/2903/2015) that will be incorporated into the FluMist Quadrivalent vaccine for the 2017-2018 influenza season to the immunogenicity and viral shedding of the previous A/H1N1 strain (A/Bolivia/559/2013) that was included in the vaccine in the 2015-2016 and 2016-2017 influenza seasons.

3.2.3 Rationale for Endpoints

Hemagglutination inhibition antibodies and neutralizing antibodies are induced by influenza vaccination and are standard assays recommended by Regulatory Authorities to evaluate the immunogenicity of different vaccine formulations (Committee for Medicinal Products for Human Use [CHMP], 2016). Additionally, for intranasally administered live attenuated vaccines, mucosal IgA responses have been associated with protective efficacy against influenza infection (Ambrose et al, 2012). The ability to successfully replicate in the nasopharynx is an important characteristic of live attenuated vaccines and is associated with the induction of immune responses. The extent and duration of replication can be assessed

through the serial collection of nasal samples in which the titer of vaccine virus can be quantified.

In combination, solicited symptoms, adverse events, and serious adverse events provide a clinically meaningful summary of both the safety and tolerability profile of FluMist vaccine formulations. Use of these endpoints, which have been widely used in previous FluMist studies, will also allow the safety data collected in this study to be compared to that collected in previous studies.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 200 subjects are planned for participation in the study.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Age 24 months to < 48 months of age at the time of screening.
2. Written informed consent and any locally required authorization (eg, data privacy) obtained from the legal representative prior to performing any protocol-related procedures, including screening evaluations.
3. Healthy by medical history and physical examination *or* presence of stable underlying chronic medical condition for which hospitalization has not been required in the previous year.
4. Child's legal representative able to be contacted by telephone throughout the study duration.
5. Child's legal representative is able to understand and comply with the requirements of the protocol, as judged by the investigator.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. History of allergic disease or reactions likely to be exacerbated by any component of the investigational product;
2. Acute illness or evidence of significant active infection (including fever ≥ 100.4°F [38.0°C]) at randomization;
3. History of asthma or history of recurrent wheezing;

4. Any drug therapy from 15 days prior to randomization or expected drug therapy through 28 days post last dose with the exception of chronic medications that have been well tolerated and were not initiated and/or did not have a dosage change within 90 days prior to randomization;
5. Any known immunosuppressive condition or immune deficiency disease; *Note: topical corticosteroids for uncomplicated dermatitis may be used throughout the study according to the judgment of the investigator; topical calcineurin inhibitors may be used in accordance with their package insert at entry and during study participation*
6. Current or expected receipt of immunosuppressive medications within a 28-day window around vaccination;
7. Use of aspirin or salicylate-containing medications within 28 days prior to randomization or expected receipt through 28 days after vaccination;
8. Use of antiviral agents with activity against influenza viruses within 48 hours prior to first dose of investigational product or anticipated use of such agents through the end of the study follow-up period;
9. Receipt of any nonstudy seasonal influenza vaccine within 90 days of Dose 1 or planned receipt of nonstudy seasonal influenza vaccine prior to 28 days after last vaccination;
10. Receipt of immunoglobulin or blood products within 90 days before randomization into the study or expected receipt during study participation;
11. Administration of intranasal medications within 10 days prior to randomization, or expected receipt through 10 days after administration of each dose of investigational product;
12. Any investigational agent from 28 days prior to randomization through the end of the study follow-up period;
13. Known or suspected mitochondrial encephalomyopathy;
14. History of Guillain-Barré syndrome.

Note: an individual who initially is excluded from study participation based on one or more of the above time-limited criteria may be reconsidered for enrollment once the condition has resolved as long as the subject continues to meet all other entry criteria and the same subject identification (SID) number is used.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (an interactive web response system, IWRS) and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive investigational product. Randomization will be stratified according to whether the subject received prior influenza vaccination (Yes/No). It is intended that approximately 50% of subjects randomized will not have been previously vaccinated.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment (withdrawal of consent). The subject's legal representative will be asked about the reason(s) and the presence of any adverse events (AEs). If possible, the subject will be seen and assessed by the investigator. Adverse events will be followed up; diary assessment worksheets should be returned by the subject's legal representative. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent from further treatment with investigational product
2. Lost to follow-up
3. An adverse event (AE) that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing or meets criteria for discontinuation from investigational product
4. Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5), the subject is lost to follow-up, or the subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Subjects will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject's legal representative may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Future Research

Samples obtained for future research will be labeled with a sample identification number linked to the SID number but will not be labeled with personal identifiers such as the subject's name. If the subject's legal representative withdraws consent for participating in the future research, the sponsor will locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject's legal representative consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 15 years after the end of the study in which they were collected. If the subject's legal representative chooses not to allow the study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

Table 4.2-1 shows all procedures to be conducted at the screening, treatment, and follow-up visits. Assessments should be performed in the order shown in the table.

Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.

Table 4.2-1 Schedule of Study Procedures

Visit (V) or Telephone Contact (TC)	V1	V2	V3	V4	V5	V6	V7	TC		V8	V9	V10	V11	TC		V12
Study Period	**Scr**	**Dose 1**	**Post Dose 1**							**Dose 2**	**Post Dose 2**					
Study Day	**-75 to 1**	**1**	**2**	**3**	**4**	**5**	**7**	**15 (+2)**	**21 (+2)**	**28 (+2)**	**30 (+2)**	**32 (+2)**	**34 (+2)**	**42 (+2)**	**48 (+2)**	**56 (± 2)**
Written informed consent/ assignment of SID number	X															
Verify eligibility criteria	X	X								X						
Medical history at screening	X															
Medical history update		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concom-itant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examina-tion including weight, height, and vital signs	X	X								X						

Table 4.2-1 Schedule of Study Procedures

Visit (V) or Telephone Contact (TC)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**TC**		**V8**	**V9**	**V10**	**V11**	**TC**		**V12**
Study Period	**Scr**	**Dose 1**	**Post Dose 1**							**Dose 2**	**Post Dose 2**					
Study Day	**-75 to 1**	**1**	**2**	**3**	**4**	**5**	**7**	**15 (+2)**	**21 (+2)**	**28 (+2)**	**30 (+2)**	**32 (+2)**	**34 (+2)**	**42 (+2)**	**48 (+2)**	**56 (± 2)**
Targeted physical examination[b]			X	X	X	X	X				X	X	X			X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize, assign investigational product via IWRS		X								X[d]						
Administer investigational product		**X**								**X**						
Observe at least 15 min post investigational product administration		X								X						

Table 4.2-1 Schedule of Study Procedures

Visit (V) or Telephone Contact (TC)	V1	V2	V3	V4	V5	V6	V7	TC		V8	V9	V10	V11	TC		V12
Study Period	**Scr**	**Dose 1**	**Post Dose 1**							**Dose 2**	**Post Dose 2**					
Study Day	**-75 to 1**	**1**	**2**	**3**	**4**	**5**	**7**	**15 (+2)**	**21 (+2)**	**28 (+2)**	**30 (+2)**	**32 (+2)**	**34 (+2)**	**42 (+2)**	**48 (+2)**	**56 (± 2)**
Collect nasal samples for shedding			X	X	X	X	X				X	X	X			
Collect nasal samples for immune response		X[a]								X[a]						X
Collect blood for assessment of immune responses		X[a]								X[a]						X
Provide thermom-eters and diary assessment worksheet		X								X[c]						
Collect and review diary assessment worksheet			X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]
Collect solicited		X	X	X	X	X	X			X	X	X	X			

Table 4.2-1 Schedule of Study Procedures

Visit (V) or Telephone Contact (TC)	V1	V2	V3	V4	V5	V6	V7	TC		V8	V9	V10	V11	TC		V12
Study Period	**Scr**	**Dose 1**	**Post Dose 1**							**Dose 2**	**Post Dose 2**					
Study Day	**-75 to 1**	**1**	**2**	**3**	**4**	**5**	**7**	**15 (+2)**	**21 (+2)**	**28 (+2)**	**30 (+2)**	**32 (+2)**	**34 (+2)**	**42 (+2)**	**48 (+2)**	**56 (± 2)**
symptoms																

AEs = adverse events; IWRS = interactive web response system; SAEs = serious adverse events; Scr = screen; SID = subject identification

[a] Collect prior to dosing.

[b] Targeted physical examination, if appropriate.

[c] Only provide thermometer if replacement is needed.

[d] Contact IWRS for assignment of investigational product kit number and sprayer number only, randomization not needed.

[e] Review diary assessment worksheet only.

[f] Collect diary assessment worksheet on Day 28 (± 2) for Days 1-15 and on Day 56 (± 2) for Days 28-42.

4.2.1 Screening Visit (Visit 1 [Days -75 to 1])

All screening procedures must be performed within 75 days before or on the same day as investigational product administration (Day -75 to Day 1). The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

1. Obtain written informed consent and appropriate privacy act document authorization
2. Assign an SID number
3. Verify eligibility criteria
4. Obtain screening medical history
5. Record concomitant medication use
6. Perform screening physical examination, including vital signs, height, and weight
7. Assess for AEs/SAEs.

4.2.2 Treatment Period, Dose 1 (Visit 2 [Day 1])

1. Verify eligibility criteria.
2. Review medical history, concomitant medication use (any new findings since screening), and perform physical examination (including height, weight, and temperature)
3. Assess for AEs/SAEs.
4. Randomize and assign investigational product kit number via IWRS..
5. Obtain nasal samples for immune responses prior to dosing.
6. Obtain blood for immune responses prior to dosing.
7. Administer investigational product.
8. Observe subject for a minimum of 15 minutes. Provide diary assessment workbook, thermometer, and instructions for completing the workbook. Ensure that the subject's legal representative understands how to take subject's temperature. Day 1 temperature is recorded by the subject's legal representative during the evening of Day 1 (day of investigational product administration). The diary assessment workbook will be used for the collection of body temperature and solicited symptoms and will be completed by the subject's legal representative to serve as a memory aid for future data collection by study staff during visits and telephone contacts. Diary assessment workbooks will be returned to the site at the study Day 28 visit.
9. Assess for post dose AEs/SAEs.

4.2.3 Follow-up Period, After Dose 1 (Visits 3 to 7 [Days 2, 3, 4, 5, 7])

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for AEs/SAEs
3. Update concomitant medications

4. Collect nasal samples for shedding evaluation
5. Review diary assessment and solicited symptoms.

4.2.4 Telephone Contact Follow-up After Dose 1 (Days 15 [+2], 21 [+2])

1. Update medical history
2. Assess AEs/SAEs
3. Update concomitant medications
4. Review diary assessment workbook information for all 14 days (at Day 15 [+2] telephone call).

4.2.5 Treatment Period, Dose 2 (Visit 8 [Day 28 (+2)])

1. Update medical history, perform physical examination including vital signs (see Section 4.3.1 for specifics) before administration of investigational product.
2. Assess AEs/ SAEs and concomitant medication use
3. Collect diary assessment workbooks for Days 1-14 (post Dose 1)
4. Verify ongoing eligibility (Section 4.1) before administration of investigational product
5. Obtain nasal sample for evaluation of immune response before administering Dose 2
6. Obtain blood for evaluation of immune response before administering Dose 2
7. Contact IWRS for assignment of investigational product kit number and sprayer number
8. Provide diary assessment workbook and instructions for completion. Ensure that the subject's legal representative understands how to contact the site to report AEs and how to take temperatures and fill out the diary assessment workbook. A thermometer is only provided if replacement is needed. The diary assessment workbook will be used for the collection of body temperature and solicited symptoms and will be completed by the subject's legal representative to serve as a memory aid for future data collection by study staff during visits and telephone contacts. Diary assessment workbooks will be returned to the site at the last subject visit (Day 56 ± 2).
9. Administer investigational product
10. Observe at least 15 minutes post investigational product administration
11. Assess for post dose AEs/SAEs.

4.2.6 Follow-up Period, After Dose 2 (Visits 9 to 11 [Days 30 (+2), 32 (+2), 34 (+2)])

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for AEs/SAEs
3. Update concomitant medications
4. Collect nasal samples for shedding evaluation
5. Review diary assessment and solicited symptoms.

4.2.7 Telephone Contact Follow-up After Dose 2 (Days 42 [+2], 48 [+2])

1) Update medical history
2) Assess AEs/SAEs
3) Update concomitant medications
4) Review diary assessment workbook information for all 14 days (at Day 42 [+2] telephone call).

4.2.8 Final Visit (Visit 12 [Day 56 +/- 2])

1) Update medical history, perform targeted physical examination if appropriate
2) Assess AEs/SAEs
3) Update concomitant medications
4) Collect diary assessment workbooks for Days 28-42
5) Obtain nasal sample for evaluation of immune response
6) Obtain blood for evaluation of immune response.

4.2.9 Optional Study Visit

Subjects will be offered and encouraged to receive commercial inactivated influenza vaccine as approved for the upcoming influenza season unless receipt is felt to be contraindicated according to the judgment of the investigator. The commercial inactivated influenza vaccine will be administered in accordance with the package insert. The optional dose(s) of influenza vaccine should be administered prior to the start of the influenza season. The optional study dose(s) must occur at least 28 days after Dose 2 has been administered. Dosing will be scheduled based on the availability of commercial inactivated influenza vaccine, the onset of influenza activity in the area, and at the convenience of the subject/legal representative and the site.

As with any vaccine, allergic reactions after administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. After vaccination, all participants will be observed for a minimum of 15 minutes by the study staff. Emergency management supplies (eg, AMBU bag, adrenaline [epinephrine], antihistamine) must be available for initial treatment of an allergic reaction if needed.

If subjects experience AEs following receipt of an optional dose of commercial influenza vaccine, the investigator will be advised to report them as required per local spontaneous postmarketing pharmacovigilance procedures. If the event is an SAE that has occurred within

the study duration, it should also be reported in accordance with Section 5.4 Reporting of SAEs.

4.3 Description of Study Procedures

4.3.1 Medical History and Physical Examination

Medical history by body system and physical examination, including vital signs (temperature [any route], heart rate, and respiratory rate), height and weight in appropriate units will be completed during screening and on Days 1 and 28, prior to dosing.

4.3.2 Clinical Laboratory Tests

No clinical laboratory tests will be performed.

4.3.3 Serum Immunogenicity Evaluation and Methods

Subjects will have 3 blood samples collected for serum influenza HAI antibody testing, serum influenza neutralizing antibody testing, and potentially other anti-influenza serology tests: one on Day 1 prior to receipt of investigational product, one on Day 28 (+ 2 days) prior to receiving Dose 2 of investigational product, and one on Day 56 (± 2 days; see time points Table 4.2-1). Serum will be separated and stored frozen at -20 ± 5°C or below until being batched and shipped to the central laboratory according to procedures specified in the Laboratory Manual. Serum can also be stored at -60°C or below.

Immune response evaluation will consist of serum HAI antibody titers and serum neutralizing antibody titers, both measurements to strains antigenically matched to those contained in the quadrivalent or trivalent vaccine formulation received. Additional assays may be performed to investigate immune responses to influenza or other respiratory viruses. Samples may also be retained for potential future testing for immune response to influenza if the subject's legal representative has given consent to potential future testing (no human genetic testing will be performed). Immunogenicity assays will be conducted following standard influenza HAI antibody and microneutralization assay procedures.

4.3.4 Shedding Evaluation and Methods

Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual. Nasopharyngeal swabs for quantification of influenza viral shedding will be obtained on Days 2, 3, 4, 5, 7, 30, 32, and 34 (see time points Table 4.2-1). All nasopharyngeal samples obtained from vaccinated subjects will have virus shedding quantified by qRT-PCR. Strain-specific qRT-PCR primer sets will be used to differentially

quantitate shedding of individual strains. A subset of the collected samples may also have influenza virus quantified by next generation sequencing.

4.3.5 Nasal HA-Specific IgA Evaluation and Methods

Quantification of influenza vaccine strain specific anti-HA IgA will be performed by collecting nasal fluid samples on Day 1 prior to receipt of investigational product, Day 28 (+ 2 days) prior to receiving Dose 2 of investigational product, and on Day 56 (± 2 days; see time points Table 4.2-1). Instructions for collecting and processing the nasal fluid samples are provided in the Laboratory Manual. Anti-HA-specific IgA quantification will be performed using an anti-HA serology assay to quantitate antibodies to the different H1, H3 and B-specific hemagglutinins.

4.3.6 Estimate of Volume of Blood to Be Collected

A maximum total of approximately 15 mL of blood will be collected over the course of this study: 5 mL for each of the 3 immunogenicity blood samples.

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Noncompliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate the study

If MedImmune determines that temporary suspension or permanent termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must

inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
FluMist Quadrivalent 2017-2018 formulation	MedImmune	$10^{7.0 \pm 0.5}$ FFU of each of 4 *ca*, *att*, *ts*, 6:2 reassortant influenza strains per 0.2 mL in the BD Accuspray device: • A/H1N1 (Slovenia/2903/2015) • A/H3N2 (A/New Caledonia/71/2014) • B (B/ Phuket/3073/2013) • B (B/Brisbane/60/2008) [redacted]
FluMist Quadrivalent 2015-2016 formulation	MedImmune	$10^{7.0 \pm 0.5}$ FFU of each of 4 *ca*, *att*, *ts*, 6:2 reassortant influenza strains per 0.2 mL in the BD Accuspray device: • A/H1N1 (A/Bolivia/559/2013) • A/H3N2 (A/Switzerland/9715293/2013) • B (B/Phuket/3073/2013) • B (B/Brisbane/60/2008) [redacted]

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
FluMist trivalent 2015-2016 formulation	MedImmune	$10^{7.0 \pm 0.5}$ FFU of each of 3 *ca*, *att*, *ts*, 6:2 reassortant influenza strains per 0.2 mL in the BD Accuspray device: • A/H1N1 (A/Bolivia/559/2013) • A/H3N2 (A/Switzerland/9715293/2013) • B (B/Phuket/3073/2013) [redacted]

att = attenuated; BD = Becton Dickinson; *ca* = cold adapted; FFU = fluorescent focus unit; *ts* = temperature sensitive; w/v = weight per volume

Investigational product will be packaged and stored at -30°C and shipped to the study site upon request of the sponsor or designee. The distributor will ship the investigational product directly to the clinical study site by express courier. Receiving departments should be notified that rapid handling of the shipment is required. Upon receipt at each study site, frozen investigational product should be immediately transferred to a -20°C (or -4°F) freezer (variations up to ± 5°C are acceptable) in a secure location with limited access.

Investigational product will be supplied to the site in devices with identical appearances in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each device within the carton). Each sprayer is also labeled with a unique number. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

4.5.1.1 Investigational Product Handling

Investigational product should not be removed from storage until the day of dosing. Remove only the sprayer to be administered; other sprayers in the kit must remain in the labeled storage conditions and must not thaw. Any broken or damaged sprayer must be identified as damaged and the sprayer number recorded on the investigational product accountability record. Damaged sprayers can be stored at room temperature until accountability is completed.

4.5.1.2 Investigational Product Inspection

At room temperature, investigational product is a colorless to pale yellow liquid, and clear to slightly cloudy. Some proteinaceous particles may be present but they do not affect the use of the product. If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions.

4.5.1.3 Treatment Administration

The first day of dosing is considered Day 1.

- Investigational product should be brought to room temperature by holding the sprayer in the palm of the hand and supporting the plunger rod with the thumb (see Appendix 10.4). The investigational product should be administered immediately thereafter.
- A single administration comprises intranasal delivery of approximately 0.2 mL total volume (0.1 mL into each nostril). Each sprayer has a divider that allows delivery of approximately half the contents of the sprayer into one nostril. Removal of the divider allows delivery of the remaining volume into the other nostril.
- The individual administering the investigational product should depress the plunger rod as rapidly as possible to generate a fine mist. Half of the contents of each sprayer will be sprayed as a fine mist into each nostril while the subject is in an upright position.
- After administration, used study sprayers must be placed immediately after use into locked containers or sealed bags.

4.5.1.4 Monitoring of Dose Administration

As with any vaccine, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. After vaccination, all subjects will be observed for a minimum of 15 minutes by the study staff. Emergency management supplies (eg, AMBU bag, adrenaline [epinephrine], antihistamine) will be made available for the initial treatment of an allergic reaction if needed. Local reactions or systemic events must be recorded.

4.5.1.5 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

[redacted]

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Investigational product must be stored in the original outer package and must not be thawed. The manufacturer's instructions for shipment and storage will be followed at all times. It is the responsibility of the investigator to maintain daily temperature logs for the freezer, at a minimum, daily Monday through Friday. The investigator will be provided with temperature monitors that record minimum/maximum temperatures, unless temperature monitors are already in place.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the

study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit and sprayer numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product to the subject.

Subjects will be randomized using a 1:1:1 ratio to receive either FluMist Quadrivalent 2017-2018 formulation, FluMist Quadrivalent 2015-2016 formulation, or FluMist trivalent 2015-2016 formulation. Investigational product (FluMist Quadrivalent 2017-2018 formulation, FluMist Quadrivalent 2015-2016 formulation, or FluMist trivalent 2015-2016 formulation) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

Subjects will receive a second dose of the same vaccine 28 days after the first dose. An IWRS will be used for assignment of the blinded investigational product kit number. Subjects are assigned the blinded investigational product kit number after the investigator notifies IWRS that the subject meets eligibility criteria for receipt of Dose 2.

4.6.2 Methods to Ensure Blinding

This is a double-blind study in which FluMist Quadrivalent 2017-2018 formulation, FluMist Quadrivalent 2015-2016 formulation, and FluMist trivalent 2015-2016 formulation are identically labeled and indistinguishable in appearance. As such, neither the subject/legal representative nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9). In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.3.2 Unblinding for Planned Analysis Purposes

Planned analyses are described in Section 4.8. The study will be fully unblinded at the time of its completion.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the electronic case report form (eCRF).

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc throughout the study is discouraged.

The following medications are exclusionary. The sponsor must be notified if a subject receives any of these during the study.

1. Any investigational agent from 28 days prior to randomization through the end of the follow-up period
2. Any intranasal medication from 10 days prior to through 10 days post investigational product administration
3. Receipt of influenza antiviral therapy or antiviral agents within 48 hours prior to investigational product administration or expected receipt of influenza antiviral therapy or antiviral agents through the end of the study period

4.8 Statistical Evaluation

4.8.1 General Considerations

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. Additional details of statistical analyses will be described in the statistical analysis plan.

Definitions of Analysis Populations

The intent-to-treat (ITT) population: The ITT includes all randomized subjects.

As-Treated Population (ATP): The ATP includes all subjects who receive any amount of investigational product. Subjects will be included in the ATP according to the investigational product received regardless of treatment assigned by randomization.

Immunogenicity population: Immunogenicity population includes all subjects in the ATP who have no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product.

4.8.2 Sample Size

HAI Immunogenicity

It is expected that for each analysis of immunogenicity, 90% of subjects will be evaluable. The resulting sample size of ~60 evaluable subjects per arm would produce a 95% confidence interval (CI) within 14 percentage points of the observed proportion of subjects seroconverting. An estimate of 40% for the proportion of subjects seroconverting was used for the purposes of CI calculations.

Assuming that the seroconversion rate in the A/Bolivia H1N1 strain (2015-2016 formulation) ranged from 10% to 40%, based on 25% of the rate difference, the sample size of 60 evaluable subjects per arm would result in approximately 80% power to detect a statistically significant difference in the seroconversion rate comparing the A/Bolivia H1N1 strain (2015-2016 formulation) to the replacement H1N1 strain selected for the 2017-2018 vaccine formulation (A/Slovenia/2903/2015). Table 4.8.2-1 summarizes the study power based on various assumptions.

Table 4.8.2-1 Power Calculations

Percentage of Subjects with Immune Response		Absolute Difference (%)	N Per Group	Power (%)
A/Bolivia Strain	A/Slovenia Strain			
10	25	15	60	58
	30	20	60	78
	35	25	60	91
	40	30	60	97
	50	40	60	99
20	35	15	60	45
	40	20	60	67
	45	25	60	84
	50	30	60	94
30	30	45	60	39
	50	20	60	61
	55	25	60	79
	60	30	60	92
40	55	15	60	37
	60	20	60	59
	65	25	60	79
	70	30	60	92

Shedding

It is expected that for each analysis of shedding, 90% of subjects will be evaluable. The resulting sample size of ~60 evaluable subjects per arm would produce a 95% CI within 15 percentage points of the observed proportion of subjects who shed. An estimate of 50% for the proportion of subjects shedding influenza vaccine virus was used for the purposes of sample size calculations, as this value was statistically conservative (ie, had the highest variability).

4.8.3 Analyses of Immunogenicity and Shedding

4.8.3.1 Primary Endpoint Analysis

The primary endpoint is the strain-specific HAI antibody seroconversion rates, defined as at least 4-fold increase from baseline through Day 28 and Day 56. The proportion of subjects who had seroconversion will be summarized at Days 28 and 56 visits by strain and treatment. Its corresponding 95% exact CI will be provided.

The difference in proportion between the A/Bolivia H1N1 strain (2015-2016) and the replacement H1N1 strain selected for the 2017-2018 vaccine formulation will be tested by Cochran–Mantel–Haenszel (CMH) test adjusting for the prior flu vaccination status. If the number of subjects in any stratum is too small, Fisher's exact test will be used without adjusting for the prior flu vaccination status. If it is evident that the proportion is confounded with some of other demographic and baseline disease characteristic variables, the confounding variables will be adjusted.

4.8.3.2 Secondary Endpoint Analyses

Geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) of HAI antibody, neutralizing antibody, and nasal IgA will be summarized by strain and treatment at Days 28 and 56 visits. Corresponding 95% CI will be calculated assuming log normal distribution.

Using the results of the qRT-PCR method, the proportion of subjects who shed vaccine will be summarized by treatment, strain, and dose number based on the same method as for the primary analysis. The number of days of shedding will be summarized descriptively by treatment, strain, dose number, and baseline serostatus. The viral titer will be calculated by day, strain, dose number, and baseline serostatus.

The strain-specific neutralizing antibody seroconversion rates (≥ 4-fold increase from baseline), and strain-specific nasal IgA increase (≥ 2-fold increase from baseline) at Days 28

and 56 visits will be summarized descriptively using the same method as for the primary endpoint.

4.8.3.3 Exploratory Endpoint Analyses

Analyses of immune response will be conducted based on newly identified specific assays to characterize immune response.

Using the results of culture-based methods, the proportion of subjects who shed vaccine, the number of days of shedding, and the viral titer will be summarized using the same methods as described in Section 4.8.3.2.

4.8.3.4 Subgroup Analyses

Subgroup analysis by baseline serostatus and vaccination status will be conducted for the primary and secondary endpoints.

4.8.4 Safety

Analysis of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same adverse event (AE) occurs multiple times within a particular subject, the highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, SAEs, and treatment discontinuations due to AEs will be provided.

4.8.5 Interim Analysis

No interim analyses are planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- 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.

5.3 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see Section 5.4). See Section 5.2 for the definition of SAEs and Section 10.2 for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.3.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period, Day 56, last contact.

All SAEs will be recorded from the time of informed consent.

For nontreatment-emergent AEs (ie, AEs that occur during the period from the time informed consent is signed but prior to the subject receiving investigational product), only AEs associated with protocol-related procedures should be reported. After the start of treatment, all treatment-emergent AEs (TEAEs; Section 5.1) should be reported.

5.3.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.3.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression should be reported and documented in the electronic case report form (eCRF) but should not be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the sponsor representative(s) within the usual timeframes (refer to Section 5.4 for additional information).

5.4 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.5 Other Events Requiring Immediate Reporting

5.5.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Package Insert, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.4. For other overdoses, reporting must occur within 30 days.

5.6 Solicited Symptoms

Solicited symptoms are events that are considered likely to occur post dosing. For this study, solicited symptoms include:

- Fever ≥ 100.4°F (38.0°C) by any route
- Runny/stuffy nose
- Sore throat
- Cough
- Headache
- Generalized muscle aches
- Decreased activity level (lethargy) OR tiredness/weakness
- Decreased appetite

Collection of specific solicited symptoms (sore throat, headache, generalized muscle aches) will be omitted when, according to the judgment of the investigator, the subject is too young to reliably report a particular symptom.

The reporting period for solicited symptoms for subjects is 14 days after each dose.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

An electronic data capture system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject's legal representative will be provided with contact information for the Principal Investigator. In addition, each subject's legal representative will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7.2 Ethics and Regulatory Review

The Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for each site must review and approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subject's legal representative. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrolment of any subject into the study.

MedImmune should approve any substantive modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IRB/IEC, and principal investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by International Council for Harmonisation (ICH)/Good Clinical Practice (GCP). MedImmune will develop a core informed consent form for use by all investigators in the clinical study. MedImmune must approve any modifications to the informed consent form that are needed to meet local requirements.

The Principal Investigator(s) at each center will:

- Ensure each subject's legal representative is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study

- Ensure each subject's legal representative is notified that they are free to discontinue the subject from the study at any time
- Ensure that each subject's legal representative is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject's legal representative provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject's legal representative
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

Substantial changes must be documented in a study protocol amendment. MedImmune will distribute amended versions of the protocol to the principle investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and according to local requirements, the national regulatory authority approval. The IRB/IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

If local regulations require, any unsubstantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

8 REFERENCES

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. These changes are summarized below.

1. Protocol Synopsis: Updated to be consistent with the changes made to the body of the protocol.
2. Section 3.1 (Description of the Study): Text was updated to reflect a change to Inclusion Criterion 1 (Section 4.1.2) from "Age 24 months to < 48 months of age at the time of randomization" to "Age 24 months to < 48 months of age at the time of screening" so that subjects close to the upper age limit who were already screened for the study before the delay in availability of the clinical trial material could still be enrolled.
3. Section 3.1 (Description of the Study): The screening period was extended from 30 days to 75 days due to a delay in the release of clinical trial material by the sponsor.
4. Section 3.1 (Description of the Study): The duration of subject participation was extended from "2 to 3 months" to "3 to 4 months" to reflect extension of the screening period from 30 days to 75 days.
5. Section 3.1 (Description of the Study): Figure 3.1-1 was updated to be consistent with the screening period extension from 30 days to 75 days.
6. Section 4.1.2 (Inclusion Criteria): Inclusion Criterion 1 (subject age criterion) was amended from "Age 24 months to < 48 months of age at the time of randomization" to "Age 24 months to < 48 months of age at the time of screening" so that subjects close to the upper age limit who were already screened for the study before the delay in availability of the clinical trial material could still be enrolled.
7. Section 4.2 (Schedule of Study Procedures): Table 4.2-1, Study Days for screening study period amended from "-30 to 1" to "-75 to 1" to reflect extension of the screening period from 30 days to 75 days.
8. Section 4.2.1 (Screening Visit): Study Days for screening study period amended from "-30 to 1" to "-75 to 1" to reflect extension of the screening period from 30 days to 75 days.

10 APPENDICES

10.1 Appendix 10.1 – Signature of Principal Investigator

Signature of Principal Investigator

A Phase 4 Double-blind Study to Evaluate the Shedding and Immunogenicity of Trivalent and Quadrivalent Formulations of FluMist in Children 24 to < 48 Months of Age

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

10.2 Appendix 10.2 - Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

10.3 Appendix 10.3 - National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Diseases (NAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.4 Appendix 10.4 – 2016-2017 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
2016-2017 Formula
Initial U.S. Approval: 2003

----------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	Dose	Schedule
2 years through 8 years	1 or 2 doses[a], 0.2 mL[b] each	If 2 doses, administer at least 1 month apart
9 years through 49 years	1 dose, 0.2 mL[b]	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.
[b] Administer as 0.1 mL per nostril.
"-" indicates information is not applicable

----------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, or after a previous dose of any influenza vaccine. (4.1, 11)
- 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 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: 7/2016

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	Dose	Schedule
2 years through 8 years	1 or 2 doses[a], 0.2 mL[b] each	If 2 doses, administer at least 1 month apart
9 years through 49 years	1 dose, 0.2 mL[b]	-

[a] 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

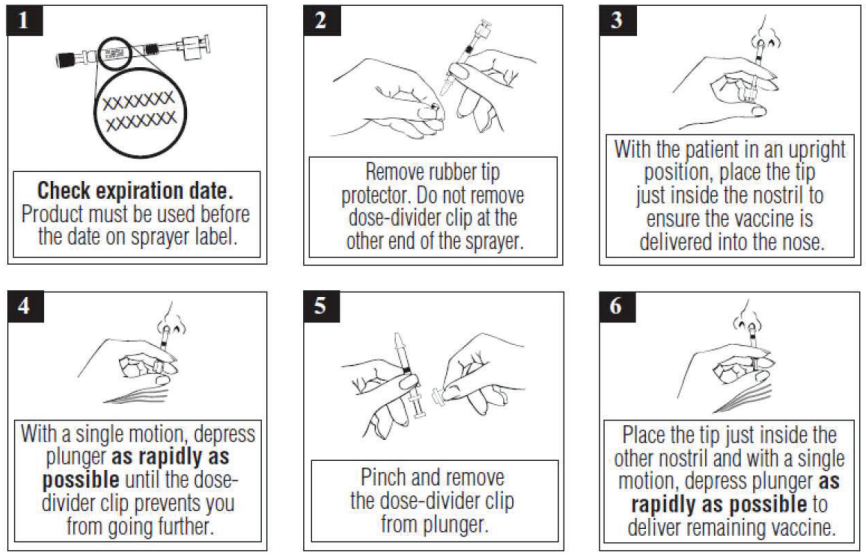
[b] Administer as 0.1 mL per nostril.

"-" indicates information is not applicable

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



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, 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 173 persons with HIV infection and 10 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] NCT00192244; 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 2016-2017 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/Bolivia/559/2013 (H1N1) (an A/California/7/2009 (H1N1)pdm09-like virus), A/New Caledonia/71/2014 (H3N2) (an A/Hong Kong/4801/2014 (H3N2)-like virus), B/Phuket/3073/2013 (B/Yamagata/16/88 lineage), and B/Brisbane/60/2008 (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

A single temperature excursion up to 25°C (77°F) for 12 hours has been shown to have no adverse impact on the vaccine. After a temperature excursion, the vaccine should be returned immediately to the recommended storage condition (2°C – 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

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

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling (Information for Patients and Their Caregivers).

Inform vaccine recipients or their parents/guardians of the need for two doses at least 1 month apart in children 2 through 8 years of age, depending on vaccination history. 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. Inform the vaccinee or their parent/guardian 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

Inform vaccine recipients or their parents/guardians that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

Instruct the vaccine recipient or their parent/guardian to report adverse reactions to their healthcare provider.

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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 is not made with natural rubber latex.
Carton containing 10 intranasal sprayers: NDC 66019-303-10

Single intranasal sprayer: NDC 66019-303-01

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. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.

DO NOT FREEZE.

Keep FluMist Quadrivalent sprayer in outer carton in order to protect from light.

A single temperature excursion up to 25°C (77°F) for 12 hours has been shown to have no adverse impact on the vaccine. After a temperature excursion, the vaccine should be returned immediately to the recommended storage condition (2°C – 8°C) and used as soon as feasible. Subsequent excursions are not permitted.

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

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling (Information for Patients and Their Caregivers).

Inform vaccine recipients or their parents/guardians of the need for two doses at least 1 month apart in children 2 through 8 years of age, depending on vaccination history. 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. Inform the vaccinee or their parent/guardian 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

Inform vaccine recipients or their parents/guardians that FluMist Quadrivalent is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

Instruct the vaccine recipient or their parent/guardian to report adverse reactions to their healthcare provider.

FluMist® is a registered trademark of MedImmune, LLC.

MedImmune

Manufactured by:

MedImmune, LLC

Gaithersburg, MD 20878

1-877-633-4411

U.S. Government License No. 1799

Information for Patients and Their Caregivers

FluMist® Quadrivalent (pronounced FLEW-mĭst Kwä-drə-VĀ-lənt)
(Influenza Vaccine Live, Intranasal)

Please read this Patient Information carefully before you or your child is vaccinated with FluMist Quadrivalent.

This is a summary of information about FluMist Quadrivalent. It does not take the place of talking with your healthcare provider about influenza vaccination. If you have questions or would like more information, please talk with your healthcare provider.

What is FluMist Quadrivalent?

FluMist Quadrivalent is a vaccine that is sprayed into the nose to help protect against influenza. It can be used in children, adolescents, and adults ages 2 through 49. FluMist Quadrivalent is similar to MedImmune's trivalent Influenza Vaccine Live, Intranasal (FluMist) except FluMist Quadrivalent provides protection against an additional influenza strain. FluMist Quadrivalent may not prevent influenza in everyone who gets vaccinated.

Who should not get FluMist Quadrivalent?

You should not get FluMist Quadrivalent if you:

- have a severe allergy to eggs or to any inactive ingredient in the vaccine (see "What are the ingredients in FluMist Quadrivalent?")
- have ever had a life-threatening reaction to influenza vaccinations
- are 2 through 17 years old and take aspirin or medicines containing aspirin. Children or adolescents should not be given aspirin for 4 weeks after getting FluMist or FluMist Quadrivalent unless your healthcare provider tells you otherwise.

Please talk to your healthcare provider if you are not sure if the items listed above apply to you or your child.

Children under 2 years old have an increased risk of wheezing (difficulty with breathing) after getting FluMist Quadrivalent.

Who may not be able to get FluMist Quadrivalent?

Tell your healthcare provider if you or your child:

- are currently wheezing
- have a history of wheezing if under 5 years old
- have had Guillain-Barré syndrome
- have a weakened immune system or live with someone who has a severely weakened immune system

- have problems with your heart, kidneys, or lungs
- have diabetes
- are pregnant or nursing
- are taking Tamiflu®, Relenza®, amantadine, or rimantadine

If you or your child cannot take FluMist Quadrivalent, you may still be able to get an influenza shot. Talk to your healthcare provider about this.

How is FluMist Quadrivalent given?

- FluMist Quadrivalent is a liquid that is sprayed into the nose.
- You can breathe normally while getting FluMist Quadrivalent. There is no need to inhale or "sniff" it.
- People 9 years of age and older need one dose of FluMist Quadrivalent each year.
- Children 2 through 8 years old may need 2 doses of FluMist Quadrivalent, depending on their history of previous influenza vaccination. Your healthcare provider will decide if your child needs to come back for a second dose.

What are the possible side effects of FluMist Quadrivalent?

The most common side effects are:

- runny or stuffy nose
- sore throat
- fever over 100 degrees F

Other possible side effects include:

- decreased appetite
- irritability
- tiredness
- cough
- headache
- muscle ache
- chills

Call your healthcare provider or go to the emergency department right away if you or your child experience:

- hives or a bad rash
- trouble breathing
- swelling of the face, tongue, or throat

These are not all the possible side effects of FluMist Quadrivalent. You can ask your healthcare provider for a complete list of side effects that is available to healthcare professionals.

Call your healthcare provider for medical advice about side effects. You may report side effects to VAERS at 1-800-822-7967 or *http://vaers.hhs.gov*.

What are the ingredients in FluMist Quadrivalent?

Active Ingredient: FluMist Quadrivalent contains 4 influenza virus strains that are weakened (A(H1N1), A(H3N2), B Yamagata lineage, and B Victoria lineage).

Inactive Ingredients: monosodium glutamate, gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, and gentamicin.

FluMist Quadrivalent does not contain preservatives.

How is FluMist Quadrivalent Stored?

FluMist Quadrivalent is stored in a refrigerator (not the freezer) between 35-46 degrees F (2-8 degrees C) upon receipt. FluMist Quadrivalent sprayer must be kept in the carton until use in order to protect from light. FluMist Quadrivalent must be used before the expiration date on the sprayer label.

If you would like more information, talk to your healthcare provider or visit www.*flumistquadrivalent.com* or call 1-877-633-4411.

MedImmune

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