A Phase 4, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety of 2 New 6:2 Influenza Virus Reassortants in Adults

Sponsor Protocol Number: D2560C00015

Application Number: [redacted]

Investigational Product: Influenza Virus Vaccine, Bivalent, Subtype A/H3N2, Type B, Live, Cold Adapted

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca
One MedImmune Way
Gaithersburg, MD 20878, USA

Medical Monitor: [redacted]

Protocol History, Date: Original Protocol, 27Mar2018

PROTOCOL SYNOPSIS

TITLE

A Phase 4, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety of 2 New 6:2 Influenza Virus Reassortants in Adults

HYPOTHESIS

The hypothesis for this study is that 2 new live attenuated influenza strains based on Ann Arbor master donor viruses (MDVs) (Maassab, 1968; Maassab et al, 1985) will have a safety and tolerability profile consistent with previously evaluated strains produced using this technology.

OBJECTIVE

The objective of this study is to assess the safety of a bivalent influenza virus vaccine of 2 new 6:2 influenza virus reassortants in healthy adults prior to the release of the quadrivalent vaccine (FluMist® Quadrivalent) containing them.

STUDY ENDPOINTS

The primary endpoint of this study is fever (Days 1 through 8), defined as oral temperature ≥ 101°F.

The secondary endpoints of this study are:

1. Solicited symptoms that occur within 7 days after vaccination (Days 1-8)
2. Adverse events (AEs) that occur within 7 days after vaccination (Days 1-8)
3. Solicited symptoms that occur within 14 days after vaccination (Days 1-15)
4. AEs that occur within 14 days after vaccination (Days 1-15)
5. Serious adverse events (SAEs) that occur within 28 days after vaccination (Days 1-29)
6. New onset chronic diseases (NOCDs) that occur within 28 days after vaccination (Days 1-29)
7. SAEs that occur within 180 days after vaccination (Days 1-181)
8. NOCDs that occur within 180 days after vaccination (Days 1-181)

STUDY DESIGN

This prospective, randomized, double-blind, placebo-controlled release study will enroll approximately 300 healthy adults 18 through 49 years of age (not yet reached their 50th birthday). Eligible subjects will be randomly assigned in a 4:1 fashion to receive a single dose of bivalent vaccine or placebo by intranasal spray. This study will be conducted at 2 sites in the United States of America (USA). Randomization will be stratified by site.

Each subject will receive one dose of investigational product on Day 1. Subjects will be followed through 180 days after receipt of investigational product.

TARGET SUBJECT POPULATION

The subjects in this study will be healthy adults 18 through 49 years of age (not yet reached their 50th birthday).

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Eligible subjects will be randomly assigned in a 4:1 ratio to receive a single dose of either bivalent vaccine (240 subjects) or placebo (60 subjects) by intranasal spray on Day 1.

STATISTICAL ANALYSIS PLAN

General Considerations

Data will be provided in data listings sorted by treatment group and subject identification number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics,

including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated.

The intent-to-treat (ITT) population is defined as all subjects that are randomized and treated with investigational product. All analyses will be performed on the ITT population unless otherwise specified.

Sample Size and Power Calculations

Based on the solicited event rates following FluMist® and placebo vaccination in healthy adults 18 to 64 years of age in Study AV009, the currently proposed study with 300 evaluable subjects (240 bivalent vaccine and 60 placebo recipients) will provide at least 98% power to rule out a rate increase of 5 percentage points assuming the true difference between the treatment groups is zero and the true fever rate is ≤ 1%. Power is lower if the true difference is different from zero. For example, if the true fever rates are 2% and 1% in vaccine and placebo recipients, respectively, the power will be 77%. For other solicited symptoms with 300 evaluable subjects (240 bivalent vaccine and 60 placebo recipients), the currently proposed study provides at least 87% power to rule out a 20 percentage point increase, assuming the true difference between the 2 treatment groups is zero. Power is lower if the true difference is greater than zero.

Assessment of Endpoints

The primary endpoint of this study is fever (Days 1 through 8), defined as oral temperature ≥ 101°F. Comparison of the rate of fever between the 2 treatment groups will be based on the upper limit of the two-sided 95% exact CIs for the rate increase (bivalent vaccine minus placebo) evaluated against the pre-specified equivalence criterion of 5 percentage points.

This corresponds to the null hypothesis of:

H0: Rate difference ≥ 5 percentage points.

The alternative hypothesis is:

HA: Rate difference < 5 percentage points.

A two-sided 95% CI will be constructed using the exact method based on the score statistic proposed by (Chan and Zhang, 1999). This method computes the lower and upper confidence limits by inverting 2 separate one-sided tests of half the nominal Type I error rate. Its test statistic is based on the score statistic that is computed as the observed difference of the 2 binomial event rates minus the hypothesized value of the rate difference (observed rate difference) divided by the standard error of this difference under the alternative hypothesis. This test assures that the Type I error does not exceed the pre-specified level. Due to discreteness when the sample size is relatively small compared to the expected event rate, the associated Type I error rate could be quite conservative, that is, smaller than the pre-specified level.

Secondary endpoints of the study include other reported solicited symptoms and AEs that occur within 7 days after vaccination (Days 1 through 8), and all solicited symptoms and AEs that occur within 14 days after vaccination (Days 1 through 15). Additional secondary endpoints include SAEs and NOCDs that occur within 28 days after vaccination (Days 1 through 29) and within 180 days after vaccination (Days 1 through 181).

Fever will be summarized according to the following thresholds:

- Oral > 100°F
- Oral ≥ 101°F
- Oral > 102°F
- Oral > 103°F

A secondary analysis comparing rates of other solicited symptoms (Days 1 through 8) between the 2 treatment groups will be performed. Exact two-sided 95% CIs (Chan and Zhang, 1999) on the rate difference (bivalent vaccine minus placebo) will be constructed. There are no pre-specified equivalence criteria for the secondary analyses.

The number of days of solicited symptoms and the proportion of subjects experiencing each event by study day will be presented without formal statistical comparison. The distribution of the number of days with each individual event will also be summarized without formal statistical comparison. The proportion of subjects using antipyretic and analgesic agents within 7 days after vaccination (Days 1 through 8) and 14 days after vaccination (Days 1 through 15) will be summarized by treatment group.

Interim Analysis

A safety analysis will be conducted after all subjects have been followed through Day 15 and all data through at least Day 8 are locked. The analysis for Days 1 through 15 will include the primary endpoint of this study (fever for Days 1 through 8, defined as oral temperature ≥ 101°F), as well as analysis of safety data (solicited symptoms and AEs), and antipyretics and analgesic use reported within 7 days and within 14 days after dosing.

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AE	adverse event
att	attenuated
BD	Becton Dickinson (Accuspray™)
BFS	blow fill seal
ca	cold-adapted
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
eCRF	electronic case report form
EDC	electronic data capture
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
MDV	Master Donor Virus
MVS	Master Virus Seed
NOCD	new onset chronic disease
SAE	serious adverse event
SID	subject identification
ts	temperature-sensitive
USA	United States of America
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1 INTRODUCTION

1.1 Disease Background

FluMist® Quadrivalent is an intranasally administered influenza vaccine that was developed as a successor vaccine to FluMist® seasonal trivalent influenza vaccine. FluMist contained 3 live reassortant strains of influenza virus, including 2 type A strains (H1N1 and H3N2) and 1 type B strain. Developed to address the issues of cocirculation of B strains from 2 lineages and mismatch between the single B strain lineage included in seasonal influenza vaccines and the predominantly circulating strain, FluMist Quadrivalent contains 4 live reassortant strains of influenza virus: A/H1N1, A/H3N2, and 2 type B strains. FluMist Quadrivalent contains biologically active components that are identical to those in FluMist except that a fourth strain is blended into the final vaccine. The 2 vaccines are produced by the same manufacturing process, beginning with the preparation of the Master Virus Seed (MVS) for each strain. The MVS for each strain contains 6 gene segments from the cold-adapted (*ca*) Master Donor Virus (MDV) and the hemagglutinin and neuraminidase gene segments from a wild-type virus isolate and is called a 6:2 reassortant. In the United States of America (USA), the strains used for influenza vaccines each season are recommended annually by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to the Center for Biologics Evaluation and Research (CBER). The wild-type strains chosen for a given year are then provided to influenza vaccine manufacturers by either CBER or the Centers for Disease Control and Prevention for preparation of vaccine.

Numerous safety tests are conducted for FluMist Quadrivalent during the manufacturing process of the vaccine including tests for absence of microorganisms; tests for absence of adventitious agents; and confirmation of the vaccine virus phenotype (cold adaptation, temperature sensitivity, and attenuation). Additionally, after new reassortants are made to match selected strains for the upcoming influenza season, their safety profile is evaluated in a clinical study in adults in order to provide further safety data prior to the release of the commercial vaccine.

The design of this clinical study will ensure that any new influenza vaccine virus reassortant has sufficient attenuation in humans, as demonstrated by the low incidence of fever ≥ 101°F (oral or equivalent). In previous clinical studies, the rate of fever in adults following administration of FluMist has been low and similar in both vaccinees and placebo recipients. For example, in Study AV009 conducted in 4,561 healthy adults 18 through 64 years of age (3,041 FluMist recipients and 1,520 placebo recipients), fever ≥ 101°F occurred in 0.57% and 0.60% of FluMist and placebo recipients, respectively. In Study MI-CP185 conducted in 1,800 adults 18 through 49 years of age (1,197 FluMist Quadrivalent recipients and 597 FluMist recipients) fever > 101.3°F occurred in 0.8% and 0.3% of FluMist Quadrivalent and FluMist recipients, respectively. Thus, in a placebo-controlled study in healthy adults to

evaluate new strains, vaccine recipients would be expected to develop temperature increases at rates similar to those of placebo recipients following vaccination.

1.2 FluMist Quadrivalent Background

FluMist Quadrivalent is briefly described below. Refer to the current package insert for details (Appendix 3).

The active agents of FluMist Quadrivalent consist of 2 *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 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.

The nonclinical program for FluMist Quadrivalent was designed to demonstrate that its immunogenicity and safety were comparable to those previously established for FluMist since 1) FluMist Quadrivalent differs from FluMist only in the number of influenza virus strains; 2) both FluMist and FluMist Quadrivalent are manufactured in an identical manner; 3) both FluMist and FluMist Quadrivalent are based on the same MDV strains; 4) the total viral content of FluMist Quadrivalent does not exceed the maximal calculated viral content of FluMist; and 5) inactive components of FluMist and FluMist Quadrivalent are identical. Because of these similarities, only select nonclinical pharmacologic studies were conducted with FluMist Quadrivalent, with FluMist as comparator. Repeat-dose and reproductive and developmental toxicology studies were repeated with FluMist Quadrivalent.

Primary pharmacodynamic studies in ferrets have been conducted to evaluate the replication and immunogenicity of live, attenuated FluMist strains. Results of replication, immunogenicity, and challenge studies in ferrets demonstrated that vaccination with 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.

Toxicology studies performed with FluMist and/or FluMist Quadrivalent include 2 repeat-dose toxicology studies in ferrets, 2 reproductive toxicology studies in rats and ferrets, and 2 ocular toxicology studies (Draize tests) in a rabbit model to evaluate the potential effects of FluMist if inadvertently sprayed into the eye.

A single- and repeat-dose toxicology study was conducted in ferrets to investigate the potential adverse effects of FluMist given once or 3 times to ferrets over a 15-week period. The regimen consisted of up to 3 human doses of 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 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 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 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 FluMist.

The potential for ocular toxicity resulting from the inadvertent instillation of 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 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. Results of an additional study (MI-CP206; 1,800 subjects), conducted in adults using FluMist Quadrivalent delivered by a novel blow fill seal (BFS) delivery system, also demonstrated that the immune responses generated by FluMist Quadrivalent were noninferior to the immune responses generated by FluMist delivered by Becton Dickinson (BD) Accuspray™, and provided support for the similar safety profile of FluMist Quadrivalent. Overall, a total of 3,783 subjects received at least 1 dose of FluMist Quadrivalent in the 3 studies, including 1,199 subjects who received FluMist Quadrivalent in the BFS device. A total of 1,386 FluMist Quadrivalent recipients were 2 years to less than 18 years of age and, of these, 1,041 subjects received 2 doses.

In addition to the clinical study experience, over 200,000 doses of FluMist have been administered in 2 post-marketing studies, and more than [redacted] 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 3).

The 2017-2018 FluMist Quadrivalent Package Insert (Appendix 3) provides the most current safety data and product use information.

1.5 Rationale for Conducting the Study

The World Health Organization (WHO) has made the following recommendation to vaccine manufacturers, effective 22Feb2018, regarding the influenza vaccine composition for the 2018-2019 influenza season:

- A/Michigan/45/2015-like virus H1N1pdm09
- A/Singapore/INFIMH-16-0019/2016-like virus (H3N2)
- B/Phuket/3073/2013-like virus (Yamagata lineage; for quadrivalent formulations)
- B/Colorado/06/2017-like virus (Victoria lineage)

Thus, in accordance with this change and these guidelines (Centers for Disease Control and Prevention [CDC], 2016), MedImmune has selected the following strains to be FluMist Quadrivalent components in the 2018-2019 influenza season:

- A/Slovenia/2903/2015 V8 (H1N1)
- A/Singapore/INFIMH-16-0019/2016 V2 (H3N2)
- B/Phuket/3073/2013 (Yamagata lineage)
- B/Colorado/06/2017 (Victoria lineage)

B/Phuket/3073/2013 (Yamagata lineage) has been 1 of the strains contained in FluMist since the 2015-2016 season, and A/Slovenia/2903/2015 (H1N1) was a new strain in the 2017-2018 season.

As a result, this study, conducted in healthy adults, will evaluate the safety of a bivalent vaccine containing 2 new influenza virus reassortants A/Singapore/INFMH-16-0019/2016 and B/Colorado/06/2017 prior to the release of the quadrivalent vaccine (FluMist Quadrivalent) containing them.

1.6 Research Hypothesis

The hypothesis for this study is that 2 new live attenuated influenza strains based on Ann Arbor MDVs (Maassab, 1968; Maassab et al, 1985) will have a safety and tolerability profile consistent with previously evaluated strains produced using this technology.

2 OBJECTIVE

2.1 Primary Objective

The objective of this study is to assess the safety of a bivalent influenza virus vaccine of 2 new 6:2 influenza virus reassortants in healthy adults prior to the release of the quadrivalent vaccine (FluMist Quadrivalent) containing them.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this study is fever (Days 1 through 8), defined as oral temperature ≥ 101°F.

2.2.2 Secondary Endpoints

1 Solicited symptoms that occur within 7 days after vaccination (Days 1-8)
2 Adverse events (AEs) that occur within 7 days after vaccination (Days 1-8)
3 Solicited symptoms that occur within 14 days after vaccination (Days 1-15)
4 AEs that occur within 14 days after vaccination (Days 1-15)
5 Serious adverse events (SAEs) that occur within 28 days after vaccination (Days 1-29)
6 New onset chronic diseases (NOCDs) that occur within 28 days after vaccination (Days 1-29)
7 SAEs that occur within 180 days after vaccination (Days 1-181)
8 NOCDs that occur within 180 days after vaccination (Days 1-181)

3 STUDY DESIGN

3.1 Description of the Study

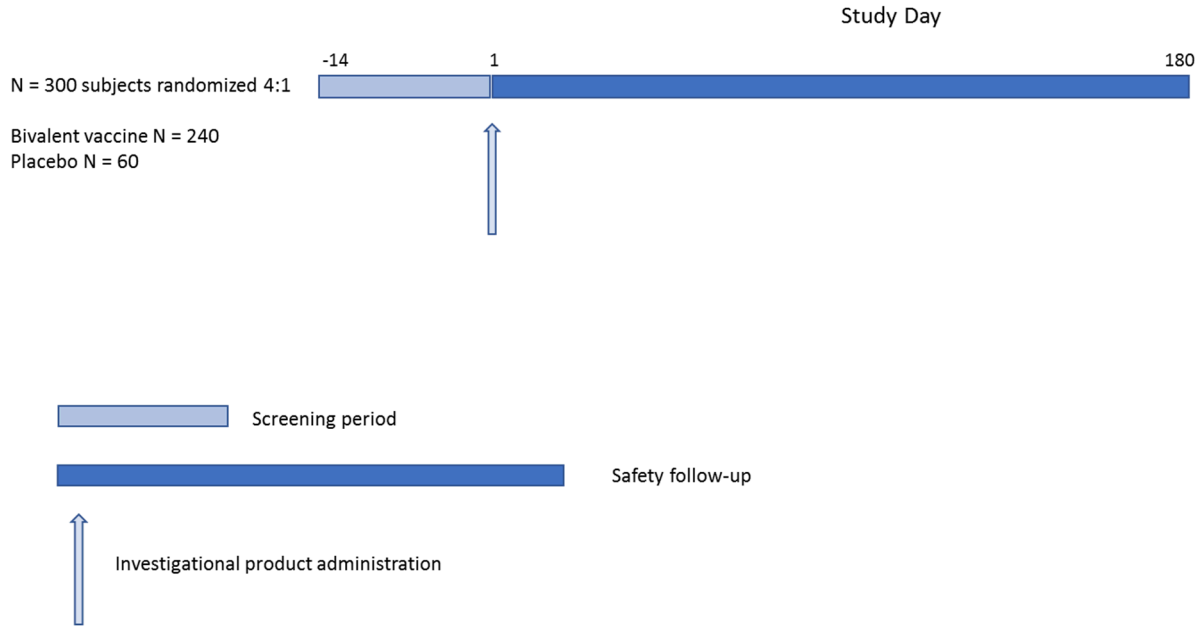
3.1.1 Overview

This prospective, randomized, double-blind, placebo-controlled release study will enroll approximately 300 healthy adults 18 through 49 years of age (not yet reached their 50th birthday). Eligible subjects will be randomly assigned in a 4:1 fashion to receive a single dose of bivalent vaccine or placebo by intranasal spray. This study will be conducted at 2 sites in the USA. Randomization will be stratified by site.

Each subject will receive one dose of investigational product on Day 1. Subjects will be followed through 180 days after receipt of investigational product.

A study schematic is provided in Figure 1.

Figure 1 Study Flow Diagram



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

3.1.2 Treatment Regimen

Subjects will be randomly assigned in a 4:1 ratio to receive a single dose of either bivalent vaccine (240 subjects) or placebo (60 subjects) by intranasal spray on Day 1.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

The influenza vaccine virus dose to be used in this study, a single dose of $10^{7.0 \pm 0.5}$ fluorescent focus units per strain, is the same as the dose that will be used in the commercial FluMist Quadrivalent product.

3.2.2 Rationale for Study Population

Healthy adults 18 through 49 years of age represent the segment of the adult population for whom FluMist Quadrivalent is indicated and, in contrast to children, are not a vulnerable population. The study's eligibility criteria are intended to prevent enrollment of individuals with medical conditions in whom FluMist Quadrivalent is not indicated, to minimize confounding circumstances that would impair the ability to interpret the study results, and to maximize the proportion of enrolled subjects completing the study.

3.2.3 Rationale for Endpoints

Fever has been chosen as a primary endpoint, because it is a common and objective consequence of infection with wild-type influenza. Fever occurring at a greater rate in the vaccine group than the placebo group would, therefore, suggest that new influenza vaccine virus strains might not be sufficiently attenuated. Regulatory authorities have accepted this measure of attenuation of new influenza vaccine virus strains over many years and have required this testing prior to their authorizing release of the FluMist or FluMist Quadrivalent vaccine containing any new influenza strains each year.

Secondary endpoints of the study include other reported solicited symptoms and AEs that occur within 7 days after vaccination (Days 1-8), and all solicited symptoms and AEs that occur within 14 days after vaccination (Days 1-15). Additional secondary endpoints include SAEs and NOCDs that occur within 28 days after vaccination (Days 1-29) and within 180 days after vaccination (Days 1-181).

The reporting period of 14 days (Days 1 through 15) for solicited symptoms, including fever, and AEs is consistent with the incubation period of influenza.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

This study will enroll approximately 300 healthy adults 18 through 49 years of age (not yet reached their 50th birthday). Eligible subjects will be randomly assigned in a 4:1 fashion to receive a single dose of bivalent vaccine or placebo by intranasal spray.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Age 18 through 49 years at the time of screening (not yet reached their 50th birthday).

2 Written informed consent and any locally required authorization (ie, Health Insurance Portability and Accountability Act [HIPAA] in the USA) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3 Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception for 30 days prior to the first dose of investigational product and must agree to continue using such precautions for 60 days after the final dose of investigational product; cessation of contraception after this point should be discussed with a responsible physician. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout

this period. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Examples of acceptable methods of contraception are described in Table 1.

4 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from Day 1 through Day 31, or at least 30 days after receipt of the final dose of investigational product. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as shown in Table 1. In addition, male subjects must refrain from sperm donation for 30 days after the final dose of investigational product as the only dose of investigational product occurs on Day 1.

Table 1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system) (eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

5 Healthy by medical history and physical examination

6 Female subjects of childbearing potential must also have a negative urine or blood pregnancy test at screening and, if screening and Day 1 do not occur on the same day, on the day of vaccination prior to randomization

7 Subject available by telephone

8 Ability to understand and comply with the requirements of the protocol, as judged by the investigator

9 Ability to complete follow-up period of 180 days after dosing as required by the protocol

4.1.3 Exclusion Criteria

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

1 Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results

2 Concurrent enrollment in another clinical study up to 180 days after receipt of investigational product (Day 181)

3 Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals

4 History of hypersensitivity to any component of the vaccine, including egg or egg proteins or serious, life threatening, or severe reactions to previous influenza vaccinations

5 History of hypersensitivity to gentamicin, gelatin, or arginine

6 Any condition for which the inactivated influenza vaccine is indicated, including chronic disorders of the pulmonary or cardiovascular systems (eg, asthma), chronic metabolic diseases (eg, diabetes mellitus), renal dysfunction, or hemoglobinopathies that required regular medical follow-up or hospitalization during the preceding year

Note: A history of asthma that requires regular medical follow-up or hospitalization during the preceding 2 years is exclusionary. Investigator judgment is required to determine whether or not a subject has a history of asthma; however, for adult subjects, a remote history of wheezing or a remote diagnosis of asthma that the investigator does not consider to be relevant to current health does not need to be considered to be a history of asthma. For example, childhood asthma that has not required treatment in adulthood is not necessarily exclusionary.

7 Acute febrile (> 100.0°F oral or equivalent) and/or clinically significant respiratory illness (eg, cough or sore throat) within 14 days prior to randomization

8 Any known immunosuppressive condition or immune deficiency disease, including human immunodeficiency virus infection, or ongoing immunosuppressive therapy

9 History of Guillain-Barre syndrome

10 A household contact who is severely immunocompromised (eg, hematopoietic stem cell transplant recipient, during those periods in which the immunocompromised individual requires care in a protective environment); additionally, subject should avoid close contact with severely immunocompromised individuals for at least 21 days after receipt of investigational product

11 Receipt of any investigational agent within 30 days prior to randomization, or expected receipt through 30 days after the dose of investigational product (use of licensed agents for indications not listed in the Package Insert is permitted)

12 Receipt of any non-study vaccine within 30 days prior to randomization, or expected receipt through 30 days after receipt of investigational product

13 Expected receipt of antipyretic or analgesic medication on a daily or every other day basis from randomization through 14 days after receipt of investigational product

Note: A daily dose of up to 81 mg of aspirin for prophylactic use is not considered a contraindication to enrollment.

14 Administration of intranasal medications within 14 days prior to randomization, or expected receipt through 14 days after administration of investigational product

15 Receipt of influenza antiviral therapy or influenza antiviral agents within 48 hours prior to investigational product administration or expected receipt of influenza antiviral therapy or influenza antiviral agents through 14 days after receipt of investigational product

16 Known or suspected mitochondrial encephalomyopathy

17 Nursing mother

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 (eg, 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.

Subjects will be randomized at a 4:1 ratio to receive either a single dose of bivalent vaccine or placebo by intranasal spray. Randomization will be stratified by site.

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 (if applicable) or receive investigational product.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up and any worksheets will be collected. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Replacement of Subjects

Subjects will not be replaced.

4.1.7 Withdrawal of Informed Consent for Data

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 may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data will be collected unless specifically required to monitor safety of the subject.

4.2 Schedule of Study Procedures

A schedule of study procedures is provided in Table 2, followed by a description of each visit. A description of study procedures is provided in Section 4.2.1.

Table 2 Schedule of Study Procedures

Study Period	Screening	Treatment	Follow-up							
Visit	Visit 1	Visit 2	Unscheduled Visit	Telephone Contact						
Procedure/Study Day	Days -14 to 1	Day 1	Days 2 to 15	Days 2 to 15	Day 31 (+7)	Day 61(+7)	Day 91(+7)	Day 121 (+7)	Day 151 (+7)	Day 181 (+14)
Written informed consent/ assignment of SID number	X									
Verify eligibility criteria	X	X								
Medical history & current medication use	X	X								
Physical examination, height, weight, & temperature	X	X[a]	X							
Pregnancy test	X	X[a]								
Collect SAEs	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Collect concomitant medications	X	X	X	X						
Collect AEs	X	X	X	X						
Collect solicited symptoms		X	X	X						
Collect NOCDs		X	X	X	X	X	X	X	X	X
Investigational Product Administration		**X**								

AE = adverse event; NOCD = new onset chronic disease; SAE = serious adverse event; SID = subject identification number

[a] If screening and dosing occur at the same visit, only one evaluation is required (female subjects only, unless exempt from pregnancy testing).

4.2.1 Screening Visit (Visit 1)

All screening procedures must be performed within 14 days before or on the same day as investigational product administration (Day -14 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 current medication use
6 Perform screening physical examination, including temperature, height, and weight
7 Collect urine sample for pregnancy test (female subjects only, unless exempt from pregnancy testing); if screening and dosing occur at the same visit, only one test is required
8 Assess for AEs, SAEs, and concomitant medication use

4.2.2 Treatment Period (Visit 2)

Day 1: Administration of Investigational Product

1 Verify eligibility criteria
2 Update screening medical history, current medication use (any new findings since screening), and physical examination (including height, weight, and temperature)
3 Collect urine sample for pregnancy test (female subjects only, unless exempt from pregnancy testing); if screening and dosing occur at the same visit, only one test is required; result must be negative for randomization and dosing to occur
4 Assess for AEs and SAEs
5 Randomize in IWRS to assign investigational product sprayer number
6 Administer investigational product
7 Observe subject for a minimum of 15 minutes. Provide safety assessment worksheets, thermometer, and instructions for completing the worksheets (see Section 5.5.2). Ensure that the subject understands how to take his/her temperature. Day 1 temperature is recorded by the subject in the evening of Day 1 (day of investigational product administration). The safety assessment worksheets will be used for the collection of solicited symptoms, AEs, and concomitant medication use, and will be completed by the subject to serve as a memory aid for future data collection by study staff during telephone contacts.

8 Record solicited symptoms, AEs, and concomitant medication use

9 Inquire about SAEs and NOCDs

4.2.3 Follow-up Period (Unscheduled Visit and Telephone Contacts)

4.2.3.1 Unscheduled Visit, Days 2 to 15 for Significant Febrile Illness

1 Perform medical evaluation

2 Record solicited symptoms, AEs, and concomitant medication use

3 Inquire about SAEs and NOCDs

4.2.3.2 Telephone Contact, Days 2 to 15

Telephone contact every day or every other day to Day 15

1 Record solicited symptoms, AEs, and concomitant medication use

2 Inquire about SAEs and NOCDs

4.2.3.3 Telephone Contact, Days 31, 61, 91, 121, 151 (+ 7 days)

One telephone contact each between Days 31 and 38, 61 and 68, 91 and 98, 121 and 128, and 151 and 158

1 Inquire about SAEs and NOCDs

4.2.3.4 Telephone Contact, Day 181 (+ 14 days): Last Follow-up Contact and Study Termination

One telephone contact between Days 181 and 195

1 Inquire about SAEs and NOCDs through 180 days post dosing

4.3 Description of Study Procedures

4.3.1 Medical History and Physical Examination, Height, Weight, and Temperature

Medical history and current medication use will be collected. A basic physical examination of the head, neck, chest, heart, abdomen, and extremities will be performed, to include collection of height, weight, and temperature (oral thermometer).

4.3.2 Clinical Laboratory Tests

The only clinical laboratory tests performed in this study will be urine pregnancy tests.

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG; at screening and day of randomization if screening and randomization/dosing do not occur on the same day).

4.4 Investigational Products

4.4.1 Identity of Investigational Products

MedImmune will provide the investigators with investigational product (Table 3) using designated distribution centers.

Table 3 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Bivalent influenza vaccine	MedImmune	$10^{7.0 \pm 0.5}$ FFU of each of 2 *ca*, *att*, *ts*, 6:2 reassortant influenza strains per 0.5 mL [redacted] in the BD Accuspray device: A/Singapore/INFIMH-16-0019/2016 V2 B/Colorado/06/2017
Placebo	MedImmune	0.5 mL of [redacted] in the BD Accuspray device

att = attenuated; BD = Becton Dickinson; *ca* = cold adapted; ; FFU = fluorescent focus unit; [redacted] *ts* = temperature sensitive

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). Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

Investigational product should not be removed from storage until the day of dosing (Day 1); investigational product may be stored at room temperature during the day of dosing. 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.

4.4.1.1 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.

4.4.1.2 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 3). The investigational product should be administered immediately thereafter.
- A single administration comprises intranasal delivery of approximately 0.5 mL total volume (0.25 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.

4.4.1.3 Monitoring of Dose Administration

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.

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.

4.4.1.4 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]

4.4.2 Additional Study Medications

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

4.4.3 Labeling

Labels for the investigational product will be prepared in accordance with GMP and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.4.4 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.

4.4.5 Treatment Compliance

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

4.4.6 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.

4.5 Treatment Assignment and Blinding

4.5.1 Methods for Assigning Treatment Groups

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product 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 sprayer numbers to the subject.

Subjects will be randomized at a 4:1 ratio to receive either bivalent influenza vaccine or placebo. The randomization will be stratified by site.

Investigational product (bivalent influenza vaccine or placebo) 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.

4.5.2 Methods for Ensuring Blinding

This is a double-blind study in which bivalent influenza vaccine and placebo 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; see Section 4.5.3.2 for unblinding related to interim planned analysis). 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*.

4.5.3 Methods for Unblinding

4.5.3.1 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. Prior to unblinding the investigational product allocation for an individual subject, the investigator must first attempt to contact the medical monitor to discuss the medical emergency and the reason for wanting to unblind. 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 SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.5.3.2 Unblinding for Interim Analysis

An interim analysis is planned for this study as described in Section 4.7.4. To ensure the blinding of each subject's treatment assignment throughout the study, the Day 15 unblinded analyses will be performed by defined MedImmune personnel, including the medical monitor, the clinical program manager, Patient Safety staff team members, Regulatory (Clinical) staff team members, a Medical Writing staff team member, a Biostatistics staff team member, Clinical Statistical Analysis System Programming staff team members, and Data Management (including data management vendor's non-MedImmune personnel) staff team members. Study site personnel and contract research organization personnel directly associated with the conduct of this study and the subjects will remain blinded to the treatment assignment for individual subjects until the completion of the study.

4.6 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).

4.6.1 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 4.6.2. 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.

4.6.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc, from Day 1-15 is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Use of antipyretic or analgesic medications for all symptoms other than temperatures ≥ 101°F oral (or equivalent) is discouraged from Day 1-15. All medications taken during the 14-day post vaccination follow-up period, the indications, the start and stop dates of the medications, and the route of administration will be recorded from the time of informed consent through Day 15.

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

1 Any vaccine or investigational agent from 30 days prior to randomization through 30 days post investigational product administration
2 Any intranasal medication from 14 days prior to through 14 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 14 days after receipt of investigational product

4.7 Statistical Evaluation

4.7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject identification number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated.

The intent-to-treat (ITT) population is defined as all subjects that are randomized and treated with investigational product. All analyses will be performed on the ITT population unless otherwise specified. Missing will be treated as missing and no data will be imputed.

4.7.2 Sample Size and Power Calculations

It is expected that almost all subjects will provide information on safety and tolerability. Table 4 summarizes the solicited event rates following FluMist and placebo vaccination in healthy adults 18 through 64 years of age in Study AV009.

Table 4 Summary of Solicited Events (Days 0 Through 7) in Study AV009

Number of Subjects	FluMist [a]	Placebo [a]	Difference in Proportions	95% CI [b]
Randomized	3,041	1,520	--	--
Who returned diary cards	2,985	1,490	--	--
Who experienced solicited events	n (%)	n (%)	--	--
Fever				
Oral temperature > 100.0°F	40 (1.34)	20 (1.34)	-0.00	(-0.01, 0.01)
Oral temperature ≥ 101.0°F	17 (0.57)	9 (0.60)	-0.00	(-0.01, 0.00)

Table 4 Summary of Solicited Events (Days 0 Through 7) in Study AV009

Number of Subjects	FluMist [a]	Placebo [a]	Difference in Proportions	95% CI [b]
Oral temperature > 102.0°F	2 (0.07)	2 (0.13)	-0.00	(-0.01, 0.00)
Oral temperature > 103.0°F	0	0	0.00	(-0.00, 0.00)
Runny nose	1,323 (44.32)	397 (26.64)	0.18	(0.15, 0.21)
Sore throat	793 (26.57)	243 (16.31)	0.10	(0.08, 0.13)
Cough	407 (13.64)	152 (10.20)	0.03	(0.01, 0.06)
Headache	1,172 (39.26)	555 (37.25)	0.02	(-0.01, 0.05)
Muscle aches	481 (16.11)	216 (14.50)	0.02	(-0.00, 0.04)
Chills	247 (8.28)	91 (6.11)	0.02	(0.00, 0.04)
Tired/weak	733 (24.56)	306 (20.54)	0.04	(0.01, 0.07)
Any solicited event	2,117 (70.92)	919 (61.68)	0.09	(0.06, 0.12)

CI = confidence interval

[a] Subjects counted if they experienced an event at least once within 7 days following vaccination.

[b] Confidence intervals for the difference in proportions are based on an exact method.

Power to show a similar fever rate with 300 evaluable subjects (240 bivalent vaccine and 60 placebo recipients) for varying true fever rates ranging from 0.5% to 2.0% in placebo recipients is presented in Table 5. Accordingly, the currently proposed study will provide at least 98% power to rule out a rate increase of 5 percentage points assuming the true difference between the treatment groups is zero and the true fever rate is ≤ 1%. Power is lower if the true difference is different from zero. For example, if the true fever rates are 2% and 1% in vaccine and placebo recipients, respectively, the power will be 77%.

Table 5 Power to Show Similar Fever Rates for N = 300 Subjects

True Fever Rate		Exact Power [a]	Exact Type I Error Rate
Vaccine	Placebo		
0.5%	0.5%	99.9%	2.2%
1.0%	1.0%	98.0%	2.3%
1.5%	1.5%	92.6%	2.3%
2.0%	2.0%	85.0%	2.3%
2.0%	1.0%	77.0%	2.3%
3.0%	1.0%	43.9%	2.3%

Note: Similar fever rates mean the ability to rule out a 5 percentage point increase in vaccine recipients. Total N includes 240 vaccine recipients and 60 placebo recipients.

[a] Power was computed using the method proposed by Chan and Zhang, 1999.

Power to show similar event rates for other solicited symptoms with 300 evaluable subjects (240 bivalent vaccine and 60 placebo recipients) for rates ranging from 6% to 37% in placebo recipients is presented in Table 6. Accordingly, the currently proposed study provides at least 87% power to rule out a 20 percentage point increase, assuming the true difference between the 2 treatment groups is zero. Power is lower if the true difference is greater than zero.

Table 6 Power For Secondary Endpoints

Solicited Events	True Event Rates		Rate Increase to be Ruled Out (PPT)	Power [a]
	Vaccine	Placebo		
Runny nose	27%	27%	20	94%
	44%	27%	20	8%
	44%	27%	36	90%
Sore throat	16%	16%	15	92%
	27%	16%	15	13%
	27%	16%	27	91%
Cough	10%	10%	15	99%
	14%	10%	15	82%
	14%	10%	17	93%
Headache	37%	37%	20	87%
Muscle aches	15%	15%	15	93%
Chills	6%	6%	10	95%
Tired/weak	21%	21%	20	98%
	25%	21%	20	86%
	25%	21%	21	90%

PPT = percentage point

Note: Total number includes 240 bivalent vaccine recipients and 60 placebo recipients.

[a] Power was computed using the method proposed by (Chan, 1998) and Proc-Stat (Version 6.2) software.

4.7.3 Endpoints

4.7.3.1 Primary Endpoint

The primary endpoint of this study is fever (Days 1 through 8), defined as oral temperature ≥ 101°F. Comparison of the rate of fever between the 2 treatment groups will be based on the upper limit of the two-sided 95% exact CIs for the rate increase (bivalent vaccine minus placebo) evaluated against the pre-specified equivalence criterion of 5 percentage points.

This corresponds to the null hypothesis of:

H0: Rate difference ≥ 5 percentage points.

The alternative hypothesis is:

HA: Rate difference < 5 percentage points.

A two-sided 95% CI will be constructed using the exact method based on the score statistic proposed by (Chan and Zhang, 1999). This method computes the lower and upper confidence limits by inverting 2 separate one-sided tests of half the nominal Type I error rate. Its test statistic is based on the score statistic that is computed as the observed difference of the 2 binomial event rates minus the hypothesized value of the rate difference (observed rate difference) divided by the standard error of this difference under the alternative hypothesis. This test assures that the Type I error does not exceed the pre-specified level. Due to discreteness when the sample size is relatively small compared to the expected event rate, the associated Type I error rate could be quite conservative, that is, smaller than the pre-specified level.

4.7.3.2 Secondary Endpoints

Secondary endpoints of the study include other reported solicited symptoms and AEs that occur within 7 days after vaccination (Days 1-8), and all solicited symptoms and AEs that occur within 14 days after vaccination (Days 1-15). Additional secondary endpoints include SAEs and NOCDs that occur within 28 days after vaccination (Days 1-29) and within 180 days after vaccination (Days 1 through 181).

Fever will be summarized according to the following thresholds:

- Oral > 100°F
- Oral ≥ 101°F
- Oral > 102°F
- Oral > 103°F

A secondary analysis comparing rates of other solicited symptoms (Days 1-8) between the 2 treatment groups will be performed. Exact two-sided 95% CIs (Chan and Zhang, 1999) on the rate difference (bivalent vaccine minus placebo) will be constructed. There are no pre-specified equivalence criteria for the secondary analyses.

The number of days of solicited symptoms and the proportion of subjects experiencing each event by study day will be presented without formal statistical comparison. The distribution of the number of days with each individual event will also be summarized without formal statistical comparison. The proportion of subjects using antipyretic and analgesic agents within 7 days after vaccination (Days 1-8) and 14 days after vaccination (Days 1-15) will be summarized by treatment group.

4.7.4 Interim Analysis

A safety analysis will be conducted after all subjects have been followed through Day 15 and all data through at least Day 8 are locked. The analysis for Days 1 through 15 will include the primary endpoint of this study (fever for Days 1-8, defined as oral temperature ≥ 101°F), as well as analysis of safety data (solicited symptoms and AEs), and antipyretics and analgesic use reported within 7 days and within 14 days after dosing. To ensure the blinding of each subject's treatment assignment throughout the study, the Day 15 unblinded analyses will be performed by defined MedImmune personnel (see Section 4.5.3.2). Subsequently the unblinded results will be reviewed by the project statistician, medical monitor, therapeutic area vice president, and the Head of Clinical Biostatistics and Data Management prior to approving the release of the unblinded study results to the project team. Since the results of the interim analysis for the primary endpoint will be final, the treatment codes will be sent to Patient Safety within 1 business day of the release of the study results to update the safety databases. Study site personnel and contract research organization personnel directly associated with the conduct of this study and the subjects will remain blinded to the treatment assignment for individual subjects until the completion of the study.

The results of the interim analysis will be reported to regulatory authorities in order to receive authorization for release of the commercial product including the tested new vaccine virus strains.

After the study is complete and the database is locked, all data through 180 days after dosing will be summarized by treatment group using the safety population.

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 electrocardiogram 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). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

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

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Solicited Symptoms

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

- Fever (> 100°F [37.8ºC] oral)
- Runny nose
- Sore throat
- Cough

- Vomiting
- Muscle aches
- Chills
- Decreased activity (tiredness)
- Headache

5.4 Definition of New Onset Chronic Diseases

An NOCD is a newly diagnosed medical condition that is of a chronic, ongoing nature and is assessed by the investigator as medically significant. Examples of NOCDs include but are not limited to diabetes, asthma, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy, autism). Events that would not be considered NOCDs are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, otitis media, bronchitis). An NOCD should also be reported as an SAE if it meets the definition in Section 5.2. If an NOCD occurs within 14 days post dosing, the event should also be reported as an AE (Section 5.1).

5.5 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events 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 MedImmune Patient Safety. See Section 5.2 for the definition of SAEs and Appendix 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.

5.5.1 Time Period for Collection of Adverse Events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period through 14 days post dosing (Days 1 through 15).

All SAEs will be recorded from the time of informed consent through 180 days post dosing (Days 1 through 181).

5.5.2 Recording of Solicited Symptoms

Solicited symptoms will be reported using the terms as defined in this protocol (Section 5.3). Oral thermometers and safety assessment worksheets will be distributed to subjects on the day of investigational product administration. Beginning on the evening of the day of investigational product administration through 14 days after receipt of investigational product (Days 1 through 15), the subject will record on the worksheets his/her temperature and the

occurrence of solicited symptoms. Temperatures should be taken at approximately the same time each day (preferably in the evening); however, if multiple temperatures are taken during a given day, the highest temperature should be recorded on the worksheet regardless of the time of day taken.

5.5.3 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. 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.

5.6 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 inform the appropriate Sponsor representative(s) within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor study representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform Sponsor study representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

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 study representative(s).

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

5.7 Other Events Requiring Immediate Reporting

5.7.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Package Insert (Appendix 3), 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 an AstraZeneca/MedImmune study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate Sponsor study representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor study 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 a SAE, the standard reporting timelines apply (see Section 5.6). For other overdoses, reporting must occur within 30 days.

5.7.2 Pregnancy

All pregnancies and outcomes of pregnancies should be reported to the Sponsor.

5.7.2.1 Maternal Exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor study representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor study representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.2) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

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 Clinical Study 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, 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)

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 Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study 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 the 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 Section 4.1.5).

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. This date will be 180 days after the final subject is entered into the study (Day 181).

6.4 Data Management

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

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the 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 will be provided with contact information for the principal investigator. In addition, each subject 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 Ethical Conduct of the Study

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.

7.2 Subject Data Protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune Medical Monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory Authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should 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 subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrolment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

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

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

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide Regulatory Authorities, IRB/IEC and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

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

7.4 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject 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
- 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

7.5 Changes to the Protocol and Informed Consent Form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

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

7.6 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 assess whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, guidelines of the 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

Centers for Disease Control and Prevention (CDC), 2016. Selecting viruses for the seasonal influenza vaccine. Available from: https://www.cdc.gov/flu/about/season/vaccine-selection.htm.

Chan IS. Exact tests of equivalence and efficacy with a non-zero lower bound for comparative studies. Stat Med. 1998;17:1403-13.

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55:1202-9.

Maassab HF. Plaque formation of influenza virus at 25 degrees C. Nature. 1968;219:645-6.

Maassab H, DeBorde D, Donabedian A, Smitka C. Development of cold-adapted master strains for type-B influenza virus vaccines. In: Lerner R, Chanock R, Brown, F, editors. Vaccines Vol 85. Cold Spring Harbor Laboratory. 1985;p. 327-32.

Appendix 1 Signature of Principal Investigator

Signature of Principal Investigator

A Phase 4, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety of 2 New 6:2 Influenza Virus Reassortants in Adults

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) _____

Appendix 2 Additional Safety Guidance

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 (mild)	An event 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 (moderate)	An event 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 (severe)	An 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 (life threatening)	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 (fatal)	Death (loss of life) 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.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

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).

Appendix 3 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
2017-2018 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: 8/2017

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.

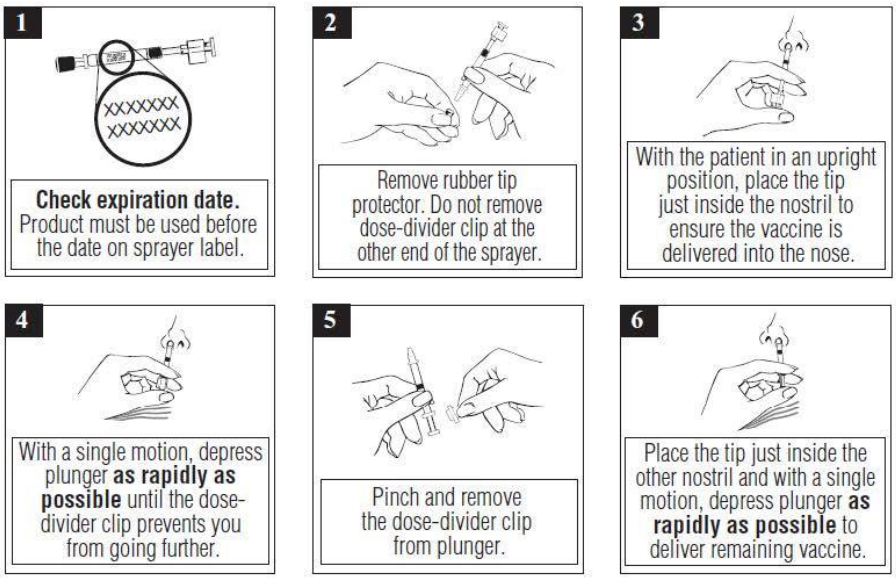
[b] Administer as 0.1 mL per nostril.

"-" 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



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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Severe Allergic Reactions

Do not administer FluMist Quadrivalent to persons who have had a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description (11)*] including egg protein, 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 2017-2018 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/Slovenia/2903/2015 (H1N1) (an A/Michigan/45/2015 (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

(< 0.024 mcg/dose), and may also contain residual amounts of gentamicin sulfate (< 0.015 mcg/mL), and ethylenediaminetetraacetic acid (EDTA) (< 0.37 mcg/dose). FluMist Quadrivalent contains no preservatives.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

Shedding Studies

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

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

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

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

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

Studies in Immunocompromised Individuals

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

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

Twenty mild to moderately immunocompromised children and adolescents 5 through 17 years of age (receiving chemotherapy and/or radiation therapy or who had received chemotherapy in the 12 weeks

prior to enrollment) were randomized 1:1 to receive FluMist or AF-SPG placebo. Frequency and duration of vaccine virus shedding in these immunocompromised children and adolescents were comparable to that seen in healthy children and adolescents. The effectiveness of FluMist and FluMist Quadrivalent in preventing influenza illness in immunocompromised individuals has not been evaluated.

Transmission Study

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

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

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

12.3 Pharmacokinetics

Biodistribution

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

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

14.1 Efficacy Studies of FluMist in Children and Adolescents

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

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

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

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

ATP Population.

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

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

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

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

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

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

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

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

14.2 Immune Response Study of FluMist Quadrivalent in Children and Adolescents

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

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

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

14.3 Effectiveness Study of FluMist in Adults

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

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

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

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

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

14.4 Immune Response Study of FluMist Quadrivalent in Adults

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

comparator vaccine, FluMist, each containing a B strain that corresponded to one of the two B strains in FluMist Quadrivalent (a B strain of the Yamagata lineage and a B strain of the Victoria lineage).

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

14.5 Concomitantly Administered Live Virus Vaccines

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FluMist Quadrivalent is supplied in a package of 10 pre-filled, single-dose (0.2 mL) intranasal sprayers.
The single-use intranasal sprayer is not made with natural rubber latex.
Carton containing 10 intranasal sprayers: NDC 66019-304-10

Single intranasal sprayer: NDC 66019-304-01

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

Issue Date: August 2017

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

Manufactured by:

MedImmune, LLC

Gaithersburg, MD 20878

Issue date: August 2017 RAL-FLUQV6

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Document Name: d2560c00015-csp-v1		
Document Title:	d2560c00015 clinical study protocol version 1	
Document ID:	Doc ID-003765938	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
06-Apr-2018 13:21 UTC	[redacted]	Author Approval
05-Apr-2018 18:45 UTC	[redacted]	Author Approval
05-Apr-2018 19:38 UTC	[redacted]	Author Approval
05-Apr-2018 18:40 UTC	[redacted]	Author Approval

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