DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DVRPA

Date: February 17, 2012

From: Meghan Ferris, M.D., M.P.H.
Medical Officer, Clinical Review Branch 1

Through: R. Douglas Pratt, M.D., M.P.H.
Chief, Clinical Review Branch 1

Subject: Clinical Review of Supplemental Biologics License Application for MedImmune's Quadrivalent Live Attenuated Influenza Vaccine (Q/LAIV)

To: BLA STN# 125020/1668

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 sBLA # 125020/1668

1.1.2 Related Master File and INDs

- IND (b)(4): MedImmune's quadrivalent live, attenuated vaccine
- IND (b)(4): BD's Accuspray nasal spray system (letter authorizing cross-reference included in this sBLA)
- IND (b)(4): MedImmune's trivalent live, attenuated vaccine

1.1.3 Reviewer Name, Division, and Mail Code

Meghan Ferris, M.D., M.P.H
Division of Vaccines and Related Products Applications
HFM-485

1.1.4 Submission Received by FDA

April 5, 2011

1.2 Product

1.2.1 Proper Name

Quadrivalent Live Attenuated Influenza Vaccine, Q/LAIV

1.2.2 Proposed Proprietary Name

FluMist Quadrivalent

1.2.3.1 Product Formulation

Each 0.2mL dose of Q/LAIV contains $10^{7.0\pm0.5}$ FFU of each of 4 cold-adapted (ca), attenuated (att), temperature sensitive (ts), 6:2 reassortant influenza strains (A/H1N1, A/H3N2, B of Victoria lineage, and B of Yamagata). Each dose also contains monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, and monobasic potassium phosphate. Each dose contains residual amounts of ovalbumin and may also contain residual amounts of gentamicin sulfate and ethylenediaminetetraacetic acid (EDTA).

1.3 Applicant

MedImmune, LLC

1.4 Pharmacologic Class

Vaccine

1.5 Proposed Indication

Active immunization for the prevention of disease caused by influenza. The proposed age range for use is 2 years through 49 years.

1.6 Dosage Forms and Route of Administration

Q/LAIV is supplied in the Becton Dickenson (BD) Accuspray device for intranasal administration.

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3 Executive Summary

With this supplement to the biologics license for FluMist, MedImmune is seeking approval to modify the formulation to include a second influenza B strain, and therefore change from a trivalent to a quadrivalent formulation (Q/LAIV) containing attenuated strains of two influenza A virus subtypes, and two influenza type B viruses. Q/LAIV safety and immunogenicity were supported by data from one pivotal pediatric study and one pivotal adult study. An additional study conducted in adults using a ------(b)(4)------ device for vaccine administration, rather than the Becton Dickinson (BD) Accuspray device, was submitted in support of the application. The studies were conducted in the United States.

Efficacy of Q/LAIV was inferred based on a non-inferiority comparison of hemagglutination inhibition (HAI) antibody responses with two different formulations of trivalent FluMist, each one containing one of the two B strain components of Q/LAIV. The primary endpoint was an upper bound of the 95% confidence interval (CI) of the ratio of HAI Geometric Mean Titers (GMT) for trivalent FluMist divided by Q/LAIV of $\leq$ 1.5 for all 4 strains included in the Q/LAIV. All pre-specified endpoints were met. While immune responses in all treatment groups appear relatively low as measured by HAI, clinical efficacy data previously obtained in studies of trivalent FluMist suggested that the immune response parameters evaluated underestimated the product's clinical efficacy, which is substantial in the pediatric population. Due to similarity in manufacturing processes, it is anticipated that Q/LAIV will have similar clinical efficacy, despite the responses measured by HAI. Data from a challenge study in ferrets following Q/LAIV administration is reassuring, as well.

In total, 1198 adults 18 – 49 years of age received Q/LAIV administered using the BD Accuspray device, and another 1199 received Q/LAIV delivered via -----(b)(4)------ device. Slightly more than half of the adult subjects were female (56.4%). The majority were White (71.9%) and non-Hispanic or non-Latino (82.3%). A total of 1382 children received Q/LAIV via BD Accuspray, of whom 299 subjects received a one dose series, and 1083 subjects received a two dose series.

Solicited reactions were monitored during Days 0-14 post-vaccination. Serious and non-serious unsolicited adverse events were monitored during Days 0-28 post-vaccination. Specific adverse events of interest (SAEs, new onset chronic disease) were followed for 6 months following the last immunization in these 3 studies. *Review of the safety data contained in studies MI-CP185, MI-CP206, and MI-CP208 did not identify any major safety concerns.*

Studies evaluating concomitant administration of other vaccines were not performed with Q/LAIV.

The applicant requested a waiver to conduct studies of Q/LAIV in children 0 to <2 years of age and because of the increased risk of wheezing noted in children < 2 years of age in previously reviewed studies of FluMist. *The Pediatric Review Committee (PeRC) concurred with the waiver at its December 14, 2011 meeting.*

The clinical reviewer recommends approval of this sBLA for the indication and age range proposed by the applicant.

4 Significant Findings from Other Review Disciplines

Please see individual review memos of the statistical analysis (Dr. Sang Ahnn), the proposed post-marketing safety evaluation (Dr. Jane Woo), and the proposed post-marketing effectiveness evaluation (Dr. Hector Izurieta).

5 Clinical and Regulatory Background

5.1.1 Epidemiology

In the United States, influenza epidemics occur yearly, usually from late Fall through early Spring. Influenza viruses cause morbidity in all age groups, although rates of infection are highest among children[1]. Serious illness and death tend to be most frequent in people < 2 years old, > 65 years old, and people with underlying medical conditions. An August 2010 Morbiditiy and Mortality Weekly Report (MMWR)[2] cited the average (from 1976 – 2007) influenza-associated mortality rate for people < 19 years of age as 0.1 per 100,000. For adults 19 - < 65 years, this rate was 0.4 per 100,000, and for adults > 65 years old, the rate was 17 per 100,000. The report did not provide a further breakdown by age of influenza-associated mortality rates for individuals < 19 years of age. However, the Centers for Disease Control summary of influenza activity for 2010 – 2011[3] provided rates of hospitalization for laboratory-confirmed influenza in children 0 - 4 years of age during the 2010 – 2011 influenza season ranging from 38.5 – 45.7 per 100,000, while similar rates for other age groups were as follows: 8.0 – 8.9 per 100,000 among 5 – 17 year olds, 10.2 – 11.1 per 100,000 among 18 – 49 year olds, 20.9 – 22.5 per 100,000 among 50 – 64 year olds, and 64.5 – 65.0 per 100,000 among individuals $\geq$ 65 years of age.

Two types of influenza viruses cause epidemic disease in people: Influenza A and B. Two surface antigens, hemagglutinin and neuraminidase, are the basis for subtyping Influenza A viruses. Influenza A subtypes and B viruses are grouped by antigenic similarities. Incremental antigenic changes in hemagglutinin and neuraminidase, or drift, produce new influenza virus variants, necessitating periodic changes in seasonal influenza vaccine formulations to protect against the circulating strains.

Vaccination is the primary method of prevention of influenza disease. In the United States, trivalent inactivated influenza vaccines are licensed for use in people $\geq$ 6 months of age, while live, attenuated influenza vaccine is licensed for use in people 2 – 49 years of age. The licensed influenza vaccines are more effective against antigenically matched strains. The strains included in these vaccines are based on annual predictions of which strains will circulate in the upcoming influenza season, as determined by global influenza surveillance. Strain selection does not always match the circulating strains. Two antigenically distinct lineages of influenza B viruses co-circulate, complicating selection of the B strain for inclusion in a trivalent vaccine. At a 2009 meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, panelists suggested expanding influenza vaccines to contain 4 virus strains: A/H1N1, A/H3N2, and 1 strain from each of the 2 type B lineages.

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[1] CDC. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010.

[2] CDC. *Morbidity and Mortality Weekly Report*. Estimates of Deaths Associated with Seasonal Influenza – United States, 1976 – 2007. August 27, 2010 / 59(33);1057-1062

[3] CDC. *FluView*. http://www.cdc.gov/flu/weekly/weeklyarchives2010-2011/10-11summary.htm

5.1.2 Immune correlates

No immune correlate of protection has been identified for influenza vaccines, although anti-hemagglutinin antibody (HI) titers of 1:32 to 1:40 represent a level at which approximately half of individuals have been shown to be protected in some studies. Previous experience with inactivated trivalent influenza vaccines suggests that HI titers may be useful in the evaluation of vaccine effectiveness. However, experience with the live, attenuated trivalent influenza vaccine suggests that HI titers appear to underestimate the vaccine's clinical efficacy or effectiveness.

5.1.3 Rationale for selected formulation

Q/LAIV is comparable to the applicant's licensed trivalent live, attenuated seasonal influenza vaccine (FluMist) other than the addition of the fourth vaccine virus strain. The virus content for each strain is based on the content for the 3 strains in FluMist. The BD Accuspray device which is used to administer trivalent FluMist is planned for use with Q/LAIV.

5.2 Regulatory Background Information

5.2.1 Chronology of Regulatory Review

06/13/03: approval of FluMist in healthy individuals 5 – 49 years of age
01/05/07: approval of the conversion from FluMist frozen formulation to liquid formulation
09/19/07: approval of FluMist in healthy individuals 2 – 49 years of age
02/17/11: pre-sBLA meeting
04/05/11: sBLA received
04/29/11: Refuse-to-File (RTF) letter sent, due to omission of datasets required for sBLA review
05/26/11: Type A meeting to discuss RTF action; sBLA filed over protest

5.2.2 Basis for Licensure

The licensure of Q/LAIV is based on the following aspects:

As the manufacturing process for Q/LAIV is the same as that for trivalent FluMist, with the addition of a second B strain, clinical efficacy data from pediatric studies of FluMist and clinical effectiveness data from adult studies of FluMist, are considered supportive of licensure of Q/LAIV. A challenge study in ferrets following vaccination with Q/LAIV was supportive, as well. Further, the applicant submitted data from two clinical trials, MI-CP185 (NCT00860067) a study conducted in adults and MI-CP208 (NCT01091246) a study conducted in children, with supportive data from MI-CP206 (NCT00952705).

- Demonstration of efficacy: Non-inferiority comparison of HAI antibody responses to the Q/LAIV when compared with the trivalent FluMist.
- Demonstration of safety comparable to trivalent FluMist

In addition, the applicant has commited to conducting post-marketing studies to confirm effectiveness and further evaluate safety.

5.2.3 Previous Human Experience with the Product including Foreign Experience

There is no previous human experience with the Q/LAIV.

Trivalent FluMist has been marketed in the United States since 2003 and in Canada since June 2010 and was approved by the European Commission in February 2011. According to the applicant, it has been approved in Brazil, Hong Kong, Israel, and the Republic of Korea, as well.

The clinical review contributing to the original FluMist approval for use in healthy subjects 5-49 years of age in June 2003 noted that FluMist recipients one and one-half to five years of age had increased rates of asthma/reactive airway disease in the 42 days after vaccination in study AV019. Also, the review included study AV010, submitted again to the current supplemental BLA, which evaluated safety of FluMist in 9 – 17 year olds with moderate to severe asthma. The review described a potential safety signal, namely an imbalance in the proportion of subjects with asthma exacerbations, with a higher incidence in the 24 FluMist recipients as compared with the 24 placebo recipients. The label included a warning that the vaccine was not to be administered to subjects with a history of asthma until this signal in children could be further evaluated.

A formulation change was approved on January 5, 2006. The original frozen formulation required frozen storage until use. The new formulation (called liquid) does not require frozen storage. In making the change of formulation from frozen to liquid, the volume was reduced from 0.5 mL to 0.2 mL, in addition to minor modifications in the excipients. Studies submitted in the current label supplement BLA used either frozen or liquid FluMist.

Extension of the indication to individuals 2 – < 60 months was approved in September 2007.

6 Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA Sections Reviewed

The following sections of the BLA were reviewed:
m 1.3.4 Financial Disclosure
m 1.14.1.1 Draft Carton and Container Labels
m 1.14.1.2 Annotated Draft Labeling Text
m 1.14.1.3 Draft Labeling Text
m 5.2 Tabular Listing of all Clinical Studies
m 5.3.5.1 Clinical Study Reports (MI-CP185, MI-CP206,)

Amendment 6 (May 18, 2011): final study report, MI-CP208
Amendment 15 (October 17, 2011): response to clinical information request
Amendment 30 (February 8, 2012): response to clinical information request

6.2 Overview of Clinical Studies

Safety and immunogenicity data from three clinical studies of Q/LAIV were submitted in the sBLA, which included pivotal immunogenicity and safety studies in adults and children, as well as a supporting study of the safety and immunogenicity of Q/LAIV administered using a ------(b)(4)---- device. Clinical study reports and/or data listings for the U.S. Package Insert tables were included for 11 additional studies of trivalent FluMist. These 11 studies were reviewed previously by Drs. Mink, Cvetkovich, and Baylor in the context of the original BLA submission or the sBLA which resulted in extending the lower age limit for trivalent FluMist from 5 years to 2 years. Therefore, only the 3 studies evaluating Q/LAIV were reviewed here. The applicant submitted data from these 11 studies to this sBLA at CBER's request so that the Q/LAIV

application would contain an electronic, easily accessible copy of these data which support the U.S. Package Insert for trivalent FluMist, which is the basis for the U.S. Package Insert for the Q/LAIV. These studies (and the FDA /CBER clinical reviewers who reviewed them previously) are: AV006 (Dr. Mink), AV008 (Dr. Mink), AV009 (Dr. Mink), AV018 (Drs. Cvetkovich and Baylor), AV019 (Dr. Mink), D145-P500 (Dr. Mink), D153-P501 (Drs. Cvetkovich and Baylor), D153-P526 (Dr. Cvetkovich), DMID 98-005 (Dr. Mink), MI-CP111 (Drs. Cvetkovich and Baylor; only the data listings for the United States Package Insert Tables included in this sBLA), and MI-CP112 (Dr. Cvetkovich). The applicant also submitted electronic tables of pooled analyses of reactogenicity events from Day 0 – Day 10 post-dose in subjects 2 – 8 years old from the placebo controlled trials AV006 and D153-P501 and of pooled analyses of safety tables for FluMist including data from studies AL002, AR001, AV002, AV002-2, AV006 Year 1, AV007, AV010, AV012 Year 1, AV012 Year 2, AV012 Year 3, AV012 Year 4, AV014, AV015, AV017, AV018, AV019, CP111, CP112, CP123, D145-P500, D153-P002, D153-P005, D153-P500, D153-P501 Year 1, D153-P501 Year 2, D153-P502 Year 1, D153-P503, D153-P504 Year 1, D153-P504 Year 2, D153-P511, D153-P513, D153-P514, D153-P515, D153-P522, D153-P526, DMID99-012, FM026, PM001.

Similarly, the report from the pharmocokinetic study and initial tolerability study "Scintigraphic Assessment of the Nasal Deposition and Clearance of a Solution Formulation Using Two Novel Dosing Devices" evaluating deposition and clearance from the nasal cavity and regions of interest was reviewed by Dr. Cvetkovich. Studies AV009, MI-CP111, D153-P510, and AV006 were efficacy studies, and study AV018 was the study of concomitant live vaccines (FluMist and MMR&V). The applicant provided some updates to the clinical study report for study D153-P500, which included a statistical report and results of a post-study Reed Frost analysis of the probability of transmission, results of genotypic analysis not available at the time of the original report, details for generating reconstructed data sets, and a comparison of the differences between the original and reconstructed databases, changes to tables generated from a statistical QC, changes to authorization signatures, and other administrative revisions.

Please refer to Dr. Jane Woo's review of study FM025, a proposal for the post-marketing safety study of Q/LAIV in children.

Table 1. Overview of Studies

Study [No.] Country	Study description	Study Start/ End	Vaccination schedule	Immunizations	Number of subjects vaccinated
MI-CP185 United States	Phase 2b/3, immunogenicity and safety study Evaluation of non-inferiority of Q/LAIV to FluMist/B/Yamagata and FluMist/B/Victoria Randomization 4:1:1 Double-blind Active control	March 23, 2009/October 9, 2009	1 dose (Day 0)	Q/LAIV 0.2 mL IN FluMist-Y 0.2 mL IN FluMist-V 0.2 mL IN	1197 298 299
MI-CP206 United States	Phase 2b/3, immunogenicity and safety study Evaluation of non-inferiority of Q/LAIV to FluMist/B/Yamagata and FluMist/B/Victoria Randomization 4:1:1 Partial-blind Active control	August 14, 2009/March 3, 2010	1 dose (Day 0)	Q/LAIV 0.2 mL IN via (b)(4) FluMist-Y 0.2 mL IN via (b)(4) FluMist-V 0.2 mL IN via (b)(4)	1198 298 298
MI-CP208 United States	Phase 3, immunogenicity and safety study Evaluation of non-inferiority of Q/LAIV to FluMist/B/Yamagata and FluMist/B/Victoria Randomization 3:1:1 Double-blind Active control	March 29, 2010/December 27, 2010	2 – 8 years: 2 doses (Day 0 and 28 – 35 days later) 9 – 17 years: 1 dose (Day 0)	Q/LAIV 0.2 mL IN FluMist-Y 0.2 mL IN FluMist-V 0.2 mL IN	1382 463 460

7 Clinical Studies

Pivotal Clinical Studies:

Study MI-CP185 (NCT00860067):
A randomized, double-blind, active controlled study to evaluate the immunogenicity of MEDI3250 in adults 18 to 49 years of age.

Objectives
Primary objective:
To demonstrate the immunologic noninferiority of Q/LAIV to 2 formulations of FluMist by comparing the strain-specific geometric mean titers (GMTs) of hemagglutination inhibition (HAI) antibody post dosing.

Secondary objectives:
1) To estimate the proportion of subjects who experienced strain-specific HAI seroresponse following Q/LAIV

2) To estimate the proportion of subjects who achieved a strain-specific HAI antibody titer $\geq$ 32 following Q/LAIV

3) To assess the safety and tolerability Q/LAIV

Study Design: This study was a randomized, double-blind, active controlled, multicenter Phase 2b/3 trial. Subjects 18 – 49 were randomized 4:1:1 to receive a single dose of either Q/LAIV, FluMist-Y, or FluMist-V during the influenza off-season.

Study Period: March 23, 2009 – October 9, 2009

Population
The study was conducted at 18 U.S. study sites.

Inclusion criteria

- Male or female
- Age 18 - 49 years at randomization
- Written informed consent and any locally required authorization in the USA obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Females of childbearing potential, unless surgically sterile; had sterile male partner; were premenarchal; or practiced abstinence; were required to use an effective method of avoiding pregnancy for 30 days prior to the first dose of investigational product, and were to agree to continue using such precautions for 60 days after the final dose of investigational product
- A subject who was considered by the investigator to be at risk of pregnancy had to have a negative urine pregnancy test at screening and, if screening and Day 0 did not occur on the same day, on the day of vaccination prior to randomization. Investigator judgment was required to assess each subject's need for pregnancy testing
- Healthy by medical history and physical examination OR presence of stable underlying chronic medical condition for which hospitalization had not been required in the previous year
- Able to complete follow-up period of 180 days post last dose of vaccine as required by the protocol
- Subject was available by telephone
- Able to understand and comply with the requirements of the protocol, as judged by the investigator

Exclusion criteria

- Acute illness or evidence of significant active infection at randomization
- Fever $\geq$ 100.4°F (38.0°C) at randomization
- History of asthma
- Any drug therapy from 15 days prior to randomization or expected drug therapy through 30 days post last dose with the exception of the following classes/types of medications, which were allowed:
  a) contraceptives
  b) chronic medications (including those taken on an as-needed basis) that had been well tolerated and were not initiated and/or did not have a dosage change within 90 days prior to randomization
- Previous medical history or evidence of an intercurrent illness that may have compromised the subject's safety
- Current or expected receipt of immunosuppressive medications within a 30 day window around vaccination, including an immunosuppressive dose of corticosteroids, which was defined as $\geq$ 20 mg/day of prednisone or its equivalent, given daily or on alternate days for $\geq$ 14 days) (inhaled, and topical corticosteroids were permitted)

- Receipt of immunoglobulin or blood products within 90 days before randomization into the study or expected receipt during study participation
- Receipt of any investigational drug therapy within 30 days prior to investigational product through 30 days post-vaccination;
- Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV);
- History of allergic disease or reactions likely to be exacerbated by any component of the investigational product including allergy to eggs, egg proteins, gentamicin, or gelatin or serious, life-threatening, or severe reactions to previous influenza vaccinations;
- History of Guillain-Barre syndrome;
- Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir, and zanamivir) within 30 days prior to first dose of investigational product or anticipated use of such agents within 30 days after last scheduled vaccination;
- Known or suspected mitochondrial encephalomyopathy
- Lactating female;
- History of alcohol or drug abuse that, in the opinion of the investigator, would have affected the subject's safety or compliance with the study;
- Any condition that, in the opinion of the investigator, might have compromised the safety of the subject in the study or would interfere with evaluation of the safety or immunogenicity of the investigational products;
- Subject or immediate family member of subject who was an employee of the clinical study site or who was otherwise involved with the conduct of the study

Reasons for deferring vaccination:

- meeting any of the above time-limited criteria

Vaccine administration

Participants received Q/LAIV, FluMist-Y, or FluMist-V as intranasal spray using the Becton Dickinson (BD) Accuspray device. The 0.2 mL dose of each FluMist vaccine was formulated to contain $10^{7.0\pm0.5}$.fluorescent focus units (FFU) of each of the 3 vaccine strains, and the final 0.2 mL dose of Q/LAIV was formulated to contain $10^{7.0\pm0.5}$ FFU of each of the 4 vaccine strains, with a maximum total calculated virus content of 10^8 FFU per 0.2 mL dose. The strains included in the Q/LAIV were: A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguary/716/2007), B/Victoria (B/Malaysia/2506/2004), and B/Yamagata (B/Florida/4/2006). The strains included in the trivalent FluMist study formulations were the same, with the exception that they each contained only one B strain. The lot numbers were as follows: Q/LAIV lot 0141700024, FluMist-Y lot 0141500588, FluMist-V lot 0141700025.

Endpoints

Primary endpoints:

Post dose strain-specific serum HAI antibody GMT, regardless of baseline serostatus. Immunologic noninferiority of Q/LAIV to FluMist would be demonstrated if the post dose strain-specific serum HAI antibody GMTs for all 4 strains in the Q/LAIV arm were noninferior to those in the combined FluMist arms for the A strains and to the relevant B-strain containing FluMist group for the B strains..

Secondary endpoints:

Immunologic:

1. The proportion of subjects who experienced post dose strain-specific HAI antibodyseroresponse by baseline serostatus (seronegative, serosusceptible, andregardless of serostatus)
2. The proportion of subjects who achieved a post dose strain-specific HAI antibody titer ≥ 32 by baseline serostatus (seronegative, serosusceptible, and regardless of serostatus)

Strain-specific baseline serostatus was defined as serosusceptible if HAI antibody titers were ≤ 8 and seropositive if > 8.

Seroresponse was defined as a ≥ 4-fold rise from baseline. Serosusceptible was defined as baseline strain specific HAI antibody titer of ≤ 8; a value of two was assigned for an HAI antibody titer reported as < 4

Safety:
1. Proportion of subjects experiencing solicited symptoms through 14 days post vaccination
2. Proportion of subjects experiencing adverse events through 28 days post vaccination
3. Serious adverse events experienced from administration of investigational product through 28 days post vaccination
4. Serious adverse events experienced through 180 days post-vaccination
5. Description of new onset chronic diseases through 180 days post-vaccination

Randomization
Subjects were randomized 4:1:1 to receive Q/LAIV, FluMist/B/Yamagata (FluMist-Y), or FluMist/B/Victoria (FluMist-V). Enrollment at each site was capped at 100 subjects. Randomization employed a block design with a fixed block size of 6. An interactive voice response system (IVRS) was used for randomization to a treatment arm and assignment of blinded investigational product kit numbers and sprayer numbers according to a computer-generated randomization schedule prepared by the ----------(b)(4)----------. The IVRS assigned each subject to the next sequential sprayer number after stratification by site.

Surveillance
Safety parameters:
Study participants were monitored for at least 15 minutes post-vaccination and for solicited symptoms days 0 – 14 after each dose, adverse events and concomitant medication use days 0 - 28 post-immunization, with reactions reported on memory aids for days 0 – 14 post vaccination. Memory aids were not collected by sites but were used to improve accuracy of reporting to sites during telephone calls and follow-up visits. Solicited adverse events included fever ≥ 100.4°F (38.0°C) by any route, runny/stuffy nose, sore throat, cough, headache, generalized muscle aches, decreased activity level (lethargy) or tiredness/weakness, and decreased appetite.

Three telephone contacts occurred: at 3 – 5 days, 7 – 10 days, and 14 – 18 days post vaccination to monitor for safety. Additional telephone contacts occurred approximately monthly from Day 60 – Day 180.

Serious adverse events and new onset chronic diseases were collected through 180 days post-vaccination.

Efficacy (immunogenicity):
Serum samples for influenza HAI antibody testing were collected pre-vaccination and at 28 – 35 days post-vaccination. The antibody testing was performed at MedImmune (---(b)(4)---).

Assay methods and laboratories:
Sera were separated at the site and stored ----------(b)(4)---------- until batched and shipped to MedImmune (---(b)(4)---). Standard HAI assays were performed in duplicate, with the GMT of the 2 results the final per-subject result. If duplicate assay runs differed by ----------(b)(4)----------, the assay was repeated. If no inhibition of hemagglutination was observed, the titer was reported as <4 (imputed as 2 for analyses of immune responses).

Statistical plan
Sample size calculations

A total of 1800 subjects randomized 4:1:1 to Q/LAIV, FluMist/B/Yamagata, and FluMist/B/Victoria provided > 97% power to rule out a > 1.5-fold difference in the post-dose serum HAI GMT ratios for each of the 4 strain-specific tests regardless of baseline serostatus. These calculations assumed a 90% evaluability rate, a true post final dose GMT ratio for serum HAI measurements of 1, and a standard deviation of the natural logarithm transformed HAI titer of 1.4 for all 4 strains. Study dropouts were not replaced.

Planned interim analyses occurred after Day 28 and included the immunologic and safety data collected through 28 days post-vaccination. This was the final analysis of the primary and secondary immunogenicity endpoints, so no statistical adjustment was applied. The second formal analysis was the analysis of SAEs and NOCDs occurring through Day 180. To ensure blinding of treatment assignment throughout the study, the Day 28 unblinded analyses were performed by a limited number of MedImmune personnel not involved in the remainder of the study. Study site personnel, MedImmune, and CRO personnel directly involved in study conduct, as well as the subjects, remained blinded to the treatment assignment for individual subjects until study completion.

Missing data were not imputed.

Primary Hypotheses
Non-inferiority of immune response was assessed by evaluating the upper bound of the two-sided 95% CIs for the strain-specific HAI antibody GMT ratios (FluMist/QLAIV) to the non-inferiority margin of 1.5. If the upper bound of CIs was $\leq$ 1.5 for all 4 strains, immunologic noninferiority of Q/LAIV compared to FluMist was declared. No adjustment was made for multiple comparisons.
H0: Rj > 1.5, for any j
HA: Rj $\leq$ 1.5, for all j
Where Rj was any of the 4 strain-specific post immunogenicity dose GMT ratios:
• (FluMist-Y) / (Q/LAIV) for B/Yamagata strain
• (FluMist-V) / (Q/LAIV) for B/Victoria strain
• (FluMist-Y + FluMist-V) / (Q/LAIV) for A/H1N1 strain
• (FluMist-Y + FluMist-V) / (Q/LAIV) for A/H3N2 strain

Populations analyzed
Safety population:
All subjects who received any investigational product and had any safety data recorded. The Evaluable Safety Population for solicited symptoms excluded subjects who had no solicited symptom data available during the summarized period.

Intent-to-treat population:
All randomized subjects.

Immunogenicity population:
All subjects who received a full dose of investigational product and had post dose HAI antibody measurement and had no protocol deviation judged by the applicant before unblinding to have potential to interfere with the generation or interpretation of an immune response.

Primary endpoint analyses were based on the Immunogenicity Population. Safety endpoint analyses were based on the Safety Population. Summaries of solicited symptoms were based on the Evaluable Safety Population for solicited symptoms.

Safety Analyses
Analyses were based on the safety population and included the number of subjects with solicited symptoms through Day 14 post-vaccination, the number of days subjects experienced solicited symptoms through Day 14 post-vaccination, and the number of subjects with solicited symptoms by study day. Tabular summaries were provided for each treatment arm and for the 2 FluMist arms combined. AEs, SAEs, and NOCDs were summarized by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0. AEs and SAEs were also summarized by severity and relationship to investigational product (as determined by the investigator and/or MedImmune). Safety evaluations were descriptive; no formal statistical comparisons of safety outcomes were planned or conducted.

Immunogenicity Analyses
Analyses were based on the immunogenicity population and included GMTs of HAI antibody at baseline and post-dose, seroconversion/seroresponse rates by baseline serostatus, number of subjects with baseline HAI titer $\geq$ 32 by baseline serostatus, and distribution of strain-specific HAI antibody titers, Strain-specific GMTs were summarized by treatment group and by sample time (i.e., baseline or post-immunogenicity dose). No multiplicity adjustment was used.

Protocol Amendments (Amendments to IND):
Amendment 1: 20 November 2008. Protocol amended to exclude subjects with known or suspected mitochondrial encephalomyopathy.

Amendment 2: 23 January 2009. Protocol amended to an adult-only study, removing all information relating to Cohort 1 (subjects 9 – 17 years of age) and Cohort 2 (subjects 2 – 8 years of age). Clarified that the diary worksheet was a memory aid and would not be collected; changed the severity grading scale from mild, moderate, or severe to Grade 1 to 5 consistent with CDISC version 3.1.1; an external safety monitoring committee was used; Appendix 1 (Toxicity Grading Scale for Solicited Symptoms) was deleted, and subsequent appendices renumbered. **All subjects were enrolled under this protocol amendment.**

Results:

Population

A total of 1924 subjects were screened, and 1800 subjects were randomized. Most subjects who were not randomized were ineligible for the study. Two randomized subjects were not dosed: 1 withdrew consent prior to dosing, and 1 was found to be pregnant prior to dosing. The subject who withdrew prior to dosing was the only withdrawal prior to Day 28. A total of 1777 subjects were dosed and followed for safety through Day 28 post-dose 1. A total of 1731 subjects (96.2%)

completed the study. Of the 69 subjects who did not complete the study, 64 (3.6%) were lost to follow-up, 4 (0.2%) withdrew consent, and 1 (0.1%) withdrew for other reasons. No one withdrew due to an AE or SAE.

> *Clinical Reviewer Comment: The distribution of subjects who did not complete the study was fairly balanced, although the proportion of subjects not completing the study was slightly higher (4.3%) in the Q/LAIV group as compared with the FluMist/B/Yamagata and FluMist/B/Victoria groups (3.0% each). There were no withdrawals of consent among the FluMist recipients, but 0.3% of Q/LAIV recipients withdrew consent.*

In the ITT Population, the mean age overall was 32.7 years and was similar across treatment groups. All groups had slightly more female than male subjects (54.8% - 56.8% females vs. 43.2% - 45.2% males). Most subjects were White (76.3% overall), and 20.9% of subjects overall were African American. The overall proportion of subjects identifying themselves as Hispanic or Latino was 22.7%. These proportions were similar across treatment groups.

Safety population:
The Evaluable Safety Population included 1794 subjects. The Evaluable Safety Population was all subjects who received any investigational product and had any solicited symptom data available.

Immunogenicity population:
The Immunogenicity Population included 1770 subjects. From the 1800 subjects randomized, 30 subjects were excluded from the Immunogenicity Population because they did not have post-dose HAI antibody measurements (28, including the 2 subjects not dosed) or took excluded anti-influenza antiviral concomitant medication for treatment of laboratory documented influenza (2). One subject was enrolled in the Q/LAIV arm as meeting all inclusion and exclusion criteria but during assessment of an SAE was found to have had a history of HIV infection prior to study screening; this subject was included in the Immunogenicity Population because this major protocol deviation was discovered after the Day 28 analysis was complete and data had been unblinded. One subject was excluded from the Immunogenicity Population for seroconversion/seroresponse analysis only because the date of this subject's Day 0 sample was recorded as 1 day after dosing in the eCRF; the investigator confirmed that the sample had been obtained prior to dosing after database lock and unblinding. Since inclusion in the Immunogenicity Population was determined prior to unblinding, the subject's data were not included in the seroconversion/seroresponse analysis. Six subjects took a potentially restricted medication (corticosteroid), but the doses and durations were in alignment with the protocol-specified allowable amount and time period, so data from these subjects were included in all analyses.

The following applicant-provided table summarizes the subject populations evaluated:

Table 2. Study MI-CP185. Overview of Subject Populations Evaluated

Population Reason for exclusion	Q/LAIV	All FluMist[a]	FluMist-Y	FluMist-V	Total
All subjects randomized	1200	600	299	301	1800
Intent-to-Treat (ITT) Population [a]	1200	600	299	301	1800
Safety Population[b]	1198	598	298	300	1796[c]
Evaluable Safety Population for Solicited Symptoms[d]	1197	597	298	299	1794
Immunogenicity Population [e]	1181	589	292	297	1770
Reason excluded					
Did not receive any investigational product	2	0	0	0	2
Did not have post-immunogenicity dose HAI measurement [g]	18	10	7	3	28
Received antiviral medication for laboratory-confirmed influenza	1	1	0	1	2

Source: Table 11.1-1, page 69/3955 of the study MI-CP185 clinical study report
HAI: hemagglutination inhibition; ITT: Intent-to-Treat; NA: not applicable
a: ITT Population included all randomized subjects
b: Safety Population included all subjects who received any investigational product and had any follow-up safety data available
c: The number of subjects in the safety population increased by 1 between the interim and final CSR. One subject was temporarily lost to follow-up and then re-contacted for the collection of safety data for SAEs and NOCDs
d: Immunogenicity Population included subjects who received a full dose of investigational product, had post-dose HAI measurements, and had no protocol violation judged to have the potential to interfere with the generation or interpretation of an immune response
e: Evaluable Safety Population for solicited symptoms included all subjects who received any investigational product and had any solicited symptom data available

Safety:

Overall safety profile: A total of 713/1197 (59.6%) Q/LAIV recipients and 358/597 (60.0%) FluMist recipients reported at least one solicited symptom. Runny nose/stuffy nose was the most commonly reported solicited symptom, slightly more common among Q/LAIV subjects (43.6%) compared with All FluMist subjects (39.5%), but with a similar frequency as the FluMist/B/Victoria recipients. Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 1 – 2. The median number of days of solicited symptoms across all groups was < 3.0.

> *Clinical Reviewer Comment: These rates are similar to those observed in pediatric study MI-CP208, in which the frequency of solicited symptoms was often more similar between the Q/LAIV subjects and the subjects who received one or the other of the trivalent vaccines, suggesting that some of the difference in reactogenicity between the Q/LAIV group and the All Flumist group may be associated with greater reactogenicity to one B strain compared with the other. In this study, MI-CP185, FluMist/B/Victoria was associated with more solicited symptoms as compared with FluMist/B/Yamagata, whereas in the pediatric study MI-CP208, the opposite was observed.*

Immediate reactions:
A 38 year-old white male reported throat tightening of 1 minute duration which occurred 4 minutes after receiving FluMist/B/Yamagata. He did not require any medical intervention, was observed for 30 minutes, rather than 15, and he recovered. One subject experienced hypersensitivity (allergic reaction with bronchospasm) approximately 26 hours after receiving FluMist/B/Victoria; this event was considered an SAE and is described in more detail below.

Solicited reactions:

The applicant provided the following table showing the rate of each solicited AE in the Q/LAIV, All FluMist, FluMist-V, and FluMist-Y treatment arms, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post Dose 1:

Table 3. Study MI-CP185. Rates of Solicited Adverse Events, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post Dose 1

Solicited symptom	Q/LAIV n (%) (N = 1197)	All FluMist n (%) (N = 597)	FluMist-Y n (%) (N = 298)	FluMist-V n (%) (N = 299)	Rate difference percentage points[a]
Any solicited symptom	713 (59.6)	358 (60.0)	167 (56.0)	191 (63.9)	- 0.4
Fever[b]					
≥ 100.4F (38.0C)	16 (1.3)	9 (1.5)	3 (1.0)	6 (2.0)	- 0.2
≥ 101.3F (38.5C)	9 (0.8)	2 (0.3)	1 (0.3)	1 (0.3)	0.4
≥ 102.2F (39.0C)	4 (0.3)	1 (0.2)	1 (0.3)	0 (0.0)	0.2
≥ 103.1F (39.5C)	1 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	- 0.1
≥ 104.0F (40.0C)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0
≥ 104.9F (40.5C)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Runny/stuffy nose	522 (43.6)	236 (39.5)	110 (36.9)	126 (42.1)	4.1
Sore throat[b]	227 (19.0)	118 (19.8)	59 (19.8)	59 (19.7)	- 0.8
Cough	163 (13.6)	75 (12.6)	40 (13.4)	35 (11.7)	1.1
Headache[b]	338 (28.2)	164 (27.5)	71 (23.8)	93 (31.1)	0.8
Generalized muscle aches[b]	121 (10.1)	59 (9.9)	26 (8.7)	33 (11.0)	0.2
Decreased activity level (lethargy) or tiredness/weakness	211 (17.6)	106 (17.8)	54 (18.1)	52 (17.4)	- 0.1
Decreased appetite	77 (6.4)	32 (5.4)	14 (4.7)	18 (6.0)	1.1

Source: Table 12.2.-1, page 101 of the MI-CP 185 CSR
a Q/LAIV rate minus All FluMist rate, where the All FluMist group refers to data from both the FluMist/B/Yamagata arm and the FluMist/B/Victoria arm combined
b Temperature by any route

Exploratory subgroup analyses of solicited symptoms by race, gender, and ethnicity provided by the applicant suggested that a larger proportion of African American subjects reported runny/stuffy nose after Q/LAIV than after FluMist (45.7% vs 33.6%), which was also true for subjects who were not of Hispanic/Latino ethnicity (47.2% vs 41.2%). A larger proportion of Hispanic/Latino subjects reported headache after Q/LAIV (26.2%) than after FluMist (21.0%). In their subgroup analyses, the applicant found that no other solicited symptoms were reported by > 5% more Q/LAIV subjects than FluMist subjects.

Unsolicited AEs:
A similar proportion of Q/LAIV and All FluMist recipients reported adverse events days 0 – 28 post-vaccination: 210 Q/LAIV recipients (17.5%) reporting 303 events and 118 (19.7%) All FluMist recipients reported 154 events. In contrast to the solicited symptoms, more FluMist/B/Yamagata recipients than FluMist/B/Victoria recipients reported unsolicited adverse events (23.8% vs 15.7%). One Q/LAIV recipient and one FluMist/B/Victoria recipient experienced laboratory-confirmed influenza.

All MedDRA preferred term AEs were reported with a rate difference of < 1.0. The preferred term AEs with the largest rate differences were sneezing, with a rate difference (Q/LAIV – All FluMist) of 0.7%, and back pain and rhinorrhea with rate differences of – 0.8%. The most commonly reported AEs among Q/LAIV subjects were sneezing, oropharyngeal pain, upper

respiratory tract infection, and cough, all reported in ≤ 1.5% of subjects in each group. Among the All FluMist subjects, in addition to these, were rhinorrhea and headache.

Nine Q/LAIV recipients (0.8%) reported 12 severe (Grade 3) events, and 6 All FluMist recipients (1.0%) reported 7 severe (Grade 3) events. By preferred term, the Grade 3 AEs among Q/LAIV recipients were diarrhea, vomiting, diverticulitis, kidney infection, upper respiratory tract infection, fibula fracture, tibia fracture, multiple injuries, cough, sneezing (1 subject each) and headache (2 subjects). Grade 3 AEs reported by subjects who received FluMist/B/Yamagata were toothache, face injury, musculoskeletal pain, and asthma (1 subject each). Grade 3 AEs reported by FluMist/B/Victoria recipients were hypersensitivity, nasopharyngitis, and cough (1 subject each).

Two events of asthma were reported, one of which was an SAE and is described in detail below. Another subject had newly diagnosed asthma 10 days post-vaccination with Q/LAIV; the event was ongoing at Day 28, but the subject did not receive any medications to treat the asthma (this event was also reported as an NOCD). Two subjects reported wheezing post-vaccination, but neither subject received treatment. These subjects were FluMist/B/Yamagata and FluMist/B/Victoria recipients who developed wheezing days 11 – 18 and 13 – 19 post-vaccination, respectively.

Four subjects reported epistaxis during Days 0 – 28 post-vaccination; 2 of these events occurred on Day 0 (1 subject each in the Q/LAIV and FluMist/B/Victoria treatment groups).

According to the applicant's exploratory subgroup analyses, proportionately more male subjects in the All FluMist group (19.8%) reported having at least one AE during Days 0 - 28 post-vaccination than did male subjects in the Q/LAIV arm (13.3%). The proportion of female subjects who reported the occurrenceof at least one AE during this time period was similar between treatment groups. Proportionally more African American subjects in the All FluMist group (17.5%) reported the occurrence of at least one AE during days 0 – 28 post-vaccination compared with African American subjects in the Q/LAIV arm (11.6%). There was no MedRA system organ class (SOC) term in which AEs were reported with a rate difference of more than 1% where more Q/LAIV subjects reported events than All FluMist subjects except for rhinorrhea (rate difference 1.2%). The proportion of White subjects who reported the occurrence of at least one AE during Days 0 – 28 post-vaccination was similar between treatment groups. There was no SOC term in which events were reported with a rate difference of more than 1%, but rhinorrhea was reported with a rate difference of 1.3% (0.7% among Q/LAIV recipients and 2.0% among All FluMist recipients).

Serious adverse events (SAEs):
There were 5 SAEs reported in 4 subjects days 0 – 28 post-vaccination. During days 0 – 180 after vaccination, 12 (0.4%) Q/LAIV recipients reported 17 SAEs, and 6 (0.5%) of All FluMist recipients reported 7 SAEs. These numbers include the SAEs reported within 28 days of vaccination. All SAEs required hospitalization except for 1 SAE which was reported as an important medical event.

The SAEs are described in more detail below, based on the provider's case narratives:
Days 0 – 28 post-vaccination:

- A 24 year-old White, Hispanic male with obesity experienced sigmoid diverticulitis with local perforation approximately 10 days post-vaccination with Q/LAIV. In the clinical reviewer's opinion, despite the temporal relationship to vaccination, due to the nature of

the event, it is unlikely that either the diverticulitis with bowel perforation or the diabetes mellitus were related to vaccination.

- A 41 year-old White male was hospitalized for a closed right tibia fracture and right fibula fracture after being involved in a mountain biking accident approximately 3 weeks post-vaccination with Q/LAIV. In the clinical reviewer's opinion, due to the nature of the event, it is unlikely related to vaccination.
- A 39 year-old White, Hispanic male with history of smoking was transported by ambulance to the emergency room complaining of throat tightening and shortness of breath of 12 hours duration (onset approximately 26 hours post-dosing) and intermittent sharp chest pain which occurred 2 days post-vaccination with FluMist/B/Victoria. The subject was in moderate respiratory distress, with inspiratory and expiratory wheezes and a respiratory rate of 20 breaths/minute. He was hospitalized and treated with intravenous (IV) methylprednisolone, nebulizers, and IV antibiotics. The investigator indicated that an allergic reaction was the etiology, and the event with bronchospasm resolved. According to the applicant, no other potential source of an allergic reaction was identified. Given that no other potential source of allergic reaction was identified, it is likely that the SAE was vaccine-related.
- A 25 year-old African American female with history of asthma since childhood with numerous hospitalizations, including an intensive care unit (ICU) admission the year prior to vaccination, and prior use of tobacco, and concomitant medications including fluticasone/salmeterol 250/50 two puffs/day, albuterol 2 puffs as needed for asthma, and ibuprofen, had an uncontrolled asthma attack unresponsive to her usual medications approximately 3 weeks post-vaccination with FluMist/B/Yamagata. Her hospital course included admission to the ICU, continuous nebulizers, Heliox 70/30, and magnesium sulfate. She recovered. In the clinical reviewer's opinion, it is possible that the SAE was related to vaccination. The subject would have met exclusion criteria for this study, based on her history of asthma. The history of an intensive care unit admission for asthma within one year suggests that her asthma may have been severe.

SAEs Occuring Days 29 – 180 post-vaccination:

- Approximately 3 months post-vaccination with Q/LAIV, a 23 year-old African American male with history of substance abuse was transferred to the ER following a 3-day stay at a rehabilitation center with complaints of abdominal pain, nausea, vomiting with blood, and diarrhea. He was diagnosed with early colitis. *Clostridium difficile* toxin was identified in a stool sample. Given the nature and timing of the event, it is unlikely related to vaccination.
- Approximately 4 months post-vaccination with Q/LAIV, a 23 year-old Native American female with history of gallstones was diagnosed with acute cholecystitis, underwent cholecystectomy and recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 33 year-old African American male with history of human immunodeficiency virus syndrome, hepatitis C, bipolar disorder, alcohol and tobacco use, polysubstance drug abuse, and allergy to haloperidol attempted to inject crystal methamphetamine IV approximately 2 months post-vaccination with Q/LAIV. Three days later, he presented to the ER with severe arm pain radiating to the right chest and right back, fever, and chills. A CT scan of the left arm showed necrosis and/or extensive abscess involvement. The postsurgical diagnosis was gas gangrene of the left upper extremity. The subject was in septic shock and was transferred to the ICU. Results of would cultures revealed *Streptococcus viridans, Bacteroides, Prevotella, Porphyromonas,* and *Fusobacterium*.

Blood cultures were negative. After a compliated hospital course, he recovered. Given the nature and timing of the event, it is unlikely related to vaccination.

- A 46 year-old White, Hispanic male developed flu-like symptoms including fever, night sweats, productive cough, and difficulty breathing 1 month post-vaccination with Q/LAIV. He was admitted for pneumonia. He was discharged on antibiotics and albuterol/ipratropium and considered recovered. Given the nature and timing of the event, it is possibly related to vaccination.
- A 42 year-old White, Hispanic female fell while stepping on the sidewalk and twisted her ankle approximately 3.5 months post-vaccination with Q/LAIV. After initial casting by a podiatrist, she was hospitalized for an open reduction internal fixation. Although the subject reported no medication use to the study site, concomitant medications reported by the admitting hospital included albuterol, fluticasone propionate, and other non-asthma medications. Neither the hospital nor the study site had a record of a history of asthma or airway disease. She was discharged from the hospital, but she returned the next day with severe, sharp pain in the lower left quadrant, with fever and intermittent nausea and vomiting. CT scan revealed diverticulitis versus focal colitis, and she was hospitalized for new onset diverticulitis. She was treated with antibiotics IV and then discharged on ciprofloxacin and metronidazole. The diverticulitis was considered recovered, but the fractures were ongoing at the time that the subject was lost to follow-up, almost 6 months post-vaccination. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 42 year-old White, Hispanic female with history of multiple sclerosis, asthma, and encephalopathy and concomitant medications including interferon B-1b. Approximately 5 months after vaccination with Q/LAIV, she felt disoriented, light-headed, and had a headache while driving to work. She drove to the hospital and was found wandering in the parking lot, confused, and stumbling. In the ER, she was evaluated as somnolent and dysarthric, and was admitted. Head CT was negative for acute intracranial hemorrhage and atrophy. ECG was normal. A psychiatric consult resulted in the diagnosis of significant psychosis of unknown etiology; possibly schizophrenia, post-traumatic stress disease, or organic etiology. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 42 year-old White male with history including cardiac catheterization in 2000 for chest pain with a diagnosis of coronary vasospasm and family history of heart disease in all males in their fifth or sixth decade of life. Approximately 3 months post-vaccination with Q/LAIV, he developed retrosternal chest pressure radiating down the right arm and associated with diaphoresis. He was discharged with a final diagnosis of coronary vasospasm and considered recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 22 year-old White female presented to the ER approximately 3.5 months post-vaccination with Q/LAIV with nausea, vomiting, diffuse abdominal pain which then localized to the right, with guarding. She was hospitalized for laparoscopic appendectomy and discharged on cephalexin and recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 36 year-old White female presented to the ER with sharp pain radiating around to her back approximately 4.5 months post-vaccination with Q/LAIV. An abdominal ultrasound showed cholelithiasis without acute cholecystitis, mild dilatation of the common bile duct, mild and diffuse fatty liver, multiple echogenic foci in the right kidney, and possible renal calculi. She was hospitalized and underwent a laparoscopic cholecystectomy. She was then discharged and considered recovered. Given the nature and timing of the event, it is unlikely related to vaccination.

- A 35 year-old White, Hispanic male was in a motorcycle accident approximately 5.5 months post-vaccination with Q/LAIV. Radiographic studies showed a closed right radiostyloid fracture, a closed tarsal navicular fracture of the right foot, a closed distal phalanx fracture of the right great toe, questionable avulsion fracture of the base of the third metatarsal, nondisplaced fracture of the right iliac crest, nondisplaced fracture of the calcaneus, and a pulmonary infiltrate with pleural effusion. He recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 47 year-old African American male with history of substance abuse and tobacco use presented to the ER with chest tightness from his throat to his chest and radiating to the left arm approximately 1 month post-vaccination with FluMist/B/Victoria and 1 hour after he stopped smoking crack. He was discharged with final diagnoses of ST segment elevation anterior wall myocardial infarction, dyslipidemia, hypertension, cocaine abuse, and tobacco dependence. Congestive heart failure secondary to myocardial injury resolved with furosemide. The event was considered recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 43 year-old White female with history including uterine fibroids, endometrial ablation, and ovarian cyst was hospitalized approximately 5 months post-vaccination with FluMist/B/Victoria for laparoscopic supracervical hysterectomy and bilateral salpingo-oopherectomy. The subject was discharged and considered recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 49 year-old White female with history of menorrhagia, polymenorrhea, and dysmenorrheal was hospitalized for leiomyoma of the uterus, and a supracervical hysterectomy was performed approximately 5.5 months post-vaccination with FluMist/B/Yamagata. She was discharged and considered recovered. Given the nature and timing of the event, it is unlikely related to vaccination.
- A 41 year-old White female with history including menorrhagia, worsening prior to enrollment, was hospitalized for a hysterectomy due to this history approximately 3 months post-vaccination with FluMist/B/Yamagata. She was discharged, and the event considered resolved. Given the nature and timing of the event, it is unlikely related to vaccination.

Notably, since the study was conducted in the influenza off-season, the study vaccines were not formulated to contain the CDC-designated influenza strains for the upcoming influenza season. Subjects were offered a dose of commercial seasonal influenza vaccine after 28 day safety data was collected but before day 180. Therefore, it is possible that some SAEs occured post-vaccination with commercial vaccine. However, since the rate of SAE occurrence was similar across treatment arms, it is unlikely that any administration of this optional commercial seasonal influenza vaccine affects the interpretation of the safety data.
No deaths were reported.

No subjects withdrew due to an AE or SAE.

<u>New Onset Chronic Diseases from Day 0 – Day 180:</u>
During Days 0 – 180 post-vaccination, new onset chronic diseases (NOCDs) were reported by 12/1198 (0.9%) Q/LAIV recipients and 6/598 (0.7%) FluMist recipients (0.7% in both the FluMist/B/Yamagata and FluMist/B/Victoria treatment groups). The NOCDs reported by Q/LAIV recipients were: Factor V Leiden mutation, repetitive strain injury, diabetes mellitus, Type 2 diabetes mellitus, anxiety, bipolar disorder, asthma (1 subject each); hypothyroidism (2 subjects), and hypertension (3 subjects). The NOCDs reported by FluMist/B/Yamagata subjects

were: bursitis, uterine leiomyoma, and anxiety (1 subject each). FluMist/B/Victoria recipients reported the following NOCDs: dyslipidemia, anxiety, and hypertension (1 subject each).

Pregnancy:
Eight pregnancies were reported. One woman was randomized but not dosed due to the positive pregnancy test; the outcome of her pregnancy was unknown. Three subjects delivered healthy babies at 38 weeks (FluMist/B/Yamagata), at 37.5 weeks (FluMist/B/Victoria), and at 39 weeks (Q/LAIV). Two FluMist/B/Victoria recipients and one Q/LAIV recipient delivered healthy babies of unspecified gestational age. The pregnancy outcome for the remaining subject, a Q/LAIV recipient, was unknown.

Other:
Due to the increased rates of wheezing and hospitalization for pneumonia among FluMist (vs placebo) recipients younger than 2 years of age in earlier studies, the number of subjects in each treatment arm who reported wheezing or asthma or pneumonia or use of medication to treat wheezing or asthma in this adult study was evaluated (post-hoc analysis by CBER reviewer). The intent of the analysis was to evaluate further whether there was a signal of increased wheezing or pneumonia among Q/LAIV recipients compared with trivalent FluMist recipients which might be associated with the addition of the fourth influenza strain. Medications to treat pneumonia were not analyzed, as only 2 subjects were reported as having pneumonia. The sources of these analyses were the adverse events and concomitant medications datasets submitted by the applicant. These analyses did not suggest an increased risk of wheezing or asthma or pneumonia among Q/LAIV subjects. The interpretation of these findings is limited by such factors as their stemming from post-hoc analyses.

Table 4. Study MI-CP185. Post-hoc Evaluation of Wheezing, Asthma, or Pneumonia or Use of Medication to Treat Wheezing or Asthma

	Q/LAIV	FluMist-Y	FluMist-V
Unsolicited AE (# subjects)			
Wheezing or asthma	1	2	1
Pneumonia	1	1	0
Medication (# subjects)			
Albuterol	0	1	1
Steroid (any) for wheezing or asthma	0	1	1
Indication asthma or wheezing for concomitant meds			
Number of subjects	0	1	1
Number of meds	0[a]	16[b]	5[c]

Source: CBER clinical reviewer
a: per concomitant medication dataset
b: albuterol, advair, atrovent, avelox, azithromycin, duoneb, epinephrine, heliox, hydrocortisone, magnesium sulfate, potassium chloride, prednisone, solumedrol, (please note that antibiotics, such as avelox, azithromycin, may be used to treat an underlying infectious etiology for an asthma exacerbation or an associated pneumonia, but are not used to treat asthma or wheezing, per se; potassium chloride is not used to treat asthma or wheezing, per se, but may be used to correct transient serum hypokalemia associated with use of beta-agonists, such as albuterol; duoneb is albuterol + ipratropium; atrovent = ipratropium; hydrocortisone, prednisone, and solumedrol are all steroids)
c: IV antibiotics, IV solution, nebulizers, prednisone, azithromycin

Immunogenicity:

Primary immunogenicity endpoint:
The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody $\leq$ 1.5 for each strain. The GMT ratios

ranged from 0.92 – 1.10, and the upper limits of the 95% CI ranged from 1.03 – 1.25. Baseline GMTs were fairly similar between Q/LAIV and comparator groups, with the largest difference in baseline GMTs between the FluMist/B/Yamagata group and the Q/LAIV group for baseline GMTs for B/Yamagata (44.3 vs 37.3, respectively). The applicant-provided table below includes the GMTs for each strain for the Q/LAIV and comparator vaccines:

Table 5. Study MI-CP185. GMTs for Each Q/LAIV and Comparator Vaccine Strain

Strain	Q/LAIV		Comparator [a]		GMT Ratio and 95% CI	
	N	GMT[b]	N	GMT[b]	Ratio[c]	95% CI[d]
A/H1N1	1181	5.9	589	6.5	1.09	1.01, 1.18
A/H3N2	1181	7.5	589	7.8	1.05	0.96, 1.14
B/Yamagata	1181	51.2	292	56.4	1.10	0.97, 1.25
B/Victoria	1181	36.5	297	33.6	0.92	0.82, 1.03

Source: Table 11.4.1.1-2 page 74/3955 of the study MI-CP185 clinical study report
GMT: geometric mean titer; HAI: hemagglutination inhibition
a: comparator = All FluMist group for A/H1N1 and A/H3N2 strains, where the All FluMist group refers to data from both the FluMist-Y arm and the FluMist-V arm combined; comparator = FluMist-Y for the B/Yamagata strain and FluMist-V for the B/Victoria strain
b: a value of 2 was assigned for an HAI antibody titer reported as < 4
c: GMT in comparator divided by GMT in Q/LAIV

Secondary immunogenicity endpoints:
Four-fold rise:
Among all subjects, regardless of baseline serostatus, seroresponse/seroconversion rates were < 10%, with the exception of those for B/Yamagata.

Table 6. Study MI-CP185. Post-Vaccination Strain-Specific Seroconversion/Seroresponse Rates

Strain	Q/LAIV	FluMist (V + Y)	FluMist/B/Victoria	FluMist/B/Yamagata
H1N1	3.6% (42/1181)	2.9% (17/589)	4.4% (13/297)	1.4% (4/292)
H3N2	3.7% (44/1181)	2.9% (17/589)	3.0% (9/297)	2.7% (8/292)
B/Victoria	11.4% (135/1181)	--	11.1% (33/297)	3.8% (11/292)
B/Yamagata	9.7% (114/1181)	--	3.7% (11/297)	9.9% (29/292)

Source: results of CBER statistical reviewer's analysis
*If the baseline titer is < 4, the post-vac titer considered as demonstrating seroconversion was ≥ 16
If the baseline titer is ≥ 4, the post-vac titer considered as demonstrating seroconversion was ≥ 4 times the baseline titer

The applicant performed additional analyses to evaluate the added benefit of the Q/LAIV in terms of the immune response to the B strain not contained in the comparator vaccine. These results are presented below.

Table 7. Study MI-CP185. Ratio of Post-Vaccination GMTs of HAI Antibody – Comparison of B Strain Antibody Responses to Q/LAIV with Those to FluMist Formulation Not Containing the Corresponding B Strain, Immunogenicity Population for Analysis of HAI Antibody

		Q/LAIV		Comparator		GMT Ratio and 95% CI	
Baseline serostatus	Strain	N	GMT (95% CI)	N	GMT (95% CI)	Ratio	95% CI
All	B/Yamagata	1181	51.2 (48.44, 54.22)	297	42.4 (37.61, 47.86)	0.83	(0.73, 0.95)
	B/Victoria	1181	36.5 (34.66, 38.59)	292	28.7 (25.48, 32.44)	0.78	(0.69, 0.90)
Serosusceptible	B/Yamagata	197	11.9 (10.51, 13.59)	45	8.3 (6.23, 11.06)	0.69	(0.50, 0.95)
	B/Victoria	250	12.3 (10.85, 13.81)	69	8.5 (6.99, 10.55)	0.70	(0.55, 0.89)
Seropositive	B/Yamagata	983	68.6 (64.45, 73.07)	252	56.9 (49.90, 64.80)	0.83	(0.72, 0.96)
	B/Victoria	930	49.1 (46.23, 52.10)	223	41.7 (36.18, 48.38)	0.85	(0.73, 1.00)

Source: Table 5.10.1.3, page 32/100 of the MI-CP185 sBLA Supplemental Tables

Summary:
Overall, Q/LAIV appeared as safe and immunogenic as the trivalent FluMist. A total of 713/1197 (59.6%) Q/LAIV recipients and 358/597 (60.0%) FluMist recipients reported at least one solicited symptom. Runny nose/stuffy nose was the most commonly reported solicited symptom, slightly more common among Q/LAIV subjects (43.6%) compared with FluMist subjects (39.5%), but with a similar frequency as the FluMist/B/Victoria recipients. Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 1 – 2. The median number of days of solicited symptoms across all groups was < 3.0. Fever (≥38°) was reported in ≤ 2% in any treatment group.

One subject, a 38 year-old white male reported throat tightening of 1 minute duration which occurred 4 minutes after receiving FluMist/B/Yamagata. He did not require any medical intervention, was observed for 30 minutes, rather than 15, and he recovered. Another subject experienced hypersensitivity (allergic reaction with bronchspasm) approximately 26 hours after receiving FluMist/B/Victoria.

One Q/LAIV recipient had a new diagnosis of asthma within 2 weeks of vaccination. CBER's post-hoc analysis of wheezing did not suggest an increased risk of wheezing in the Q/LAIV group compared to the trivalent FluMist groups.

The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody ≤ 1.5 for each strain. The GMT ratios ranged from 0.92 – 1.10, and the upper limits of the 95% CI ranged from 1.03 – 1.25. Baseline GMTs were fairly similar between Q/LAIV and comparator groups.

Study MI-CP208 (NCT01091246):

A phase III, randomized, double-blind, active controlled study, double-to evaluate the immunogenicity of quadrivalent LAIV in children.

Objectives

Primary objective:
To demonstrate the immunologic noninferiority of Q/LAIV to FluMist in children 2 – 17 years of age by comparing the post dose strain-specific geometric mean titers (GMTs) of serum hemagglutination inhibition (HAI) antibody.

Secondary objectives:
1) To estimate the proportion of subjects 2 – 17 years of age who experienced post dose strain-specific HAI antibody response

2) To estimate the proportion of subjects 2 – 17 years of age who achieved a post dose strain-specific HAI antibody titer $\geq$ 32

3) To assess the safety and tolerability of Q/LAIV in individuals 2 – 17 years of age, as two doses in subjects 2 – 8 years of age and as a single dose in subjects 9 – 17 years of age

Study Design: This study was a randomized, active controlled, multicenter Phase 3 trial. Randomization was 3:1:1 to receive Q/LAIV, trivalent FluMist containing an influenza B strain from the Yamagata lineage (FluMist-Y), or trivalent FluMist containing an influenza B strain from the Victoria lineage (FluMist-V). Randomization was stratified by age (2 – 8 years, 9 – 17 years). For subjects 2 – 8 years of age, randomization was stratified by history or previous seasonal influenza vaccination.

Study Period: March 29, 2010 – December 27, 2010

Population
The study was conducted at 97 U.S. study sites. Enrollment in Canada was planned but did not occur due to the time required for Canadian regulatory approval.

Inclusion criteria
- Male or female
- Age 2 – 17 years at randomization
- Written informed consent and any locally required authorization in the USA and written informed assent, if applicable, obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
- Females of childbearing potential, unless surgically sterile; had sterile male partner; were premenarchal; or practiced abstinence; were required to use an effective method of avoiding pregnancy for 30 days prior to the first dose of investigational product, and were to agree to continue using such precautions for 60 days after the final dose of investigational product
- A subject who was considered by the investigator to be at risk of pregnancy had to have a negative urine pregnancy test at screening and, if screening and Day 0 did not occur on

the same day, on the day of vaccination prior to randomization. Investigator judgment was required to assess each subject's need for pregnancy testing
- Healthy by medical history and physical examination OR presence of stable underlying chronic medical condition for which hospitalization had not been required in the previous year
- Able to complete follow-up period of 180 days post last dose of vaccine as required by the protocol
- Subject/legal representative was available by telephone
- Child's legal representative was able to understand and comply with the requirements of the protocol, as judged by the investigator

Exclusion criteria
- Acute illness or evidence of significant active infection at randomization
- Fever $\geq$ 100.4°F (38.0°C) at randomization
- History of asthma, or in children < 5 years of age, history of recurrent wheezing
- Any drug therapy from 15 days prior to randomization or expected drug therapy through 28 days post last dose with the exception of the following classes/types of medications, which were allowed:
  a) contraceptives (change in contraceptive type or method was acceptable as long as guidelines were followed for prevention of pregnancy during change);
  b) topical corticosteroids, calcineurin inhibitors, or antifungals for uncomplicated dermatitis;
  c) chronic medications (including those taken on an as-needed basis) that had been well tolerated and were not initiated and/or did not have a dosage change within 90 days prior to randomization
- current or expected receipt of immunosuppressive medications within a 28 day window around any dose, including an immunosuppressive dose of corticosteroids, which was defined as $\geq$ 20 mg/day of prednisone or its equivalent, given daily or on alternate days for $\geq$ 15 days) (intranasal, intra-articular, and topical corticosteroids were permitted)
- Receipt of immunoglobulin or blood products within 90 days before randomization into the study or expected receipt during study participation
- Receipt of any investigational drug therapy within 28 days prior to Dose 1 or planned receipt of any investigational drug therapy through 90 days after final dosing of investigational product (use of licensed agents for indications not listed in the package insert was permitted);
- Receipt of any nonstudy vaccine within 28 days prior to randomization or planned receipt of nonstudy vaccine through 28 days after final dosing;
- Receipt of any nonstudy seasonal influenza vaccine within 90 days of Dose 1 or planned receipt of nonstudy seasonal influenza vaccine prior to 35 days post last dose of investigational product;
- Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV);
- History of allergic disease or reactions likely to be exacerbated by any component of the investigational product including allergy to eggs, egg proteins, gentamicin, or gelatin or serious, life-threatening, or severe reactions to previous influenza vaccinations;
- Use of aspirin or salicylate-containing medications within 28 days prior to randomization or expected receipt through 28 days after final vaccination;
- History of Guillain-Barre syndrome;
- Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir, and zanamivir) within 28 days prior to first dose of

investigational product or anticipated use of such agents within 28 days after last scheduled vaccination;
- Known or suspected mitochondrial encephalomyopathy
- Pregnant or lactating female;
- History of alcohol or drug abuse that, in the opinion of the investigator, would have affected the subject's safety or compliance with the study;
- Any condition that, in the opinion of the investigator, might have compromised the safety of the subject in the study or would interfere with evaluation of the safety or immunogenicity of the investigational products;
- Subject, legal representative, or immediate family member of subject who was an employee of the clinical study site or who was otherwise involved with the conduct of the study;
- A history of epilepsy, seizure, or an evolving neurological condition except that a single febrile seizure that occurred 3 or more years prior to enrollment would not disqualify a subject

Reasons for deferring vaccination:
- meeting any of the above time-limited criteria

Exclusion criteria (dose 2):
- Withdrawal of consent
- Fever $\geq$ 100.4°F (38.0°C) or evidence of significant active infection on the day of dosing
- Anaphylactic reaction or other hypersensitivity reaction assessed as possibly, probably, or definitely related to investigational product by study investigator or medical monitor
- Receipt or expected receipt within a 28 days window around Dose 2 of:
  a) immunosuppressive medications, including an immunosuppressive dose of corticosteroids, defined as above
  b) nonstudy vaccine
  c) antiviral agents with activity against influenza
  d) aspirin or salicylate-containing medications
- Investigational drug therapy within 28 days prior to Dose 1 or planned receipt of any investigational drug therapy through 90 days after final dosing of investigational product (use of licensed agents for indications not listed in the package insert was permitted)
- Receipt or expected receipt of immunoglobulin or blood products or any nonstudy seasonal influenza vaccine from the period between 90 days prior to Dose 1 to when the final blood sample was obtained or 28 days after the last study dose, whichever was later
- Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with HIV
- A virologically confirmed case of influenza. Virologic confirmation was a positive result for influenza of any type in a laboratory assay of any type
- Any condition that, in the opinion of the investigator, might have compromised the safety of the subject upon repeat dosing or that would have interfered with evaluation of the safety or immunogenicity of the investigational products.

Vaccine administration
Participants received Q/LAIV, FluMist-Y, or FluMist-V as intranasal spray using the Becton Dickinson (BD) Accuspray device. The 0.2 mL dose of each FluMist vaccine was formulated to contain $10^{7.0\pm0.5}$.fluorescent focus units (FFU) of each of the 3 vaccine strains, and the final 0.2 mL dose of Q/LAIV was formulated to contain $10^{7.0\pm0.5}$ FFU of each of the 4 vaccine strains, with a maximum total calculated virus content of 10^8 FFU per 0.2 mL dose. The lot numbers were as follows: Q/LAIV lot 0141700024, FluMist-Y lot 0141500588, FluMist-V lot 0141700025.

Endpoints
Primary endpoints:
Post dose strain-specific serum HAI antibody GMT, regardless of baseline serostatus. Immunologic noninferiority of Q/LAIV to FluMist would be demonstrated if the post dose strain-specific serum HAI antibody GMTs for all 4 strains in the Q/LAIV arm were noninferior to those in the FluMist arms.

Secondary endpoints:
Immunologic:

1. The proportion of subjects who experienced post dose strain-specific HAI antibody seroresponse by baseline serostatus (seronegative, serosusceptible, and regardless of serostatus)
2. The proportion of subjects who achieved a post dose strain-specific HAI antibody titer $\geq$ 32 by baseline serostatus (seronegative, serosusceptible, and regardless of serostatus)

Strain-specific baseline serostatus was defined as seronegative if HAI antibody titers were $\leq$ 4 and serosusceptible if HAI antibody titers were $\leq$ 8.

Seroresponse was defined as a $\geq$ 4-fold rise from baseline. Seronegative was defined as baseline strain-specific HAI antibody titer $\leq$ 4; serosusceptible was defined as baseline strain specific HAI antibody titer of $\leq$ 8; a value of two was assigned for an HAI antibody titer reported as < 4

Safety:

1. Solicited symptoms experienced from administration of investigational product through 14 days post vaccination by dose number (as appropriate)
2. Adverse events experienced from administration of investigational product through 28 days post vaccination by dose number (as appropriate)
3. Serious adverse events experienced from administration of investigational product through 28 days post vaccination by dose number (as appropriate)
4. Serious adverse events and new onset chronic disease (NOCD) through 180 days after the final dose.

Randomization
Performed using an interactive voice response system (IVRS) at screening (all subjects screened), at randomization/assignment of Dose 1 (all eligible subjects), and assignment of Dose 2 (for randomized subjects age 2 to 8 years of age). The IVRS used to assign the SID number to each subject at screening was used again for randomizing each eligible subject to a treatment arm and assigning investigational product kit number(s) and BD Accuspray device number(s). Randomization incorporated a block design and stratification by age (2 – 8 years, 9 – 17 years). For subjects 2 – 8 years of age only, randomization was also stratified by previous seasonal influenza vaccination history.

Surveillance

Safety parameters:

Study participants were monitored for at least 15 minutes post-vaccination and for solicited symptoms days 0 – 14 after each dose, adverse events and concomitant medication use days 0 - 28 post-immunization, with reactions reported on memory aids by subjects' guardians for days 0 – 14 post vaccination. Solicited adverse events included fever ≥ 100.4°F (38.0°C) by any route, runny/stuffy nose, sore throat, cough, headache, generalized muscle aches, decreased activity level (lethargy) or tiredness/weakness, and decreased appetite. Certain symptoms were not collected if the investigator determined that the subject was too young to report a particular symptom reliably. Temperature logs were collected day 28 – 35.

Three telephone contacts occurred: at 3 – 5 days, 7 – 10 days, and 14 – 18 days post vaccination to monitor for safety. Additional telephone contacts occurred approximately monthly from Day 60 – Day 180.

Serious adverse events and new onset chronic diseases were collected through 180 days post-vaccination.

Effectiveness (immunogenicity):

Serum samples for influenza HAI antibody testing were collected pre-vaccination and during the designated immunogenicity sample time point. For all subjects who received one dose (9 – 17 year olds), this timepoint was 28 – 35 days after vaccination. For the two-dose group (2 – 8 years old), subjects who previously had received a dose of any seasonal influenza vaccine had blood collected 28 – 35 days post dose 1, and subjects who had never received a seaonsal influenza vaccine had blood collected 28 – 35 days post dose 2. The antibody testing was performed at MedImmune (---(b)(4)---).

Statistical plan

Sample size calculations

A sample size of 1380 subjects in the Q/LAIV arm provided > 98% confidence to detect an AE that occurred at a rate of 0.3%. For the primary endpoint, 1380 subjects in the Q/LAIV arm and 460 subjects in each of the two FluMist arms and the noninferiority margin of 1.5 for GMT ratios, the study provided ≥ 92% power to demonstrate immunologic noninferiority of Q/LAIV compared to FluMist measured by the post immunogenicity dose serum HAI antibody GMT ratios (FluMist divided by Q/LAIV) for all of the 4 strains simultaneously if the true GMT ratio was ≤ 1.1 for all 4 strains.

Primary Hypotheses

Non-inferiority of immune response was assessed by evaluating the upper bound of the two-sided 95% CIs for the strain-specific HAI antibody GMT ratios (FluMist/QLAIV) to the non-inferiority margin of 1.5. If the upper bound of CIs was ≤ 1.5 for all 4 strains, immunologic noninferiority of Q/LAIV compared to FluMist was declared. No adjustment was made for multiple comparisons.

H0: $R_j > 1.5$, for any j
HA: $R_j \leq 1.5$, for all j
Where Rj was any of the 4 strain-specific post immunogenicity dose GMT ratios:

- (FluMist-Y) / (Q/LAIV) for B/Yamagata strain
- (FluMist-V) / (Q/LAIV) for B/Victoria strain
- (FluMist-Y + FluMist-V) / (Q/LAIV) for A/H1N1 strain
- (FluMist-Y + FluMist-V) / (Q/LAIV) for A/H3N2 strain

Populations analyzed
Safety population:
All subjects who received any investigational product and had safety data available.

Intent-to-treat population:
All randomized subjects.

As-treated population:
All subjects who received any investigational product. Used only in the analysis of vaccine exposure.

Immunogenicity population:
All subjects who received any investigational product and had post dose HAI antibody measurement as defined below and had no protocol deviation judged by the applicant to have potential to interfere with the generation or interpretation of an immune response. Protocol deviations were identified prior to unblinding for the analysis of 28-day post-vaccination data. In fact, no subjects were excluded from the Immunogenicity Population except for those subjects who were not dosed or who did not have HAI results.

- One dose group (9 – 17 years of age): received a dose of investigational product and had post dose HAI antibody measurement
- Two-dose group (2 – 8 years of age) with history of prior seasonal influenza vaccination: received a dose of investigational product at dose 2 and had post dose 2 HAI antibody measurement
- Two-dose group (2 – 8 years of age) without history of prior seasonal influenza vaccination: received a dose of investigational product at doses 1 and 2 and had post dose 2 HAI antibody measurement

Subjects who received different vaccines at dose 1 and dose 2 were excluded from all immunogenicity analyses except for recipients of one of the trivalent vaccines who received the other trivalent vaccine at the other dose; these subjects were included in the FluMist immunogenicity analyses for H1N1 and H3N2.

Primary endpoint analyses were based on the Immunogenicity Population.

Safety Analyses
Analyses based on the safety population which includes the number of subjects with solicited symptoms through Day 14 post-vaccination, the number of days subjects experienced solicited symptoms through Day 14 post-vaccination, and the number of subjects with solicited symptoms by study day. Tabulations and rate differences were provided for the proportion of subjects experiencing each solicited symptom. Descriptive statistics were also used. The following AE summaries were provided: number of subjects with AEs through 28 days post-dose, number of subjects with AEs through 28 days post-dose by highest severity, number of subjects with AEs through 28 days post-dose sorted by frequency, number of subjects with related AEs through 28 days, number of subjects with SAEs through 28 days, number of subjects with SAEs through 28 days by SAE criteria, number of subjects with related SAEs through 28 days, number of subjects with SAEs through 180 days, number of subjects with SAEs through 180 days post-last dose by SAE criteria, number of subjects with related SAEs through day 180.

Immunogenicity Analyses

Analyses based on the immunogenicity population include the ratio of post-immunogenicity dose GMTs and GMFRs of HAI antibody, GMTs of HAI antibody at baseline and post-immunogenicity dose, post-immunogenicity dose seroconversion/seroresponse rates by baseline

serostatus, number of subjects with baseline HAI titer ≥ 32 by baseline serostatus, and distribution of strain-specific HAI antibody titers, Strain-specific GMTs were summarized by treatment group and by sample time (i.e., baseline or post-immunogenicity dose). No multiplicity adjustment was used.

Protocol Amendments (Amendments to IND):
Amendment 1: 17 September 2009. Protocol amended to remove the --------(b)(4)--------- arm, changing the number of subjects enrolled but permitting blinding. The primary endpoint was amended such that it was met if the UL of the 95% CI for the strain-specific HAI antibody GMT ratios (FluMist divided by Q/LAIV) was ≤ 2 for all 4 strains. The definition of seronegative and serosusceptible was amended to include HAI antibody values that were not whole numbers because each time point was assayed in duplicate, and if the results were --------(b)(4)-------, the GMT was calculated and used for analysis. If values differed ----------(b)(4)---------- for a single specimen the assays were repeated.

Amendment 2: 8 March 2010. Protocol amended to add unblinded MI-CP185 safety and immunogenicity data and to change the noninferiority margin from 2.0 to 1.5 in accordance with CBER advice. Also, "site" was removed as a stratification for randomization because the study was to be conducted in approximately 120 sites in the USA and Canada and given the 3:1:1 randomization ratio and stratification by age group and vaccine history, there would have been so many strata that stratification by site would not have been meaningful. Clarified that all MedImmune staff were unblinded for the Day 28 safety and immunogenicity analyses but site staff, CRO staff, and subjects were to remain blinded until the Day 180 final database lock. **All subjects were enrolled under this protocol amendment.**

Results:

Population

A total of 2481 subjects were screened, and 2312 subjects were randomized. Most screened subjects who were not randomized were ineligible for the study or because randomization had closed. A total of 2305 subjects received at least one dose of Q/LAIV, FluMist-Y, or FluMist-V. A total of 2277 subjects were dosed and followed for safety through Day 28 post-dose 1. Seven of the 2312 randomized subjects were not vaccinated: one subjects received a nonstudy vaccine in the 28 days prior to Dose 1; 1 subject was randomized despite a time-limited exclusion criterion which resolved after randomization had closed; 1 subject was wheezing at screening; and 4 subjects or their guardians decided against vaccination.

Safety population:
The Safety Population included 2305 subjects. The Evaluable Safety Population was all subjects who received any investigational product at Dose 1 and had any solicited symptom data available post-Dose 1 and included 2297 subjects. The Evaluable Safety Population for post-Dose 2 solicited symptoms included 1731 subjects.

Immunogenicity population:
The Immunogenicity Population included 2210 subjects. From the 2312 subjects randomized, 102 subjects were excluded from the Immunogenicity Population because they did not receive investigational product in accordance with the protocol (32 subjects) or did not have post-dose HAI antibody measurements (70). Of the 32 subjects who were excluded because they did not receive investigational product according to the protocol, 7 subjects were not dosed, 3 two-dose group subjects without a history of influenza vaccine received Dose 1 and Dose 2 but did not

receive the same product at both doses, 22 two-dose subjects without a history of influenza vaccine received Dose 1 but did not receive Dose 2. Subjects who received FluMist at Dose 1 and a different FluMist at Dose 2 were included in the Immunogenicity Population but only contributed data to A strain assessments. The true collection window for immunogenicity samples was 22 – 56 days post-dosing.

> *Clinical Reviewer Comment*: t*he clinical reviewer agrees with exclusion of these subjects from the immunogenicity population.*

The following applicant-provided table summarizes the subject populations evaluated:

Table 8. Study MI-CP208. Overview of Evaluated Subject Populations

Population Reason for exclusion	Q/LAIV	All FluMist[a]	FluMist-Y	FluMist-V	Total
All subjects randomized	1385	927	464	463	2312
Intent-to-Treat (ITT) Population [b]	1385	927	464	463	2312
One-dose group	300	204	103	101	504
Two-dose group	1085	723	361	362	1808
History of prior seasonal influenza vaccination	773	517	260	257	1290
History of no prior seasonal influenza vaccination	312	206	101	105	518
Immunogenicity Population [c]	1327	883	446	437	2210
One-dose group	297	203	104	99	500
Two-dose group	1030	680	342	338	1710
History of prior seasonal influenza vaccination	750	494	252	242	1244
History of no prior seasonal influenza vaccination	280	186	90	96	466
Reason not evaluable					
Did not receive any investigational product	NA [d]	NA [d]	NA [d]	NA [d]	7
Received Dose 1 but not Dose 2 [e]	14	8	2	6	22
Received Doses 1 and 2 but did not receive the same investigational product [e,f]	2	1	1	0	3
Received correct dose(s) but did not have post-immunogenicity dose HAI measurement [g]	39	31	14	17	70
Other protocol deviations	0	0	0	0	0
Total number not evaluable	55	40	17	23	102
Safety Population [c]	1382	923	463	460	2305
One-dose group	299	204	104	100	503
Two-dose group	1083	719	359	360	1802
Reasons not evaluable					
Did not receive any investigational product	NA [d]	NA [d]	NA [d]	NA [d]	7
Received investigational product but did not have any post-dose safety follow-up	0	0	0	0	0
Evaluable Safety Population for post-Dose 2 safety analyses [h]	1041	693	347	346	1734
Reasons not evaluable					
Did not receive any investigational product	NA [d]	NA [d]	NA [d]	NA [d]	6
Received Dose 1 but did not receive Dose 2	36	21	9	12	57
Received Doses 1 and 2 but did not receive the same investigational product [c]	6	5	3	2	11
Received correct doses but did not have any safety follow-up post-Dose 2	0	0	0	0	0
Evaluable subjects for post-Dose 1 solicited symptoms analyses	1377	920	462	458	2297
One-dose group	299	204	104	100	503
Two-dose group	1078	716	358	358	1794
Evaluable subjects for post-Dose 2 solicited symptoms analyses	1039	692	347	345	1731

Source: Table 11.1-1, page 98/6316 of the study MI-CP208 interim clinical study report

HAI: hemagglutination inhibition; ITT: Intent-to-Treat; NA: not applicable

a: All FluMist refers to data from both the FluMist-Y and FluMist-V arms combined

b: Treatment was summarized according to the treatment assigned at randomization

c: Treatment was summarized according to the treatment actually received at Dose 1

d: Not applicable for summarization by treatment received

e: Only applies to subjects in two-dose group who had no history of prior seasonal influenza vaccination

f: Subjects who received different FluMist (either FluMist-Y or FluMist-V) at Dose 1 and Dose 2 were included in the Immunogenicity Population. They were included in the immunogenicity analyses for A/H1N1 and A/H3N2 strains only

g: Post-immunogenicity dose HAI measurement was defined as HAI antibody result post-dose for one-dose group subjects; post Dose 1 for two-dose group subjects with history of prior seasonal influenza vaccination; and post-Dose 2 for two-dose group subjects without history of prior seasonal influenza vaccination

h: Only applies to subjects in two-dose group

Safety:

Overall safety profile: Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 2 – 3. The median number of days of solicited symptoms across all groups was < 4.0.

Immediate reactions:
None.

Solicited reactions:
The rate of each solicited AE in the Q/LAIV, All FluMist, FluMist-V, and FluMist-Y treatment arms, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post Dose 1 are shown in Table 10. Runny/stuffy nose was the most frequently reported solicited reaction, occurring in 32.3% of Q/LAIV recipients and 32.0% of All FluMist recipients.

Table 9. Study MI-CP208. Rate of Solicited Adverse Events, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post-Dose 1, Subjects 2 – 17 years old

	Q/LAIV n/N (%)	All FluMist n/N (%)	FluMist-Y n/N (%)	FluMist-V n/N (%)	Rate difference percentage points[a]
Any solicited symptom	659/1377 (47.9)	436/920 (47.4)	242/462 (52.4)	194/458 (42.4)	0.5
Fever[b]					
≥ 100.4F (38.0C)	79/1375 (5.7)	36/920 (3.9)	24/462 (5.2)	12/458 (2.6)	1.8
≥ 101.3F (38.5C)	46/1375 (3.3)	21/920 (2.3)	11/462 (2.4)	10/458 (2.2)	1.1
≥ 102.2F (39.0C)	19/1375 (1.4)	7/920 (0.8)	5/462 (1.1)	2/458 (0.4)	0.6
≥ 103.1F (39.5C)	4/1375 (0.3)	2/290 (0.2)	2/462 (0.4)	0/458 (0.0)	0.1
≥ 104.0F (40.0C)	1/1375 (0.1)	0/920 (0.0)	0/462 (0.0)	0/458 (0.0)	0.1
≥ 104.9F (40.5C)	0/1375 (0.0)	0/920 (0.0)	0/462 (0.0)	0/458 (0.0)	0.0
Runny/stuffy nose	445/1377 (32.3)	294/920 (32.0)	167/462 (36.1)	127/458 (27.7)	0.4
Sore throat[c]	127/1343 (9.2)	95/902 (10.3)	57/453 (12.3)	38/449 (8.3)	- 1.1
Cough	217/1377 (15.8)	155/920 (16.8)	79/462 (17.1)	76/458 (16.6)	- 1.1
Headache[c]	172/1345 (12.5)	112/901 (12.2)	54/453 (11.7)	58/448 (12.7)	0.3
Generalized muscle aches[c]	60/1341 (4.4)	42/902 (4.6)	24/453 (5.2)	18/449 (3.9)	- 0.2
Decreased activity level (lethargy) or tiredness/weakness	135/1377 (9.8)	91/920 (9.9)	49/462 (10.6)	42/458 (9.2)	- 0.1
Decreased appetite	76/1377 (5.5)	61/920 (6.6)	36/462 (7.8)	25/458 (5.5)	- 1.1

Source: Table 12.2.1-1, page 141 – 142 of the MI-CP 208 CSR
a proportion of Q/LAIV recipients – proportion of All FluMist recipients
b Temperature by any route
c Collection of sore throat, headache, and generalized muscle aches was omitted when the subject was too young to report these symptoms reliably

Number of subjects with solicited symptoms from Day 0 – Day 14 Post Dose 1 and Post Dose 2, Evaluable Safety Population for Solicited Symptoms (Two-Dose Group). Again, runny/stuffy nose was the most frequently reported solicited reaction after either dose 1 or dose 2. Reactogenicity events were reported at a higher rate following dose 1 than after dose 2. Fever was reported in more Q/LAIV recipients after dose 1 (6.6%) compared with All FluMist recipients after dose 1 (4.2%) but was reported in a more similar proportion of FluMist-Y recipients after dose 1 (5.6%). However, there was no apparent increase in associated sequelae associated with the higher rate of fever (e.g., there were no febrile convulsions reported). After dose 2, fever was reported in fewer Q/LAIV recipients compared to the other groups.

Table 10. Study MI-CP208. Rates of Solicited Adverse Events from Days 0 – 14 Post-Dose 1 and Post-Dose 2, Evaluable Safety Population for Solicited Symptoms, Subjects 2 – 8 Years of Age

Solicited symptom	Post Dose	Q/LAIV n/N (%)	All FluMist n/N (%)	FluMist-Y n/N (%)	FluMist-V n/N (%)	Rate difference percentage points[a]
Any solicited symptom	Dose 1	519/1078 (48.1)	340/716 (47.5)	190/358 (53.1)	150/358 (41.9)	0.7
	Dose 2	326/1039 (31.4)	212/692 (30.6)	103/347 (29.7)	109/345 (31.6)	0.7
Fever[b]						
≥ 100.4F (38.0C)	Dose 1	71/1076 (6.6)	30/716 (4.2)	20/358 (5.6)	10/358 (2.8)	2.4
	Dose 2	28/1037 (2.7)	29/691 (4.2)	12/346 (3.5)	17/345 (4.9)	- 1.5
≥ 101.3F (38.5C)	Dose 1	43/1076 (4.0)	16/716 (2.2)	8/358 (1.4)	1/358 (0.3)	0.8
	Dose 2	16/1037 (1.5)	16/691 (2.3)	7/346 (2.0)	9/345 (2.6)	- 0.8
≥ 102.2F (39.0C)	Dose 1	18/1076 (1.7)	6/716 (0.8)	5/358 (1.4)	1/358 (0.3)	0.8
	Dose 2	8/1037 (0.8)	7/691 (1.0)	4/346 (1.2)	3/345 (0.9)	- 0.2
≥ 103.1F (39.5C)	Dose 1	4/1076 (0.4)	2/716 (0.3)	2/358 (0.6)	0/358 (0.0)	0.1
	Dose 2	3/1037 (0.3)	2/691 (0.3)	1/346 (0.3)	1/345 (0.3)	0.0
≥ 104.0F (40.0C)	Dose 1	1/1076 (0.1)	0/716 (0.0)	0/358 (0.0)	0/358 (0.0)	0.1
	Dose 2	0/1037 (0.0)	1/691 (0.1)	1/346 (0.3)	0/345 (0.0)	- 0.1
≥ 104.9F (40.5C)	Dose 1	0/1076 (0.0)	0/716 (0.0)	0/358 (0.0)	0/358 (0.0)	0.0
	Dose 2	0/1037 (0.0)	0/691 (0.0)	0/346 (0.0)	0/345 (0.0)	0.0
Runny/stuffy nose	Dose 1	364/1078 (33.8)	227/716 (31.7)	131/358 (36.6)	96/358 (26.8)	2.1
	Dose 2	217/1039 (20.9)	135/692 (19.5)	66/347 (19.0)	69/345 (20.0)	1.4
Sore throat[c]	Dose 1	88/1044 (8.2)	64/698 (8.9)	39/349 (10.9)	25/349 (7.0)	- 0.8
	Dose 2	43/1008 (4.1)	32/674 (4.6)	15/338 (4.3)	17/336 (4.9)	- 0.5
Cough	Dose 1	185/1078 (17.2)	129/716 (18.0)	68/358 (19.0)	61/358 (17.0)	- 0.9
	Dose 2	132/1039 (12.7)	81/692 (11.7)	37/347 (10.7)	44/345 (12.8)	1.0
Headache[c]	Dose 1	105/1046 (9.7)	72/697 (10.1)	35/349 (9.8)	37/348 (10.3)	- 0.3
	Dose 2	56/1011 (5.4)	38/673 (5.5)	21/338 (6.1)	17/335 (4.9)	- 0.1
Generalized muscle aches[c]	Dose 1	49/1042 (4.5)	31/698 (4.3)	19/349 (5.3)	12/349 (3.4)	0.2
	Dose 2	12/1006 (1.2)	6/674 (0.9)	3/338 (0.9)	3/336 (0.9)	0.3
Decreased activity level (lethargy) or tiredness/weakness	Dose 1	100/1078 (9.3)	59/716 (8.2)	34/358 (9.5)	25/358 (7.0)	1.0
	Dose 2	61/1039 (5.9)	37/692 (5.3)	22/347 (6.3)	15/345 (4.3)	0.5
Decreased appetite	Dose 1	60/1078 (5.6)	48/716 (6.7)	28/358 (7.8)	20/358 (5.6)	- 1.1
	Dose 2	38/1039 (3.7)	23/692 (3.3)	13/347 (3.7)	10/345 (2.9)	0.3

Source: Combined applicant-provided Tables 12.2.1-2 and 12.2.1-3, pages 143-145 of the MI-CP208 CSR
a Proportion of Q/LAIV subjects – proportion of All FluMist subjects
b Temperature by any route
c Collection of sore throat, headache, and generalized muscle aches was omitted when the subject was too young to report these symptoms reliably

Exploratory subgroup analyses performed by the applicant suggested similar proportions of subjects reported any solicited symptom and each specific solicited symptom in the age group 9 – 17 years except for headache, which was reported in 2.8% more Q/LAIV recipients than All FluMist subjects. Post-dose 1 among 2 – 8 year old subjects, fever and runny/stuffy nose were reported by > 1% more of the Q/LAIV recipients compared with All FluMist subjects. Fever among 2 – 8 year old subjects was reported in more than twice as many Q/LAIV recipients as compared to FluMist/B/Victoria recipients. The rate of fever among Q/LAIV recipients was slightly higher than the rate of fever among FluMist/B/Yamagata recipients. Post-dose 1, similar

proportions of male subjects reported any solicited symptom after Q/LAIV (45.7%) or FluMist (48.2%); findings were similar for females: 49.9% of Q/LAIV recipients and 46.6% of All FluMist subjects). In the two-dose group, following both doses, solicited symptoms were reported in similar proportions across treatment groups. For all subjects post-dose 1, similar proportions of White subjects reported any solicited symptom after either Q/LAIV (51.0%) of FluMist (51.1%); similar proportions of African Americans reported any solicited symptoms after either product (37.6% Q/LAIV vs 35.5% All FluMist). By ethnicity, rates were similar across treatment groups.

Unsolicited AEs:
Among all subjects, the AEs days 0 – 28 days post-vaccination with dose 1 in the Safety Population included 460 events in 290 subjects (21.0%) who received Q/LAIV, 263 events in 191 subjects (20.7%) in the All FluMist group [151 events in 108 (23.3%) FluMist-Y recipients and 112 events in 83 (18.0%) FluMist-V recipients]. The nature of the unsolicited AEs was common pediatric illnesses and events, and the proportion of subjects in each group experiencing the AEs was similar. All these events were reported in < 3% of subjects. The most commonly reported unsolicited AEs (> 1% of the total subjects) during this time period were rhinorrhea, sneezing, cough, diarrhea, pyrexia, upper abdominal pain, upper respiratory tract infection, and vomiting all reported in ≤ 2.6% of subjects in any group. Headache was reported in a greater proportion of Q/LAIV recipients (0.9%) compared with the All FluMist (0.2%), FluMist-Y (0.4%), or FluMist-V (0.0%). Wheezing was reported in 0.2% of Q/LAIV subjects, 0.1% of All FluMist subjects, 0.2% of FluMist-Y recipients, and 0 FluMist-V subjects. A breakdown of the number of subjects in each age group reporting wheezing or pneumonia is provided in Table 12, below (CBER analysis).

Table 11. Study MI-CP208. Numbers of Subjects with AEs of Wheezing or Pneumonia, or with Use of Beta-Agonist or Steroids, or an Indication of Asthma or Wheezing for Concomitant Medications

	Age group	Q/LAIV	FluMist-Y	FluMist-V
Unsolicited AE				
Wheezing	9 - 17	1*	0	0
	2 - 8	3	3	0
Pneumonia	9 - 17	0	0	0
	2 - 8	4[a]	1[b]	0
Medication				
Albuterol	9 - 17	1	0	0
	2 - 8	5	6	2
Steroid (any) for wheezing	9 - 17	0	0	0
	2 - 8	0	1	0
Indication asthma or wheezing for concomitant meds				
Number of subjects	9 – 17	1	0	0
	2 – 8	3	4	0
Number of meds	9 – 17	2	0	0
	2 - 8	5	7	0

* This subject is listed as having 2 episodes of wheezing in the adverse event dataset: one moderate episode reported 9 days after dose 1, and one mild episode reported 13 days after dose 1. Insufficient detail is provided to determine whether these were 2 discrete episodes or part of one episode
a: these subjects included: a 4 year old male with pneumonia of moderate severity 7 days post-dose 2; a 4 year old female with pneumonia of mild severity 28 days post-dose 1; an 8 year old female with pneumonia of moderate severity 28 days post-dose 2, and a 5 year old female with pneumonia of mild severity 18 days post-dose 1
b: this subject was a 6 year old male with pneumonia of moderate severity 22 days post-dose 1

Clinical Reviewer Comment: given the randomization scheme of 3:1:1, there does not seem to be a signal for increased wheezing or pneumonia with the addition of a 4th live, attenuated influenza virus.

Among subjects in the two dose group, the AEs days 0 – 28 days post-vaccination 1 in the Safety Population included 356 events in 220 (20.3%) Q/LAIV recipients, 229 events in 165 (22.9%) All FluMist subjects, 126 events in 90 (25.1%) of FluMist-Y recipients, and 103 events in 75 (20.8%) of FluMist-V recipients. Post-dose 2, the AEs included 214 events in 140 (13.4%) Q/LAIV recipients, 169 events in 116 (16.7%) All FluMist subjects, 85 events in 62 (17.9%) FluMist-Y recipients, and 84 events in 54 (15.6%) FluMist-V recipients. The events were mainly routine pediatric medical conditions, and the most commonly reported events were similar to those described in the preceding paragraph.

The majority of unsolicited AEs were of mild to moderate severity. After dose 1, 3 subjects (0.2%) in the Q/LAIV arm, all in the two-dose group, and 4 subjects (0.4%) in the All FluMist group, all in the two-dose group, reported a severe (Grade 3). For the two-dose group post Dose 2, 4 Q/LAIV recipients (0.4%) reported 5 severe (Grade 3) events, and 2 FluMist recipients (0.3%) reported 2 severe (Grade 3) events.

Exploratory subgroup analyses provided by the applicant suggested that AEs in all subjects post-dose 1 were reported by proportionately more male subjects in the Q/LAIV group (20.8%) compared with the All FluMist group (18.3%). By preferred term, proportionately more male subjects who received Q/LAIV reported streptococcal pharyngitis than did male subjects who received FluMist (rate difference 1.1). Proportionately more female subjects who received Q/LAIV reported pyrexia than did female subjects who received FluMist (rate difference 1.4). A similar pattern was observed by gender in two-dose subjects 2 – 8 years of age post-dose 1. Post dose 2, proportionately more male subjects who received Q/LAIV reported cough than did FluMist recipients (rate difference 1.0). Post-dose 1, more African American subjects in the Q/LAIV group (19.6%) reported AEs than in the All FluMist group (13.9%). By preferred term, more African American subjects who received Q/LAIV reported abdominal pain, diarrhea, vomiting, pyrexia, cough, and rhinorrhea (rate differences 1.0 – 2.2). Post dose 2, more African American Q/LAIV recipients (12.3%) reported AEs than African American All FluMist recipients (7.7%). For White subjects, there were similar proportions of subjects in both study groups who reported any AE or specific preferred term AEs for all subjects post dose 1 and for the 2 dose subjects after either dose. AEs were reported in similar proportions of Q/LAIV recipients and FluMist recipients post dose 1 in both Hispanic/Latino and non-Hispanic/Lation or in more subjects who had received FluMist. In subjects 9 – 17 years of age, AEs were reported by more Q/LAIV recipients (23.1%) compared with All FluMist recipients (12.7%). Due to limited numbers of subjects in the subgroup analyses, these data should be interpreted with caution.

Serious adverse events (SAEs):
In the Evaluable Safety Popularion, there were no SAEs reported days 0 – 28 post-dose 1. Following dose 2, four SAEs were reported in 3 subjects: 3 SAEs were reported in 2 (of 1041) Q/LAIV recipients (appendicitis, salmonella gastroenteritis, and dehydration), and 1 SAE was reported in 1 (out of 346) FluMist-V recipient or 1 (out of 693) All FluMist subjects (major depression). All 3 SAEs were considered as such because they required inpatient hospitalization.

During days 0 – 180 after vaccination, 6/1382 (0.4%) Q/LAIV recipients reported 7 SAEs, and 5/923 (0.5%) of FluMist recipients reported 9 SAEs. These numbers include the SAEs reported within 28 days of vaccination and described above. All SAEs were reported in the subset of

subjects 2 – 8 years old. New onset chronic diseases (NOCDs) were reported by 19/1382 (1.4%) Q/LAIV recipients and 7/923 (0.8%) FluMist recipients.

The SAEs are described in more detail below, based on the provider's case narratives:
Days 0 – 28 post-vaccination:

- A 7 year-old African American female with several day history of decreased appetite awoke with abdominal pain and tenderness 4 days post-dose 2 of Q/LAIV. While other evaluations were negative, an abdominal ultrasound revealed acute appendicits with appendicolith. The event resolved following laparoscopic appendectomy. Given the nature of the event and the noted appendicolith, it is unlikely related to vaccination.
- A 27 month-old White female developed Salmonella gastroenteritis and dehydration 24 days after Q/LAIV dose 2. She was hospitalized, received sulfamethoxazole and trimethoprim, recovered, and was discharged. Given the nature of the event, it is unlikely related to vaccination.
- An 8 year-old White male presented with "wanting to kill himself and others" 28 days post-dose 2 of FluMist (which strain not specified). His mother reported that in the last year, the child had displayed aggressive behavior and complained of hearing voices. He was hospitalized; diagnosed with psychotic state, major depressive disorder, and hypothyroidism; and treated with fluoxetine, risperidone, and levothyroxine. He was discharged and was considered recovered with sequelae. Given the nature of the event, it is unlikely related to vaccination.

Days 29 – 180 post-vaccination:

- A 7 year-old White male with history of knee arthralgia and elbow cellulites developed tenderness over the right side of his face and upper tooth pain 92 days post-dose 2 of Q/LAIV. A CT scan of the face contrast showed cellulites, possibly with an area of phlegmon. The infection did not appear to be dental or sinus in origin. He was discharged after approximately 3 days, on oral clindamycin and had resolution a few days later. Given the timing and nature of the event, it is unlikely related to vaccination.
- An 8 year-old White female fell off an all-terrain vehicle 33 days post-dose 2 of Q/LAIV. She was hospitalized for closed reduction and percutaneous pinning of the right elbow supracondlyar fracture. The event resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 6 year-old White female subject presented 84 days post-dose 2 of Q/LAIV with diabetic ketoacidosis (DKA) with elevated serum glucose of 308 mg/dL, leukocytosis with WBC count of 31,500, bicarbonate of < 5.0 mmol/L, hemoglobin A1C of 14.7%, and ketonuria. She was discharged on insulin, and the DKA was resolved with sequelae. Given the the complex relationship between potential environmental triggers and onset of diabetes mellitus type I, it is impossible to determine that these events were unrelated to vaccination. However, it is important to consider that an intercurrent viral illness, among other events, could have served as a trigger.
- A 27 month-old White female with history of chronic intermittent diarrhea and family history of celiac disease and diabetes had glucosuria 58 days post-dose 2 of Q/LAIV following a few days of polydipsia and polyuria. On admission, her glucose was 330 mg/dL, and pH was 7.33. She was discharged on insulin. Given the the complex relationship between potential environmental triggers and onset of diabetes mellitus type I, it is impossible to determine that these events were unrelated to vaccination. However, it is important to consider that an intercurrent viral illness, among other events, could have served as a trigger.

- A 38 month-old White female with history of developmental delays had an unwitnessed fall from her bed 59 days post-dose 2 of FluMist. She was unable to control her body movements above her waist, and unable to walk or maintain posture. She developed vomiting, dizziness, and a headache. After an extensive workup, she was presumed to have had a cerebrovascular event (CVA) and was discharged close to baseline and on oral aspirin. She had a similar episode a few days after discharge. A neurologist concluded that her only potential risk factor was the presence of methylenetetrahydrofolate reductase (MTHFR) mutation. She continued on aspirin therapy. A few months later, she was reported as having returned to baseline except for pain in the lower extremities. Also, she had a cognitive deficit, with speech and motor delays, which was attributed to the CVA. The outcome was resolved with sequelae. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 6 year-old White male was hospitalized for pulmonary contusion, pneumothorax, and head injury after being hit and run over by a sport utility vehicle while crossing the street 90 days post-dose 2 of FluMist. He was discharged "in excellent condition" according to the applicant. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 39 month-old White female developed fever and vomiting 39 days post-dose 2 of FluMist. She was found to have fever, leukocytosis, injected pharynx, mild suprapubic tenderness, and dehydration. She was hospitalized for urinary tract infection (UTI) and sepsis. The events resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 4 year-old White female was hospitalized 117 days post-dose 2 of FluMist for hydronephrosis and urinary tract infection. Urinalysis showed 20 – 40 WBC/HPF, and culture was positive for E. coli. The UTI resolved. A MAG3 scan demonstrated significant high-grade right kidney obstruction. The subject was readmitted for a right open dismembered pyeloplasty with ureteral stent placement was performed, and ureteropelvic junction (UPJ) obstruction resolved, and she was discharged on oral antibiotics. The UPJ obstruction was considered a congenital anomaly. Given the timing and nature of the event, it is unlikely related to vaccination.

Notably, since the study was conducted in the influenza off-season, the study vaccines were not formulated to contain the CDC-designated influenza strains for the upcoming influenza season. Subjects were offered a dose of commercial seasonal influenza vaccine after 28 day safety data was collected but before day 180. Therefore, it is possible that some SAEs occured post-vaccination with commercial vaccine. However, since the rate of SAE occurrence was similar across treatment arms, it is unlikely that any administration of this optional commercial seasonal influenza vaccine affects the interpretation of the safety data.

No deaths were reported.

Two subjects were withdrawn from dosing by the parent/legal guardian, but not by the investigator, due to AEs of vomiting and dizziness (one Q/LAIV recipient) and gastroenteritis (one FluMist recipient).

<u>New Onset Chronic Diseases from Day 0 – Day 180:</u>
In the Safety Population, NOCDS were reported in 19/1382 (1.4%) of Q/LAIV recipients and 7/923 (0.8%) All FluMist recipients. All diagnoses were reported in one subject each, except fo attention deficit/hyperactivity disorder (4 Q/LAIV subjects), asthma (3 Q/LAIV recipients and 4 FluMist recipients, 2 among FluMist-Y and 2 among FluMist-V recipients), type I diabetes

mellitus (2 Q/LAIV recipients), migraine (2 Q/LAIV recipients), anxiety (1 Q/LAIV recipient and 1 FluMist recipient), and food allergy (1 Q/LAIV subject and 1 FluMist subject). The 2 subjects who developed type I diabetes mellitus are described in greater detail in the above section on SAEs. According to meeting minutes of the independent DMC, the applicant discussed these 2 cases in an open session of the DMC. The applicant was concerned initially because of the known association of viral infections with potential triggers of the disease onset. At that time, the applicant apparently performed a review of VAERS data and concluded that there was no signal detected in that database. Given the the complex relationship between potential environmental triggers and onset of diabetes mellitus type I, it is impossible to determine that these events were unrelated to vaccination. However, it is important to consider that an intercurrent viral illness, among other events, could have served as a trigger. The applicant's search of its databases provides some reassurance. Separately, with respect to wheezing, newly diagnosed asthma was not more common among Q/LAIV recipients.

Pregnancy:
Two pregnancies were reported; both subjects received Q/LAIV, although neither subject was pregnant when dosed. In both cases, the subjects delivered reportedly healthy babies.

Immunogenicity:

Primary immunogenicity endpoint:
The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody $\leq$ 1.5 for each strain. The ratios ranged from 1.04 – 1.21. Baseline GMTs were similar between Q/LAIV and comparator groups. The applicant-provided table 12 below includes the GMTs and 95% CI for each strain for the Q/LAIV and comparator vaccines:

Table 12. Study MI-CP208. GMTs in Individuals Receiving Q/LAIV or Comparator

Strain	Q/LAIV			Comparator [a]			GMT Ratio and 95% CI	
	N	GMT[c]	95% CI	N	GMT[c]	95% CI	Ratio[d]	95% CI[b]
A/H1N1	1327	16.7	15.9, 17.6	883	17.9	16.8, 19.1	1.07	0.98, 1.16
A/H3N2	1327	27.7	26.1, 29.4	883	28.8	26.7, 31.1	1.04	0.94, 1.14
B/Yamagata	1327	49.6	46.6, 52.8	445	59.8	53.7, 66.7	1.21	1.07, 1.37
B/Victoria	1327	35.4	33.3, 37.7	437	37.0	33.4, 41.0	1.05	0.93, 1.18

Source: Table 11.4.1.1-1 page 104/6316 of the study MI-CP208 interim clinical study report
GMT: geometric mean titer; HAI: hemagglutination inhibition
a: comparator = All FluMist group for A/H1N1 and A/H3N2 strains, where the All FluMist group refers to data from both the FluMist-Y arm and the FluMist-V arm combined; comparator = FluMist-Y for the B/Yamagata strain and FluMist-V for the B/Victoria strain
b: Q/LAIV immune response was non-inferior to that of FluMist if the upper bound for each of the strains's 95% CIs for post-dose strain-specific GMT ratios was $\leq$ 1.5
c: a value of 2 was assigned for an HAI antibody titer reported as < 4
d: GMT in comparator divided by GMT in Q/LAIV

Secondary immunogenicity endpoints:
Four-fold rise:
Among all subjects, regardless of baseline serostatus, seroconversion/seroresponse rates were greater for the B strains than for the A strains but were similar between the Q/LAIV and comparator groups.

Table 13. Study MI-CP208. Strain-Specific HAI Seroconversion/Seroresponse Rates* in Individuals Receiving Q/LAIV or Comparator†

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

Source: results of CBER statistical reviewer's analysis
*If the baseline titer is < 4, the post-vac titer considered as demonstrating seroconversion was ≥ 16
If the baseline titer is ≥ 4, the post-vac titer considered as demonstrating seroconversion was ≥ 4 times the baseline titer
† The timepoint at which immune response was measured was 28 to 35 days after Dose 1 for subjects 9 – 17 years of age and for subjects 2 – 8 years of age with history of prior seasonal influenza vaccination or at 28 to 35 days after Dose 2 for subjects 2 – 8 years of age with no history of prior seasonal influenza vaccination

Table 14. Study MI-CP208. Comparison of B Strain HAI Antibody Responses to Q/LAIV with Those to FluMist Formulation Not Containing the Corresponding B Strain

		Q/LAIV		Comparator		GMT Ratio and 95% CI	
Baseline serostatus	Strain	N	GMT (95% CI)	N	GMT (95% CI)	Ratio	95% CI
All	B/Yamagata	1327	49.6 (47.03, 52.26)	437	20.8 (19.09, 22.86)	0.42	(0.38, 0.47)
	B/Victoria	1327	35.4 (33.55, 37.35)	446	20.6 (18.72, 22.57)	0.58	(0.52, 0.65)
Serosusceptible	B/Yamagata	483	27.9 (25.82, 30.21)	152	4.4 (4.02, 4.86)	0.16	(0.14, 0.18)
	B/Victoria	487	14.8 (13.72, 15.97)	161	4.6 (4.19, 5.04)	0.31	(0.28, 0.35)
Seropositive	B/Yamagata	588	29.6 (27.40, 31.85)	191	5.9 (5.39, 6.45)	0.20	(0.18, 0.22)
	B/Victoria	620	17.2 (16.08, 18.51)	209	6.1 (5.59, 6.81)	0.36	(0.32, 0.40)

Source: Table 5.10.1.1, page 37/254 of the MI-CP208 sBLA Supplemental Tables

Summary:
Overall, Q/LAIV appeared as safe and immunogenic as the trivalent FluMist formulated with either influenza type B lineage.

In the one dose group (subjects 9 – 17 years of age), runny/stuffy nose was the most frequently reported solicited reaction, occurring in 32.3% of Q/LAIV recipients and 32.0% of All FluMist recipients. Fever was slightly more common among Q/LAIV recipients (5.7%) compared with the All FluMist group (3.9%) but was similar to the fever rate reported in the FluMist-Y group and within the range of fever among children as noted in the FluMist Package Insert.
Runny/stuffy nose was the most frequently reported solicited reaction after either dose 1 or dose 2 in the two dose group (subjects 2 – 8 years of age), as well. Reactogenicity events were reported at a higher rate following dose 1 than after dose 2. Fever was reported in more Q/LAIV recipients after dose 1 (6.6%) compared with All FluMist recipients after dose 1 (4.2%) but was reported in a more similar proportion of FluMist-Y recipients after dose 1 (5.6%). After dose 2, fever was reported in fewer Q/LAIV recipients compared to the other groups.

Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 2 – 3. The median number of days of solicited symptoms across all groups was < 4.0.

The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody $\leq$ 1.5 for each strain. The ratios ranged from 1.04 – 1.21.

Baseline GMTs were similar between Q/LAIV and comparator groups.
Among all subjects, regardless of baseline serostatus, the proportion of subjects achieving at least a 4-fold rise in HAI antibody titer from baseline was < 10% for A/H1N1 and A/H3N2 and approximately 40% for the relevant B strains.

Study MI-CP206:
A randomized, partially blind active controlled study to evaluate the immunogenicity of MEDI8662 [Q/LAIV] in adults 18 to 49 years of age

> *Clinical Reviewer Comment: this study was performed with a delivery device which differed from that of the licensed product and which was used in studies MI-CP185 and MI-CP208. CBER did not consider the study as pivotal to support effectiveness because of the different presentation, which could result in a different distribution of the vaccine in the respiratory mucosa, and because it is not the licensed presentation. However, the study enrolled 1800 subjects, and CBER evaluated the safety data for potential safety signals that might be associated with the Q/LAIV.*

Objectives
Primary objective:
To demonstrate the immunologic noninferiority of Q/LAIV administered intranasally through a ---------(b)(4)---------- delivery system to 2 formulations of FluMist, delivered intranasally using the Becton Dickinson Accuspray delivery device, comparing the strain-specific geometric mean titers (GMTs) of hemagglutination inhibition (HAI) antibody post dosing.

Secondary objectives:
1) To estimate the proportion of subjects who experienced strain-specific HAI seroresponse following Q/LAIV-(b)(4), defined as a minimum 4-fold rise in post-vaccination HAI antibody titer, by baseline serostatus
2) To estimate the proportion of subjects who achieved a strain-specific HAI antibody titer $\geq$ 32 following Q/LAIV-(b)(4), by baseline serostatus
3) To assess the safety and tolerability Q/LAIV-(b)(4)

4) To determine the acceptability of the (b)(4) dosing unit as a vaccine delivery system to vaccine recipients.

Study Design: A randomized (4:1:1), partially blind, active controlled study assessing the safety and immunogenicity of a single intranasal dose of quadrivalent live attenuated influenza virus vaccine (Q/LAIV) using a --------(b)(4)-------- delivery system in comparison with two formulations of FluMist in adults 18 to 49 years of age. The study was conducted during the influenza off-season.

Study Period: August 14, 2009 – March 3, 2010

Population
The study was conducted at 18 U.S. study sites.

Inclusion criteria
- Male or female
- Age 18 - 49 years at randomization
- Written informed consent and any locally required authorization in the USA obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
- Females of childbearing potential, unless surgically sterile; had sterile male partner; were at least one year post-menopausal; or practiced abstinence; were required to use an effective method of avoiding pregnancy for 30 days prior to the first dose of investigational product, and were to agree to continue using such precautions for 60 days after the final dose of investigational product
- A subject who was considered by the investigator to be at risk of pregnancy had to have a negative urine pregnancy test at screening and, if screening and Day 0 did not occur on the same day, on the day of vaccination prior to randomization. Investigator judgment was required to assess each subject's need for pregnancy testing
- Healthy by medical history and physical examination OR presence of stable underlying chronic medical condition for which hospitalization had not been required in the previous year
- Able to complete follow-up period of 180 days post last dose of vaccine as required by the protocol
- Subject was available by telephone
- Able to understand and comply with the requirements of the protocol, as judged by the investigator

Exclusion criteria
- Acute illness or evidence of significant active infection at randomization
- Fever $\geq$ 100.4°F (38.0°C) at randomization
- History of asthma
- Any drug therapy from 15 days prior to randomization or expected drug therapy through 30 days post last dose with the exception of the following classes/types of medications, which were allowed:
    - **a.** contraceptives
    - **b.** chronic medications (including those taken on an as-needed basis) that had been well tolerated and were not initiated and/or did not have a dosage change within 90 days prior to randomization
    - **c.** topical corticosteroids or antifungals for uncomplicated dermatitis

- Previous medical history or evidence of an intercurrent illness that may have compromised the subject's safety
- Current or expected receipt of immunosuppressive medications within a 30 day window around vaccination, including an immunosuppressive dose of corticosteroids, which was defined as ≥ 20 mg/day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days) (inhaled and topical corticosteroids were permitted)
- Receipt of immunoglobulin or blood products within 90 days before randomization into the study or expected receipt during study participation
- Receipt of any investigational drug therapy within 30 days prior to investigational product through 30 days post-vaccination;
- Receipt of any nonstudy vaccine within 30 days prior to randomization or planned receipt of nonstudy vaccine through 30 days after dosing
- Receipt of any influenza vaccine (investigational or licensed) in 2009 prior to randomization or anticipated receipt prior to the collection of the post-dose immunogenicity blood sample for this study
- Any known immunosuppressive condition or immune deficiency disease including known or suspected infection with human immunodeficiency virus (HIV);
- History of allergic disease or reactions likely to be exacerbated by any component of the investigational product including allergy to eggs, egg proteins, gentamicin, or gelatin or serious, life-threatening, or severe reactions to previous influenza vaccinations;
- History of Guillain-Barre syndrome;
- Use of antiviral agents with activity against influenza virus (including amantadine, rimantadine, oseltamivir, and zanamivir) within 30 days prior to first dose of investigational product or anticipated use of such agents within 30 days after last scheduled vaccination;
- Known or suspected mitochondrial encephalomyopathy
- Pregnant or lactating female;
- History of alcohol or drug abuse that, in the opinion of the investigator, would have affected the subject's safety or compliance with the study;
- Any condition that, in the opinion of the investigator, might have compromised the safety of the subject in the study or would interfere with evaluation of the safety or immunogenicity of the investigational products;
- Subject or immediate family member of subject who was an employee of the clinical study site or who was otherwise involved with the conduct of the study

Reasons for deferring vaccination:

- meeting any of the above time-limited criteria

Vaccine administration

Participants received Q/LAIV-(b)(4) using a (b)(4) delivery system or, FluMist-Y or FluMist-V as intranasal spray using the Becton Dickinson (BD) Accuspray device. The 0.2 mL dose of each FluMist vaccine was formulated to contain $10^{7.0\pm0.5}$.fluorescent focus units (FFU) of each of the 3 vaccine strains, and the final 0.2 mL dose of Q/LAIV-(b)(4) was formulated to contain $10^{7.0\pm0.5}$ FFU of each of the 4 vaccine strains, with a maximum total calculated virus content of 10^8 FFU per 0.2 mL dose. The strains included in the Q/LAIV were: A/H1N1 (A/South Dakota/6/2007), A/H3N2 (A/Uruguary/716/2007), B/Victoria (B/Malaysia/2506/2004), and B/Yamagata (B/Florida/4/2006). The strains included in the trivalent FluMist study formulations were the same, with the exception that they each contained only 1 B strain. The lot numbers were as follows: Q/LAIV lot 0141000604, FluMist-Y lot 0141500588, FluMist-V lot 0141700025.

Endpoints

Primary endpoints:

Post dose strain-specific serum HAI antibody GMT, regardless of baseline serostatus. Immunologic noninferiority of Q/LAIV-(b)(4) to FluMist would be demonstrated if the post dose strain-specific serum HAI antibody GMTs for all 4 strains in the Q/LAIV arm were noninferior to those in the FluMist arms.

Secondary endpoints:

Immunologic:

1. The proportion of subjects who experienced post dose strain-specific HAI antibody seroresponse by baseline serostatus (seronegative, serosusceptible, and regardless of serostatus)
2. The proportion of subjects who achieved a post dose strain-specific HAI antibody titer $\geq$ 32 by baseline serostatus (seronegative, serosusceptible, and regardless of serostatus)

Strain-specific baseline serostatus was defined as serosusceptible if HAI antibody titers were $\leq$ 8 and seropositive if > 8.

Seroresponse was defined as a $\geq$ 4-fold rise from baseline.

Safety:

1. Proportion of subjects experiencing solicited symptoms through 14 days post vaccination
2. Proportion of subjects experiencing adverse events through 28 days post vaccination
3. Serious adverse events experienced from administration of investigational product through 28 days post vaccination
4. Serious adverse events experienced through 180 days post-vaccination
5. Description of new onset chronic diseases through 180 days post-vaccination

Randomization

Subjects were randomized by site 4:1:1 to receive Q/LAIV-(b)(4), FluMist/B/Yamagata (FluMist-Y), or FluMist/B/Victoria (FluMist-V). Enrollment at each site was capped at 100 subjects. Randomization employed a block design with a fixed block size of 6. An interactive voice response system (IVRS) was used for randomization to a treatment arm and assignment of blinded investigational product kit numbers and sprayer numbers according to a computer-generated randomization schedule prepared by the ----------(b)(4)----------. The IVRS assigned each subject to the next sequential sprayer number after stratification by site.

Surveillance

Safety parameters:

Study participants were monitored for at least 15 minutes post-vaccination and for solicited symptoms days 0 – 14 after each dose, adverse events and concomitant medication use days 0 - 28 post-immunization, with reactions reported on memory aids for days 0 – 14 post vaccination. Memory aids were not collected by sites but were used to improve accuracy of reporting to sites during telephone calls and follow-up visits. Solicited adverse events included fever $\geq$ 100.4°F (38.0°C) by any route, runny/stuffy nose, sore throat, cough, headache, generalized muscle aches, decreased activity level (lethargy) or tiredness/weakness, and decreased appetite.

Three telephone contacts occurred: at 3 – 5 days, 7 – 10 days, and 14 – 18 days post vaccination to monitor for safety. Additional telephone contacts occurred approximately monthly from Day 60 – Day 180.

Serious adverse events and new onset chronic diseases were collected through 180 days post-vaccination.

Effectiveness (immunogenicity):
Serum samples for influenza HAI antibody testing were collected pre-vaccination and at 28 – 35 days post-vaccination. The antibody testing was performed at MedImmune (---(b)(4)---).

Assay methods and laboratories:
Serum was separated at the site and stored ----------(b)(4)---------- until batched and shipped to MedImmune (---(b)(4)---). Standard HAI assays were performed in duplicate, with the GMT of the 2 results the final per-subject result. If duplicate assay runs differed ----------(b)(4)----------, the assay was repeated. If no inhibition of hemagglutination was observed, the titer was reported as <4 (imputed as 2 for statistical purposes).

Statistical plan
Sample size calculations

A total of 1800 subjects randomized 4:1:1 to Q/LAIV-(b)(4), FluMist/B/Yamagata, and FluMist/B/Victoria provided > 97% power to rule out a > 1.5-fold difference in the post-dose serum HAI GMT ratios for each of the 4 strain-specific tests regardless of baseline serostatus. These calculations assumed a 90% evaluability rate, a true post final dose GMT ratio for serum HAI measurements of 1, and a standard deviation of the natural logarithm transformed HAI titer of 1.4 for all 4 strains. Study dropouts were not replaced.

Planned interim analyses occurred after Day 28 and included the immunologic and safety data collected through 28 days post-vaccination. This was the final analysis of the primary and secondary immunogenicity endpoints, so no statistical adjustment was applied. The second formal analysis was the analysis of SAEs and NOCDs occurring through Day 180.

Missing data were treated as missing; no data were imputed.

Primary Hypotheses
Non-inferiority of immune response was assessed by evaluating the upper bound of the two-sided 95% CIs for the strain-specific HAI antibody GMT ratios (FluMist/QLAIV-(b)(4)) to the non-inferiority margin of 1.5. If the upper bound of CIs was $\leq$ 1.5 for all 4 strains, the immunologic noninferiority of Q/LAIV compared to FluMist was declared. No adjustment was made for multiple comparisons.
H0: Rj > 1.5, for any j
HA: Rj $\leq$ 1.5, for all j
Where Rj was any of the 4 strain-specific post immunogenicity dose GMT ratios:
• (FluMist-Y) / (Q/LAIV-(b)(4)) for B/Yamagata strain
• (FluMist-V) / (Q/LAIV-(b)(4)) for B/Victoria strain
• (FluMist-Y + FluMist-V) / (Q/LAIV-(b)(4)) for A/H1N1 strain
• (FluMist-Y + FluMist-V) / (Q/LAIV-(b)(4)) for A/H3N2 strain

Populations analyzed
Safety population:

All subjects who received any investigational product and had any safety data recorded. The Evaluable Safety Population for solicited symptoms excluded subjects who had no solicited symptom data available during the summarized period.

Intent-to-treat population:
All randomized subjects.

Immunogenicity population:
All subjects who received investigational product, had post dose HAI antibody measurement, and had no protocol deviation judged to have potential to interfere with the generation or interpretation of an immune response.

Primary endpoint analyses were based on the Immunogenicity Population. Safety endpoint analyses were based on the Safety Population. Summaries of solicited symptoms were based on the Evaluable Safety Population for solicited symptoms.

Safety Analyses
Analyses based on the safety population and include the number of subjects with solicited symptoms through Day 14 post-vaccination, the number of days subjects experienced solicited symptoms through Day 14 post-vaccination, and the number of subjects with solicited symptoms by study day. Tabular summaries were provided for each treatment arm and for the 2 FluMist arms combined. AEs, SAEs, and NOCDs were summarized by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0. AEs and SAEs were also summarized by severity and relationship to investigational product (as determined by the investigator and/or MedImmune). Safety evaluations were descriptive; no formal statistical comparisons of safety outcomes were planned or conducted.
Immunogenicity Analyses
Analyses based on the immunogenicity population and include the ratio of post-immunogenicity dose GMTs and GMFRs of HAI antibody, GMTs of HAI antibody at baseline and post-immunogenicity dose, post-immunogenicity dose seroconversion/seroresponse rates by baseline serostatus, number of subjects with baseline HAI titer $\geq$ 32 by baseline serostatus, and distribution of strain-specific HAI antibody titers, Strain-specific GMTs were summarized by treatment group and by sample time (i.e., baseline or post-immunogenicity dose). No multiplicity adjustment was used.

Protocol Amendments (Amendments to IND):
Amendment 1: 29 November 2009. Protocol amended to clarify that SAEs through Day 28 would be included in the unblinded interim analysis and additional information on personnel who were blinded or would have access to unblinded data was provided; (b)(4) administration instructions were clarified and updated; language regarding the schedule of study procedures was clarified; recording and reporting of AEs, SAEs was clarified; the definition of the immunogenicity population was clarified to include all subjects who received any dose of investigational product, who had post-dose HAI blood draws, and who did not have a protocol deviation that would have interfered with interpretation of immunogenicity results; definitions of serosusceptible and seropositive were more clearly defined. **All subjects were enrolled under this protocol.**

Results:

Population

A total of 1888 subjects were screened, and 1800 subjects were randomized (1202 to the Q/LAIV-(b)(4) group, 300 to the FluMist/B/Yamagata group, and 298 to the FluMist/B/Victoria group). Three subjects randomized to the Q/LAIV-(b)(4) group did not receive Q/LAIV-(b)(4) for the following reasons: 2 subjects withdrew consent on the same day they were scheduled to be dosed, and 1 subject received FluMist/B/Yamagata. One subject randomized to the FluMist/B/Yamagata group failed to meet ongoing eligibility criteria and was not treated. A total of 1199 subjects received Q/LAIV-(b)(4), 300 subjects received FluMist/B/Yamagata, and 298 subjects received FluMist/B/Victoria. All subjects randomized to the FluMist/B/Victoria group received FluMist/B/Victoria. Of the 1797 subjects vaccinated, a total of 1770 (98.3%) subjects were followed for safety through Day 28. A total of 1747 subjects (97.1%) completed the study. Of the 53 subjects who did not complete the study, 41 (2.3%) were lost to follow-up, 4 (0.2%) withdrew consent, 2 (0.1%) died, and 6 (0.3%) withdrew for other reasons. Withdrawal for other reasons included 5 subjects from the Q/LAIV-(b)(4) group who were incarcerated post-vaccination and one subject who did not receive treatment as a result of not meeting one of the exclusion criteria. No one withdrew due to an AE or SAE.

In the ITT Population, the mean age overall was 33.9 years and was similar between treatment groups. All groups had slightly more female than male subjects (56.0% - 58.3% females vs. 41.7% - 44.0% males). Most subjects were White (67.4% overall), and 28.3% of subjects overall were African American (ranging from 25.2% of FluMist/B/Victoria recipients to 29.2% of Q/LAIV-(b)(4) recipients). The overall proportion of subjects identifying themselves as Hispanic or Latino was 12.8%. These proportions were similar between treatment groups.

Safety population:

Of the 1797 vaccinated subjects, 1794 subjects were included in the Safety Population (1198 Q/LAIV-(b)(4) recipients, 298 FluMist/B/Yamagata recipients, and 298 FluMist/B/Victoria recipients). Three subjects who received treatment (1 Q/LAIV-(b)(4) recipient and 2 FluMist/B/Yamagata recipients) were not included in the Safety Population; these subjects were lost to follow-up on Day 0 post-vaccination. The Evaluable Safety Population included 1791 subjects. The Evaluable Safety Population was all subjects who received any investigational product and had any solicited symptom data available. Safety endpoints were assessed in the Safety Population, while solicited symptoms were assessed in the Evaluable Safety Population.

Immunogenicity population:

Of the 1800 randomized subjects, 1762 subjects (1176 Q/LAIV subjects, 294 FluMist/B/Yamagata subjects, and 292 FluMist/B/Victoria subjects) were included in the Immunogenicity Population. The 38 subjects eliminated from the total number of randomized subjects were excluded from the Immunogenicity Population for the following reasons: 3 sujbects were not vaccinated; 3 subjects (all Q/LAIV-(b)(4) recipients) were excluded due to prohibited concomitant medications per study protocol (Tamiflu, Relenza); 29 subjects did not have post-dose HAI measurements taken; 2 subjects did not have post-dose HAI measurements taken within the 24- to 58-day window; and 1 subject had confirmed influenza disease. One subject randomized to the Q/LAIV-(b)(4) group received the incorrect kit number and was vaccinated with FluMist/B/Yamagata; this subject was included in the Q/LAIV-(b)(4) group for the ITT Population but included in the FluMist/B/Yamagata group for the Immunogenicity Population.

The following applicant-provided table summarizes the subject populations evaluated:

Table 15. Study MI-CP206. Summary of Subject Populations Evaluated

Population Reason for exclusion	Q/LAIV	All FluMist	FluMist-Y	FluMist-V	Total
All subjects randomized	1202	598	300	298	1800
Intent-to-Treat (ITT) Population [a]	1202	598	300	298	1800
Safety Population[b]	1198	596	298	298	1794[c]
Evaluable Safety Population for Solicited Symptoms[c]	1196	595	298	297	1791
Immunogenicity Population [d]	1176	586	294	292	1762
Reason excluded from Immunogenicity Population					
Did not receive any investigational product	N/A	N/A	N/A	N/A	3
Did not have post-immunogenicity dose HAI measurement [g]	17	12	6	6	29
Post dose HAI measurements not within 24 to 58 days	2	0	0	0	2
Received antiviral medication	3	0	0	0	3
Laboratory-confirmed influenza disease	1	0	0	0	1

Source: Table 11.1-1, page 70/5438 of the study MI-CP206 clinical study report
HAI: hemagglutination inhibition; ITT: Intent-to-Treat; NA: not applicable
a: ITT Population included all randomized subjects
b: Safety Population included all subjects who received any investigational product and had any follow-up safety data available
c: Evaluable Safety Population for solicited symptoms included all subjects who received any investigational product and had any solicited symptom data available
d: Immunogenicity Population included subjects who received a full dose of investigational product, had post-dose HAI measurements, and had no protocol violation judged to have the potential to interfere with the generation or interpretation of an immune response

Safety:

Overall safety profile: A total of 605/1196 (50.6%) Q/LAIV recipients and 323/595 (60.0%) FluMist recipients reported at least one solicited symptom. Runny nose/stuffy nose was the most commonly reported solicited symptom, more common among FluMist subjects (37.6%) compared with Q/LAIV subjects (31.3%). In this study, MI-CP206, FluMist/B/Victoria was associated with more solicited symptoms as compared with FluMist/B/Yamagata, which is similar to what was observed in adult study MI-CP185, but the opposite of what was observed in the pediatric study MI-CP208. Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 1 – 2. However, the proportion of subjects with solicited symptoms was $\geq$ 10% in every treatment group Days 0 – 6. The median number of days of solicited symptoms across all groups was $\leq$ 3.0.

Immediate reactions:
None reported.

Solicited reactions:
The applicant provided the following table showing the rate of each solicited AE in the Q/LAIV, All FluMist, FluMist-V, and FluMist-Y treatment arms, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post Vaccination.

Table 16. Study MI-CP206. Rates of Solicited AEs, Evaluable Safety Population for Solicited Symptoms, Days 0 – 14 Post-Vaccination

Solicited symptom	Q/LAIV n (%) (N = 1196)	All FluMist n (%) (N = 595)	FluMist-Y n (%) (N = 298)	FluMist-V n (%) (N = 297)	Rate difference percentage points[a]
Any solicited symptom	605 (50.6%)	323 (54.3%)	154 (51.7%)	169 (56.9%)	- 3.7%
Fever[b]					
≥ 100.4F (38.0C)	19 (1.6%)	12 (2.0%)	4 (1.3%)	8 (2.7%)	- 0.4%
≥ 101.3F (38.5C)	8 (0.7%)	4 (0.7%)	0 (0.0%)	4 (1.3%)	- 0.0%
≥ 102.2F (39.0C)	3 (0.3%)	1 (0.2%)	0 (0.0%)	1 (0.3%)	0.1%
≥ 103.1F (39.5C)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.1%
≥ 104.0F (40.0C)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0%
≥ 104.9F (40.5C)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0%
Runny/stuffy nose	374 (31.3%)	224 (37.6%)	104 (34.9%)	120 (40.4%)	- 6.4%
Sore throat[b]	207 (17.3%)	89 (15.0%)	43 (14.4%)	46 (15.5%)	2.3%
Cough	115 (9.6%)	47 (7.9%)	23 (7.7%)	24 (8.1%)	1.7%
Headache[b]	285 (23.8%)	145 (24.4%)	71 (23.8%)	74 (24.9%)	- 0.5%
Generalized muscle aches[b]	101 (8.4%)	66 (11.1%)	26 (8.7%)	40 (13.5%)	- 2.6%
Decreased activity level (lethargy) or tiredness/weakness	194 (16.2%)	104 (17.5%)	52 (17.4%0	52 (17.5%)	- 1.3%
Decreased appetite	63 (5.3%)	34 (5.7%)	10 (3.4%)	24 (8.1%)	- 0.4%

Source: Table 12.2.-1, page 101 of the MI-CP 206 CSR
a Q/LAIV rate minus All FluMist rate, where the All FluMist group refers to data from both the FluMist/B/Yamagata arm and the FluMist/B/Victoria arm combined
b Temperature by any route

Unsolicited AEs:
A similar proportion of Q/LAIV and All FluMist recipients reported adverse events days 0 – 28 post-vaccination: 187 Q/LAIV recipients (15.6%) reporting 318 events, and 89 (14.9%) All FluMist recipients reporting 149 events. In contrast to the solicited symptoms, slightly more FluMist/B/Yamagata recipients than FluMist/B/Victoria recipients reported unsolicited adverse events (15.4% vs 14.4%), but this small difference is unlikely to be of clinical significance. Two Q/LAIV recipients experienced influenza.

All MedDRA preferred term AEs were reported with a rate difference of < 1.0. The preferred term AEs with the largest rate differences were vomiting, with a rate difference (Q/LAIV – All FluMist) of -0.7%, and headache, with a rate difference of 0.8% and cough, with a rate difference of 0.7%. The most commonly reported AEs among all subjects were headache, diarrhea, nausea, vomiting, cough, rhinorrhea, and upper respiratory tract infection, all reported in ≤ 1.7% of subjects in each group.
The majority of unsolicited AEs reported Days 0 – 28 were of mild to moderate severity. Six Q/LAIV-(b)(4) recipients (0.5%) reported 19 severe (Grade 3) events, and 4 FluMist recipients (0.7%) reported 4 severe (Grade 3) events. By preferred term, the Grade 3 AEs among Q/LAIV-(b)(4) recipients were tooth ache, pyrexia, gallbladder disorder, bronchitis (2 subjects), pharyngitis, contusion, ligament rupture, electrolyte imbalance, back pain, headache (2 subjects), migraine, asthma, dyspnea, hypoxia, nasal congestion, rhinorrhea, and status asthmaticus. Grade 3 AEs reported by subjects who received FluMist were sinusitis, headache, abdominal pain upper and migraine (1 subject each). Grade 4 (life-threatening) AEs were reported in 2 subjects who received Q/LAIV-(b)(4), which included cardiac aneurysm and cholecystitis. The subject who experienced cholecystitis (25 days post vaccination) subsequently died on Day 44 from complications of cholecystitis, sepsis, and multiorgan failure. One Q/LAIV-(b)(4) recipient had a Grade 5 (fatal) event of pneumonia within 28 days of vaccination.

Two additional unsolicited AEs of Grade 4 (life-threatening) severity were reported outside the 28 day period: a Q/LAIV-(b)(4) recipient who experienced acute renal failure 50 days after vaccination, and a FluMist/B/Yamagata recipient who experienced cellulitis of the left upper lip 30 days post-vaccination. These events were SAEs are are included below.

One event of asthma was reported, in a Q/LAIV-(b)(4) subject.

Twelve subjects reported epistaxis during Days 0 – 28 post-vaccination, 9 (0.8%) Q/LAIV-(b)(4) recipients and 3 (0.5%) All FluMist subjects.

Serious adverse events (SAEs):
There were 4 SAEs reported in 4 subjects days 0 – 28 post-vaccination; these subjects were all Q/LAIV-(b)(4) recipients. During days 0 – 180 after vaccination, 15 (1.3%) Q/LAIV recipients reported 18 SAEs, and 2 (0.3%) of FluMist recipients reported 6 SAEs (all FluMist/B/Yamagata recipients). These numbers include the SAEs reported within 28 days of vaccination. Most SAEs resolved.

The SAEs are described in more detail below, based on the provider's case narratives:
Days 0 – 28:

- A 33 year old African American male with history of bipolar disorder and Stage IIIB/IV anaplastic non-Hodgkin's lymphoma (in remission since approximately 9 months prior to vaccination) developed nausea, abdominal cramping, heartburn, decreased appetite, and fever approximately 3 weeks post-vaccination with Q/LAIV-(b)(4) and 3 days after having 2 teeth extracted. After 4 days of symptoms, he was evaluated in the ER and hospitalized. An abdominal ultrasound was read as normal. His fever persisted, and a few days later, he was assessed as having possible pneumonia (vs atelectasis), abdominal distention, anemia, leukocytosis, and increasing renal insufficiency. Three days later, he underwent cholecystectomy for cholecystitis. Approximately one week later, he had acute respiratory distress syndrome (ARDS), severe sepsis with organ damage, severe leukocytosis, urinary tract infection, decreased effective circulatory volume, elevated lactate dehydrogenase (LDH), and protein-calorie malnutrition. One week later, he died of complications from cholecystitis, sepsis, and multiorgan failure. Given the nature of the SAE, it is unlikely related to vaccination.
- A 38 year old White female with positive family history of aneurysm (mother died at age 30) and history of episodes of tachycardia prior to dosing had an MRI which noted a left ventricular wall aneurysm 28 days post-vaccination with Q/LAIV-(b)(4). Her scheduled electrophysiology study was cancelled due to this finding. She was hospitalized for initiation of amiodarone therapy, discharged, and then readmitted for surgical removal of the left ventricular wall aneurysm. She was hospitalized for one week post-operatively, and the event was considered resolved on the day of surgery. However, she refused to sign a release of medical records to the site, and no further information is available. Given the nature of the SAE, it is unlikely related to vaccination.
- A 30 year-old African American female with history of morbid obesity, hypertension, sleep apnea, hyperlipidemia, depression, asthma (disclosed after the SAE), diabetes, and menstrual irregularities; with concomitant medications including clonidine, albuterol, prednisone 5 mg, amlodipine/benazepril, bupropion, divalproex sodium, lorazepam, cyclobenzaprine, hydrochlorothiazide, metformin, potassium, hydrocodone + acetaminophen, amoxicillin/clavulanate, spironolactone, indomethacin, and diclofenac presented to the ER approximately 28 days post-vaccination with Q/LAIV-(b)(4) with blood-streaked sputum and a 4 day history of cough. A chest X-ray was read as

consistent with pulmonary vascular congestion. She was seen the next day at the site for a scheduled follow-up visit and reported no AEs. That night, she was hospitalized for shortness of breath, bilateral pneumonia, and hypoxemia requiring intubation. The following day, an echocardiogram revealed an ejection fraction of 55%, no pericardial effusion, and no obvious source of emboli or vegetations. Rapid influenza antigen test was negative for A and B strains. During the hospitalization, her renal function deterioriated, and a follow-up chest X-ray showed severe pulmonary air space disease from bilateral pneumonia, atelectasis, or ARDS; repeat rapid influenza antigen test was negative, but an influenza A antibody level of $\geq$ 64 was found. She developed acute renal failure requiring Continuous Renal Replacement Therapy. Her family decided to withdraw life support, and she died, with cause of death listed as respiratory failure due to ARDS secondary to bilateral pneumonia. While a relationship to vaccination cannot be entirely ruled out due to the nature of the SAE (pneumonia), the subject had multiple co-morbidities, including morbid obesity and diabetes, which may have contributed to the development of pneumonia.

- A 26 year old African American female with history of dysmenorrhea, tension headaches, anemia, and menorrhagia and last menstrual period (LMP) of July 11, 2009 was vaccinated with Q/LAIV-(b)(4) on August 21, 2009. On -------(b)(6)--------, she presented to the ER for abnormal vaginal bleeding. Serum pregnancy test was positive. Ultrasound showed the uterine size of 10.8 x 6.6 x 5.9 cm, as well as a gestational sac of 1.85 cm (6 weeks 2 days) and a crown-rump length of 1.27 cm (7 weeks 3 days). Fetal heart rate was confirmed at 152 beats per minute. Intravenous saline was given for dehydration, and acetaminophen was given for low back pain. RhoD human immune globulin was administered. Four days later, she was seen in the ER for vaginal bleeding; a transvaginal pregnancy ultrasound was performed and revealed a crown-rump length suggesting a gestational age of 8 weeks 2 days and no fetal heartbeat. RhoD immune globulin was administered, and the subject was discharged from the ER with a diagnosis of fetal demise. The ISMC reviewed the case and unanimously assessed the miscarriage to be unrelated to investigational product. A relationship to vaccination cannot be determined, and the event is possibly related. The product package insert cautions against using it in pregnant women.
- A 30 year old African American female with history of childhood asthma, tobacco abuse, seasonal allergies, possible cat allergies, and obesity; concomitant medications included albuterol. She was hospitalized 22 days post-vaccination with Q/LAIV-(b)(4) with report of bad sinus and allergy symptoms, coughing, wheezing, severe dyspnea, and a one time fever the previous day. Chest X-ray showed no acute pneumonic process. A CT of the face showed findings consistent with acute sinusitis. Influenza A and B antigens were negative, but her white blood cell count was mildly elevated. She was diagnosed with status asthmaticus, acute bronchitis, and acute sinusitis. She was treated with albuterol, ceftriaxone, montelukast, prednisone, fluticasone/salmeterol, fluticasone, guaifenesin, and amoxicillin clavulanate. The event resolved. The event is possibly related to vaccination. However, status asthmaticus could be related to tobacco use and seasonal allergies, as well, assuming they were current at the time of the SAE.

Days 29 – 180 post-vaccination:

- A 27 year old White female with history of seasonal allergies, tension headaches, and depression was hospitalized 177 days post-vaccination with Q/LAIV-(b)(4) for upper respiratory tract infection and pyelonephritis. She was discharged, and the events were considered not resolved. Given the timing of the events, it is unlikely they were related to vaccination.

- A 45 year old African American male with history of possible untreated hypertension experienced dysarthria and right-sided weakness 140 days post-vaccination with Q/LAIV-(b)(4). He was evaluated in the ER, and the final head CT showed an acute 3.7 cm intraparenchymal hematoma centered in the left lentiform nucleus with mild edema and associated mild mass effect and suggestive of an acute hypertensive hemorrhage.. Also noted were chronic small vessel ischemic disease including a small right anterior frontal infarct and lacunar infarcts in the left caudate head and right thalamus. During hospitalization, the subject's systolic blood pressure was 120s – 160s mmHg. He was discharged to an acute rehabilitation facility; the outcome of the stroke was recovered with sequelae of right hemiparesis and dysarthria. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 43 year old African Amercian male with history of arthritis, right hip arthroplasty, heterotopic ossification, and bilateral hip pain was hospitalized 85 days post-vaccination with Q/LAIV-(b)(4) for a left total hip arthroplasty for worsening arthritis. A nondisplaced fracture of the proximal femur was noted in the operating room, requiring cable fixation. He underwent radiation therapy for prophylaxis of heterotopic ossification, and was discharged, with the event resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 41 year old Native Hawaiian or other Pacific Islander female was diagnosed with esophageal cancer approximately 4 months post-vaccination with Q/LAIV-(b)(4). She declined further discussion of information related to her diagnosis. The outcome is unknown. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 48 year old White female was evaluated for dizziness and cognitive dysfunction and diagnosed with cranial meningioma 3 months post-vaccination with Q/LAIV-(b)(4). She underwent a right frontotemporal craniotomy for removal of olfactory groove meningioma. She was discharged from the hospital, and the event was considered resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 27 year old White female was hospitalized for crisis evaluation and observation after presenting to the ER for newly emerging depressive symptoms without suicidal ideation 34 days post-vaccination with Q/LAIV-(b)(4). She was treated with divalproex sodium and advised to follow-up with a counselor. The outcome was resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 37 year old White male was hospitalized 76 days post-vaccination with Q/LAIV-(b)(4) with symptoms of sore throat and fever. Chest X-ray showed minimal streaky basilar opacity on the lateral view. Blood cultures were negative. CT chest showed infiltrate vs atelectasis. Nasopharyngeal specimen by rapid enzyme immunoassay was negative for influenza A and B, but PCR detected H1N1 influenza. Arterial blood gas (ABG) showed hypoxia (pO2 52 mmHg). He was treated with antibiotics, an antiviral (oseltamivir), steroids, and fluticasone propionate (for bilateral wheezing). The SAE resolved. Given the PCR findings of H1N1, it is possible that the event is related to vaccination, although the timing is unexpected. It may be more probable that either a different H1N1 strain infected the subject, or that a vaccine failure occurred.
- A 43 year old White female was hospitalized 109 days post-vaccination with Q/LAIV-(b)(4) for severe vomiting, treated with ciprofloxacin, and discharged, with the SAE of gastroenteritis resolved. Given the timing and nature of the event, it is unlikely related to vaccination.
- A 27 year old White male with history of gastroparesis, anxiety, psoriasis, seasonal allergies, tension headaches, biliary dyskinesia, and Gilbert's syndrome developed diarrhea, nausea, and vomiting and was hospitalized for intractable nausea and vomiting 155 days post-vaccination with Q/LAIV-(b)(4). Hepatobiliary iminodiacetic acid (HIDA)

scan and CT showed gastritis and a hiatal hernia. His bilirubin was 1.6 (range not provided). Laparoscopic cholecystectomy was performed, and the event resolved. Given the timing and nature of the event, it is unlikely related to vaccination.

- A 27 year old White female with history including asthma, obesity, hyponatremia, and 130 pound weight loss over the preceding year was evaluated at an urgent care center 73 days post-vaccination with FluMist/B/Yamagata for swelling and pain of the right foot which had been ongoing for 10 months. There, her glucose was 679, and her sodium was 129 (reviewer's note: probably pseudohyponatremia due to hyperglycemia), and she was prescribed cyclobenzaprine for muscle spasms and hydrochlorothiazide for elevated blood pressure of 142/84 mmHg. She was transferred to the ER for x-rays. In the ER, her serum glucose was > 1000 mg/dL. X-rays were negative for acute changes. She was diagnosed with new onset diabetes mellitus, anemia, hyponatremia, increased serum glutamic oxaloacetic transaminase, electrolyte abnormality, and obesity. She was treated with subcutaneous insulin and discharged on insulin, atorvastatin, and iron sulfate. The right lower extremity edema resolved, and the diabetes mellitus was ongoing. Given the timing and nature of the events, they are unlikely related to vaccination.
- A 43 year old African American female with history including insulin-dependent diabetes type 2, hypertension, depression, obstructive sleep apnea, obesity, irregular heartbeat, hypercholesterolemia, allergic rhinitis, right foot bunionectomy, carbuncles of the posterior neck presented to the ER with few day history of left buccal commissure edema and pain, and was hospitalized for possible abscess and cellulites 30 days post-vaccination with FluMist/B/Yamagata. She was treated with antibiotics, underwent incision and drainage, and was discharged with a diagnosis of methicillin-resistant staphylococcus aureus cellulitis and abscess of the left upper lip. The event resolved. Given the timing and nature of the events, they are unlikely related to vaccination.
- A 45 year old female vaccinated with Q/LAIV----------(b)(4)---------- on August 24, 2009, with estimated date of conception January 14, 2010, experienced a miscarriage in the beginning of her ninth week of pregnancy.

Two deaths were reported during the study, both in Q/LAIV subjects. One subject died 44 days post-vaccination of complications from cholecystitis, sepsis, and multiorgan failure. The other subject died 52 days post-vaccination due to bilateral pneumonia and acute renal failure. Additional details were provided in the above summaries of the SAE case narratives.

No subjects withdrew due to an AE or SAE.

New Onset Chronic Diseases from Day 0 – Day 180:
During Days 0 – 180 post-vaccination, new onset chronic diseases (NOCDs) were reported by 6/1198 (0.5%) Q/LAIV recipients and 3/596 (0.5%) FluMist recipients (0.7% in the FluMist/B/Yamagata and 0.3% in the FluMist/B/Victoria treatment groups). The NOCDs reported by Q/LAIV recipients were: autoimmune thyroiditis, type 2 diabetes mellitus, thyroid neoplasm, restless legs syndrome, anxiety, and hypertension (1 subject each). The NOCDs reported by FluMist/B/Yamagata subjects were: mitral valve prolapse and diabetes mellitus, (1 subject each). One FluMist/B/Victoria recipients reported attention deficit/hyperactivity disorder.

Pregnancy:
One subject was randomized and received Q/LAIV-(b)(4) after having a negative pregnancy test at screening. She had a miscarriage 33 days post-vaccination. According to the applicant, based on sonography and laboratory results, it appeared that the subject was approximately 8 weeks pregnant at vaccination, and that the screening pregnancy test result was a false negative. This event was reported as an SAE. An additional 6 subjects were reported as pregnant within 60 days

post-vaccination. Three of these subjects (2 FluMist recipients and 1 Q/LAIV-(b)(4) recipient) delivered healthy infants, and one subject (Q/LAIV-(b)(4) recipient) had an unknown pregnancy outcome, one Q/LAIV recipient had a spontaneous abortion (date of vaccination August 21 2009; last menstrual period September 23, 2009, and end of pregnancy November 22, 2009). The other pregnancy occurred in a 45 year old female approximately 4.5 months post-vaccination with Q/LAIV----------(b)(4)----------; in the beginning of her ninth week of pregnancy, the subject had an SAE of miscarriage.

Wheezing:
Due to the increased rates of wheezing and hospitalization for pneumonia among FluMist (vs placebo) recipients younger than 2 years of age, the number of subjects in each treatment arm who reported wheezing or asthma or pneumonia or use of medication to treat wheezing or asthma in this adult study was evaluated (post-hoc analysis by CBER reviewer). The intent of the analysis was to evaluate further whether there was a signal of increased wheezing or pneumonia among Q/LAIV recipients compared with trivalent FluMist recipients which might be associated with the addition of the fourth influenza strain. Medications to treat pneumonia were not analyzed, as only 2 subjects were reported as having pneumonia. The sources of these analyses were the adverse events and concomitant medications datasets submitted by the applicant. These analyses did not suggest an increased risk of wheezing or asthma or pneumonia among Q/LAIV subjects (randomization scheme was 4:1:1). The interpretation of these findings is limited by such factors as their stemming from post-hoc analyses.

Table 17. Study MI-CP206. Occurrence of Wheezing and Pneumonia

	Q/LAIV	FluMist-Y	FluMist-V
Unsolicited AE (# subjects)			
Wheezing or asthma	1	0	0
Pneumonia	1	1	0
Medication (# subjects)			
Albuterol	4	0	0
Steroid (any) for wheezing or asthma	2	0	0
Indication asthma or wheezing for concomitant meds			
Number of subjects	4	0	0
Number of meds	9	0	0

Source: CBER clinical reviewer analysis

Immunogenicity:

Primary immunogenicity endpoint:
The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody $\leq$ 1.5 for each strain. The GMT ratios (comparator divided by Q/LAIV-(b)(4)) ranged from 0.90 – 0.97, and the upper limits of the 95% CI ranged from 1.00 – 1.10. Baseline GMTs were fairly similar between Q/LAIV and

comparator groups. The table below includes the Day 28 GMTs for each strain for the Q/LAIV and comparator vaccines; the geometric mean fold rise ratios were provided by the applicant.

Table 18. Study MI-CP206. Post-Vaccination GMTs and GMT Ratios

Strain	Q/LAIV-(b)(4)		Comparator [a]		GMT Ratio and 95% CI	
	N	GMT[b]	N	GMT[b]	Ratio[c]	95% CI[d]
A/H1N1	1176	8.1	586	7.7	0.95	0.87, 1.03
A/H3N2	1176	8.3	586	7.7	0.93	0.85, 1.00
B/Yamagata	1176	60.3	294	54.1	0.90	0.79, 1.02
B/Victoria	1176	27.4	292	26.7	0.97	0.87, 1.10

Source: Tables 11.4.1.1-1, 11.4.1.1-2, page 73/5438 of the study MI-CP206 clinical study report
GMT: geometric mean titer; HAI: hemagglutination inhibition
a: comparator = All FluMist group for A/H1N1 and A/H3N2 strains, where the All FluMist group refers to data from both the FluMist-Y arm and the FluMist-V arm combined; comparator = FluMist-Y for the B/Yamagata strain and FluMist-V for the B/Victoria strain
b: a value of 2 was assigned for an HAI antibody titer reported as < 4
c: GMT in comparator divided by GMT in Q/LAIV
d: Confidence Interval calculated based on bootstrapping method

Method of Dose Delivery
According to the applicant, the proportion of subjects receiving the entire dose of Q/LAIV-(b)(4) was 98.7% compared to 99.3% of subjects receiving one of the 2 FluMist comparators delivered via the BD Accuspray device. While 6 subjects received half a dose or less of the Q/LAIV delivered by (b)(4), additional issues such as incomplete openings of the twist-off tabe were noted by 8 sites in administering the vaccine. Based on a subject questionnaire about the dose delivery method, 92% of Q/LAIV-(b)(4) recipients and 94% of FluMist recipients reported overall satisfaction with their delivery devices. The applicant reported that the rate of delivery system opening malfunctions was incompatible with consistent vaccine dose delivery and reports its evaluation of the delivery system for optimization of the opening and dose delivery is ongoing.

Summary:
Study MI-CP206 was considered a supportive, but not pivotal, evaluation of the safety and immunogenicity of Q/LAIV as the -----(b)(4)----- delivery differs from the BD Accuspray device used in the pivotal studies and currently licensed for administration of FluMist. Findings of this study were similar to those of the pivotal studies and raised no additional concerns regarding the Q/LAIV safety and immunogenicity in comparison to FluMist.

Runny nose/stuffy nose was the most commonly reported solicited symptom, more common among FluMist subjects (37.6%) compared with Q/LAIV subjects (31.3%). In this study, MI-CP206, FluMist/B/Victoria was associated with more solicited symptoms as compared with FluMist/B/Yamagata, which is similar to what was observed in adult study MI-CP185, but the opposite of what was observed in the pediatric study MI-CP208. Among all subjects, the peak number of vaccine recipients reported solicited symptoms Days 1 – 2. However, the proportion of subjects with solicited symptoms was $\geq$ 10% in every treatment group Days 0 – 6. The median number of days of solicited symptoms across all groups was $\leq$ 3.0.

The study met its primary immunogenicity endpoint, with the upper limit of the 95% confidence interval (CI) for the ratios of GMTs of HAI antibody $\leq$ 1.5 for each strain. The GMT ratios (comparator divided by Q/LAIV-(b)(4)) ranged from 0.90 – 0.97, and the upper limits of the 95% CI ranged from 1.00 – 1.10.

Study D145-P500:
A randomized, double-blinded trial of the safety, transmissibility, and phenotypic and genotypic stability of influenza virus vaccine, trivalent, types A & B, live cold-adapted (CAIV-T) in children who attended day care.

This sBLA contains an update to the report submitted to BLA 125020/0 as part of a response to a Complete Response Letter (CRL) on 7 January 2002 (Volume 16 through 18). The updates include incorporation of the statistical report and results of a post-study Reed Frost analysis of the probability of transmission, results of genotypic analysis not available at the time of the original report, details for generating reconstructed data sets and a comparison of the differences between the original and reconstructed databases, changes to tables generated from a statistical QC, changes to authorization signatures, and other administrative revisions. Wyeth, the sponsor of this study, compared the original and reconstructed analysis data sets and assessed the impact of any differences on the statistical analysis and clinical study report results and conclusions. As it did not find any differences which it judged clinically significant, the original analysis data sets were the basis of the statistical analysis and CSR included.

The study was performed in healthy children 8 - < 36 months of age in daycare in Finland from November 16, 1999 to May 29, 2000. The primary objective was to assess whether CAIV-T was transmitted from vaccinated children to their unvaccinated placebo contacts in a day care setting; if so, the rate of transmission was to be estimated. Secondary objectives included assessment of safety and tolerability of CAIV-T in children attending day care; assessment of the safety and tolerability of transmitted vaccine virus in placebo recipients if transmission occurred; assessment of whether CAIV-T isolates obtained from vaccine recipients or placebo recipients for transmitted virus maintains the cold-adapted and temperature sensitive phenotypes; assessment of whether CAIV-T maintained the 6:2 reassortant genotype in viral isolates obtained from vaccinated participants and recipients of transmitted virus.

The study was reviewed under BLA 125020/0. Please see the clinical review of that submission for details, including review of the safety data. Briefly, 197 healthy Finnish children 8 months - < 36 months of age who attended day care at least 3 days per week and for 4 hours per day received either CAIV-T (98 subjects) or placebo (99 subjects). Nasal swab specimens for culture were obtained from all subjects on day 0, day 1, and on 3 alternating days per week for the remainder of a 21-day collection period. Specimens were analyzed by culture at designated local laboratories to detect vaccine virus shedding. Any influenza-positive isolates were typed A or B at the local laboratory, and culture supernatant was frozen for future analysis. The original nasal swab and culture supernatants were shipped to Aviron (Mountain View, CA) for subtype, phenotype, and genotype analysis. The primary endpoint for placebo recipients was the first nasal swab positive for any influenza vaccine virus strain. An exploratory, post-hoc analysis was performed for this endpoint using the Reed-Frost model to estimate probability of transmission. The endpoint for CAIV-T recipients (secondary endpoint) was the first nasal swab positive for viral shedding in which the vaccine virus phenotype (cold-adapted and temperature sensitive) or genotype (6:2 reassortant) was not preserved.

Seventy-eight (80%) CAIV-T recipients and 7 (7%) of placebo recipients had shedding detected. No vaccine recipients were found to be shedding wildtype virus. Thirteen CAIV-T recipients (6 who shed type A virus and 7 who shed type B virus) had virus recovered from nasal swab specimens that could not be subtyped or phenotyped. According to the applicant, vaccine-like phenotype was preserved in all viral isolates from the nasal swabs of CAIV-T and placebo recipients, including the transmitted type B vaccine virus recovered from one placebo subject. Virus could not be recovered successfully for genotypic sequence analysis to identify the origin of these isolates according to the CSR, but the applicant reported that the genotype for the definite case of transmission was consistent with that of the type B vaccine strain.

> *Clinical Reviewer Comment: This re-analysis does not prompt revision of the existing information about shedding and transmission in the Package Insert.*

8 Overview of Immunogenicity (Effectiveness) Across Trials

The two pivotal studies of immunogenicity were performed in such different age populations (1 in adults and 1 in children) that combining the data for an integrated summary of immunogenicity would not be informative.

9 Overview of Safety Across Trials

The two pivotal studies were performed in such different age populations (1 in adults and 1 in children) that combining the data for an integrated summary of safety would not be informative. The applicant provided an integrated summary of safety findings from the two adult trials. However, it is unclear what effect the device used for vaccination in the two studies in adults affects the safety profile. Since the Q/LAIV administered via BD Accuspray is the subject of this application for licensure, only the SAEs from the 2 adult trials were analyzed for an integrated summary of safety.

Combining studies MI-CP185 and MI-CP206, the 3600 total adult subjects were randomized to each treatment group were: Q/LAIV 2402, All FluMist 1198 (FluMist-Y 599, FluMist-V 599); numbers of subjects in the safety population were: Q/LAIV 2396, All FluMist 1194 (FluMist-Y 596, FluMist-V 598). Overall, more female subjects were randomized than male subjects (56 % vs 44%). The majority of total subjects were White (2588/3600 or 72%), while African Americans comprised the next largest racial group (885/3600 or 25%). The most common ethnicity was not Hispanic or Latino (2961/3600 = 82%). The mean age of the overall combined groups was 33.3 years. By age group, 1447/3600 (40%) subjects were 18 – 29 years old, 1114/3600 (31%) were 30 – 40 years old, and 1039/3600 (29%) were 41 – 49 years old. The number of subjects vaccinated in the 2 adults studies combined was 3595, of whom 2397 were Q/LAIV recipients, 599 were FluMist-Y recipients, and 599 were FluMist-V recipients, contributing to the 1198 All FluMist subjects. Loss to follow-up was similar across treatment groups. The numbers of subjects completing the study were as follows: 2317 Q/LAIV recipients, 1161 All FluMist recipients (581 FluMist-Y subjects and 580 FluMist-V subjects). There were 2 deaths in the Q/LAIV group. Details of the deaths are included in the respective study review section.

The rate difference between the Q/LAIV recipients and the All FluMist recipients for any adverse events which were reported as occurring at any time during days 0 – 28 post-vaccination was less than 1% for all subjects in these 2 trials combined. For African American subjects, rhinorrhea was more commonly reported in Q/LAIV recipients, with a rate difference of 1.2%. For Whites, all rate differences were <1%. For other racial groups, rate differences were greater, but given

the small numbers of subjects in each of the other contributing racial groups, the clinical significance of these differences is difficult to interpret.

Serious adverse events through 180 days post-vaccination were reported as follows in the combined adult trials: 35 SAEs in 27 (1.1%) Q/LAIV recipients, 7 SAEs in 5 (0.8%) FluMist-Y recipients, and 4 SAEs in 3 (0.5%) FluMist-V recipients. Six of the 35 SAEs among Q/LAIV recipients were fractures. One Q/LAIV recipient had status asthmaticus, while one FluMist-Y recipient had an SAE of asthma. Additionally, the following SAEs were reported once in Q/LAIV recipients but not in any FluMist recipients: cardiac aneurysm, coronary arteriospasm, multi-organ failure, appendicitis, bacteremia, C. difficile colitis, gas gangrene, gastroenteritis, influenza, lobar pneumonia, pneumonia, pyelonephritis, upper respiratory tract infection, arthritis, meningioma, esophageal carcinoma, cerebrovascular event, depression, psychotic disorder, acute renal failure. There were 2 cases of diverticulitis and spontaneous abortions, respectively in the Q/LAIV group and none in the other groups. Please see the full review section corresponding to the individual studies for additional information and reviewer conclusions about each SAE. Overall, there was no pattern of SAEs which raised concerns about Q/LAIV's safety in the studied population.

New onset chronic diseases through 180 days were reported as follows in the combined adult trials: 18 NOCDs in 17 (0.7%) Q/LAIV subjects, 5 NOCDs in 4 FluMist-Y (0.7%) subjects, and 4 NOCDs in 3 (0.5%) FluMist-V subjects. There was no pattern to suggest safety concerns with respect to Q/LAIV.

10 Pediatric Research Equity Act (PREA) requirements

The applicant requested that the requirement to study FluMist Q/LAIV in all pediatric populations be waived for children younger than 2 years of age. This request was presented to the PeRC on December 14, 2011, and the PeRC agreed. Previous studies with the trivalent CAIV suggested an increased risk of wheezing and hospitalization for pneumonia in children younger than 2 years of age in previous studies. This was discussed with the VRBPAC and informed CBER's decision not to license the product for use in children younger than 2 years of age. Therefore, due to this safety concern, a waiver in this portion of the pediatric population is reasonable. The applicant has safety and immunogenicity data in the rest of the pediatric population.

11 Conclusions—Overall

The two pivotal studies raised no new safety concerns. In general, the safety and reactogenicity profile of Q/LAIV appeared similar to that of FluMist in both adults and children. Runny/stuffy nose was the most frequently reported solicited reaction, and the median duration of any reactogenicity symptoms was $\leq$ 4 days. Among children 2 – 8 years of age, fever was reported in more Q/LAIV recipients after dose 1 (6.6%) compared with All FluMist recipients after dose 1 (4.2%) but was reported in a more similar proportion of FluMist-Y recipients after dose 1 (5.6%). However, there was no apparent increase in associated sequelae associated with the higher rate of fever (e.g., there were no febrile convulsions reported). After dose 2, fever was reported in fewer Q/LAIV recipients compared to the other groups.

Effectiveness of Q/LAIV was inferred based on a non-inferiority comparison with two different formulations of trivalent FluMist, each one containing one of the two B strain components of Q/LAIV. The primary endpoint was an upper bound of the 95% confidence interval (CI) of the

ratio of FluMist GMTs divided by Q/LAIV of ≤ 1.5 for all 4 strains included in the Q/LAIV. All pre-specified primary endpoints were met. The immune response to Q/LAIV overall appears non-inferior to the immune response elicited by trivalent FluMist. While immune responses in all treatment groups appear relatively low as measured by HAI, clinical efficacy data previously obtained in studies of trivalent FluMist suggested that the immune response parameters evaluated underestimated the product's clinical efficacy, which is substantial in the pediatric population. It is anticipated that Q/LAIV will have similar clinical efficacy, despite the low responses measured by HAI. Post-hoc immunogenicity analyses performed by the applicant suggested that the inclusion of the second B strain did result in higher seroresponse rates to the second B strain than was afforded by the single B strain contained in the trivalent comparator.

Given the theoretical potential for viral interference among the 4 replicating vaccine strains that could result in reduced effectiveness, MedImmune has agreed to conduct additional studies post-marketing studies to confirm effectiveness of this product. MedImmune has also agreed to conduct an observational safety study post-licensure.

12 Recommendation

The clinical reviewer recommends approval of the supplement to the license of FluMist allowing reformulation with the addition of a second influenza B strain. An acceptable proper name would be FluMist Quadrivalent. The clinical reviewer also recommends that the applicant conduct the post-marketing case-control study to confirm effectiveness of Q/LAIV in children 2 years through 17 years of age.