DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA

BLA/Supplement Number:	STN 125020/1668
Product Name:	FluMist® Quadrivalent, Influenza Vaccine Live, Intranasal
Indication(s):	Influenza disease caused by influenza virus subtypes A and type B contained in the vaccine
Applicant:	MedImmune
Date(s):	Date submitted: April 29, 2011 Action due date: February 29, 2012
Review Priority:	Standard
Statistical Branch:	Vaccine Evaluation Branch
Primary Statistical Reviewer:	Sang Ahnn
Concurring Reviewer (1):	Tsai-Lien Lin, Team Leader Viral and Bioassay Team
Concurring Reviewer (2):	Dale Horne, Branch Chief Vaccine Evaluation Branch
Medical Office/Division:	OVRR/DVRPA
Clinical Reviewer:	Meghan Ferris (HFM-475)
Project Manager:	Daryll Miller / Bernard McWatters (HFM-478)

EXECUTIVE SUMMARY

This supplemental BLA presents data to support licensure of a new 4-strain formulation of FluMist, FluMist Quadrivalent, Live Attenuated Influenza Vaccine, for active immunization of individuals 2 to 49 years of age against influenza disease caused by influenza virus subtypes A and both influenza B lineages contained in the vaccine.

Clinical data presented in this supplement includes two clinical trials, MI-CP185 (adult; in subjects 18 to 49 years of age) and MI-CP208 (pediatric; in children 2 to 17 years of age) along with supportive safety data from an adult clinical trial (MI-CP206) which utilized Q/LAIV administered with an alternative delivery device.

RECOMMENDATION: For subjects of 2-49 years of age, noninferior immunogenicity of FluMist Quadrivalent to FluMist was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criteria [The upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by FluMist Quadrivalent) be ≤ 1.5].

MI-CP185

This is a randomized, double-blind, active controlled, multicenter study to evaluate the immunogenicity of Q/LAIV in adults 18 to 49 years of age.

A total of 1,800 subjects were randomized by site at a 4:1:1 ratio to receive a single dose of either Q/LAIV or 1 of 2 formulations of FluMist, each containing a B strain that matched 1 of the 2 B strains in the Q/LAIV vaccine [B/Yamagata or B/Victoria]. Among 1,800 subjects randomized, 1,798 were dosed. Immunogenicity analyses were performed on 1,770 subjects (98.3% of the randomized). The safety population included 1,796 subjects, and the evaluable safety population for solicited symptoms included 1,794 subjects.

Primary analysis of immunogenicity

The statistical criterion to show the noninferior immune response of Q/LAIV to FluMist is that the upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by Q/LAIV) be ≤ 1.5. The comparators for the GMT ratios for the primary endpoint were subjects in the two FluMist groups combined for A/H1N1 and A/H3N2 strains and subjects who received FluMist with a matching B strain for the B/Yamagata and B/Victoria strains.

Post dose GMT ratios and their corresponding 95% CIs (in the parenthesis) for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.09 (1.01, 1.18), 1.05 (0.96, 1.14), 1.10 (0.97, 1.25), and 0.92 (0.82, 1.03).

The results showed [based on the pre-specified noninferiority criteria] that the immune response to vaccination with each of the 4 influenza vaccine strains contained in Q/LAIV was noninferior to that occurring after vaccination with the same strains contained in a licensed (trivalent) FluMist vaccine.

Safety

There were no SAEs considered to be related to the investigational product that occurred in subjects in the Q/LAIV arm. There was an SAE of hypersensitivity (allergic reaction with brochospasm) considered to be related to the FluMist/B/Victoria vaccine.

Subgroup Analyses

(Post hoc) subgroup analyses of immunogenicity by gender, race (white vs. non-white) or age (18-34 years vs. 35-49 years) did not show any remarkable difference in immunogenicity between the genders, age groups or the race groups.

(Post hoc) subgroup analyses of serious adverse events (SAE's) by gender, race (white vs. non-white), or age (18-34 years vs. 35-49 years) did not show any noteworthy difference in the distribution of SAE's between the genders, age groups, or race groups.

MI-CP208

This is a randomized, double-blind, active controlled, multicenter study to evaluate the immunogenicity of Q/LAIV in children 2 to 17 years of age.

A total of 2,312 subjects were randomized (by age strata; 2 to 8 years of age and 9 to 17 years of age) at a 3:1:1 ratio to receive either Q/LAIV or 1 of 2 formulations of FluMist, each containing a B strain that matched 1 of the 2 B strains in the Q/LAIV vaccine [B/Yamagata or B/Victoria]. Among 2,312 subjects randomized, 2,305 received at least one dose of vaccine.

Primary analysis of immunogenicity

Immunogenicity analyses were performed on 2,210 subjects (95.6% of the randomized).

The statistical criterion to show noninferior immune response of Q/LAIV to FluMist is that the upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by Q/LAIV) be ≤ 1.5. The comparators for the GMT ratios for the primary endpoint were subjects in the two FluMist groups combined for A/H1N1 and A/H3N2 strains and subjects who received FluMist with a matching B strain for the B/Yamagata and B/Victoria strains.

Post dose GMT ratios and their corresponding 95% CIs (in parentheses) for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, respectively, were 1.07 (0.98, 1.16), 1.04 (0.94, 1.14), 1.21 (1.07, 1.37), and 1.05 (0.93, 1.18).

The results showed [based on the pre-specified noninferiority criteria] that the immune response to vaccination with each of the 4 influenza vaccine strains contained in Q/LAIV was noninferior to that occurring after vaccination with the same strains contained in a licensed (trivalent) FluMist vaccine.

Safety

No deaths and no SAEs considered to be related to investigational product were reported in study subjects. No SAEs occurred within 28 days of Dose 1. Within 28 days of Dose 2, 3 subjects reported 4 SAEs (appendicitis[Q/LAIV group], salmonella gastroenteritis with dehydration[Q/LAIV group], and major depression[FluMist/B/Victoria group]).

Subgroup Analyses

(Post hoc) subgroup analyses of immunogenicity by gender, race (white vs. non-white) or age (2-8 years vs. 9-17 years) did not show any remarkable difference in immunogenicity between the genders, age groups or the race groups.

(Post hoc) subgroup analyses of serious adverse events (SAE's) by gender, race (white vs. non-white), or age (2-8 years vs. 9-17 years) did not show any noteworthy difference in the distribution of SAE's between the genders, age groups, or race groups.

Reviewer's Comments

1. For subjects 2-49 years of age, noninferior immunogenicity of FluMist Quadrivalent to FluMist was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criteria [the upper bound for each of the four 95% CIs for the GMT ratios (FluMist divided by FluMist Quadrivalent) be ≤ 1.5].
2. Numerical accuracy of the applicant's primary immunogenicity results and major safety results were verified by the reviewer.