

FDA Statistical Review and Evaluation

BLA: 125020\0\20 and 125020\0\36

Sponsor: MedImmune Vaccines (formerly Aviron)

Product: Trivalent influenza virus vaccine, live, cold adapted, intranasal (FluMist)

Re: Asthma/Reactive Airway Disease (RAD) among FluMist recipients

From: Wasima N. Rida, Ph.D.

For: December 17, 2002 VRBPAC

Background

On October 31, 2000, Aviron submitted a BLA for FluMist, a live, cold-adapted, intranasally administered trivalent influenza virus vaccine. A label indication for active immunization for the prevention of influenza in children, adolescents, and adults 1 to 64 years of age was sought. The data submitted in the BLA were presented to VRBPAC on July 26-27, 2001. Upon review of the data, the committee raised a number of concerns about the safety and efficacy of FluMist. The safety concerns involved: (1) a potential increase in the rate of asthma and other respiratory events among vaccine recipients, (2) shedding and transmission of vaccine strains to contacts, (3) limited safety data in the very young and those over 50, (4) no data on concurrent immunizations, (5) potential for genotype or phenotype reversion, and (6) limited data on re-vaccination. Efficacy concerns involved the number and timing of doses. Two doses given 28 days apart were proposed for children under 9 years of age who are receiving the vaccine for the first time. All others would receive a single dose annually. There are also no efficacy or effectiveness data in subjects between 6 and 17 years of age.

After VRBPAC, the agency completed its review of the BLA and issued a complete response letter to the sponsor on August 31, 2001. The following January the sponsor submitted an amended BLA which among other things contained the completed data from a large, randomized safety trial AV019. The agency issued another complete response letter in July 2002 that was followed by the sponsor's response in August. In late October, MedImmune indicated that it would now seek a labeling indication for active immunization in healthy children, adolescents, and adults 5 to 64 years of age.

The statistical review herein focuses on the safety concerns raised about asthma at the July 2001 VRBPAC and is based on the sponsor's submissions of January 7 and August 26, 2002. Special attention is given to those subjects less than 5 years of age as well as those 5 years of age and older. Analysis is limited to the three large trials involving pediatric populations: AV019, AV012, and AV006.

Protocol AV019 (large, randomized safety trial)

AV019 was a randomized, double-blinded, placebo-controlled study of the safety of FluMist in healthy children and adolescents between 1 and 17 years of age. A total of 9,733 participants were enrolled from sites of the Northern California Kaiser Permanente (NCKP) health care system between October 2 and December 22, 2000. Subjects were randomized 2:1 to receive FluMist or placebo (normal allantoic fluid). Participants less than 9 years of age were to receive two doses of FluMist or placebo with the second dose to be administered 28 to 42 days after the first. Subjects 9 years of age and older received a single dose. Follow-up for safety was for 42 days after each dose. Medically attended events (MAEs) were extracted from the NCKP computerized health care utilization databases for hospitalizations, emergency department visits, and clinic visits. Information on drug prescriptions was not extracted.

Vaccine:

The vaccine consisted of single 0.5 mL doses of FluMist containing approximately 10^7 TCID₅₀ of each of three strains for the 1999-2000 influenza season: A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2), and B/Yamanashi/166/98 given intranasally, 0.25 mL in each nostril. The influenza strains recommended for 2000-2001 included the same B strain. However, both of the A strains were different.

Primary Objectives:

A number of pre-specified grouped diagnoses were selected to capture illness syndromes that have been reported to occur in association with wild-type influenza infection and theoretically might occur after administration of FluMist. These diagnoses included acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. Individual diagnoses were analyzed as well. Note that NCKP's medical diagnoses were provided rather than ICD-9-CM codes.

Asthma Exclusion Criterion:

Subjects with a history of asthma or possible asthma by parent/guardian report at the time of recruitment were to be excluded.

Prior History of Asthma/RAD:

In the January 2002 submission, history of asthma/RAD for each subject was determined by a retrospective search of the HMO database beginning in January 1998 up to the time of enrollment of that subject. The database search was only for the term "asthma/RAD."

Based on this search, 857 (8.8%) of the 9,733 subjects were classified as history positive. For children less than 9 years of age, 545 (9.6%) of 5,669 subjects were classified as history positive.

Prior History of Asthma/RAD/Wheezing:

In the August 2002 submission, subjects were re-classified according to their history of asthma and/or wheezing illness. History of asthma/RAD/wheezing for each subject was determined by a retrospective search of the HMO database beginning in January 1995 up to the time of enrollment of that subject. The database search was for the terms asthma, RAD, bronchospasm, bronchiolitis, and wheezing. Terms such as “dyspnea” and “shortness of breath” were not used to identify history because of their non-specificity in identifying asthma or wheezing illness. Based on this search, 1,533 (26.7%) of 5,685 subjects less than 9 years of age were considered history positive for asthma/RAD/wheezing.

Asthma/RAD/Wheezing Outcomes:

Subjects experiencing shortness of breath were coded as experiencing wheezing/shortness of breath.

Protocol AV012 (large, non-randomized herd immunity trial)

AV012 was a multi-year, non-randomized, open label study of the herd effect of FluMist on medically attended acute respiratory illness (MAARI) in children and adolescents 18 months through 18 years of age. In Year 1, 4,298 children were enrolled between August 17 and December 19, 1998 at the Scott and White HMO in Temple-Belton, Texas. Three thousand four hundred six (79.2%) subjects received their medical care primarily at the Scott and White HMO while the remainder received care outside of the HMO. All children received a single dose of FluMist. In Year 2, 5,251 children were enrolled between September 13 and December 30, 1999. Of the 5,251 enrolled, 2,101 (40.0%) were re-enrolled from Year 1 and thus received a second dose of FluMist. Also, 3,748 (71.4%) children reported receiving their medical care primarily at Scott and White. Data from Years 3 and 4 have not been submitted to the BLA.

Vaccines:

In Year 1, the vaccine consisted of a single 0.5 mL dose of FluMist containing approximately 10^7 TCID₅₀ of each of three strains for the 1998-1999 influenza season: A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2), and B/Harbin/7/94-like given intranasally, 0.25 mL in each nostril. The vaccine in Year 2 contained the same strains as Year 1 although a different vaccine lot was used.

Primary Objectives:

MAARI events and rare events potentially related to wild-type influenza were extracted from the Scott and White HMO database using pre-specified ICD-9-CM codes. For Year 1, these data were collected for each subject from the time the first subject was enrolled and vaccinated on August 17, 1998 through January 30, 1999, 42 days after the last subject was vaccinated. Thus, all subjects were followed for a minimum of 42 days after vaccination. For Year 2, events were extracted from the database from September 13, 1999 through February 10, 2000. The database search included hospital admissions, hospital observations without admission, outpatient surgery, and emergency room visits. In addition, all participants were asked to contact the study site if a new significant health problem occurred within 42 days of FluMist administration. A Day 42 Health Report Postcard that captured serious adverse events was to be returned to the site as well.

Asthma Exclusion Criterion:

Children with moderate, persistent asthma or any other condition for whom the licensed inactivated influenza vaccine is recommended were to be excluded. However, children with a history of wheezing illness were eligible.

Prior History of Asthma/RAD/Wheezing:

History of asthma/RAD/wheezing was determined by a retrospective search of the HMO database (from January 1, 1997 for Year 1 and from January 1, 1998 for Year 2 to the day prior to vaccination) for ICD-9 codes for asthma (493.00-493.91) **or** a prior history of asthma, RAD, or wheezing as identified by the parent/guardian at the time of enrollment. In Year 1, a retrospective search determined that 505 (11.7%) subjects had a history of asthma/RAD/wheezing. For the 3,406 subjects who received their medical care at Scott and White, 453 (13.3%) were classified as history positive. In Year 2, 754 (14.4%) subjects were designated as history positive while 622 (16.6%) of the 3748 subjects who received care at Scott and White were history positive.

Asthma/RAD/Wheezing Outcomes:

Medically attended events in which an ICD-9 code for asthma (493.0-493.91), bronchiolitis (466.1), or wheezing (786.07) was entered into the HMO database were counted as outcomes.

Acute Asthma/RAD/Wheezing Outcomes:

In this study, asthma/RAD/wheezing was further classified as “acute” if (1) the participant has reactive airway disease, asthma, or cough variant asthma, (2) the

participant has acute symptoms and/or signs consistent with asthma exacerbation, such as increased cough at night or early morning, post-tussive emesis, shortness of breath, wheezing, or increase work of breathing, (3) the examination of a participant reveals at least one finding suggesting respiratory distress resulting from an asthma exacerbation, such as increased respiratory rate, wheezing, labored breathing, accessory muscle use, decreased O₂ saturation, chest x-ray finding of hyperinflation or improvement of air movement or reduction in wheezing after Beta-agonist treatment, (4) the participant is started or continued on Beta-agonist therapy, or (5) the participant is started on oral steroid therapy.

Protocol AV006 Year 1 (efficacy trial in healthy children 15-71 months of age)

AV006 was a multi-center, randomized, double-blinded, placebo-controlled study of the efficacy and safety of FluMist in healthy children between the ages of 15 and 71 months. In Year 1, a total of 1,602 subjects were enrolled between August 21 and December 5, 1996. Subjects were randomized 2:1 to receive FluMist or placebo (normal allantoic fluid). One thousand three hundred fourteen children receive a two-dose regimen with the second dose given approximately 60 days after the first. The remaining children received a single dose.

Vaccine:

In Year 1, the vaccine consisted of a single 0.5 mL dose of FluMist containing approximately 10⁷ TCID₅₀ of each of three strains for the 1996-1997 influenza season: A/Texas/36/91 (H1N1), A/Wuhan/359/95 (H3N2), and B/Harbin/7/94-like given intranasally, 0.25 mL in each nostril.

Safety Evaluations:

Parents/guardians were to complete a 10 day diary card for pre-specified reactogenicity events. However, there was no monitoring plan specified in the protocol for the collection of adverse events within 42 days of each vaccination or for the duration of the study. Some adverse events were captured on illness forms when children were seen by study personnel to obtain cultures for influenza virus detection.

Asthma Exclusion Criterion:

Individuals with a history of wheezing or bronchodilator use within 3 months prior to vaccination or with a significant underlying chronic illness for whom inactivated influenza vaccines are recommended were to be excluded.

Prior History of Asthma/RAD/Wheezing:

History was obtained retrospectively “based on historical information in records.”

Asthma/RAD/Wheezing Outcomes:

Outcomes were captured on adverse event case report forms (CRFs), comment CRFs, and illness forms during study follow-up.

Demographics of AV006, AV012, and AV019

FDA Table 1.
Demographic Characteristics of Study Participants

| Characteristic | AV006 Year 1 | AV012 Year 1 | AV012 Year 2 | AV019 |
|--------------------|-----------------|-----------------|-----------------|-------|
| Race/Ethnicity (%) | | | | |
| African American | 9.1 | 6.8 | 6.5 | 6.3 |
| American Indian | - | - | - | 0.1 |
| Asian/Pacific Is. | 0.9 | 1.1 | 1.1 | 10.1 |
| Hispanic | 3.4 | 16.6 | 14.5 | 19.8 |
| Multiracial | - | - | - | 4.5 |
| None noted | - | 1.9 | 1.9 | 0.0 |
| Other | 2.1 | 2.5 | 3.4 | 3.9 |
| White | 84.6 | 71.0 | 72.5 | 55.4 |
| Sex (%) | | | | |
| Male | 47.4 | 50.4 | 50.4 | 49.1 |
| Female | 52.6 | 49.6 | 49.6 | 50.9 |

Sponsor’s Analyses of Asthma/RAD/Wheezing/SOB

AV019

As presented at the VRBPAC meeting in July 2001, medically attended asthma/RAD events for Days 0-42 post dose one were significantly increased for FluMist recipients between 18 and 35 months of age. A preliminary analysis showed 6 cases among 728 FluMist recipients and 0 cases among 369 placebo recipients. The lower bound of the 90% confidence interval for the binomial relative risk was 1.08.

The final clinical study report for AV019 was submitted in January 2002. In that report, separate analyses for the outcomes asthma/RAD and wheezing/shortness of breath were presented. For children between 18 and 35 months, there were now 11 episodes of asthma in 10 of 728 FluMist recipients post dose one as compared to 0 episodes among 369 placebo recipients. The lower bound of the 90% confidence interval for the binomial relative risk was 1.95. Seven more cases occurred following dose two, 5 among FluMist recipients and 2 among placebo recipients. Of note, 7 of the 16 cases among FluMist recipients were in children with a prior history of asthma/RAD.

An increase in asthma/RAD was not observed for FluMist recipients 12 to 17 months of age, but this may be due to the small number of subjects in this age group. To better understand the possible association between vaccination and asthma in this study, the sponsor examined the asthma event rates for a range of cumulative age groups by increasing increments of six months of age (MedImmune Table 18, Volume 14, January 2002 submission). Using this approach, the estimates of relative risk increased initially as older children were included in the analysis, peaked in the 12 to 53 month age group, and declined thereafter. This pattern may suggest an age-dependent risk of asthma in susceptible children who received FluMist.

Table 18
Asthma Event Rates by Cumulative Age Range,
All Settings Combined, All Doses Combined

| Age | Number of Participants | | Rate per 1000- Person Months ^a FluMist/Placebo | Binomial Relative Risk ^a (90% CI) |
|--------------|------------------------|----------------|---|--|
| | FluMist n/N | Placebo n/N | | |
| 12-17 Months | 1/171 | 3/90 | 2.77/16.16 | 0.17 (0.01, 1.15) |
| 12-23 Months | 6/381 | 4/208 | 7.22/8.79 | 0.82 (0.28, 2.58) |
| 12-29 Months | 12/633 | 5/323 | 8.84/7.32 | 1.21 (0.51, 3.10) |
| 12-35 Months | 17/899 | 5/459 | 8.74/5.03 | 1.74 (0.77, 4.31) |
| 12-41 Months | 23/1189 | 6/623 | 8.88/4.50 | 1.98 (0.95, 4.45) |
| 12-47 Months | 26/1457 | 7/760 | 8.24/4.33 | 1.91 (0.96, 4.02) |
| 12-53 Months | 30/1741 | 7/882 | 7.96/3.71 | 2.15 (1.10, 4.49) |
| 12-59 Months | 33/2021 | 10/1011 | 7.54/4.57 | 1.65 (0.92, 3.08) |
| 12-65 Months | 33/2263 | 13/1129 | 6.70/5.35 | 1.25 (0.74, 2.19) |
| 12-71 Months | 37/2454 | 15/1234 | 6.92/5.62 | 1.23 (0.75, 2.07) |
| 12-78 Months | 40/2736 | 17/1373 | 6.71/5.73 | 1.17 (0.73, 1.92) |
| 12-83 Months | 42/2912 | 18/1470 | 6.65/5.65 | 1.18 (0.74, 1.90) |

^a Based on participant-incidence.

For the outcome wheezing/shortness of breath, there was no statistically significant increase post dose one or two. For both doses combined, there were 7 cases among 728 FluMist recipients and 5 cases among 369 placebo recipients. The estimated relative risk and 90% confidence interval were 0.71 and (0.27, 1.98), respectively.

Subsequently to the January submission, a systematic chart review was conducted on participants 12 to 53 months of age who were assigned a coded diagnosis of either asthma/RAD or wheezing/shortness of breath. In general, the coded diagnosis of asthma/RAD was more likely assigned to children who had a prior diagnosis of asthma/RAD, who presented with more severe clinical signs, or who were prescribed oral or inhaled corticosteroids. Also, the vast majority of wheezing/shortness of breath outcomes were in fact wheezing events. However, it was evident that the two diagnostic codes were often assigned by the health care providers to describe very similar clinical scenarios. Thus, there was considerable overlap in the use and treatment of the two diagnoses. Because of this overlap, these two outcomes were combined into the broader diagnosis of “asthma/RAD/wheezing/shortness of breath.”

Based on data presented in the sponsor’s Tables 43.20, 43.24, and 43.28 (August 2002 submission), asthma/RAD events, relative risks, and their corresponding 90% confidence intervals for children less than 5 years of age and for children between 5 and 9 years of age by prior history of asthma/RAD/ wheezing are as follows.

FDA Table 2a.
 Number of Events and Relative Risk of Asthma/RAD
 by Dose, Age Group, and Prior History of Asthma/RAD/Wheezing
 (All Utilization Settings Combined)

| Population | Age Group (in months) | Dose | <u>42 Day Summary Period</u> | | RR (90% CI) | |
|--|--|-------|------------------------------|------------------|-------------------|--------------------|
| | | | FluMist (n/N) | Placebo (n/N) | | |
| All | 12-59 | One | 14/2,032 | 2/1,025 | 3.53 (1.10,15.66) | |
| | | Two | 23/1,729 | 8/ 861 | 1.43 (0.74, 2.92) | |
| | 60-107 | One | 9/1,759 | 6/ 869 | 0.74 (0.31, 1.76) | |
| | | Two | 4/1,513 | 6/ 739 | 0.33 (0.11, 0.94) | |
| | Hx Positive (Asthma/RAD/ Wheezing) | 12-59 | One | 9/ 557 | 2/ 290 | 2.30 (0.67, 10.61) |
| | | | Two | 14/ 472 | 5/ 249 | 1.48 (0.64, 3.73) |
| 60-107 | | One | 7/ 465 | 3/ 221 | 1.11 (0.36, 3.45) | |
| | | Two | 2/ 406 | 4/ 188 | 0.23 (0.06, 0.96) | |
| Hx Negative (Asthma/RAD/ Wheezing) | | 12-59 | One | 5/1,475 | 0/ 735 | NA (0.92, NA) |
| | | | Two | 9/1,257 | 3/ 612 | 1.46 (0.50, 5.02) |
| | 60-107 | One | 2/1,294 | 3/ 648 | 0.33 (0.07, 1.50) | |
| | | Two | 2/1,107 | 2/ 551 | 0.50 (0.10, 2.58) | |

Based on data presented in the sponsor's Tables 43.21, 43.25, and 43.29 (August 2002 submission), asthma/RAD/wheezing/SOB events, relative risks, and their corresponding 90% confidence intervals for children less than 5 years of age and for children between 5 and 9 years of age by prior history of asthma/RAD/ wheezing are as follows.

FDA Table 2b.
 Number of Events and Relative Risk of Asthma/RAD/Wheezing/SOB
 by Dose, Age Group, and Prior History of Asthma/RAD/Wheezing
 (All Utilization Settings Combined)

| Population | Age Group (in months) | Dose | <u>42 Day Summary Period</u> | | RR (90% CI) |
|--|--------------------------|------|------------------------------|------------------|-------------------|
| | | | FluMist (n/N) | Placebo (n/N) | |
| All | 12-59 | One | 25/2,032 | 8/1,025 | 1.58 (0.82, 3.20) |
| | | Two | 34/1,729 | 16/ 861 | 1.06 (0.65, 1.77) |
| | 60-107 | One | 12/1,759 | 10/ 869 | 0.59 (0.29, 1.20) |
| | | Two | 11/1,513 | 8/ 739 | 0.67 (0.31, 1.44) |
| Hx Positive (Asthma/RAD/ Wheezing) | 12-59 | One | 13/ 557 | 4/ 290 | 1.66 (0.66, 4.67) |
| | | Two | 20/ 472 | 9/ 249 | 1.17 (0.61, 2.34) |
| | 60-107 | One | 8/ 465 | 5/ 221 | 0.76 (0.30, 1.94) |
| | | Two | 7/ 406 | 6/ 188 | 0.54 (0.22, 1.35) |
| Hx Negative (Asthma/RAD/ Wheezing) | 12-59 | One | 12/1,475 | 4/ 735 | 1.51 (0.59, 4.27) |
| | | Two | 14/1,257 | 7/ 612 | 0.97 (0.46, 2.18) |
| | 60-107 | One | 4/ 1,294 | 5/ 648 | 0.40 (0.13, 1.21) |
| | | Two | 4/ 1,107 | 2/ 551 | 1.00 (0.24, 4.16) |

AV012 Years 1 and 2

In the original protocol for AV012 Year 1, the sponsor proposed to compare the MAARI event rates to rates from unvaccinated controls from two neighboring communities, PCA in Austin, Texas and Scott and White HMO in Bryan-College Station, Texas. However, the problem of identifying a subset of the comparison communities that was comparable to the vaccinees proved to be problematic. In addition, PCA changed ownership and data

access became impossible. As a result, the Data and Safety Monitoring Board for AV012 recommended an epidemiological method as described by Griffin et al. (1990, 1991) for analyzing the MAARI event data. With this approach, MAARI event rates during a specified post-vaccination period are compared to rates during a control or reference period for each participant. The post-vaccination periods assessed were Days 0-14 and Days 0-42. In Year 1, the reference period for each participant was constructed by combining the pre-vaccination period (time from August 17, 1998 through one day prior to the date of vaccination) plus the post-vaccination period (time from Day 15 or Day 43 after vaccination to January 30, 1999). The sponsor also made an attempt to adjust the analyses for the seasonal effects of parainfluenza virus (October 4 through November 14) and respiratory syncytial virus (November 15 through January 30). Reference periods for Year 2 were similarly defined.

For Year 1 and the post-vaccination period Days 0-14, the sponsor calculated an adjusted relative risk of 0.77 for acute asthma/wheezing with a 90% confidence interval (0.45, 1.32) for all participants receiving health care at Scott and White HMO (Volume 10, January 2002 submission). For the post-vaccination period Days 0-42, the adjusted relative risk was 0.87 with a 90% confidence interval (0.65, 1.17). For the subset of participants with a history of asthma/wheezing, the adjusted relative risks and 90% confidence intervals were 1.11 (0.62, 1.98) and 0.77 (0.52, 1.13) for Days 0-14 and Days 0-42, respectively. The sponsor did not carry out similar analyses for restricted age groups such as children 12 to 59 months old.

For Year 2 and the post-vaccination period Days 0-14, the sponsor calculated an adjusted relative risk of 0.88 for acute asthma/wheezing with a 90% confidence interval of (0.52, 1.50) for all participants receiving care at Scott and White HMO prior to the greatest intensity of the influenza season (Volume 12, January 2002 submission). For the post-vaccination period Days 0-42, the adjusted relative risk was 1.83 with a 90% confidence interval (1.26, 2.67). For the subset of participants with a history of asthma/wheezing, the adjusted relative risks and 90% confidence intervals were 0.82 (0.44, 1.52) and 1.47 (0.95, 2.28) for Days 0-14 and Days 0-42, respectively. The sponsor did not carry out similar analyses for restricted age groups such as children 12 to 59 months old.

AV006 Year 1

Based on data presented in the sponsor's Tables 43.20, 43.24, and 43.28 (August 2002 submission), asthma/RAD events, relative risks, and their corresponding 90% confidence intervals for children less than 5 years of age and for children between 5 and 6 years of age by prior history of asthma/RAD/ wheezing are as follows.

FDA Table 3a.
 Number of Events and Relative Risk of Asthma/RAD
 by Dose, Age Group, and Prior History of Asthma/RAD/Wheezing

| Population | Age Group (in months) | Dose | <u>42 Day Summary Period</u> | | RR (90% CI) |
|--|--------------------------|------|------------------------------|------------------|-------------------|
| | | | FluMist (n/N) | Placebo (n/N) | |
| All | 12-59 | One | 2/ 853 | 0/ 437 | NA (0.24, NA) |
| | | Two | 3/ 691 | 2/ 343 | 0.74 (0.15, 4.20) |
| | 60-71 | One | 1/ 217 | 0/ 95 | NA (0.06, NA) |
| | | Two | 1/ 163 | 0/ 75 | NA (0.06, NA) |
| Hx Positive (Asthma/RAD/ Wheezing) | 12-59 | One | 0/ 16 | 0/ 8 | NA (NA) |
| | | Two | 0/ 14 | 0/ 6 | NA (NA) |
| | 60-71 | One | 0/ 4 | 0/ 1 | NA (NA) |
| | | Two | 0/ 4 | 0/ 1 | NA (NA) |
| Hx Negative (Asthma/RAD/ Wheezing) | 12-59 | One | 2/ 837 | 0/ 429 | NA (0.24, NA) |
| | | Two | 3/ 677 | 2/ 337 | 0.75 (0.15, 4.21) |
| | 60-71 | One | 1/ 213 | 0/ 94 | NA (0.06, NA) |
| | | Two | 1/ 159 | 0/ 74 | NA (0.06, NA) |

Based on data presented in the sponsor's Tables 43.21, 43.25, and 43.29 (August 2002 submission), asthma/RAD/wheezing/SOB events, relative risks, and their corresponding 90% confidence intervals for children less than 5 years of age and for children between 5 and 6 years of age by prior history of asthma/RAD/ wheezing are as follows.

FDA Table 3b.
Number of Events and Relative Risk of Asthma/RAD/Wheezing/SOB
by Dose, Age Group, and Prior History of Asthma/RAD/Wheezing

| Population | Age Group (in months) | Dose | 42 Day Summary Period | | RR (90% CI) |
|--|--------------------------|------|-----------------------|------------------|-------------------|
| | | | FluMist (n/N) | Placebo (n/N) | |
| All | 12-59 | One | 28/ 853 | 13/ 437 | 0.91 (0.51, 1.81) |
| | | Two | 21/ 691 | 8/ 343 | 1.31 (0.66, 2.68) |
| | 60-71 | One | 4/ 217 | 0/ 95 | NA (0.65, NA) |
| | | Two | 3/ 136 | 0/ 75 | NA (0.57, NA) |
| Hx Positive (Asthma/RAD/ Wheezing) | 12-59 | One | 3/ 16 | 2/ 8 | 0.75 (0.15, 4.25) |
| | | Two | 2/ 14 | 0/ 6 | NA (0.28, NA) |
| | 60-71 | One | 0/ 4 | 0/ 1 | NA (NA) |
| | | Two | 0/ 4 | 0/ 1 | NA (NA) |
| Hx Negative (Asthma/RAD/ Wheezing) | 12-59 | One | 20/ 837 | 11/ 429 | 0.93 (0.50, 1.77) |
| | | Two | 19/ 677 | 8/ 337 | 1.18 (0.60, 2.45) |
| | 60-71 | One | 4/ 213 | 0/ 94 | NA (0.66, NA) |
| | | Two | 3/ 159 | 0/ 74 | NA (0.48, NA) |

FDA Analysis

AV019

The protocol specified that children under the age of 9 years were to receive two doses of FluMist or placebo 28 to 42 days apart. However, only 4,911 (86.6%) of 5,669 subjects received two doses. For those receiving two doses, the median time to second dose was 35 days. Also, 886 (18.0%) of 4,911 received their second dose more than 42 days after the first. In the most extreme case, one subject received his second dose 122 days later. A higher proportion of non-white subjects than white subjects did not receive a second dose. Four hundred forty five (16.9%) of 2,629 non-whites did not receive a second dose while 312 (10.9%) of 3,038 whites did not. The primary reasons for not receiving dose

two were “unable to contact” and “protocol non-compliance.” Given this non-compliance, the relative risk for asthma/RAD or asthma/RAD/wheezing/SOB post dose two should be interpreted with care.

Based on data contained in the sponsor’s SAS transport files (January 2002 submission), asthma/RAD events, relative risks, and their corresponding 90% confidence intervals for children less than 5 years of age and for children between 5 and 9 years of age by prior history of asthma/RAD/ wheezing are as follows.

FDA Table 4.
 Number of Participants and Relative Risk of Asthma/RAD
 by Dose, Age Group, and Prior History of Asthma/RAD
 (All Utilization Settings Combined)

| Population | Age Group (in months) | Dose | 42 Day Summary Period ¹ | | RR (90% CI) |
|-----------------------------|--------------------------|------|------------------------------------|------------------|--------------------|
| | | | FluMist (n/N) | Placebo (n/N) | |
| All | 12-59 | One | 14/2,020 | 2/1,011 | 3.50 (1.01, 12.15) |
| | | Two | 21/1,728 | 8/ 861 | 1.31 (0.66, 2.59) |
| | 60-107 | One | 8/1,748 | 5/ 858 | 0.78 (0.31, 2.01) |
| | | Two | 4/1,514 | 6/ 739 | 0.33 (0.11, 0.94) |
| Hx Positive (Asthma/RAD) | 12-59 | One | 6/ 207 | 2/ 97 | 1.41 (0.37, 5.39) |
| | | Two | 8/ 179 | 1/ 83 | 3.71 (0.65, 21.23) |
| | 60-107 | One | 3/ 155 | 2/ 85 | 0.82 (0.18, 3.69) |
| | | Two | 2/ 135 | 2/ 74 | 0.55 (0.11, 2.84) |
| Hx Negative (Asthma/RAD) | 12-59 | One | 8/1,813 | 0/ 914 | NA (1.59, NA) |
| | | Two | 13/1,549 | 7/ 778 | 0.93 (0.43, 2.02) |
| | 60-107 | One | 5/1,593 | 3/ 773 | 0.81 (0.24, 2.69) |
| | | Two | 2/1,379 | 4/ 665 | 0.24 (0.06, 1.00) |

¹ For Dose One, subjects are censored at the time of administration of Dose Two if Dose Two is given before Day 42.

Note that there are differences between FDA Tables 2a and 4. In Table 2a, history is defined by a prior history of asthma, RAD, or wheezing. In Table 4, history is defined

per the January 2002 submission and is defined by a prior history of asthma/RAD only. There were many more children with a prior history that included wheezing than children with a history of asthma/RAD only. Also, Table 4 counts the number of participants rather than events. Since some subjects had more than one event in the 42 day reference period, the numerators in Table 4 are somewhat smaller. But because the proportion of subjects with multiple events was small, the relative risks for all subjects combined are very similar between Tables 2a and 4.

The characteristics of the 14 cases among FluMist recipients 12 to 59 months of age post dose one were as follows. Nine were white, 5 were non-white. Six were male, 8 were female. Eight had no prior history of asthma/RAD, 6 did. The 14 cases were identified at 10 different sites. Among the 2 placebo cases, one was white and one was non-white. One was male and one was female. Both had a prior history of asthma/RAD. While no cases were hospitalized, one FluMist recipient was seen in the emergency department. The other 13 were seen in outpatient clinic. There does not appear to be any temporal clustering in the time of asthma/RAD post dose one. Cases occurred fairly uniformly between Days 12 and 42.

AV012 Years 1 and 2

The method of Griffin et al. (1990, 1991) makes the assumption that any increase in risk of a MAARI event due to vaccination occurs only in the specified post-vaccination period. Thus, for the post-vaccination period Days 0-42, one assumes that any increased risk that may occur after vaccination is gone after Day 42. This may not be a reasonable assumption for a more chronic condition such as asthma. As an alternative approach to the analysis of the AV012 data, a Cox proportional hazards model with vaccination status as a time dependent covariate was fit to the Year 1 and 2 data. For a given study year, time is measured from the date that the first subject was enrolled and vaccinated. Thus, time zero refers to August 17, 1998 for Year 1 while time zero refers to September 13, 1999 for Year 2. All subjects were censored 42 days after the last subject was enrolled. This corresponds to censoring on January 30, 1999 for Year 1 and February 10, 2000 for Year 2. Subjects in Year 1 were followed for the same 166 days while subjects in Year 2 were followed 150 days.

The exponential of the estimated beta coefficient associated with the time dependent covariate vaccination status is a measure of the relative increase (or decrease) in the hazard for a given medically attended acute respiratory illness (MAARI) due to FluMist vaccination. For this measure to be unbiased, one must assume that subjects enrolled later in the recruitment period do not differ from subjects enrolled earlier with respect to factors that are predictive of a MAARI outcome. The Cox model also assumes that the increase (or decrease) in risk is immediate following vaccination and persists for the duration of follow-up. Alternative models that fit separate time dependent covariates that reflect various post-vaccination periods were considered. In particular, models that measured the effect of vaccination between Days 0 and 42 post-vaccination versus beyond Day 42 were explored.

FDA Table 5a presents the results from the fit of a Cox proportional hazards model with vaccination status as a single time dependent covariate to the data on acute asthma/wheezing. Relative risk estimates and their 95% confidence intervals are presented by age group for Years 1 and 2. The model is applied to the data of subjects who received their medical care primarily at Scott and White HMO only as MAARI events from subjects who received their care elsewhere were not fully captured in the Scott and White database.

While a number of subjects had recurrent episodes of acute asthma/wheezing, these analyses consider the time to first episode only. Episodes that were coded as unclassified cases of asthma/wheezing were treated as non-acute cases. This should be an anti-conservative approach to the estimate of relative risk. In Year 1, there were 19 unclassified diagnoses in 16 individuals of which 13 were first events. In Year 2, there were 21 unclassified diagnoses in 15 subjects of which 15 were first events. Also, if an episode occurred on the day of vaccination, it was treated as occurring post-vaccination. Fortunately, there were only a handful of such cases and these should not impact the estimate of relative risk materially. There were X such cases in Year 1 and 2 cases in Year 2.

In Year 1, 118 (3.5%) of 3,406 subjects who received their medical care at Scott and White HMO had at least one diagnosis of acute asthma/wheezing between August 17, 1998 and January 30, 1999. This yielded a relative risk estimate of 1.61 with a 95% confidence interval of (0.86, 3.20) for children and adolescents between 1 and 18 years of age. For children less than 5 years of age, 55 (6.5%) of 852 subjects experienced at least one diagnosis during the observation period. A relative risk of 1.57 was observed with a 95% confidence interval of (0.52, 4.45). This estimate is very similar to the estimate of 1.58 for asthma/RAD/wheezing/SOB for the same age group in AV019 (FDA Table 2a). While estimates of relative risk ranged from 1.54 to 2.18 for age groups under 12 years, none was statistically significantly greater than 1.0. Thus, in Year 1, FluMist does not appear to have increased the risk of acute asthma/wheezing appreciably.

Note that an analysis stratified by prior history of asthma/RAD was not possible since history was not defined at baseline which is August 17, 1998, the first day of follow-up for Year 1.

In Year 2, 140 (3.7%) of 3748 subjects had at least one diagnosis of acute asthma/wheezing between September 13, 1999 and February 10, 2000. A relative risk of 1.79 with 95% confidence interval of (1.02, 3.13) was observed. For children less than 5 years of age, 69 (7.1%) of 974 subjects had at least one acute diagnosis. A relative risk of 2.01 with 95% confidence interval (0.94, 4.27) was observed. Thus, in Year 2, there is some suggestion for an elevated risk of acute asthma/wheezing due to FluMist.

Given that 1,616 (40.0%) of 3,748 subjects in Year 2 had been vaccinated in Year 1, separate Cox models were fit to the data of new enrollees and re-vaccinated subjects. The results of these analyses are presented in FDA Table 5b. For re-vaccinated subjects, 59 (3.7%) of 1,616 had at least one acute diagnosis with a relative risk estimate of 1.23 with a 95% confidence interval of (0.56, 2.70). For all age groups under 12 years,

relative risks on the order of 1.0 were observed suggesting no increased risk of acute asthma/wheezing due to FluMist in these subjects. However, for subjects who were new enrollees, there appears to be an elevated risk. For children 1 to 18 years, 81 (3.8%) of 2,132 had at least one acute diagnosis. A relative risk estimate of 2.40 with a 95% confidence interval of (1.08, 5.30) was observed. For children less than 5 years, 43 (6.2%) of 698 subjects had at least one diagnosis. A relative risk estimate of 2.61 with a 95% confidence interval of (1.01, 6.46) was observed.

In AV012, all subjects were followed for at least 42 days after vaccination. However, for subjects vaccinated on Day 0, post-vaccination follow-up was 166 days in Year 1 and 150 days in Year 2. The median length of post-vaccination follow-up was 100 and 103.5 days for Years 1 and 2, respectively. Thus, unlike AV019 which only followed subjects for 42 days after each dose, AV012 had longer post-vaccination follow-up on average. With AV012, one may be able to examine the risk of asthma beyond 42 days post-vaccination. Cox models with separate effects for Days 0 to 42 post-vaccination and for beyond Day 42 were fit to the data from new enrollees in Year 2. For children under 5 years of age, the relative risk for Days 0 to 42 post-vaccination was 2.68 (95% CI: 1.04, 6.88) while the relative risk for beyond Day 42 was 2.11 (95% CI: 0.60, 7.44). For children between 5 and 9 years of age, the corresponding relative risks were 1.53 (95% CI: 0.27, 8.68) and 1.48 (95% CI: 0.19, 11.73).

The Cox proportional hazards model with vaccination status as a time dependent covariate makes the strong assumption that subjects enrolled later in the recruitment period do not differ from subjects enrolled earlier with respect to factors that are predictive of a given MAARI. Given that a history of moderate to severe asthma was an exclusion criterion for subjects in AV012, there is a potential for positive bias in the estimates of relative risk for acute asthma/wheezing. Theoretically, subjects who do not enroll early have more time to develop asthma/wheezing and hence to be excluded from the study. This does not appear to be the case, at least for subjects enrolled in Year 2. Of the 3,406 subjects who were enrolled in Year 1 and received their medical care at Scott and White HMO, 1,616 (47.7%) re-enrolled into the Year 2 study and were re-vaccinated with the same vaccine as Year 1 although the vaccine was from a different manufactured lot. Of the 118 subjects who were diagnosed with at least one episode of acute asthma/wheezing in Year 1, 54 (45.8%) were among those subjects who re-enrolled. This would suggest that a prior diagnosis of acute asthma/wheezing did not limit participation in Year 2.

FDA Table 5a.
AV012 Years 1 and 2
Relative Risk of a Medically Attended Event
with a Diagnosis of Acute Asthma/Wheezing
after a Single Dose of FluMist

| Age Group | Year 1 | | | | Year 2 | | | |
|-----------|-----------|------|------|--------------|-----------|------|------|--------------|
| | First Dxs | N | RR | 95% CI | First Dxs | N | RR | 95% CI |
| All | 118 | 3406 | 1.61 | (0.86, 3.20) | 140 | 3748 | 1.79 | (1.02, 3.13) |
| < 12 Yrs | 106 | 2612 | 1.90 | (0.97, 3.75) | 133 | 2812 | 1.53 | (0.88, 2.66) |
| < 9 Yrs | 96 | 1910 | 1.85 | (0.90, 3.81) | 106 | 2041 | 1.66 | (0.91, 3.03) |
| < 8 Yrs | 90 | 1636 | 1.92 | (0.91, 4.07) | 104 | 1751 | 1.64 | (0.90, 2.99) |
| < 7 Yrs | 84 | 1368 | 1.71 | (0.77, 3.82) | 89 | 1493 | 1.55 | (0.81, 2.97) |
| < 6 Yrs | 70 | 1119 | 2.12 | (0.90, 4.98) | 83 | 1228 | 1.64 | (0.82, 3.28) |
| < 5 Yrs | 55 | 852 | 1.57 | (0.55, 4.45) | 69 | 974 | 2.01 | (0.94, 4.27) |
| < 4.5 Yrs | 51 | 750 | 1.54 | (0.52, 4.56) | 63 | 843 | 2.15 | (1.00, 4.62) |
| < 4 Yrs | 45 | 625 | 1.81 | (0.51, 6.39) | 56 | 708 | 2.07 | (0.93, 4.63) |
| < 3.5 Yrs | 37 | 494 | 2.18 | (0.57, 8.32) | 47 | 577 | 1.99 | (0.77, 5.14) |
| < 3 Yrs | 30 | 371 | 1.62 | (0.37, 7.03) | 33 | 444 | 3.55 | (1.33, 9.42) |
| ? 5 Yrs | 63 | 2553 | 1.66 | (0.76, 3.60) | 71 | 2774 | 1.53 | (0.67, 3.49) |
| ? 6 Yrs | 48 | 2287 | 1.17 | (0.48, 2.87) | 57 | 2520 | 1.88 | (0.73, 4.87) |
| ? 7 Yrs | 34 | 2038 | 1.40 | (0.55, 3.52) | 51 | 2255 | 2.24 | (0.76, 6.59) |
| ? 8 Yrs | 28 | 1770 | 0.88 | (0.30, 2.57) | 36 | 1997 | 1.99 | (0.52, 7.63) |
| ? 9 Yrs | 22 | 1496 | 0.92 | (0.28, 3.01) | 34 | 1707 | 1.99 | (0.51, 7.79) |

FDA Table 5b.
 AV012 Year 2
 Relative Risk of a Medically Attended Event
 with a Diagnosis of Acute Asthma/Wheezing
 after a Single Dose of FluMist
 by prior enrollment in Year 1

| Age Group | New Enrollees | | | | Re-Vaccinated Subjects | | | |
|-----------|---------------|------|------|--------------|------------------------|------|------|--------------|
| | First Dxs | N | RR | 95% CI | First Dxs | N | RR | 95% CI |
| All | 81 | 2132 | 2.40 | (1.08, 5.30) | 59 | 1616 | 1.23 | (0.56, 2.70) |
| < 12 Yrs | 76 | 1630 | 2.11 | (0.98, 4.53) | 57 | 1182 | 1.03 | (0.46, 2.27) |
| < 9 Yrs | 62 | 1244 | 2.25 | (0.98, 5.20) | 44 | 797 | 1.09 | (0.48, 2.48) |
| < 8 Yrs | 61 | 1098 | 2.26 | (0.99, 5.18) | 43 | 653 | 1.03 | (0.45, 2.37) |
| < 7 Yrs | 55 | 975 | 2.33 | (0.95, 5.71) | 34 | 518 | 0.83 | (0.34, 2.06) |
| < 6 Yrs | 51 | 844 | 2.57 | (1.02, 6.46) | 32 | 384 | 0.79 | (0.29, 2.15) |
| < 5 Yrs | 43 | 698 | 2.61 | (1.01, 6.74) | 26 | 276 | 1.20 | (0.36, 4.06) |
| < 4.5 Yrs | 40 | 626 | 3.07 | (1.18, 8.00) | 23 | 217 | 1.12 | (0.32, 3.96) |
| < 4 Yrs | 39 | 558 | 2.94 | (1.12, 7.69) | 17 | 150 | 0.83 | (0.18, 3.84) |
| < 3.5 Yrs | 35 | 477 | 3.31 | (1.18, 9.29) | 12 | 100 | 0.34 | (0.04, 2.72) |
| < 3 Yrs | 28 | 393 | 4.39 | (1.46, 13.2) | 5 | 51 | 0.64 | (0.13, 3.09) |
| ? 5 Yrs | 38 | 1434 | 1.97 | (0.51, 7.71) | 33 | 1340 | 1.20 | (0.43, 3.33) |
| ? 6 Yrs | 30 | 1288 | 1.85 | (0.40, 8.45) | 27 | 1232 | 1.91 | (0.61, 6.04) |
| ? 7 Yrs | 26 | 1157 | 2.34 | (0.41, 13.3) | 25 | 1098 | 2.14 | (0.57, 8.03) |
| ? 8 Yrs | 20 | 1034 | 2.35 | (0.52, 7.63) | 16 | 963 | 1.73 | (0.34, 8.89) |
| ? 9 Yrs | 19 | 888 | 2.44 | (0.27, 22.1) | 15 | 819 | 1.67 | (0.30, 9.20) |

FDA Conclusions

From AV019, there appears to be a 3.5-fold increase in the rate of asthma/RAD in the 42 days following the first dose of FluMist in children less than 5 years of age. While this increase is only statistically significant at the 10% level, it is of concern as many of these children were treated medically. A relative risk of 3.5 would imply 5 excess cases per 1,000 first doses of vaccine if the increased risk were limited to the first 42 days post-vaccination. There does not appear to be any clustering in the timing of asthma with cases among FluMist recipients occurring fairly uniformly between Days 12 and 42. If the risk continues beyond Day 42, then the number of excess cases would increase.

Furthermore, the increased risk does not appear to be limited to children with a prior history of asthma/RAD. For children with a prior history, the relative risk is 1.41 (90% CI: 0.37, 5.39) Days 0 to 42 post dose one. For children without a prior history, there were no cases of asthma observed among 914 placebo recipients under 5 years while there were 8 cases among 1,814 FluMist recipients. Thus, most of the excess cases of asthma appear to come from children with no prior history.

There does not appear to be an increased risk of asthma/RAD following the second dose of vaccine. However, because nearly 14% of children less than 9 years of age did not receive the intended second dose, these results should be considered carefully.

There does not appear to be an increased risk of asthma/RAD in children between 5 and 8 years of age after a first dose. A relative risk of 0.78 was observed with a 90% confidence interval of (0.31, 2.01).

Wheezing/shortness of breath does not appear to be increased with the administration of FluMist in any age group.

Based on FDA analyses using a Cox proportional hazards model with vaccination status as a time dependent covariate, there appears to be a 1.57-fold increase in the rate of acute asthma/wheezing in children less than 5 years of age for AV012 Year 1. This is nearly identical to the risk observed in AV019 for the same age group. Year 2 suggests a 2-fold increase for new and repeat vaccinees combined and a 2.57-fold increase among first time vaccinees. The data from Year 2 also suggest that the elevated risk of acute asthma/wheezing may persist beyond Day 42.

Further study is warranted of the association between FluMist and asthma/RAD in children under the age of 5 years with and without a history of asthma/RAD or wheezing. Clear outcome definitions for asthma/RAD and wheezing are needed as well as some measure of the severity and rate of recurrence of these outcomes. Post-vaccination follow-up should be more than 42 days, possibly for the entire duration of an influenza season.

References

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