FDA Clinical Briefing Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

May 16, 2007

Liquid formulation of FluMist®: Influenza Virus Vaccine, Trivalent, Types A and B, Cold-adapted, Live Attenuated, Liquid Formulation (CAIV-T)

Proposed Indication: Prevention of disease caused by influenza A and B viruses for children 12 to 59 months of age without a history of wheezing or asthma.

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MEMORANDUM

To:	Committee Members, VRBPAC
From:	Office of Vaccine Research and Review and the Division of Vaccines and Related Product Applications
Re:	May 16-17, 2007 Meeting Topic 1: Safety and Efficacy of CAIV-T in a Pediatric Population Less Than 59 Months of Age

Background:

FluMist® Influenza Virus Vaccine, Live, Intranasal (CAIV-T), is a live, attenuated, cold-adapted, temperature-sensitive trivalent vaccine that contains two Type A (H1N1 and H3N2) and one Type B influenza viruses. CAIV-T is administered via the intranasal route and is indicated for active immunization of healthy children and adolescents 5-17 years of age, and healthy adults, 18-49 years of age against influenza disease caused by influenza types A and B contained in the vaccine. The applicant (MedImmune, Inc.) provided clinical data in a BLA supplement to support an extension of the licensed indication to children less than 5 years of age. The data provided in this BLA supplement will be discussed during the first session of the May 16, 2007, Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting.

The original FluMist® BLA was presented to the VRBPAC on July 26-27, 2001. The clinical efficacy/effectiveness data that supported approval and that were presented for discussion were primarily from Study AV006, "A Phase 3, Randomized, Double-blind, Placebo-controlled, Trial to Assess the Safety, Immunogenicity and Efficacy of Influenza Virus Vaccine, Trivalent, Types A&B, Live, Cold-Adapted (CAIV-T) in Healthy Children." Study AV006 was conducted in children 15-71 months of age; the primary efficacy endpoint was culture confirmed influenza illness. Additional data from studies of CAIV-T in adults that evaluated the incidence of symptomatic illness without culture confirmation were also presented.

Safety data from additional studies of FluMist® were discussed. Three deaths were identified in the overall safety database. An 18-month old child died due to bronchopneumonia approximately 1 month after receipt of the second dose of CAIV-T. Two adult subjects with pre-existing chronic pulmonary disease died from complications of their pulmonary disease after receipt of CAIV-T. Bacterial pneumonia within 21 days of vaccination was observed in both CAIV-T and placebo treatment groups. An imbalance in asthma/wheezing adverse events was noted in subjects less than 5 years of age following receipt of CAIV-T in the preliminary safety results of study AV019,

“Randomized, double-blinded, placebo-controlled study of the safety of FluMist®.” Study AV019 was a placebo-controlled study conducted in a population of children receiving care in an HMO setting. Subjects were randomized 2:1 to receive FluMist® or placebo. Adverse events were ascertained by evaluation of the health care utilization databases. Study AV019 had not been completed at the time of the original BLA submission so that only preliminary results were available for review. The majority of the committee voted against approval pending additional evaluation of these adverse events.

A second VRBPAC was held December 17, 2002, to discuss the applicant’s proposal for an indication in the pediatric age group 5 years and above as well as in adults 18-64 years of age. On the basis of analysis of the completed data from study AV019, and additional analyses of the safety data, the applicant sought licensure in persons 5 to 64 years of age with exclusion of the age populations where asthma/wheezing safety signals were noted.

An exploratory analysis of cumulative asthma events by 6 month age increments in study AV019 identified an increased relative risk (RR = 3.5, 90% CI [1.0, 12.2]) in the 12-59 month age subgroup. There was no increased relative risk observed in study subjects 5 years of age and older. In the subgroup of children ages 18-35 months there were 11 cases of asthma/reactive airways disease among CAIV-T recipients (N=728) and 0 cases among placebo recipients (N=369) identified among the health care utilization visits. All 11 cases had concurrent respiratory tract diagnoses (e.g., URI, bronchitis, acute otitis media, croup) at the time of the asthma/reactive airways event. Approximately 44% of the 11 children who had asthma/reactive airways disease in the CAIV-T group had a history of asthma or wheezing, in contrast to approximately 9% of the children overall in the study. A separate evaluation of children 18-35 months of age who received coded diagnoses of both "wheezing" and "shortness of breath" revealed 7 cases in CAIV-T group and 5 cases in placebo group (RR =0.71, 90% CI [0.27, 1.98]).

Two hospitalizations due to asthma/wheezing were identified; both were enrolled in study AV006; one in a CAIV-T recipient and one in a placebo recipient. Among children 5 years and older and adults, the rates of wheezing or asthma among CAIV-T recipients were similar to or lower than the rates among placebo recipients.

The applicant conducted a small study in 48 children 9-17 years of age who had moderate asthma. In this study, two CAIV-T recipients experienced asthma exacerbations while there were no asthma exacerbations among placebo recipients.

After review and discussion of the safety data it was concluded that the possible pneumonia associated with administration of CAIV-T, which was noted at the first VRBPAC, was not confirmed.

FluMist® (CAIV-T) was approved for use in healthy individuals 5-49 years of age on June 17, 2003. There was concurrence with the applicant that the frequency of wheezing or asthma in children 5 years of age and younger was increased after vaccination with CAIV-T. However, because these age subgroups had not been pre-specified and

therefore no longer represented a randomized comparison, firm conclusions about the incidence of respiratory adverse events could not be made. For this reason, additional study to address these concerns was recommended.

Current BLA Supplement:
The applicant submitted the results of five studies to support the safety and efficacy of FluMist® (CAIV-T) in children 5 years of age and younger. Four of these studies are described below and outlined in Table 1.

- Study MICP 111, "A Randomized Double-blind Trial to Assess the Safety and Relative Efficacy of CAIV-T Against Inactivated Influenza Vaccine in Children 6-59 Months of Age", was a randomized, active-controlled, double-blinded, multi-national study with culture-confirmation of cases of influenza-like illness as the primary efficacy endpoint in children 6-59 months of age."
- Safety and efficacy data from study AV006 in children 15-71 months of age submitted to the original BLA were included in this supplement.
- Study D153 P 501, "A Prospective, Randomized, Double-Blind, Placebo-Controlled, Trial to Determine the Safety and Efficacy of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold-Adapted (CAIV-T) in Healthy Children" provided safety and culture confirmed influenza efficacy data in children 12-36 months of age."
- Study AV018, "Trial to Assess Safety, Tolerability, and Immunogenicity of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold-Adapted (FluMist®) and Measles, Mumps, Rubella, and Varicella Vaccines Administered Concurrently to Healthy Children," evaluated immune responses following concomitant administration of the live viral vaccines MMR and varicella with CAIV-T in children 12-15 months of age.

Table 1: Clinical Studies included in supplemental BLA

Study number	Country (-ies)	Study Design	CAIV-T :numbers of subjects	Age
MI CP111, MedImmune	U.S., Europe, Middle East, Asia	Randomized, active controlled, double-blind	4243	6 months to 59 months
AV006, MedImmune	U.S.	Randomized, placebo controlled	1070	15 months to 71 months
D153 P 501, Wyeth	Asia	Randomized, placebo controlled	1900	12 months to 36 months
AV018, MedImmune	U.S., Australia	Randomized, active and placebo controlled	1245	12 months to 15 months

The results of study MICP 123 were submitted in this application. This study was intended to document immune responses in the same age groups using the same vaccine. However, only one half of the population was enrolled due to limited availability of the appropriate formulation of TIV in that season. The applicant has agreed to further study of immune responses to CAIV-T in those five years and younger; results from this study will not be further considered.

Efficacy Results

Study AV006:
In AV006, children 15-71 months of age were randomized 2:1 to receive CAIV-T or placebo. Active surveillance for influenza was performed; clinical specimens were obtained from subjects who experienced influenza-like illness. The primary endpoint was culture-confirmed influenza illness due to wild-type (w-t) virus subtype antigenically similar to the strains contained in the vaccine.

Vaccine efficacy of approximately 90% was observed in this study, as demonstrated in Table 2.

Table 2: Efficacy data from original BLA

Table AV006 – 2: Year 1 Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness for All subjects (15 through 71 months of age) by Dosing Regimen.

Analysis Group	Strain	Estimated Efficacy % (95% CI)
Participants Receiving Two Doses	Any	93.4 (87.5, 96.5)
	H3N2	96.0 (89.4, 98.5)
	B	90.5 (78.0, 95.9)
Participants in Two Dose Regimen	Any	93.2 (87.6, 96.3)
	H3N2	95.5 (89.3, 98.1)
	B	90.5 (78.0, 95.9)
Participants in One Dose Regimen	Any	88.8 (64.5, 96.5)
	H3N2	86.9 (46.6, 96.8)
	B	91.3 (45.6, 98.6)
All Randomized Participants	Any	92.6 (87.3, 95.7)
	H3N2	94.5 (88.3, 97.4)
	B	79.5 (79.5, 95.7)

Table from MedImmune, original BLA, October 2000, Volume 16.

Study MICP 111
MICP 111 was a randomized, active controlled, multi-center, double-blinded study of CAIV-T vs. trivalent inactivated influenza vaccine (TIV) in children 6-59 months of age. The study was conducted in 16 countries including the US, Europe, the Middle East and Asia. Approximately 50% of subjects were enrolled at sites in the United States.

Study vaccines contained the recommended three strains for the 2004-2005 influenza season. Children who had previously received influenza vaccine received one dose of assigned study vaccine; all previously unvaccinated subjects were given two doses of the assigned study vaccine; the first dose was administered on day 0 and the second dose was administered 4-6 weeks later. Study subjects, parents/guardians, and study personnel

were blinded to treatment assignment. That is, subjects who were randomized to receive live attenuated vaccine also received an intramuscular injection of saline placebo, and subjects who were randomized to receive inactivated vaccine also received an intranasal mist of saline placebo. Parents/guardians were contacted every 7 to 10 days throughout the influenza surveillance period. Nasal swabs for culture of influenza were obtained if a subject developed symptoms suggestive of influenza.

Solicited and unsolicited adverse events were documented on diary cards for 42 days following the administration of each dose. Diagnoses of adverse events could be made by a health care provider (HCP) not involved in the study. Serious adverse events (SAEs) were collected during the entire study period.

The primary efficacy endpoint was the Centers for Disease Control-defined Influenza-like Illness (fever, plus sore throat or cough) modified for this age group to include runny nose or nasal congestion ("modified CDC-ILI") with a positive culture for influenza caused by wild-type strains antigenically similar to those contained in the vaccine.

Randomization was stratified by the following baseline characteristics: Age (6-23 months or 24-59 months), country, history of prior influenza vaccination, and wheezing history. In addition to the age stratification, which was based upon power calculations intended to allow efficacy to be evaluated in the youngest age group, an additional age stratification subgroup (23- 35 months) was included to reflect the age differences in recommended TIV dosing, in which those older than 36 months received a 0.5 mL dose and those younger received a dose of 0.25 mL.

The demographic/baseline characteristics were well-balanced between the treatment groups. The following tables are taken from the applicants analyses provided in the study report. The numbers of cases due to individual strains may include culture results not represented in the analysis of "all" strains; however these differences are small and do not impact the comparisons made.

Table 3 shows analysis of the primary endpoint, which evaluated modified CDC-ILI due to w-t antigenically similar influenza strains; Table 4 shows a supportive analysis of modified CDC-ILI due to w-t antigenically dissimilar strains. Table 5 shows an additional supportive analysis of modified CDC-ILI due to all w-t strains combined. It was notable that approximately 70% of influenza strains that circulated in the 2004-05 season were antigenically dissimilar to those contained in the vaccines.

Table 3: Primary endpoint: Culture confirmed modified CDC ILI/ATP* population *Antigenically similar* w-t influenza strains

Strain	CAIV-T 3916		TIV 3936		Absolute difference	Relative efficacy	95% C.I.
	Cases N	Rate %	Cases N	Rate %			
All	53	1.4	93	2.4	1.0	45	22, 61
A/H1	3	0.1	27	0.7	0.6	89	68, 97
A/H3	0	0	0	0			
B	50	1.3	67	1.7	0.4	27	-5, 50

ATP= according to protocol

Table 4: Culture confirmed modified CDC ILI/ ATP population
Antigenically dissimilar w-t influenza strains

Strain	CAIV-T 3916		TIV 3936		Absolute difference	Relative efficacy	95% C.I.
	Cases N	Rate %	Cases N	Rate %			
All	102	2.6	245	6.2	3.6	58	47, 67
A/H1	0	0	0	0			
A/H3	37	0.9	178	4.5	3.6	79	71, 86
B	66	1.7	71	1.8	0.1	6	-32, 33

ATP= according to protocol

Table 5: Culture confirmed modified CDC ILI/ ATP population
All w-t influenza strains

Strain	CAIV-T 3916		TIV 3936		Absolute difference	Relative efficacy	95% C.I.
	Cases N	Rate %	Cases N	Rate %			
All	153	3.9	338	8.6	4.7	55	45, 63
A/H1	3	0.1	27	0.7	0.6	89	68, 97
A/H3	37	0.9	178	4.5	3.6	79	71, 86
B	115	2.9	136	3.5	0.6	16	-8, 35

ATP= according to protocol

Study MICP111 was adequately powered to evaluate efficacy in the pre-specified age strata 6-23 and 24 – 59 months. Table 6 shows efficacy data by these age subgroups.

Table 6 MI CP 111: Subgroup efficacy analysis by pre-stratified age group
Primary endpoint, subgroups: Pre-specified age groups

	CAIV-T			TIV					
	N	Cases N	Rate %	N	Cases N	Rate %	Ab.D.	R.E.	95% C.I.*
6-23m	1834			1852					
AS		23	1.3		32	1.7	0.4	29	-21, 59
AD		35	1.9		98	5.3	3.4	64	47, 76
All		59	3.2		133	7.2	4.0	56	40, 68
24-59m	2082			2084					
AS		30	1.4		61	32.9	1.6	53	27, 70
AD		67	3.2		147	7.1	3.9	54	39, 66
All		94	4.5		205	9.8	5.3	54	42, 65

*R. E. and 95% CI in this table for 24 – 59 months were calculated by reviewer
AS= antigenically similar; AD= antigenically dissimilar

The relative efficacy of CAIV-T versus TIV in preventing culture confirmed lower respiratory tract infection (LRI) was examined as a secondary efficacy endpoint. LRI was defined as a health care provider diagnoses of shortness of breath, pulmonary congestion, pneumonia, wheezing, bronchitis, croup, and bronchiolitis. Results of this analysis are provided in Table 7.

Table 7: Secondary efficacy: LRI / ATP

	CAIV-T			TIV					
	N	Cases N	Rate %	N	Cases N	Rate %	Absolute difference	Relative efficacy	95% C.I.
ATP	3916			3936					
AS		8	0.2		11	0.3	0.1	25	-90, 71
AD		8	0.2		21	0.5	0.3	63	19, 85
All		18	0.5		33	0.8	0.3	46	4, 70

ATP= according to protocol
AS= antigenically similar; AD= antigenically dissimilar

Study D153 P 501

Study D153 P 501 was a placebo-controlled study that evaluated efficacy of culture-confirmed influenza in healthy children 12-36 months of age. The study was conducted in Asia over two years from 2000 to 2002, with the primary efficacy endpoint of culture confirmation to be tabulated during the first influenza season. Tables 8 and 9 summarize the efficacy data from the primary efficacy endpoint. Tables are taken from the clinical study report submitted in the BLA.

Table 8: D153 P 501. Primary endpoint: Community acquired culture positive for strains *antigenically related* to strains contained in the vaccine; symptomatic influenza

	CAIV N=1653	Placebo N= 1111	Vaccine Efficacy	95% CI
All strains, N (%)	56 (3.4)	139 (12.5)	73%	63, 81
H1N1	23 (1.4)	81 (7.3)	81%	69, 89
H3N2	4 (0.2)	27 (2.4)	90%	71, 98
B	29 (1.8)	35 (3.2)	44%	6, 67

Table 9: D153 P501. Community acquired culture positive for any influenza strain, *antigenically related or unrelated*

	CAIV N=1653	Placebo N= 1111	Vaccine Efficacy	95% CI
All strains, N (%)	81 (4.9)	182 (16.4)	70%	61, 77
H1N1	23 (1.4)	82 (7.4)	81%	69, 89
H3N2	14 (0.8)	60 (5.4)	84%	72, 92
B	44 (2.7)	52 (4.7)	43%	13, 63

Safety Review

Deaths/SAEs

In study MI CP 111, there were two deaths, one in each treatment group; these were due to accidents unrelated to administration of vaccine. The total number and types of serious adverse events were similar between treatment groups, which did not reveal a

safety signal.

Wheezing events

MSW:

Medically significant wheezing was evaluated through 42 days after vaccination. The protocol defined medically significant wheezing as wheezing on examination plus one of the following: signs of respiratory distress (increased respiratory rate, retractions, or dyspnea), hypoxemia (oxygen saturation < 95%), or new prescription for daily bronchodilator treatment. Table 10 shows the results of analysis of this safety endpoint by treatment group, by number of doses, and in those 6 – < 24 months and in those 24 months – 59 months.

Table 10: Medically Significant Wheezing Observed In Study MI CP 111:

	ONE DOSE GROUP		TWO DOSE GROUP		TWO DOSE GROUP		TOTAL	
			After 1st Dose		After 2nd Dose			
	CAIV-T	TIV	CAIV-T	TIV	CAIV-T	TIV	CAIV-T	TIV
All subjects	19 (2.0%)	17 (1.8%)	74 (2.3%)	48 (1.5%)	73 (2.4%)	67 (2.2%)	164 (3.9%)	131 (3.1%)
Subjects ≥ 24 months	12 (1.8%)	14 (2.1%)	19 (1.2%)	14 (0.9%)	16 (1.1%)	28 (1.9%)	47 (2.1%)	56 (2.5%)
Subjects < 24 months	7 (2.6%)	3 (1.1%)	55 (3.2%)	34 (2.0%)	57 (3.6%)	39 (2.4%)	117 (5.9%)	75 (3.8%)

Source: Table provided by applicant

Asthma, Bronchiolitis, Bronchospasm, and Wheezing (All Wheezing):

The protocol pre-specified the preferred adverse event terms asthma, bronchiolitis, bronchospasm, and wheezing to be used collectively as a safety endpoint in the evaluation of wheezing. These four terms together are referred to as "all wheezing" in this review. The tables were generated by the clinical reviewer and were tabulated directly from the electronic datasets submitted to the BLA.

Serious adverse events were defined as recommended in 21 CFR 312.32: Any AEs that resulted in death, were life-threatening, resulted in an in-patient hospitalization, prolonged an in-patient hospitalization, resulted in persistent or significant disability or incapacity, resulted in congenital anomaly/birth defect in offspring, required significant medical or surgical intervention, or any event that may have jeopardized the study subject per medical judgment. As specified in the study protocol, serious adverse events were documented for the entire 180 day study period. All wheezing SAEs by treatment group are shown in Table 11.

Table 11: Serious Adverse Events (SAEs) Of All Wheezing During the Entire Study Period:

	After 1st Dose		After 2nd Dose	
	CAIV-T N=4179	TIV N=4173	CAIV-T N=3002	TIV N=3034
Asthma	1 (<0.1%)	0	0	0
Bronchiolitis	2 (<0.1%)	2 (<0.1%)	5 (0.1%)	4 (0.1%)
Bronchospasm	4 (<0.1%)	2 (<0.1%)	0	1 (<0.1%)
Wheezing	4 (<0.1%)	2 (<0.1%)	0	0

Source: Reviewer generated table from Adverse Event dataset provided by applicant

A summary of the four preferred terms for wheezing events is shown in Table 12. Because the pathophysiology of wheezing after vaccination with FluMist® is poorly understood, events from the entire study period, not only those reported in the first 42 days post-vaccination, were included in this analysis.

Table 12: Evaluation of All Wheezing in Study MI CP 111:

	CAIV-T	TIV
#Events	905	872
#Subjects with wheezing events	575	554
Gender: female/male	254/321	249/305
Age (Months): mean, median Range	22.03, 20 6-59	22.68, 20 6-58
# of Subjects with hx of wheezing per protocol	99	80
# of Subjects with any hx of wheezing	244	211
Preferred Terms (#events/#subjects)		
Asthma	74/65	72/59
Bronchiolitis	142/120	136/121
Bronchospasm	29/25	23/21
Wheezing	660/463	641/437
Wheezing events after dose:		
#1	426	378
#2	479	494
Day of onset: mean, median Range	70.07, 57 0-215	72.24, 62 0-218
Severity: (#events/#subjects)		
Mild	614/431	637/433
Moderate	270/196	226/163
Severe	21/17	8/8
HCP visit for wheezing (#events/#subjects)	729/490	687/470
Hospitalized for wheezing (#events/#subjects)	15/12	11/11

No dose #2 because of wheezing (#events/#subjects)	38/34	29/22

Source: Reviewer generated table from Adverse Event dataset provided by applicant

Of note, there is one more serious adverse event (Table 11) in the CAIV-T arm than hospitalizations (Table 12) due to the inclusion of one patient as a serious AE and not as a hospitalization. This study subject was a 14 month old female enrolled in the United States who developed wheezing and shortness of breath; she was treated at the hospital and discharged in less than 24 hours.

The majority of episodes of wheezing beyond 42 days after vaccination: 58% of wheezing events in the CAIV-T arm and 62.9% in the TIV arm occurred after the 42 day time period. There were 29 events of wheezing (3.2%) in the first two days post-vaccination in the CAIV-T arm and 27 (3.1% of all wheezing events) in the same time period in the TIV arm.

An analysis of all wheezing by age is presented in the Table 13.

Table 13: All Wheezing By Age During The Entire Study Period Of MI-CP111

	CAIV-T				TIV			
Age in Months	6-11 N=684	12-23 N=1308	24-35 N=1372	≥ 36 N=815	6-11 N=683	12-23 N=1292	24-35 N=1379	≥ 36 N=819
#Subjects with events	131	212	164	68	130	178	174	72
# Events	233	345	238	89	215	290	268	99
Gender: female/male	54/77	104/108	64/100	32/36	56/74	81/97	78/96	34/38
Preferred terms (events/subj)								
Asthma	16/15	27/24	19/16	12/10	5/5	23/17	32/27	12/10
Bronchiolitis	64/51	54/46	22/21	2/2	61/54	43/39	29/26	3/2
Bronchospasm	6/5	13/11	10/9	0	5/4	9/8	8/8	1/1
Wheezing	147/98	251/168	187/137	75/60	144/92	215/144	199/139	83/62
Severity:								
Mild	154	222	180	58	152	199	210	76
Moderate	74	113	54	29	59	87	57	23
Severe	5	10	4	2	3	4	1	0
Serious AEs	5	9	1	1	5	3	2	1

Source: Reviewer generated table from Adverse Event dataset provided by applicant

Hospitalizations

The safety of CAIV-T was also examined by analyses of hospitalizations in Study MI-CP111. Data on hospitalizations were collected for the entire study period. Table 14 was generated by the applicant and shows the number of hospitalizations in the one and two dose groups of the study.

Table 14: Overall Inpatient Hospitalizations MI-CP111

ONE DOSE GROUP		TWO DOSE GROUPS		TOTAL	
CAIV-T N=933	TIV N=947	CAIV-T N=3246	TIV N=3226	CAIV-T N=4179	TIV N=4173
14 1.5%	23 2.4%	116 3.6%	96 3.0%	130 3.1%	119 2.9%

Source: Subset of table provided by applicant.

Table 15 shows further analysis of hospitalizations by age subgroups. Of note, there were more hospitalizations in the youngest children and the majority of hospitalizations occurred 42 days or more post-vaccination.

Table 15: Number of Hospitalizations by Age and Time Post-Vaccination MI-CP111

	CAIV-T			TIV		
Age, months	≤ 42 Days	> 42 Days	Total	≤ 42 Days	> 42 Days	Total
6-11	15	27	42	9	9	18
12-<24	17	25	42	16	29	45
24-59	13	33	46	22	34	56

Source: Table provided by applicant

Because more hospitalizations were observed in the CAIV-T group in subjects 6-11 months of age, the reasons for hospitalizations in this age group were examined further. Table 16 shows the applicant's analysis of the reasons for hospitalization.

Table 16: Reasons for Hospitalization for Subjects 6-11 Months of Age

Number of subjects with:	CAIV-T N=684	TIV N=683
All-cause hospitalization	42 (6.1%)	18 (2.6%)
Respiratory hospitalization	22 (3.2%)	8 (1.2%)

Source: Table provided by applicant

Respiratory hospitalizations included all hospitalizations with a diagnosis of one the following MedDRA terms: Acute sinusitis, acute tonsillitis, bronchiolitis, bronchitis, bronchopneumonia, infectious croup, influenza, mastoiditis, acute otitis media,

pharyngitis, laryngitis, pharyngotonsillitis, pneumonia, sinusitis, upper respiratory tract infection, viral infection, asthma, bronchospasm, tonsillar hypertrophy, wheezing, adenoidal disorder, pulmonary congestion, tonsillitis, and viral upper respiratory tract infection.

Early hospitalizations were examined in detail in order to identify any serious AEs that occurred soon after vaccination, and therefore, may be more likely to be related to study vaccination; These diagnoses are described in Table 17.

Table 17: Diagnoses For Hospitalizations In The First Two Weeks Post-Vaccination

6-11 Months N=1367	12-23 Months N=2600	24-35 Months N=2751	≥ 36 Months N=1634
CAIV-T			
Pneumonia - 3	Pneumonia - 3	Gastroenteritis -2	Bronchiolitis
Gastroenteritis-2	Bronchiolitis	Herpangina	
AOM	Pharyngitis	Pneumonia – 3	
Wheezing	Asthma	Seizure	
Periorbital cellulitis	AOM / URTI		
	Drug hypersensitivity		
	Anuria		
TIV			
Gastroenteritis-2	Pneumonia	Pneumonia	Wheezing
Bronchiolitis - 2	Bronchiolitis	Wheezing	Croup
	Viral infection	Gastroenteritis	Jaw fracture
	Gastroenteritis-2	Herpangina	Pneumonia
	Febrile Seizure		Gastroenteritis
	Viral Infection		URTI
	Sinusitis		Head injury

Source: Reviewer generated table from Adverse Event dataset provided by applicant

As shown in Table 17, pneumonia was reported more often in CAIV-T recipients in the two weeks post-vaccination (nine events in the CAIV-T arm compared to three in the TIV arm). However, the numbers of events are small.

Other Studies

Safety data from studies AV018 and D153 P501 are currently under review and will be presented during the VRBPAC session.

Consultation

A consultation from CDER's Division of Pulmonary and Allergy Products was requested to provide input on the respiratory safety data by those with expertise in the field of asthma.

The conclusion from the pulmonary consultation is provided here:

"With the above limitations in mind, this reviewer's conclusion is that in Study MI-CP 111 there are more wheezing serious adverse events and wheezing adverse events in patients who received CAIV-T than in patients who received the trivalent inactivated vaccine. However, the difference between the treatment groups is small, approximately 0.1% and 0.4% for wheezing SAEs and wheezing AEs, respectively. There were more severe wheezing events in the CAIV-T group than in the TIV group, however, again the difference between treatment groups is small. The data for the "medically significant wheezing" is consistent with the findings for the wheezing AEs and SAEs. There were no ICU admissions or requirements for mechanical ventilation for medically significant wheezing in either treatment group.

The subgroup analyses performed by the Applicant do suggest that the imbalance in wheezing AEs between the CAIV-T and TIV groups is primarily driven by patients < 24 months of age. Further subgroup analysis suggests that a history of asthma or wheezing is associated with an increase in wheezing AEs/REs in the CAIV-T compared to the TIV group, particularly in patients < 24 months of age. In addition, the subgroup analysis of the medically significant wheezing data suggests that the imbalance is driven by patients < 24 months of age, primarily in children 6 to 11 months of age.

While this reviewer acknowledges the imbalance in wheezing AEs, SAEs, and medically significant wheezing between the CAIV-T and TIV treatment groups, the difference between treatment groups is quite small. The subgroup analysis does suggest that the difference is driven primarily by patients < 24 months of age. However, it is important to note that there were no drug-related deaths, ICU admissions, or requirement for mechanical ventilation in either treatment group for medically significant wheezing. From a pulmonary standpoint, our interpretation is that the data do not suggest a clinically significant safety signal for wheezing. However, the significance of the imbalance in wheezing adverse events will have to be weighed in the risk/benefit assessment of FluMist® when compared to injectable influenza vaccine."

SUMMARY

The results from MICP 111 support the efficacy of CAIV-T in the prevention of culture-confirmed CDC-ILI in children 6 months to 59 months of age. Efficacy results from two other studies with a primary endpoint of culture confirmed influenza illness also provide supportive efficacy data in the age groups 15 months to 71 months (AV006) and 12 months to 36 months (D 153 P 501).

An imbalance between the two treatment groups in wheezing events was noted in MICP 111, with more events observed in subjects in the CAIV-T group than in the TIV group. This imbalance appears to be due to increased wheezing events in the age subgroup 6-23 months. More frequent hospitalizations were seen in the CAIV-T group, particularly in the < 24 month age subgroup, as were hospitalizations due to respiratory diagnoses. However, more than half of these hospitalizations occurred > 42 days after vaccination. Assessment of the outcomes of respiratory adverse events did not reveal any deaths, requirement for mechanical ventilation, or ICU admissions.

It should be noted that MICP 111 was a large study, allowing the detection of small differences. It is the clinical relevance of the imbalance in respiratory adverse events identified in MICP 111 that will be the basis of discussion. Risks associated with CAIV-T use must be weighed against the increased hospitalization rates in children less than 24 months of age due to influenza. Any risk benefit determination in younger children would also be affected by strategies to minimize risk, availability of treatment, and adverse events associated with treatment

FDA Statistical Briefing Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

May 16, 2007

Liquid formulation of FluMist®: Influenza Virus Vaccine, Trivalent, Types A and B, Cold-adapted, Live Attenuated, Liquid Formulation (CAIV-T)

Proposed Indication: Prevention of disease caused by influenza A and B viruses for children 12 to 59 months of age without a history of wheezing or asthma.

Sang Ahnn, Ph.D.
FDA/CBER/OBE

Introduction

In the application for licensure of the liquid formulation of FluMist® (CAIV-T) for children 12-59 months of age without a history of wheezing or asthma, MedImmune submitted results from five controlled clinical studies pertinent to the claimed indication (D153-P501, AV006, AV018, AV019, and MI-CP111). This statistical briefing document covers the trial (MI-CP111) that forms the basis for this supplemental BLA.

MI-CP111 was performed in children 6-59 months of age, including those children with a history of wheezing or asthma. The applicant is seeking an indication extension of the liquid formulation of FluMist (CAIV-T) for children 12-59 months of age, excluding those children with a history of wheezing or asthma.

MI-CP111

This was a multi-center (249 sites: 133 sites in the U.S., 15 sites in Hong Kong/Korea/ Taiwan, and 101 sites in Belgium/Czech Republic/Finland/Germany/Greece/Iceland/ Israel/Italy/Lebanon/Spain/Sweden/UK), double-blind, randomized study to compare the efficacy and safety of CAIV-T vs. TIV. A total of 8,475 (4,117 in the U.S.) subjects were randomized (1:1 ratio) to either CAIV-T or TIV, stratified by age (6-23 months, 24-35 months, 36-59 months), prior influenza vaccination (yes/no), wheezing history status (≥ 3 wheezing illnesses requiring medical follow-up or hospitalization: yes/no), and country.

MedImmune's Analyses

Efficacy

The primary endpoint is culture-confirmed modified CDC-ILI caused by community-acquired wild-type strains antigenically similar ('matched') to those contained in the vaccine. The definition of modified CDC-ILI is as follows (quoted from page 93 in Mod.5/Vol.49 of the applicant's submission):

> CDC-ILI (CDC-defined influenza-like illness), defined as fever (temperature ≥100°F oral or equivalent) plus cough or sore throat on the same or consecutive days, was modified ("*modified CDC-ILI*") to fever plus cough, sore throat, *or runny nose/nasal congestion* as a means of capturing age-appropriate influenza illness symptoms per discussions with CBER (13/Aug/04 CBER Comments on 21/Jul/04 Type B Pre-Phase III Meeting). Modified CDC-ILI was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI symptoms.

The analysis of the primary efficacy endpoint is on the According-To-Protocol (ATP) population. The applicant's criterion of non-inferiority of CAIV-T to TIV is that the lower bound of the 2-sided 95% CI on the relative efficacy of CAIV-T compared to TIV is > -30%. The applicant's criterion of superiority of CAIV-T to TIV is that the lower bound of the 2-sided 95% CI on the relative efficacy of CAIV-T compared to TIV is > 0%.

The applicant's conclusion was "CAIV-T demonstrated statistically significant superior efficacy compared to TIV against culture-confirmed influenza endpoints due to both matched and mismatched strains in children 6-59 months of age."

Safety

The primary endpoint is medically significant wheezing occurring through 42 days after vaccination. The definition of medically significant wheezing is as follows (quoted from page 132 in Mod.5/Vol.49 of the applicant's submission):

Medically significant wheezing was defined as the presence of wheezing on physical examination and accompanied by at least one of the following:

- Sign of respiratory distress: tachypnea, retractions, or dyspnea
- Hypoxemia (O_2 saturation <95%)
- New prescription for daily bronchodilator therapy (not on an "as needed" basis)

The applicant's conclusion was: "In children **12-59** months of age without a prior history of wheezing or asthma, CAIV-T has been demonstrated to be safe."

Reviewer's Comments

1. CBER did not agree with the applicant's superiority criterion, "The lower bound of 2-sided 95% CI on the relative efficacy of CAIV-T compared to TIV is > 0%." CBER's position on this matter was as follows (quoted from the meeting minutes dated 8/13/2004. The meeting was between MedImmune and CBER on 7/21/2004):

We caution you that we would consider an analysis of superiority to be pertinent only to this specific study. That is, data obtained regarding specific vaccine strains administered to a limited population exposed to certain seasonal circulating strains could not be extrapolated to apply to other strains and populations. Should you choose to pursue such a claim, we would anticipate that your study results demonstrate a robust increase in efficacy as compared to TIV and in the prevention of influenza illness. Specifically, we do not view that demonstration of a relative efficacy of >0 as supportive of a claim of superiority for the study being conducted. Should you conduct additional clinical endpoint studies such that you are able to demonstrate significantly greater efficacy against multiple strains of influenza (which should include A/H1, A/H3, and B strains) over several influenza seasons, at that point, less restrictive labeling could be considered.

2. The following Tables 1 and 2 provide the reviewer-generated results on the primary efficacy endpoint, based on the ATP population.

FDA Table 1. MI-CP111 Primary Efficacy Results

					CAIV-T	TIV		
Endpoint	Population	Country	Age* (months)	Subjects with Previous History of Wheezing/asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	All	6 ~ 59	Included	54/3916	93/3936	41.6%	(18.8, 58.1)
	ATP	U.S.	6 ~ 59	Included	22/1919	33/1925	33.1%	(-13.5, 60.6)

*Age of SUBJID= 44270068 (COUNTRY= LEBANON) is 60 months.

FDA Table 2. MI-CP111 Primary Efficacy Results by Strain

					CAIV-T	TIV		
Endpoint	Population	Country	Age* (months)	Subjects with Previous History of Wheezing/asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	All	6 ~ 59	Included	54/3916	93/3936	41.6%	(18.8, 58.1)
				H1N1	3/3916	28/3936	89.2%	(66.7, 96.5)
				H3N2	0/3916	0/3936	-	-
				B	51/3916	66/3936	22.3%	(-11.4, 45.9)
	ATP	U.S.	6 ~ 59	Included	22/1919	33/1925	33.1%	(-13.5, 60.6)
				H1N1	0/1919	0/1925	-	-
				H3N2	0/1919	0/1925	-	-
				B	22/1919	33/1925	33.1%	(-13.5, 60.6)

*Age of SUBJID= 44270068 (COUNTRY= LEBANON) is 60 months.

3. The following Table 3 provides the reviewer-generated results on the primary efficacy endpoint by pre-specified age strata based on the ATP population.

FDA Table 3. MI-CP111 Primary Efficacy Results by Age Strata

					CAIV-T	TIV		
Endpoint	Population	Country	Age (months)	Subjects with Previous History of Wheezing/asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	All	6 ~ 23	Included	24/1834	32/1852	24.3%	(-27.4, 55.0)
	ATP	All	24 ~ 35	Included	17/1311	23/1301	26.7%	(-35.3, 60.3)
	ATP	All	36 ~59	Included	13/771	38/783	65.3%	(36.0, 81.2)

4. The reviewer performed additional efficacy analyses based on the ITT population. The efficacy results, shown in Table 4, are similar to the results performed on the ATP population, shown in Table 1.

FDA Table 4. MI-CP111 Efficacy Results on ITT population

					CAIV-T	TIV		
Endpoint	Population	Country	Age (months)	Subjects with Previous History of Wheezing/asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ITT	All	6 ~ 59	Included	56/4243	98/4232	43.0%	(21.1, 58.8)
	ITT	U.S.	6 ~ 59	Included	23/2058	34/2059	32.3%	(-13.8, 59.8)

5. The reviewer also performed exploratory efficacy analyses based on qualifying symptoms* and modified CDC-ILI. These results are shown in Table 5 below.

FDA Table 5. MI-CP111 Exploratory Efficacy Results on ITT population

					CAIV-T	TIV		
Endpoint	Population	Country	Age (months)	Subjects with Previous History of Wheezing/asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Qualifying Symptoms*	ITT	All	6 ~ 59	Included	292/4243	423/4232	31.1%	(20.6, 40.3)
Modified CDC-ILI	ITT	All	6 ~ 59	Included	181/4243	354/4232	49.0%	(39.3, 57.1)

*The definition of Qualifying Symptom is as follows (quoted from Pages 45-46 in Mod.5/Vol.49 of the applicant's submission):

Qualifying symptoms for symptomatic influenza infection were defined as the **new onset of one** (or more) of the following symptoms occurring during the influenza surveillance period:

- **ANY** fever (temperature ≥99.8°F oral or ≥100.4°F rectal/tympanic or ≥99.5°F axillary)
- **ANY** wheezing
- **ANY** shortness of breath (SOB)
- **ANY** pulmonary congestion (including bronchitis, bronchiolitis, and croup)
- **ANY** pneumonia
- **ANY** ear infection (acute otitis media [AOM], suspected or diagnosed)

***Or* at least two** of the following symptoms concurrently:

- Runny/stuffy nose (rhinorrhea)
- Sore throat (pharyngitis)
- Cough
- Muscle aches
- Chills
- Headache
- Irritability
- Decreased activity
- Vomiting

6. According to the pre-specified success criterion, CAIV-T demonstrated non-inferior efficacy compared to TIV (i.e., all lower confidence limits on relative efficacy of CAIV-T compared to TIV exceed -30%).

7. The reviewer generated additional subgroup results, by gender, race, and other factors, for information purpose. Please see Tables A1 ~ A4 in the Appendix.

8. The following Table 6 provides the reviewer-generated results on the primary safety endpoint, medically significant wheezing, based on the safety population. The safety population includes subjects who received any vaccination and had any safety follow-up.

FDA Table 6. MI-CP111 Safety Results on Safety population
Relative Risk of CAIV-T to TIV
Based on Medically Significant Wheezing (MSW)

	CAIV-T		TIV		
Age (months)	N	# of Subjects with Medically Significant Wheezing (MSW)	N	# of Subjects with Medically Significant Wheezing (MSW)	Relative Risk of CAIV-T compared to TIV (95% CI)
6 ~59	**4179**	**163 (3.9%)**	**4173**	**131 (3.1%)**	**1.24 (0.99, 1.56)**
6-23	1992	117 (5.9%)	1975	75 (3.8%)	1.55 (1.17, 2.05)
24-35	1372	33 (2.4%)	1379	32 (2.3%)	1.04 (0.64, 1.67)
36-59	815	13 (1.6%)	819	24 (2.9%)	0.54 (0.28, 1.05)

9. The following Table 7 provides the reviewer-generated results on Medically Significant Wheezing-related hospitalization based on the safety population.

FDA Table 7. MI-CP111 Safety Results on Safety population
Relative Risk of CAIV-T to TIV
Based on Medically Significant Wheezing-related Hospitalization

	CAIV-T		TIV		
Age (months)	N	# of Subjects with Medically Significant Wheezing Hospitalization	N	# of Subjects with Medically Significant Wheezing (MSW) Hospitalization	Relative Risk of CAIV-T Compared to TIV (95% CI)
6 ~59	**4179**	**12 (0.29%)**	**4173**	**8 (0.19%)**	**1.50 (0.63, 3.56)**
6-23	1992	10 (0.50%)	1975	4 (0.20%)	2.48 (0.82, 7.46)
24-35	1372	1 (0.07%)	1379	2 (0.15%)	0.50 (0.07, 3.83)
36-59	815	1 (0.12%)	819	2 (0.24%)	0.50 (0.07, 3.83)

10. The applicant stated "In children 6-11 months of age, rates of medically significant wheezing and rates of hospitalizations were higher in CAIV-T vs. TIV recipients." This result is the basis for the applicant excluding the 6-11 month subgroup from the sought indication. There are two main statistical issues regarding this subgroup exclusion:

    a) As shown in Tables 8 and 9, in children 12-23 months of age, rates of medically significant wheezing and rates of hospitalizations are also higher in the CAIV-T group.

FDA Table 8. MI-CP111 Safety Results on Safety population
Relative Risk of CAIV-T to TIV
Based on Medically Significant Wheezing (MSW)

	CAIV-T		TIV		
Age (months)	N	# of Subjects with Medically Significant Wheezing (MSW)	N	# of Subjects with Medically Significant Wheezing (MSW)	Relative Risk of CAIV-T compared to TIV (95% CI)
6-23	1992	117 (5.9%)	1975	75 (3.8%)	1.55 (1.17, 2.05)
6-11	684	47 (6.9%)	683	29 (4.2%)	1.62 (1.04, 2.53)
12-23	1308	70 (5.4%)	1292	46 (3.6%)	1.50 (1.05, 2.16)

FDA Table 9. MI-CP111 Safety Results on Safety population
Relative Risk of CAIV-T to TIV
Based on Medically Significant Wheezing-related Hospitalization

	CAIV-T		TIV		
Age (months)	N	# of Subjects with Medically Significant Wheezing-related Hospitalization	N	# of Subjects with Medically Significant Wheezing-related Hospitalization	Relative Risk of CAIV-T compared to TIV (95% CI)
6-23	1992	10 (0.50%)	1975	4 (0.20%)	2.48 (0.82, 7.46)
6-11	684	4 (0.58%)	683	2 (0.29%)	2.00 (0.43, 9.31)
12-23	1308	6 (0.46%)	1292	2 (0.15%)	2.96 (0.69, 12.8)

    b) Since the 6-11 month age group (12-23 month group likewise) is a post-hoc, non-randomized subgroup, any statistical results could be misleading and therefore should be interpreted with caution. On the other hand, the results based on the pre-specified 6-23 month age stratum are less problematic in this regard, since the stratified randomization was performed separately within this age stratum.

11. Based on the safety signals in the 6-23 month age stratum, as shown in Tables 6, and 7, the need for further evaluation of the safety of CAIV-T in this age stratum may warrant consideration.

12. Appendix Tables A5 and A6 contain the reviewer's risk/benefit analysis results, based on pre-specified primary efficacy and safety endpoints. These tables are re-analyses of data presented by MedImmune at the 2/21/2007 Advisory Committee on Immunization Practices (ACIP) meeting in Atlanta, GA. MedImmune presented risk/benefit analyses based on post hoc safety and efficacy endpoints, such as Medically Significant Wheezing occurring within 180 days after vaccination (rather than the pre-specified 42 days after vaccination), and cc-m-CDC-ILI regardless of antigenic match (rather than the pre-specified 'matched' cc-m-CDC-ILI). The FDA reviewer's analyses are presented here to help clarify the context and interpretation of MedImmune's analyses. However, although the reviewer's risk/benefit analyses are based on pre-specified criteria, they would not necessarily support comparative label claims, which would be dependent on a determination of the clinical and public health relevance of the findings.

APPENDIX

FDA Table A1. MI-CP111 Primary Efficacy Results by Gender

				CAIV-T	TIV		
Endpoint	Population	Gender	Subjects with Previous History of Wheezing/Asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	Female	Included	30/1907	49/1920	38.4%	(3.7, 60.6)
	ATP	Male	Included	24/2009	44/2016	45.3%	(10.8, 66.4)

FDA Table A2. MI-CP111 Primary Efficacy Results by Race

				CAIV-T	TIV		
Endpoint	Population	Race	Subjects with Previous History of Wheezing/Asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	Asian	Included	1/290	5/297	79.5%	(-31.3, 96.8)
	ATP	Black	Included	2/156	2/140	10.3%	(-405, 84.0)
	ATP	Hispanic	Included	0/224	3/244	-	-
	ATP	Other	Included	1/78	3/71	69.7%	(-7.9, 95.6)
	ATP	White (non-Hispanic)	Included	50/3168	80/3184	37.2%	(11.0, 55.7)

FDA Table A3. MI-CP111 Primary Efficacy Results by Prior Flu Vaccination

				CAIV-T	TIV		
Endpoint	Population	Previously Received Flu Vaccine	Subjects with Previous History of Wheezing/Asthma	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	No	Included	36/2987	65/2999	44.4%	(17.0, 62.8)
	ATP	Yes	Included	18/929	28/937	35.2%	(-15.4, 63.6)

FDA Table A4. MI-CP111 Primary Efficacy Results by History of 3+ Wheezing Episodes

			CAIV-T	TIV		
Endpoint	Population	History of 3 or More Wheezing Episodes	Attack Rate (cases/N)	Attack Rate (cases/N)	Relative Efficacy	95% CI
Culture-confirmed modified CDC-ILI caused by wild-type strains matched to vaccine	ATP	No	46/3670	84/3720	44.5%	(20.9, 61.1)
	ATP	Yes	8/246	9/216	22.0%	(-92.9, 68.4)

FDA Table A5. MI-CP111 Risk/Benefit Analysis on Subjects with or without a History of Wheezing or Asthma

(Based on Risk of getting MSW / Benefit of preventing 'matched' cc-m-CDC-ILI)

If CAIV-T is used rather than TIV

Age (months)	Risk (per 1000)	Benefit (per 1000)
6 ~ 59	**7.6 additional MSW**	**9.8 less cc-m-CDC-ILI**
6 ~ 23	20.8 additional MSW	4.2 less cc-m-CDC-ILI
24 ~ 35	0.8 additional MSW	4.7 less cc-m-CDC-ILI
36 ~59		13.4 less MSW 31.7 less cc-m-CDC-ILI

FDA Table A6. MI-CP111 Risk/Benefit Analysis on Subjects without a History of Wheezing or Asthma

(Based on Risk of getting MSW / Benefit of preventing 'matched' cc-m-CDC-ILI)

If CAIV-T is used rather than TIV

Age (months)	Risk (per 1000)	Benefit (per 1000)
6 ~ 59	**6.3 additional MSW**	**9.4 less cc-m-CDC-ILI**
6 ~ 23	11.8 additional MSW	1.0 less cc-m-CDC-ILI
24 ~ 35	3.7 additional MSW	8.3 less cc-m-CDC-ILI
36 ~59		4.9 less MSW 35.5 less cc-m-CDC-ILI

The applicant is seeking an indication extension of the liquid formulation of FluMist (CAIV-T) for children 12-59 months of age, *excluding children with a history of wheezing or asthma*. The reviewer's risk/benefit analysis, based on the pre-specified primary efficacy and safety endpoints, and after excluding the subjects with a history of wheezing or asthma, is shown in Table A6 above. Note that the subjects with a history of wheezing or asthma are a non-randomized subgroup (i.e., this subgroup was not a defined category for the stratified randomization). Thus, the remaining subjects, after excluding the subjects with a history of wheezing or asthma, are also a non-randomized subgroup. Therefore, these subgroup results should be interpreted with caution.