Sponsor: Novartis Vaccines and Diagnostics

Investigational Product: MF59-adjuvanted monovalent influenza virus vaccine containing 7.5 µg of the A/Vietnam/1194/2004-like (H5N1) influenza antigen

Indication: Prophylaxis Pandemic Influenza

Protocol Number: V87P4

Protocol Title: A Phase III, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity, Safety and Tolerability of Two Doses of FLUAD-H5N1 InfluenzaVaccine in Adult and Elderly Subjects

Phase of Development: Phase III

Study Period:
Date of first enrolment: 30 JAN 07

Date of last visit: 03 OCT 07

Methodology:

In this phase III study, randomized, multi-center study, approximately 4400 subjects were to be enrolled into two groups according to age (18-60 years and 61 years and over) and randomly assigned at a 3:1 ratio to receive two injections, 3 weeks apart and given intramuscularly (IM) in the deltoid muscle, preferably of the non-dominant arm, of either 7.5 µg of H5N1 influenza antigen or 15 µg each of A/H1N1, A/H3N2 and B antigens (Fluad) over a period of approximately 8 months at multiple study sites in several countries. Subjects were enrolled over a period of approximately 7 weeks on the basis of their medical history and physical examination to ensure that they were in good health according to the investigator's opinion and met all the inclusion criteria and none of the exclusion criteria. A copy of the signed informed consent form was given to each subject.

Number of Subjects (Planned and Analyzed):

In total 4560 subjects were enrolled and randomized in this study, 1042 of which were from centers 12, 14, 16, and 31, which are excluded from all main analyses presented in this report. Of the remaining 3518 subjects, 2637 were randomized to receive Fluad-H5N1 influenza vaccine and 881 to receive Fluad. A total of 3196 subjects were aged 18-60 (adults) and 322 were aged 60 years and older (elderly). In total, 3516 out of these

3518 subjects were included in the safety population; two 2 subjects were excluded because of missing or unreliable safety data.
In total, 398 subjects were included in the immunogenicity full analysis set (FAS). Of these 297 received Fluad- H5N1 virus influenza vaccine and 101 received Fluad.
Elderly subjects were only enrolled at site in Poland and in the Czech Republic.

Study Centers:

The study was conducted in 23 study centers in Poland, Lithuania and Czech Republic.

Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:

NCT00434733.

Objectives:

Immunogenicity Objective:
To evaluate the magnitude of antibody responses to two doses of MF59-adjuvanted A/Vietnam/1194/2004 (H5N1 Clade 1) influenza antigen, each containing 7.5 µg of the H5N1 antigen.

Safety Objective
Primary:
To assess the safety profile of Fluad- H5N1 virus influenza vaccine and to rule out an occurrence of an AE with a rate of 0.1% in adults and 1% in elderly subjects.
Secondary:
To evaluate the safety profile of Fluad-H5N1 when compared with the interpandemic influenza virus vaccine Fluad.

Test Product, Dose, Mode of Administration, Lot Number:

Two 0.5 mL injections of Fluad-H5N1MF59-adjuvanted monovalent H5N1 virus influenza vaccine containing 7.5 µg of H5N1 antigen, administered 3 weeks apart, IM in the deltoid muscle, preferably of the non-dominant arm. Lot number: 050203; expiry date: April 2007.

Duration of Study:
The actual subject enrollment interval was approximately 7 weeks. Duration of individual subject's participation was approximately 31 weeks. The total duration of the study was approximately 38 weeks.

Reference Therapy, Dose, Mode of Administration, Lot Number:

Two 0.5 mL injections of interpandemic Fluad vaccine (2006/2007) containing 15 µg each of A/H1N1, A/H3N2 and B antigens, administered 3 weeks apart, IM in the deltoid

muscle, preferably of the non-dominant arm. Lot number: 067721; expiry Date: July 2007.

Statistical Methods:

Statistical Hypothesis and Power Considerations:
There was no statistical (null) hypothesis associated with the immunogenicity or safety objective, which was analyzed descriptively. The probability of detection of at least one adverse event in the Fluad- H5N1 group is consistent with the European Medicines Agency (EMEA) Guideline for influenza vaccines with avian strains (EMEA/CHMP/VWP/171037/2006).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

Subjects 18 years of age who signed the informed consent.

Exclusion Criteria:

- Receipt of another investigational agent within 4 weeks;
- Receipt of influenza vaccination for current season 2006/2007;
- Experienced any acute disease or infection, history of neurological symptoms or signs, known or suspected impairment of immune function, any serious disease, bleeding diathesis;
- Experienced fever (defined as axillary temperature ≥38.0°C) within 3 days (prior to Visit 1);
- Pregnant or breastfeeding or females of childbearing potential who refuse to use an acceptable method of birth control;
- Surgery planned during the study period;
- Hypersensitivity to eggs, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin or any other component of the study vaccine;
- Receipt of another vaccine within 3 weeks prior to Visit 1 or planned vaccination within 3 weeks following the last study vaccination;
- History of (or current) drug or alcohol abuse;
- Any condition, which, in the opinion of the investigator, might have interfered with the evaluation of the study objectives.

Criteria for Evaluation:

Immunogenicity

Immune response after two immunizations of Fluad-H5N1 vaccine containing 7.5 µg of H5N1 influenza antigen was evaluated. In the interpretation of hemagglutination inhibition (HI) and single radial hemolysis (SRH) immunogenicity results, Committee for Medicinal Products for Human Use (CHMP) criteria (CPMP/BWP/214/96) were taken into consideration.

Safety

Safety was assessed in accordance with available safety data on influenza vaccines.

Results:

Table 1: Population Analyzed

	Number (%) of Subjects		
	Fluad-H5N1	**Fluad**	**Total**
Enrolled	2637 (100%)	881 (100%)	3518 (100%)
FAS Population*	297 (11%)	101 (11%)	398 (11%)
PP Population*	288 (11%)	100 (11%)	388 (11%)
Safety Population	2635 (100%)	881 (100%)	3516 (100%)

Abbreviations: FAS = full analysis set; PP = per protocol.

*Immunogenicity subset.

Table 2: Summary of Study Terminations – Adults and Elderly

		Number (%) of Subjects		
	Vaccine Group	**Fluad-H5N1**	**Fluad**	**Total**
Adults	Enrolled	2396	800	3196
	Completed study	2285 (95%)	757 (95%)	3042 (95%)
	Premature withdrawals	111 (5%)	43 (5%)	154 (5%)
	AE or death	2 (<1%)	3 (<1%)	5 (<1%)[a]
	Withdrew consent	23 (<1%)	8 (1%)	31 (<1%)
	Lost to follow-up	85 (4%)	31 (4%)	116 (4%)
	Protocol deviation	1 (<1%)	1 (<1%)	2 (<1%)
Elderly	Enrolled	241	81	322
	Completed study	237 (98%)	79 (98%)	316 (98%)
	Premature withdrawals	4 (2%)	2 (2%)	6 (2%)
	AE or death	2 (<1%)	0	2 (<1%)
	Withdrew consent	0	0	0
	Lost to follow-up	2 (<1%)	2 (2%)	4 (1%)
	Protocol deviation	0	0	0

[a]One subject reported an adverse event (AE) leading to withdrawal of study after the first injection, but the primary reason for withdrawal was withdrawal of consent.

Table 3: Demographic and Other Baseline Characteristics – Safety Set

Variable		Adult			Elderly		
		Fluad-H5N1 N=2394	Fluad N=800	Total N=3194	Fluad-H5N1 N=241	Fluad N=81	Total N=322
Mean age (years) ± SD		33.3±12.6	32.1±12.0	33.0±12.5	68.3±5.4	67.8±5.1	68.1±5.3
Sex	Male	1123 (47%)	396 (50%)	1519 (48%)	122 (51%)	39 (48%)	161 (50%)
	Female	1271 (53%)	404 (51%)	1675 (52%)	119 (49%)	42 (52%)	161 (50%)
Race	Caucasian	2393 (100%)	799 (100%)	3192 (100%)	241 (100%)	81 (100%)	322 (100%)
	Hispanic	1 (<1%)	0	1 (<1%)	0	0	0
	Other	0	1 (<1%)	1 (<1%)	0	0	0
Mean weight (kg) ± SD		72.33±15.49	72.35±15.72	72.33±15.55	80.36±14.56	81.79±15.14	80.72±14.70
Mean height (cm) ± SD		171.5±9.4	171.9±9.5	171.6±9.5	167.0±9.1	166.3±8.4	166.8±8.9
Inclusion criteria met		2392 (100%)	800 (100%)	3192 (100%)	241 (100%)	81 (100%)	322 (100%)
Previous vaccination		866 (36%)	273 (34%)	1139 (36%)	149 (62%)	49 (60%)	198 (61%)

Abbreviation: SD = standard deviation.

Categorical parameters: N (%); non-categorical parameters: Mean±Std

Table 4: Evaluation of Committee for Medicinal Products for Human Use (CHMP) Criteria by Hemagglutination Inhibition (HI) Assay (Full Analysis Set)

Number (%) of Subjects (n/N[a]) and GMTs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=147	Fluad N=51	Fluad-H5N1 N=147	Fluad N=50
Baseline (day 1)	GMT	5.23 (4.89-5.59)	5.36 (4.78-6.00)	5.57 (5.08-6.1)	5.7 (4.88-6.65)
	Seroprotection[b]	2 (1%) (0-5)	1 (2%) (0.05-10)	3 (2%) (0-6)	3 (6%) (1-17)
Post-1st (day 22)	Seroprotection[b]	38 (26%) (19-34)	1 (2%) (0.05-10)	47 (32%) (25-40) N=146	6 (12%) (5-24)
	GMR[c]	2.34 (1.91-2.86)	1.03 (0.73-1.45)	2.74 (2.19-3.43) N=146	1.37 (0.94-2.01)
	SC[e]/SI[f]	36 (24%) (18-32)	0 (0%) (0-7)	45 (31%) (23-39)	3 (6%) (1-17)
Post-2nd (day 43)	Seroprotection[b]	87 (60%) (52-68) N=144	1 (2%) (0.05-10)	100 (68%) (60-76) N=146	6 (12%) (5-24)
	GMR[d]	9.43 (7.20-12) N=144	1.01 (0.64-1.59)	12 (9.33-16) N=146	1.5 (0.97-2.32)
	SC[ge]/SI[f]	86 (60%) (51-68) N=144	0 (0%) (0-7)	97 (66%) (58-74)	3 (6%) (1-17)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer.
[a] n/N - responders (n) (i.e, subjects who met the HI definition of seroprotection [pre- and post-vaccination] and seroconversion or significant increase) as part of the total number of subjects in the population (N).[b] Seroprotection - HI titers ≥40.[c] GMR - the geometric mean of the day 22 to day 1 ratio;[d] GMR - the geometric mean of the day 43 to day 1 ratio; [e] Seroconversion (SC) - negative pre-vaccination serum (i.e, HI titer <10) and post-vaccination HI titer ≥40.[f] Significant increase (SI) - at least a 4-fold increase in HI titers in subjects who were positive pre-vaccination (i.e, HI titer ≥10).

Table 5: HI Geometric Mean Titers (GMTs) and Geometric Mean Ratios (GMRs) (Full Analysis Set)

GMTs and GMRs With 95% CIs					
	Parameter	**Adult**		**Elderly**	
		Fluad-H5N1	**Fluad**	**Fluad-H5N1**	**Fluad**
	N	N=147	N=51	N=147	N=50
Baseline (day 1)	GMT (95% CI)	5.23 (4.89-5.59)	5.36 (4.78-6.00)	5.57 (5.08-6.10)	5.70 (4.88-6.65)
Post-1st (day 22)	N	N=147	N=51	N=146	N=50
	GMT (95% CI)	12 (9.88-15)	5.50 (3.84-7.88)	15 (12-20)	7.82 (5.17-12)
	GMR[a] (95% CI)	2.34 (1.91-2.86)	1.03 (0.73-1.45)	2.74 (2.19-3.43)	1.37 (0.94-2.01)
Post-2nd (day 43)	N	N=144	N=51	N=146	N=50
	GMT (95% CI)	48 (37-63)	5.41 (3.42-8.56)	67 (51-87)	8.53 (5.44-13)
	GMR[a] (95% CI)	9.43 (7.2-12)	1.01 (0.64-1.59)	12 (9.33-16)	1.50 (0.97-2.32)

Abbreviation: CI = confidence interval.
[a] GMR - the geometric mean of the ratios over day 1.

Table 6: Evaluation of CHMP Criteria by Single Radial Hemolysis (SRH) Assay (Full Analysis Set)

Number (%) of Subjects (n/N[a]) and GMAs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=146	Fluad N=51	Fluad-H5N1 N=150	Fluad N=50
Baseline (day 1)	GMA	5.43 (4.94-5.98)	5.58 (4.74-6.57)	5.62 (5.07-6.22)	4.9 (4.11-5.83)
	Seroprotection[b]	4 (3%) (1-7)	4 (8%) (2-19)	9 (6%) (3-11)	2 (4%) (0-14)
Post-1st (day 22)	Seroprotection[b]	57 (39%) (31-47)	13 (25%) (14-40)	51 (34%) (27-42) N=149	15 (30%) (18-45)
	GMR[c]	2.12 (1.8-2.49)	1.53 (1.17-2.02)	1.91 (1.63-2.24) N=149	1.78 (1.36-2.34)
	SC[e]/SI[f]	56 (38%) (30-47)	9 (18%) (8-31)	46 (31%) (24-39) N=149	13 (26%) (15-40)
Post-2nd (day 43)	Seroprotection[b]	116 (81%) (74-87) N=143	17 (33%) (21-48)	105 (70%) (62-78) N=149	23 (46%) (32-61)
	GMR[d]	6.32 (5.33-7.49) N=143	1.77 (1.33-2.35)	5.01 (4.16-6.03) N=149	2.67 (1.95-3.67)
	SC[e]/SI[f]	113 (79%) (71-85) N=143	13 (25%) (14-40)	99 (66%) (58-74) N=149	21(42%) (28-57)

Abbreviations: CI = confidence interval; CHMP = Committee for Medicinal Products for Human Use; GMR = geometric mean ratio; GMT = geometric mean titer.

[a] n/N - responders (n) (i.e., subjects who met the SRH definition of seroprotection [pre- and post-vaccination] and seroconversion or significant increase) as part of the total number of subjects in the population (N); [b] Seroprotection - SRH area $\geq 25mm^2$; [c] GMR - the geometric mean of the day 22 to day 1 ratio; [d] GMR - the geometric mean of the day 43 to day 1 ratio; [e] Seroconversion (SC) - negative pre-vaccination serum (i.e., SRH titer $\leq$ 4mm2) and post-vaccination SRH area ≥ 25 mm^2; [f] Significant increase (SI) - at least a 50% increase in SRH area in subjects who were positive pre-vaccination (i.e., SRH area >4 mm^2).

Table 7: SRH Geometric Mean Areas (GMAs) and GMRs (Full Analysis Set)

GMAs and GMRs With 95% CIs					
	Parameter	**Adult**		**Elderly**	
		Fluad-H5N1	**Fluad**	**Fluad-H5N1**	**Fluad**
Baseline (day 1)	**N**	N=146	N=51	N=150	N=50
	GMA (95% CI)	5.43 (4.94-5.98)	5.58 (4.74-6.57)	5.62 (5.07-6.22)	4.9 (4.11-5.83)
Post-1st (day 22)	**N**	N=146	N=51	N=149	N=50
	GMA (95% CI)	12 (9.73-14)	8.56 (6.43-11)	11 (9.08-13)	8.73 (6.51-12)
	GMR[a] (95% CI)	2.12 (1.8-2.49)	1.53 (1.17-2.02)	1.91 (1.63-2.24)	1.78 (1.36-2.34)
Post-2nd (day 43)	**N**	N=143	N=51	N=149	N=50
	GMA (95% CI)	34 (29-40)	9.87 (7.64-13)	28 (24-33)	13 (9.81-17)
	GMR[a] (95% CI)	6.32 (5.33-7.49)	1.77 (1.33-2.35)	5.01 (4.16-6.03)	2.67 (1.95-3.67)

Abbreviations: CI = confidence interval; SRH = single radial hemolysis.
[a] GMR - the geometric mean of the ratios over day 1.

Table 8: Subjects With Microneutralization (MN) Assay Titers ≥ 1:20, ≥ 1:40, ≥ 1:80 (Full Analysis Set)

Number (%) of Subjects (n/N)[a] With 95% CIs					
	MN titer	Adult		Elderly	
		Fluad-H5N1 N=147	Fluad N=51	Fluad-H5N1 N=150	Fluad N=50
Baseline (day 1)	≥1: 20	2 (1%) (0-5)	1 (2%) (0.05-10)	4 (3%) (1-7)	2 (4%) (0-14)
	≥1: 40	1 (1%) (0.017-4)	0 (0%) (0-7)	3 (2%) (0-6)	0 (0%) (0-7)
	≥1: 80	0 (0%) (0-2)	0 (0%) (0-7)	2 (1%) (0-5)	0 (0%) (0-7)
Post-1st (day 22)	≥1: 20	37 (25%) (18-33)	2 (4%) (0-13)	42 (28%) (21-36) N=149	10 (20%) (10-34)
	≥1: 40	18 (12%) (7-19)	2 (4%) (0-13)	29 (19%) (13-27) N=149	4 (8%) (2-19)
	≥1: 80	6 (4%) (2-9)	0 (0%) (0-7)	19 (13%) (8-19) N=149	1 (2%) (0.051-11)
Post-2nd (day 43)	≥1: 20	112 (78%) (70-84) N=144	2 (4%) (0-13)	111 (74%) (67-81) N=149	8 (16%) (7-29)
	≥1: 40	92 (64%) (55-72) N=144	2 (4%) (0-13)	83 (56%) (47-64) N=149	2 (4%) (0-14)
	≥1: 80	44 (31%) (23-39) N=144	1 (2%) (0.050-10)	55 (37%) (29-45) N=149	1 (2%) (0.051-11)

Abbreviation: CI = confidence interval.
[a] n/N - responders (n) (i.e., subjects who met the criteria) as part of the total number of subjects in the population (N).

Table 9: GMTs and GMRs Determined by MN Assay (Full Analysis Set)

GMAs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=147	Fluad N=51	Fluad-H5N1 N=150	Fluad N=50
Baseline (day 1)	GMT	10 (9.91-11)	10 (9.77-11)	11 (9.95-11)	10 (9.35-12)
Post-1st (day 22)	GMT	15 (13-16)	11 (8.97-13)	17 (15-20) N=149	13 (10-17)
	GMR[a]	1.43 (1.3-1.58)	1.04 (0.88-1.23)	1.61 (1.4-1.84) N=149	1.24 (0.98-1.56)
Post-2nd (day 43)	GMT	49 (42-57) N=144	11 (8.32-14)	52 (43-61) N=149	13 (9.44-17)
	GMR[a]	4.8 (4.13-5.58) N=144	1.05 (0.81-1.35)	4.87 (4.13-5.74) N=149	1.22 (0.92-1.61)

Abbreviations: CI = confidence interval; GMR = geometric ratio; GMT = geometric mean titer; MN = microneutralization.
[a] GMR - the geometric mean of the ratio over day 1.

Table 10: Four-fold Increase in MN Titer Above Baseline (Full Analysis Set)

Number (%) of Subjects (n/N)[a] With 95% CIs				
	Adult		Elderly	
	Fluad-H5N1 N=147	Fluad N=51	Fluad-H5N1 N=149	Fluad N=50
Post-1st (day 22)	17 (12%) (7-18)	1 (2%) (0.05-10)	25 (17%) (11-24)	3 (6%) (1-17)
Post-2nd (day 43)	91 (63%) (55-71) N=144	1 (2%) (0.05-10)	80 (54%) (45-62)	1 (2%) (0.051-11)

Abbreviations: CI = confidence interval; MN = microneutralization.
[a] n/N - responders (n) (ie, subjects who met the criteria) as part of the total number of subjects in the population (N).

Table 11: HI Seronegative Subjects Population – CHMP Criteria

Number (%) of Subjects (n/N)[a] and GMAs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=145	Fluad N=50	Fluad-H5N1 N=138	Fluad N=47
Baseline (day 1)	GMT	5.00 (5.00-5.00)	5.00 (5.00-5.00)	5.00 (5.00-5.00)	5.00 (5.00-5.00)
	Seroprotection[b]	0 (0%) (0-3)	0 (0%) (0-7)	0 (0%) (0-3)	0 (0%) (0-8)
Post-1st (day 22)	Seroprotection[b]	36 (25%) (18-33)	0 (0%) (0-7)	39 (28%) (21-37) N=137	3 (6%) (1-18)
	GMR[c]	2.35 (1.91-2.88)	1.03 (0.72-1.46)	2.65 (2.11-3.34) N=137	1.38 (0.94-2.05)
	SI[e]	36 (25%) (18-33)	0 (0%) (0-7)	39 (28%) (21-37) N=137	3 (6%) (1-18)
Post-2nd (day 43)	Seroprotection[b]	86 (60%) (52-68) N=143	0 (0%) (0-7)	94 (68%) (60-76)	3 (6%) (1-18)
	GMR[d]	9.53 (7.26-13) N=143	1.02 (0.64-1.62)	13 (9.72-16)	1.46 (0.93-2.29)
	SI[e]	86 (60%) (52-68) N=143	0 (0%) (0-7)	94 (68%) (60-76)	3 (6%) (1-18)

Abbreviations: CI = confidence interval; CHMP = Committee for Medicinal Products for Human Use; GMR = geometric mean ratio; GMT = geometric mean titer; HI = hemagglutination inhibition.
[a] n/N - responders (n) (i.e., subjects who met the HI definition of seroprotection [pre- and postvaccination]) as part of the total number of subjects in the population (N); [b] Seroprotection - HI titers ≥40; [c] GMR - the geometric mean of the day 22 to day 1 ratio; [d] GMR - the geometric mean of the day 43 to day 1 ratio; [e]Significant increase (SI) - at least a 4-fold increase in HI titers in subjects who were positive prevaccination (i.e., HI titer ≥10).

Table 12: SRH Seronegative Subset Population – CHMP Criteria

Number (%) of Subjects (n/N)[a] and GMAs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=111	Fluad N=39	Fluad-H5N1 N=113	Fluad N=42
Baseline (day 1)	GMA	4.00 (4.00-4.00)	4.00 (4.00-4.00)	4.00 (4.00-4.00)	4.00 (4.00-4.00)
	Seroprotection[b]	0 (0%) (0-3)	0 (0%) (0-9)	0 (0%) (0-3)	0 (0%) (0-8)
Post-1st (day 22)	Seroprotection[b]	41 (37%) (28-47)	8 (21%) (9-36)	36 (32%) (24-42) N=112	12 (29%) (16-45)
	GMR[c]	2.36 (1.92-2.89)	1.73 (1.23-2.44)	2.12 (1.74-2.58) N=112	1.93 (1.4-2.66)
	SC[e]/SI[f]	41 (37%) (28-47)	8 (21%) (9-36)	36 (32%) (24-42) N=112	12 (29%) (16-45)
Post-2nd (day 43)	Seroprotection[b]	91 (83%) (75-90) N=109	12 (31%) (17-48)	83 (74%) (65-82) N=112	19 (45%) (30-61)
	GMR[d]	8.41 (6.96-10) N=109	2.08 (1.52-2.85)	6.78 (5.5-8.36) N=112	2.99 (2.13-4.21)
	SC[e]/SI[f]	91 (83%) (75-90) N=109	12 (31%) (17-48)	83 (74%) (65-82) N=112	19 (45%) (30-61)

Abbreviations: CI = confidence interval; CHMP = Committee for Medicinal Products for Human Use; GMA = geometric mean area; GMR = geometric mean ratio; SRH = single radial hemolysis.
[a] n/N - responders (n) (i.e., subjects who met the SRH definition of seroprotection [pre- and post-vaccination]) as part of the total number of subjects in the population (N); [b] Seroprotection – SRH area ≥ 25 mm^2; [c] GMR - the geometric mean of the day 22 to day 1 ratio; [d] GMR - the geometric mean of the day 43 to day 1 ratio; [e] Seroconversion - negative pre-vaccination serum (i.e., SRH titer ≤ 4 mm^2) and post-vaccination SRH area ≥ 25 mm^2; [f] Significant increase- at least a 50% increase in SRH area in subjects who were positive pre-vaccination (i.e., SRH area >4 mm^2).

Table 13: SRH GMAs and GMRs - SRH Seronegative Subset

GMAs and GMRs With 95% CIs					
	Parameter	Adult		Elderly	
		Fluad-H5N1 N=111	Fluad N=39	Fluad-H5N1 N=113	Fluad N=42
Baseline (day 1)	GMA	4.00 (4.00-4.00)	4.00 (4.00-4.00)	4.00 (4.00-4.00)	4.00 (4.00-4.00)
Post-1st (day 22)	GMA	9.42 (7.68-12)	6.92 (4.92-9.75)	8.48 (6.96-10) N=112	7.7 (5.59-11)
	GMR[a]	2.36 (1.92-2.89)	1.73 (1.23-2.44)	2.12 (1.74-2.58) N=112	1.93 (1.4-2.66)
Post-2nd (day 43)	GMA	34 (28-41) N=109	8.32 (6.06-11)	27 (22-33) N=112	12 (8.5-17)
	GMR[b]	8.41 (6.96-10) N=109	2.08 (1.52-2.85)	6.78 (5.5-8.36) N=112	2.99 (2.13-4.21)

Abbreviations: CI = confidence interval; GMA = geometric mean area; GMR = geometric mean ratio; SRH = single radial hemolysis.
[a] GMR - the geometric mean of the day 22 to day 1 ratio; [b] GMR - the geometric mean of the day 43 to day 1 ratio.

Table 14: MN Seronegative Subset Population - Percentages of Subjects With a MN Titer ≥ 40

Number (%) of Subjects (n/N)[a] With 95% CIs					
	MN titer	Adult		Elderly	
		Fluad-H5N1 N=145	Fluad N=50	Fluad-H5N1 N=146	Fluad N=48
Baseline (day 1)	≥1: 40	0 (0%) (0-3)	0 (0%) (0-7)	0 (0%) (0-2)	0 (0%) (0-7)
Post-1st (day 22)	≥1: 40	16 (11%) (6-17)	1 (2%) (0.051-11)	25 (17%) (11-24) N=145	3 (6%) (1-17)
Post-2nd (day 43)	≥1: 40	91 (64%) (55-72) N=143	1 (2%) (0.051-11)	79 (54%) (46-63) N=145	1 (2%) (0.053-11)

Abbreviations: CI = confidence interval; MN = microneutralization.
[a] n/N - responders (n) (i.e., subjects who met the criteria) as part of the total number of subjects in the population (N).

Table 15: MN Seronegative Subset Population: 4-fold Increase

Timepoint of 4-fold increase	Number (%) of Subjects With 95% CIs			
	Adult		Elderly	
	Fluad-H5N1 N=145	Fluad N=50	Fluad-H5N1 N=145	Fluad N=48
Day 22[a]	16 (11%) (6-17)	1 (2%) (0.051-11)	25 (17%) (11-24)	3 (6%) (1-17)
Day 43[b]	91 (64%) (55-72) N=143	1 (2%) (0.051-11)	79 (54%) (46-63)	1 (2%) (0.053-11)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; MN = microneutralization.
[a] GMR - the geometric mean of the day 22 to day 1 ratio; [b] GMR - the geometric mean of the day 43 to day 1 ratio.

Table 16: Overview of Solicited Reactions After 2 Injections, up to Day 43, by Injection

Number (%) of Subjects					
Parameter	**Injection**	**1st injection**		**2nd injection**	
	Type of reaction	**Fluad-H5N1**	**Fluad**	**Fluad-H5N1**	**Fluad**
		N=2394	**N=800**	**N=2356**	**N=783**
Adult	**Any Reaction**	1579 (66)	594 (74)	1077 (46)	380 (49)
	Local Reaction	1375 (57)	535 (67)	896 (38)	325 (42)
	Systemic Reaction	887 (37)	381 (48)	518 (22)	191 (24)
	Other Reaction	174 (7)	81 (10)	82 (3)	25 (3)
Elderly		**N=241**	**N=81**	**N=240**	**N=81**
	Any Reaction	121 (50)	39 (48)	91 (38)	22 (27)
	Local Reaction	79 (33)	26 (32)	63 (26)	13 (16)
	Systemic Reaction	75 (31)	25 (31)	53 (22)	12 (15)
	Other Reaction	15 (6)	6 (7)	19 (8)	4 (5)

Table 17: Overview of Severe Solicited Reactions After 2 Injections, up to Day 43, by Injection

		Number (%) of Subjects					
Parameter	**Injection**	**1st injection**			**2nd injection**		
	Type of reaction	**Fluad-H5N1**	**Fluad**	**P value[1]**	**Fluad-H5N1**	**Fluad**	**P value[1]**
		N=2394	**N=800**	**N=3194**	**N=2356**	**N=783**	**N=3139**
Adult	**Any Reaction**	79 (3%)	63 (8%)	<0.001***	54 (2%)	20 (3%)	0.68
	Local Reaction	28 (1%)	29 (4%)	<0.001***	24 (1%)	11 (1%)	0.37
	Systemic Reaction	59 (2%)	42 (5%)	<0.001***	38 (2%)	13 (2%)	0.93
Elderly		**N=241**	**N=81**	**N=322**	**N=240**	**N=81**	**N=321**
	Any Reaction	4 (2%)	1 (1%)	1.0	5 (2%)	2 (2%)	1.0
	Local Reaction	0	1 (1%)	0.25	3 (1%)	2 (2%)	0.60
	Systemic Reaction	4 (2%)	0	0.58	2 (<1%)	0	1.0

[1]12-sided p-value for categorical variables computed by the chi-square test if <= 20% of the cells have expected cell counts less than 5, or by Fisher's Exact test if > 20% of the cells have expected cell counts less than 5. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 18: Summary of Local Reactions 1 Week After Each Injection

		Number (%) of Subjects					
	Injection	**1st injection (Day 1 – 7)**			**2nd injection (Day 22 – 29)**		
	Local reaction (Any and Severe)	**Fluad-H5N1**	**Fluad**	**P value[1]**	**Fluad-H5N1**	**Fluad**	**P value[1]**
		N=2394	**N=800**		**N=2356**	**N=783**	
	Any	1579 (66)	594(74)		1077 (46)	380 (49)	
Adult	Erythema Any	219 (9)	90 (11)	0.082	170 (7)	71 (9)	0.093
	Severe	7 (<1)	4 (1)		5 (<1)	4 (1)	
	Induration Any	182 (8)	104 (13)	<0.001***	152 (6)	55 (7)	0.58
	Severe	4 (<1)	5 (1)		1 (<1)	2 (<1)	
	Swelling Any	127 (5)	70 (9)	<0.001***	93 (4)	46 (6)	0.023*
	Severe	8 (<1)	6 (1)		4 (<1)	3 (<1)	
	Ecchymosis Any	46 (2)	17 (2)	0.72	28 (1)	11 (1)	0.64
	Severe	1 (<1)	1 (<1)		0	0	
	Pain Any	1289 (54)	500 (63)	<0.001***	793 (34)	283 (36)	0.21
	Severe	15 (1)	19 (2)		17 (1)	7 (1)	
Elderly		**N=241**	**N=81**		**N=240**	**N=81**	
	Any	121 (50)	39 (48)		91 (38)	22 (27)	
	Erythema Any	13 (5)	7 (9)	0.29	8 (3)	3 (4)	1.0
	Severe	0	1(1)		0	1(1)	
	Induration Any	17 (7)	10 (12)	0.14	12 (5)	6 (7)	0.41
	Severe	0	1 (1)		1 (<1)	0	
	Swelling Any	6 (2)	5 (6)	0.15	9 (4)	4 (5)	0.74
	Severe	0	1 (1)		1 (<1)	1 (1)	
	Ecchymosis Any	0	0	1.0	2 (1)	1 (1)	1.0
	Severe	0	0		1 (<1)	0	
	Pain Any	67 (28)	20 (25)	0.59	55 (23)	8 (10)	0.011*
	Severe	0	0		1(<1)	0	

[1]P-value from Pearson's chi-square test for vaccine group differences: * p < 0.05; ** p < 0.01; *** p <0.001.

Table 19: Summary of Solicited Local Reactions Continuing Past Day 7

		Number (%) of Subjects					
	Injection	**1st injection (Day 1 – 7)**			**2nd injection (Day 22 – 29)**		
		Fluad-H5N1	**Fluad**	**Total**	**Fluad-H5N1**	**Fluad**	**Total**
		N=2394	**N=800**	**N=3194**	**N=2354**	**N=783**	**N=3137**
Adult	Erythema Any	3 (<1)	2 (<1)	5 (<1)	2 (<1)	0	2 (<1)
	Severe	0	1 (<1)	1 (<1)	0	0	0
	Induration Any	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
	Severe	0	1 (<1)	1 (<1)	0	0	0
	Swelling Any	0	0	0	1 (<1)	0	1 (<1)
	Severe	0	0	0	0	0	0
	Ecchymosis Any	12 (1)	6 (1)	18 (1)	3 (1)	1 (<1)	4 (<1)
	Severe	0	1 (<1)	1 (<1)	0	0	0
	Pain Any	2 (<1)	1 (<1)	3 (<1)	2 (<1)	0	2 (<1)
	Severe	1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	1 (<1)
Elderly		**N=241**	**N=81**	**N=322**	**N=240**	**N=81**	**N=321**
	Erythema Any	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Induration Any	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Swelling Any	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
	Ecchymosis Any	0	0	0	1 (<1)	0	1 (<1)
	Severe	0	0	0	1 (<1)	0	1 (<1)
	Pain Any	0	0	0	0	0	0
	Severe	0	0	0	0	0	0

Table 20: Summary of Solicited Systemic Reactions 1 Week After Each Injection - Adults

		Number (%) of Subjects					
		1st injection (Day 1 – 7)			2nd injection (Day 22 – 29)		
Solicited Systemic Reactions		**Fluad-H5N1 N=2394**	**Fluad N=800**	**P value[1]**	**Fluad-H5N1 N=2354**	**Fluad N=783**	**Pvalue[1]**
Chills	Any	180 (8)	102 (13)	<0.001***	99 (4)	28 (4)	0.44
	Severe	14 (1)	7 (1)		8 (<1)	4 (1)	
Malaise	Any	285 (12)	156 (20)	<0.001***	175 (7)	66 (8)	0.37
	Severe	27 (1)	18 (2)		15 (1)	5 (1)	
Myalgia	Any	400 (17)	208 (26)	<0.001***	225 (10)	93 (12)	0.063
	Severe	10 (<1)	16 (2)		13 (1)	7 (1)	
Arthralgia	Any	141 (6)	95 (12)	<0.001***	95 (4)	42 (5)	0.12
	Severe	6 (<1)	7 (1)		6 (<1)	3 (<1)	
Headache	Any	428 (18)	216 (27)	<0.001***	241 (10)	94 (12)	0.17
	Severe	29 (1)	21 (3)		8 (<1)	6 (1)	
Sweating	Any	151 (6)	89 (11)	<0.001***	91 (4)	29 (4)	0.84
	Severe	13 (1)	7 (1)		2 (1)	2 (1)	
Fatigue	Any	455(19)	214 (27)	<0.001***	255 (11)	87 (11)	0.83
	Severe	33 (1)	18 (2)		13 (1)	4 (1)	
Nausea	Any	101 (4)	46 (6)	0.074	46(2)	19(2)	0.42
	Severe	5 (<1)	2 (<1)		4 (<1)	2 (<1)	
Fever	≥ 38°C	54 (2)	38/799 (5)	<0.001***	44(2)	8(1)	0.11
	≥ 40°C	1(<1)	0		0	1(<1)	
Other Reactions							
Stay home		37/2385 (2)	21/798 (3)	0.048*	21/2349 (1)	3/779 (<1)	0.16
Analge. Antipyr. Med.Used		164 (7)	78 (10)	0.007**	76 (3)	24 (3)	0.82

[a] P-value from Pearson's chi-square test for vaccine group differences: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 21: Summary of Solicited Systemic Reactions 1 Week After Each Injection - Elderly

		Number (%) of Subjects					
		1st injection (Day 1 – 7)			2nd injection (Day 22 – 29)		
Solicited Systemic Reactions		**Fluad-H5N1 N=226**	**Fluad N=75**	**P-value**	**Fluad-H5N1 N=235**	**Fluad N=80**	**P-value**
Chills	Any	15 (6)	6 (7)	0.71	5 (2)	1 (1)	1.0
	Severe	1 (<1)	0		0	0	
Malaise	Any	25 (10)	10 (12)	0.62	18 (8)	5 (6)	0.69
	Severe	1 (<1)	0		0	0	
Myalgia	Any	30 (12)	8 (10)	0.53	14 (6)	4 (5)	1.0
	Severe	2 (1)	0		0	0	
Arthralgia	Any	23 (10)	6 (7)		14 (6)	0	0.58
	Severe	3 (1)	0	0.56	1 (<1)	3 (4)	
Headache	Any	39 (16)	16 (20)	0.46	32 (13)	5 (6)	0.081
	Severe	0	0		0	0	
Sweating	Any	19 (8)	9 (11)	0.37	15 (6)	2 (2)	0.26
	Severe	0	0		1 (<1)	0	
Fatigue	Any	34 (14)	15 (19)	0.34	32 (13)	8 (10)	0.42
	Severe	0	0		0	0	
Nausea	Any	6 (2)	4 (5)	0.28	4 (2)	1 (1)	1.0
	Severe	1 (<1)	0		0	0	
Fever	≥ 38°C	3 (1)	1 (1)	1.0	1 (<1)	0	1.0
	≥ 40°C	0	0		0	0	
Other Reactions							
Stay home		4 (2)	1 (1)	1.0	1 (<1)	0	1.0
Analge. Antipyr. Med.Used		15 (6)	6 (7)	0.71	19 (8)	4 (5)	0.37

Table 22: Summary of Solicited Systemic Reactions Continuing Past Day 7 – Adults

		Number (%) of Subjects					
		1st injection			2nd injection		
Solicited Systemic and Other Reactions		Fluad-H5N1 N=2394	Fluad N=800	Total N=3194	Fluad-H5N1 N=2354	Fluad N=783	Total N=3137
Chills	Any	17 (1)	3 (<1)	20 (1)	7 (<1)	1 (<1)	8 (<1)
	Severe	3 (<1)	0	3 (<1)	3 (<1)	0	3 (<1)
Malaise	Any	29 (1)	7 (1)	36 (1)	12 (1)	1 (<1)	13 (<1)
	Severe	9 (<1)	6 (1)	15 (<1)	3 (<1)	0	3 (<1)
Myalgia	Any	15 (1)	8 (1)	23 (1)	11 (<1)	1 (<1)	12 (<1)
	Severe	2 (<1)	3 (<1)	5 (<1)	1 (<1)	0	1 (<1)
Arthralgia	Any	16 (1)	4 (1)	20 (1)	4 (<1)	0	4 (<1)
	Severe	0	2 (<1)	2 (<1)	0	0	0
Headache	Any	23 (1)	12 (2)	35 (1)	9 (<1)	7 (1)	16 (1)
	Severe	7 (<1)	6 (1)	13 (<1)	1 (<1)	1 (<1)	2 (<1)
Sweating	Any	22 (1)	5 (1)	27 (1)	4 (<1)	3 (<1)	7 (<1)
	Severe	3 (<1)	0	3 (<1)	0	0	0
Fatigue	Any	31 (1)	12 (2)	43 (1)	19 (1)	5 (1)	24 (1)
	Severe	10 (<1)	5 (1)	15 (<1)	1 (<1)	0	1 (<1)
Nausea	Any	8 (<1)	1 (<1)	9 (<1)	1 (<1)	0	1 (<1)
	Severe	1 (<1)	0	1 (<1)	0	0	0

The numbers (N) in the header is the total number of subjects with documented reactions.

Table 23: Summary of Systemic Reactions Continuing Past Day 7 – Elderly

		Number (%) of Subjects					
		1st injection			2nd injection		
Solicited Systemic and Other Reactions		**Fluad-H5N1 N=241**	**Fluad N=81**	**Total N=322**	**Fluad-H5N1 N=240**	**Fluad N=81**	**Total N=321**
Chills	Any	2 (1)	0	2 (1)	0	0	0
	Severe	0	0	0	0	0	0
Malaise	Any	4 (2)	0	4 (1)	0	0	0
	Severe	0	0	0	0	0	0
Myalgia	Any	4 (2)	0	4 (1)	2 (1)	0	2 (1)
	Severe	1 (<1)	0	1 (<1)	0	0	0
Arthralgia	Any	8 (3)	1 (1)	9 (3)	4 (2)	0	4 (1)
	Severe	2 (1)	0	2 (1)	1 (<1)	0	1 (<1)
Headache	Any	6 (2)	1 (1)	7 (2)	1 (<1)	0	1 (<1)
	Severe	0	0	0	0	0	0
Sweating	Any	3 (1)	1 (1)	4 (1)	1 (<1)	0	1 (<1)
	Severe	0	0	0	1 (<1)	0	1 (<1)
Fatigue	Any	6 (2)	1 (1)	7 (2)	0	0	0
	Severe	0	0	0	0	0	0
Nausea	Any	0	0	0	0	0	0
	Severe	0	0	0	0	0	0

Table 24: Overview of Other Adverse Events (AEs) – 3 Weeks After Injection, by Injection

		Number (%) of Subjects					
	Injection	3 weeks after 1st injection			3 weeks after 2nd injection		
	Type of reaction	Fluad-H5N1	Fluad	Total	Fluad-H5N1	Fluad	Total
		N=2394	N=800	N=3194	N=2356	N=783	N=3139
Adult	Any AE	363 (15)	113 (14)	476 (15)	191 (8)	55 (7)	246 (8)
	At least possibly related AE	91 (4)	39 (5)	130 (4)	58 (2)	18 (2)	76 (2)
	AE leading to vaccine discontinuation	12 (1)	9 (1)	21 (1)	NA	NA	NA
	AE leading to withdrawal from study	2 (<1)	2 (<1)	4 (<1)	0	0	0
	Serious AEs	8 (<1)	2 (<1)	10 (<1)	4 (<1)	2 (<1)	6 (<1)
	At least possibly related serious AE	0	0	0	0	0	0
	Death	0	0	0	0	0	0
Elderly		N=241	N=81	N=322	N=240	N=81	N=321
	Any AE	46 (19)	15 (19)	61 (19)	36 (15)	12 (15)	48 (15)
	At least possibly related AE	14 (6)	2 (2)	16 (5)	8 (3)	0	8 (2)
	AE leading to vaccine discontinuation	1 (<1)	0	1 (<1)	NA	NA	NA
	AE leading to withdrawal from study	0	0	0	0	0	0
	Serious AEs	1 (<1)	0	1 (<1)	4 (2)	1 (1)	5 (2)
	At least possibly related serious AE	0	0	0	0	0	0
	Death	0	0	0	0	0	0

Table 25: Overview of Other Adverse Events (AEs) – More Than 3 Weeks Postvaccination

		Number (%) of Subjects		
	Injection	**3 weeks after 1st injection**		
	Type of reaction	**Fluad-H5N1**	**Fluad**	**Total**
		N=2300	**N=767**	**N=3067**
Adult	**Any AE**	263 (11)	79 (10)	342 (11)
	At least possibly related AE	0	0	0
	AE leading to vaccine discontinuation	NA	NA	NA
	AE leading to withdrawal from study	0	0	0
	Serious AEs	40 (2)	8 (1)	48 (2)
	At least possibly related serious AE	0		0
	Death	1 (<1)	1 (<1)	2 (<1)
Elderly		**N=239**	**N=79**	**N=318**
	Any AE	50 (21)	18 (23)	68 (21)
	At least possibly related AE	0	0	0)
	AE leading to vaccine discontinuation	NA	NA	NA
	AE leading to withdrawalfrom study	0	0	0
	Serious AEs	14 (6)	7 (9)	21 (7)
	At least possibly related serious AE	0	0	0
	Death	2 (<1)	0	2 (<1)

Table 26: Summary of Serious Adverse Events- Age Group: Adults 18-60 Years of Age

	Number (%) of Subjects		
MedDRA System Organ Class MedDRA Preferred Term	**Fluad-H5N1 N=2394**	**Fluad N=800**	**Total N=3194**
Any serious adverse event	51 (2)	12 (2)	63 (2)
Blood & lymphatic system disorders			
Iron deficiency anaemia	1 (<1)	0	1 (<1)
Cardiac disorders			
Acute myocardial infarction	1 (<1)	0	1 (<1)
Arteriospasm coronary	1 (<1)	0	1 (<1)
Coronary artery disease	1 (<1)	0	1 (<1)
Myocardial infarction	1 (<1)	0	1 (<1)
Ventricular arrhythmia	1 (<1)	0	1 (<1)
Congen. & famil./genetic disorders			
Hydrocele	1 (<1)	0	1 (<1)
Eye disorder			
Glaucoma	1 (<1)	0	1 (<1)
Gastrointestinal disorders			
Crohn’s disease	1 (<1)	0	1 (<1)
Duodenal ulcer	1 (<1)	0	1 (<1)
Duodenal ulcer perforation	0	1 (<1)	1 (<1)
Intestinal polyp	1 (<1)	0	1 (<1)
Malocclusion	1 (<1)	0	1 (<1)
Oesophagitis	1 (<1)	0	1 (<1)
Pancreatitis acute	0	1 (<1)	1 (<1)
Peritonitis	0	1 (<1)	1 (<1)
Rectal polyp	1 (<1)	0	1 (<1)
Gen. Disorders & admin. Site cond.			
Chest pain	1 (<1)	0	1 (<1)
Death	0	1 (<1)	1 (<1)
Multi-organ failure	1 (<1)	0	1 (<1)
Sudden cardiac death	1 (<1)	0	1 (<1)
Hepato-biliary disorders			
Cholelithiasis	2 (<1)	2 (<1	4 (<1)
Infections & infestations			
Acute tonsillitis	1 (<1)	0	1 (<1)
Appendicitis	1 (<1)	0	1 (<1)
Bronchitis	1 (<1)	0	1 (<1)
Lyme disease	1 (<1)	0	1 (<1)

	Number (%) of Subjects		
Orchitis	1 (<1)	0	1 (<1)
Otitis media chronic	1 (<1)	0	1 (<1)
Peritonsillar abscess	1 (<1)	0	1 (<1)
Pneumonia	1 (<1)	0	1 (<1)
Scrotal abscess	1 (<1)	0	1 (<1)
Sepsis	1 (<1)	0	1 (<1)
Subcutaneous abscess	1 (<1)	0	1 (<1)
Syphilis	1 (<1)	0	1 (<1)
Injury & poisoning			
Concussion	1 (<1)	0	1 (<1)
Eye injury	1 (<1)	0	1 (<1)
Head injury	1 (<1)	1 (<1)	2(<1)
Joint injury	2(<1)	2(<1)	4 (<1)
Meniscus lesion	0	1 (<1)	1 (<1)
Road traffic accident	0	1 (<1)	1 (<1)
Musculo., connect. Tis. & bone dis.			
Arthropathy	1 (<1)	0	1 (<1)
Back pain	1 (<1)	0	1 (<1)
Osteochondrosis	1 (<1)	0	1 (<1)
Neo. Ben./malig.(inc. Cysts/polyps)			
Breast cancer	1 (<1)	1 (<1)	2(<1)
Cervix carcinoma	1 (<1)	0	1 (<1)
Lipoma	1 (<1)	0	1 (<1)
Thyroid cancer	1 (<1)	0	1 (<1)
Uterine leiomyoma	1 (<1)	1 (<1)	2(<1)
Nervous system disorders			
Brain stem stroke	1 (<1)	0	1 (<1)
Carpal tunnel syndrome	1 (<1)	0	1 (<1)
Headache	1 (<1)	0	1 (<1)
Preg., puerperium & perinatal cond.			
Abortion missed	1 (<1)	0	1 (<1)
Reproduct. Sys. & breast disorders			
Breast cyst	0	1 (<1)	1 (<1)
Ovarian cyst	1 (<1)	0	1 (<1)
Pelvic pain	1 (<1)	0	1 (<1)
Uterine polyp	2 (<1)	0	2 (<1)
Vaginal haematoma	1 (<1)	0	1 (<1)
Resp., thoracic & mediastinal dis.			
Asthma	1 (<1)	0	1 (<1)
Nasal septum deviation	2 (<1)	0	2 (<1)
Surgical & medical procedures			
Abortion induced	1 (<1)	0	1 (<1)
Appendicectomy	1 (<1)	0	1 (<1)
Breast operation	0	1 (<1)	1 (<1)
Cholecystostomy	1 (<1)	0	1 (<1)
Myomectomy	1 (<1)	0	1 (<1)
Polypectomy	1 (<1)	0	1 (<1)
Uterine dilation and curettage	1 (<1)	0	1 (<1)
Uterine operation	1 (<1)	0	1 (<1)
Vascular disorders			

		Number (%) of Subjects	
Varicose vein	1 (<1)	0	1 (<1)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

Table 27: Summary of Serious Adverse Events- Age Group: Elderly >60 Years

	Number (%) of Subjects		
MedDRA System Organ Class **MedDRA Preferred Term**	**Fluad-H5N1** **N=241**	**Fluad** **N=81**	**Total** **N=322**
Any serious adverse event	19 (8)	8 (10)	27 (8)
Blood & lymphatic system disorders			
Anaemia	1 (<1)	0	1 (<1)
Hypochromic anaemia	1 (<1)	0	1 (<1)
Cardiac disorders			
Atrial fibrillation	2 (1)	0	2 (1)
Myocardial ischaemia	2 (1)	0	2 (1)
Ear & labyrinth disorders			
Acute vestibular syndrome	0	1 (1)	1 (<1)
Deafness neurosensory	1 (<1)	0	1 (<1)
Eye disorder			
Cataract nuclear	1 (<1	0	1 (<1)
Gastrointestinal disorders			
Abdominal pain	1 (<1)	0	1 (<1)
Inguinal hernia	0	1 (1)	1 (<1)
Subileus	0	1 (1)	1 (<1)
Vomiting	1 (<1)	0	1 (<1)
Gen. Disorders & admin. Site cond.			
Pyrexia	1 (<1)	0	1 (<1)
Infections & infestations			
Urinary tract infection	1 (<1)	0	1 (<1)
Injury & poisoning			
Humerus fracture	1 (<1)	0	1 (<1)
Lumbar vertebral fracture	1 (<1)	0	1 (<1)
Investigations			
Arteriogram coronary	0	1 (1)	1 (<1)
Metabolism & nutrition disorders			
Diabetes mellitus	1 (<1)	0	1 (<1)
Musculo., connect. Tis. & bone dis			
Bursitis	1 (<1)	0	1 (<1)
Neo. Ben./malig.(inc. Cysts/polyps)			
Oesophageal carcinoma	1 (<1)	0	1 (<1)
Oral fibroma	1 (<1)	0	1 (<1)
Nervous system disorders			
Cerebral infarction	1 (<1)	0	1 (<1)
Cerebral ischaemia	0	1 (1)	1 (<1)
Cerebrovascular accident	2 (1)	0	2 (1)
Headache	0	1 (1)	1 (<1)
Intracranial aneurysm	0	1 (1)	1 (<1)
Thalamus haemorrhage	1 (<1)	0	1 (<1)
Renal & urinary disorders.			

	Number (%) of Subjects		
Dysuria	1 (<1)	0	1 (<1)
Haematuria	1 (<1)	0	1 (<1)
Resp., thoracic & mediastinal dis.			
Epistaxis	1 (<1)	0	1 (<1)
Pulmonary embolism	0	1 (1)	1 (<1)
Surgical & medical procedures			
Cardiac pacemaker replacement	1 (<1)	0	1 (<1)
Medical device removal	0	1 (1)	1 (<1)
Transurethral prostatectomy	1 (<1)	0	1 (<1)
Vascular disorders			
Circulatory collapse	1 (<1)	0	1 (<1)
Embolism	0	1 (1)	1 (<1)
Hypotension	0	1 (1)	1 (<1)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

Table 28: Other Adverse Events Reported in > 5% of Subjects by Preferred Term Sorted by System Organ Class - Elderly >60 Years

	Number (%) of Subjects	
MedDRA Preferred Term	**Fluad-H5N1 N=241**	**Fluad N=81**
Rhinitis	<5%	6 (7)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

Conclusion:

By all serological assessments and criteria for evaluation, the immune response to Fluad-H5N1 formulated with 7.5 µg was adequate and similar to earlier studies after each of the two injections.
Analysis of Single Radial Hemolysis (SRH) results showed that all three Committee for Medicinal Products for Human Use (CHMP) criteria were met by the Fluad- H5N1 group in the adult and elderly subjects after two injections of Fluad- H5N1 containing 7.5 µg A/H5N1 influenza antigen. When antibody titers were assessed by Hemagglutination Inhibition (HI) assay, two out of three CHMP criteria (CPMP/BWP/214/96) were met for the adult (i.e., 18-60 years) Fluad- H5N1 subjects (the required proportion of subjects achieving seroprotection was not met), while all three criteria were met for elderly subjects (i.e., >60 years).
Fluad- H5N1 influenza vaccine and seasonal Fluad vaccination were well tolerated. With the exception of a lower percentage of adult Fluad- H5N1 influenza vaccine recipients reporting severe local reactions after the first injection, there was no clear and consistent difference in the reactogenicity profile between the two vaccines.

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