Sponsor:	Novartis Vaccines and Diagnostics S.r.l.
Investigational Product:	Fluad-H5N1 influenza vaccine containing 7.5 µg of A/turkey/Turkey-like H5N1
Indication:	Prophylaxis Influenza
Protocol Number:	V87P1E1
Protocol Title:	A Phase II, Open-label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Booster Dose of Fluad-H5N1 (Surface Antigen Adjuvanted with MF59C.1) Influenza Vaccine in Non-elderly Adult and Elderly Subjects
Phase of Development:	Phase II
Study Period:	
Date of first enrolment:	18 October 2007
Date of last visit:	14 June 2008

Methodology:

This study was an extension of a previous study (V87P1) performed over a period of approximately 6 months at multiple study sites. In the phase II, open-label, multi-center, extension study, approximately 60 subjects (age 18 years and above) previously vaccinated with 2 doses of either 7.5 µg or 15 µg Fluad-H5N1 vaccine (Adjuvanted trivalent influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived; aTIV) (A/Vietnam strain) in study V87P1, who did not receive a booster dose 6 months after the last primary vaccination, were invited to participate. In extension study V87P1E1, all subjects received one booster dose of aTIV-H5N1 influenza vaccine containing 7.5 µg of H5N1 influenza antigen (A/turkey/Turkey strain), on study day 382, 17- 18 months (actually 492 to 578 days) after the last primary vaccination in V87P1.

Number of Subjects (planned and analyzed):

Approximately 60 subjects who had previously participated in study V87P1 were planned for this study and 47 subjects (29 adult and 18 elderly subjects) actually were enrolled. All subjects enrolled in this study received the same vaccine.

Study Centers:

Three study centers in Italy.

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

NCT00561184.

Objectives:

Immunogenicity

- To assess persistence of antibody titers 17-18 months after primary immunization with two 0.5 mL intramuscular (IM) doses of aTIV-H5N1 influenza vaccine containing either 7.5 µg or 15 µg of H5N1 influenza antigen (A/Vietnam strain) as measured by HI, SRH and MN assays.
- To assess immunogenicity of one 0.5 mL IM booster dose of aTIV-H5N1 influenza vaccine containing 7.5 µg of H5N1 influenza antigen (A/turkey/Turkey), as measured by HI and SRH assays in compliance with the requirements of the current European Union recommendations (CPMP/BWP/214/96), and by MN assay.

Safety

- To evaluate the safety of the administration of one 0.5 mL IM booster dose of aTIV-H5N1 influenza vaccine containing 7.5 µg of H5N1 influenza antigen 17-18 months after primary immunization.

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

aTIV-H5N1 influenza vaccine containing of A/turkey/Turkey-like H5N1 influenza 7.5 µg antigen, Novartis Vaccines (Lot number: X52D18H1, Expiry Date: July 2008). One 0.5 mL IM injection of aTIV-H5N1 was administered in the deltoid muscle of the (preferably) non-dominant arm.

Duration of Study:

The actual subject enrollment interval was approximately 5 weeks. Duration of an individual subject's participation was approximately 26 weeks. The total duration of the study was approximately 33 weeks.

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

None.

Statistical Methods:

There was no statistical null hypothesis associated with the immunogenicity objectives, which were analyzed descriptively. The sample size of this study was limited by the availability of previously vaccinated subjects who did not receive a booster dose 6 months after the last primary vaccination in study V87P1.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:
Subjects eligible for enrollment in this study were male and female adults who were: 18 years of age or older and had previously participated in study V87P1, but did not receive the booster dose on study day 202 of study V87P1, willing and able to give written informed consent prior to study entry; able to comply with all the study requirements and in general good health as determined by medical history, physical examination, and the clinical judgment of the investigator. Informed consent was obtained from all the subjects before enrollment in the study.

Exclusion Criteria:
Subjects not eligible for enrollment in this study were adults who were: pregnant or breastfeeding; who received another vaccine or any investigational agent within the past 4 weeks; who had surgery planned during the study period

Criteria for Evaluation:

Immunogenicity
Persistence of antibody titers 17-18 months after primary vaccination with aTIV-H5N1 influenza vaccine containing A/Vietnam/1194/2004-like influenza antigen (in study V87P1) and immune response after booster injection of aTIV-H5N1 influenza vaccine (in study V87P1E1) containing a heterologous H5N1 influenza antigen (A/turkey/Turkey) was evaluated by dose of the primary vaccination (7.5 or 15 μg) and by age group (18-60 years of age and older than 60 years of age).

All statistical analyses for Hemagglutination Inhibition (HI), Microneutralization (MN) and Single Radial Hemolysis (SRH) assays were performed on the logarithmically (base 10) transformed titer/area values. Titers below the limit of detection for HI and MN assay were set to half that limit for the purposes of analysis.

The lower detection limit of the SRH assay was at an area of 4 mm^2. All areas below the lower limit of detection were set to 4 for the immunogenicity analysis. Measures of

immunogenicity included the geometric mean titer (GMT) of HI and MN or the geometric mean area (GMA) of SRH; percentage of subjects with seroconversion or significant increase in HI titer or SRH area.

Committee for Medicinal Products for Human Use (CHMP) criteria (CPMP/BWP/214/96) were taken into consideration for the interpretation of HI and SRH immunogenicity results. The primary immunogenicity analyses was based on the per protocol (PP) set. All immunogenicity analyses were evaluated by primary vaccine dose (i.e, 7.5 μg, 15 μg and overall) and by age group. Generally, all confidence intervals (CIs) were regarded as descriptive, and therefore, no adjustment was made to account for multiplicity.

Safety

Safety was assessed in accordance with available safety data on influenza vaccines. Safety was assessed by solicited local and systemic reactions, Adverse Events (AEs) and Serious Adverse Events (SAEs).

Results:

Table 1. Time and Events

Study Visit	**6**	**7**	**8**	**9** ☎
Study Day (window)[1]	**382 (+210)**	**389 (+/-1)**	**403 (-1/+7)**	**562 (+/-28)**
Informed Consent	X			
Inclusion/Exclusion Criteria Assessment	X			
Medical History	X			
Physical Examination	X			
Brief Physical Examination		X	X	
Pregnancy Test	X[2]			
Blood Sample for Antibody Assay	X	X	X	
Vaccination	X			
Local and Systemic Reactions	X	X		
Adverse Events	X	X	X	X[3]
Concomitant Medications	X	X	X	X
Diary Card Dispensed	X	X	X[4]	
Diary Card Review		X	X	X
Study Termination				X

Abbreviations: AEs, adverse events; SAEs, serious adverse events.

[1] The scheduled time for visit 6 refers to the date of the last vaccination within study V87P1, i.e, 360 days after the last primary vaccination. For visit 7 to 9 it refers to the date of the booster vaccination within study V87P1E1.

[2] Pregnancy test was done in the clinic prior to vaccination for all females of childbearing potential.

[3] Only SAEs, AEs necessitating a physician's visit or consultation, AEs that lead to withdrawal from the study, and concomitant medications associated with these events were recorded from study day 403 to study day 562.

[4] On study day 403 memory aid was dispensed.

Table 2. Overview of Subject Populations

	aTIV-H5N1 7.5 µg	aTIV-H5N1 15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**
Enrolled Set:	15 (100%)	14 (100%)	29 (100%)
Per Protocol Set:	15 (100%)	14 (100%)	29 (100%)
Full Analysis Set:	15 (100%)	14 (100%)	29 (100%)
Safety Set:	15 (100%)	14 (100%)	29 (100%)
Elderly > 60 years	**N=7**	**N=11**	**N=18**
Enrolled Set:	7 (100%)	11 (100%)	18 (100%)
Per Protocol Set: Excluded due to Protocol Violation	7 (100%) 0	10 (91%) 1 (9%)	17 (94%) 1 (6%)
Full Analysis Set:	7 (100%)	11 (100%)	18 (100%)
Safety Set:	7 (100%)	11 (100%)	18 (100%)

Table 3. Demography and Baseline Characteristics – Per Protocol Set

		aTIV-H5N1 7.5 µg	aTIV-H5N1 15 µg	Total
Adults 18-60 years		**N=15**	**N=14**	**N=29**
Age at enrollment in V87P1 (years):		44.8±7.6	35.0±10.4	40.1±10.2
Sex	Male	7 (47%)	6 (43%)	13 (45%)
	Female	8 (53%)	8 (57%)	16 (55%)
Ethnic Origin	Caucasian	15 (100%)	14 (100%)	29 (100%)
Weight at enrollment in V87P1 (kg):		70.59±17.30	66.00±12.94	68.37±15.26
Height at enrollment in V87P1 (cm):		168.8±9.8	170.6±9.1	169.7±9.3
Met Study Entry Criteria:		15 (100%)	14 (100%)	29 (100%)
Elderly > 60 years		**N=7**	**N=10**	**N=17**
Age at enrollment in V87P1 (years):		71.9±6.5	68.9±4.8	70.1±5.6
Sex	Male	4 (57%)	7 (70%)	11 (65%)
	Female	3 (43%)	3 (30%)	6 (35%)
Ethnic Origin	Caucasian	7 (100%)	10 (100%)	17 (100%)

	aTIV-H5N1 7.5 µg	aTIV-H5N1 15 µg	Total
Weight at enrollment in V87P1 (kg):	71.86±5.61	77.00±14.97	74.88±12.03
Height at enrollment in V87P1 (cm):	165.3±5.6	166.1±10.5	165.8±8.6
Met Study Entry Criteria:	7 (100%)	10 (100%)	17 (100%)

Categorical parameters: N (%), non-categorical parameters: Mean ± Standard Deviation.

Table 4. Geometric Mean HI Titers and GMRs, by Age Group - GMR Calculated From Study Day 382 - PPS

	GMT and (95% CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	15 µg	Total	7.5 µg	15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 382 (pre-booster)	5 (5-5)	5 (5-5)	5 (5-5)	7.24 (4.87-11)	5.52 (3.66-8.32)	6.35 (4.78-8.44)
day 389	46 (19-113)	29 (11-74)	37 (19-70)	133 (52-340)	78 (30-206)	103 (53-201)
GMR[a]	9.18 (3.72-23)	5.79 (2.27-15)	7.35 (3.86-14)	18 (6.99-48)	14 (5.19-38)	16 (8.17-32)
day 403	111 (40-309)	45 (16-131)	72 (34-151)	192 (65-568)	125 (41-383)	156 (73-336)
GMR[b]	22 (7.9-62)	9.05 (3.12-26)	14 (6.82-30)	27 (8.89-80)	23 (7.28-70)	25 (11-53)
Elderly > 60 years	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**
day 382 (pre-booster)	24 (6.3-94)	9.33 (3.01-29)	14 (5.79-33)	38 (6.99-207)	13 (3.09-53)	20 (6.75-59)
day 389	119 (31-450)	15 (4.99-46)	35 (13-95)	186 (40-859)	26 (7.33-95)	59 (20-173)
GMR[a]	4.88 (1.68-14)	1.63 (0.67-3.97)	2.56 (1.25-5.24)	4.88 (1.3-18)	2.07 (0.68-6.26)	2.95 (1.26-6.87)
day 403	186 (39-881)	67 (18-247)	102 (38-277)	250 (51-1232)	144 (38-547)	181 (67-490)

	GMT and (95% CI)					
GMR[b]	7.62 (1.54-38)	7.21 (1.89-28)	7.38 (2.74-20)	6.57 (1.1-39)	11 (2.53-51)	9.04 (2.97-28)

Abbreviations: CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titer; HI, hemagglutination inhibition; PPS, per protocol set.

[a] GMR - the geometric mean of the post-vaccination study day 389 to study day 382 titer ratio; [b] GMR - the geometric mean of the post-vaccination study day 403 to study day 382 titer ratio; Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 µg on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 5. Geometric Mean SRH Area and GMRs, by Age Group - GMR Calculated From Study Day 382 - PPS

	GMA and (95% CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	**15 µg**	**Total**	**7.5 µg**	**15 µg**	**Total**
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 382 (pre-booster)	11 (6.94-16)	6.46 (4.2-9.93)	8.31 (6.11-11)	11 (7.36-16)	6.8 (4.57-10)	8.64 (6.49-11)
day 389	40 (29-57)	39 (27-56)	40 (31-51)	35 (23-55)	28 (17-44)	31 (23-43)
GMR[a]	3.83 (2.54-5.79)	6.07 (3.96-9.31)	4.79 (3.53-6.49)	3.27 (2.11-5.06)	4.07 (2.59-6.41)	3.64 (2.66-4.96)
day 403	53 (36-79)	49 (32-74)	51 (38-68)	45 (29-70)	37 (23-59)	41 (30-56)
GMR[b]	5.04 (3.16-8.03)	7.57 (4.67-12)	6.13 (4.37-8.6)	4.14 (2.64-6.51)	5.45 (3.41-8.7)	4.73 (3.43-6.53)
Elderly > 60 years	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**
day 382 (pre-booster)	28 (14-58)	11 (6.11-20)	16 (9.87-27)	25 (12-53)	12 (6.12-22)	16 (9.5-26)
day 389	47 (28-80)	28 (18-43)	34 (24-49)	41 (23-72)	22 (14-35)	28 (19-41)
GMR[a]	1.66 (0.92-3)	2.49 (1.52-4.08)	2.11 (1.44-3.08)	1.64 (0.93-2.9)	1.89 (1.18-3.04)	1.79 (1.26-2.54)
day 403	62 (34-113)	43 (26-71)	50 (34-73)	48 (25-92)	39 (22-67)	42 (28-63)

	GMA and (95% CI)					
GMR[b]	2.18 (1.09-4.35)	3.87 (2.17-6.92)	3.05 (1.94-4.81)	1.92 (0.96-3.83)	3.37 (1.89-6)	2.67 (1.7-4.19)

Abbreviations: CI, confidence interval; GMA, geometric mean area; GMR, geometric mean ratio; PPS, per protocol set; SRH, single radial hemolysis.

[a] GMR - the geometric mean of the post-vaccination study day 389 to study day 382 titer ratio; [b] GMR - the geometric mean of the post-vaccination study day 403 to study day 382 titer ratio; Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 µg on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 6. Geometric Mean MN and GMRs, by Age Group - GMR Calculated From Study Day 382 - PPS

	GMT and (95% CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	15 µg	Total	7.5 µg	15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 382 (pre-booster)	12 (9.8-15)	11 (8.59-13)	11 (9.76-13)	19 (11-32)	16 (9.14-28)	17 (12-25)
day 389	122 (65-231)	127 (66-245)	124 (79-195)	152 (75-307)	125 (60-260)	138 (84-228)
GMR[a]	10 (5.56-19)	12 (6.39-23)	11 (7.18-17)	8.09 (4.15-16)	7.88 (3.95-16)	7.99 (4.99-13)
day 403	280 (126-620)	175 (77-400)	223 (126-394)	349 (149-815)	202 (84-486)	268 (146-492)
GMR[b]	23 (11-50)	17 (7.53-37)	20 (12-34)	19 (8.93-39)	13 (5.95-27)	15 (9.18-26)
Elderly > 60 years	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**	**N=7 (95% CI)**	**N=10 (95% CI)**	**N=17 (95% CI)**
day 382 (pre-booster)	33 (11-101)	15 (5.7-37)	20 (9.88-42)	48 (13-175)	21 (7.03-61)	29 (13-67)
day 389	150 (53-426)	41 (17-99)	70 (34-145)	175 (65-472)	48 (21-109)	81 (40-164)
GMR[a]	4.55 (1.71-12)	2.83 (1.25-6.41)	3.44 (1.85-6.38)	3.63 (1.59-8.25)	2.3 (1.16-4.58)	2.78 (1.65-4.68)
day 403	343 (115-1020)	124 (50-309)	189 (91-389)	290 (75-1125)	170 (54-528)	211 (90-495)

	GMT and (95% CI)					
GMR[b]	10 (2.93-37)	8.5 (2.95-25)	9.23 (4.22-20)	6 (1.38-26)	8.2 (2.4-28)	7.21 (2.89-18)

Abbreviations: CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titer; MN, microneutralization; PPS, per protocol set.

[a] GMR - the geometric mean of the post-vaccination study day 389 to study day 382 titer ratio; [b] GMR - the geometric mean of the post-vaccination study day 403 to study day 382 titer ratio; Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 ug on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 7. Percentages of Subjects with Seroconversion[a] or Significant Increase[b] in HI Titers, by Age Group - PPS

	% and (95% CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	15 µg	Total	7.5 µg	15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 389	67% (38-88)	43% (18-71)	55% (36-74)	73% (45-92)	57% (29-82)	66% (46-82)
day 403	73% (45-92)	50% (23-77)	62% (42-79)	73% (45-92)	79% (49-95)	76% (56-90)
Elderly > 60 years	**N=7**	**N=10**	**N=17**	**N=7**	**N=10**	**N=17**
day 389	43% (10-82)	20% (3-56)	29% (10-56)	43% (10-82)	30% (7-65)	35% (14-62)
day 403	71% (29-96)	50% (19-81)	59% (33-82)	43% (10-82)	60% (26-88)	53% (28-77)

Abbreviations: CI, confidence interval; HI, hemagglutination inhibition; PPS, per protocol set.

a Seroconversion is defined as negative pre-booster vaccination serum (i.e, HI titer <10) and post-booster vaccination HI titer ≥40; b Significant increase is defined as at least a 4-fold increase from non-negative (≥10) prebooster HI titer; Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 µg on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 8. Percentages of Subjects with Seroconversion or Significant Increase in SRH Areas, by Age Group - PPS

	% and (95% CI)	
	Strain H5N1 A/turkey/Turkey (Clade 2.2)	Strain H5N1 A/Vietnam (Clade 1)

	% and (95% CI)					
	7.5 µg	**15 µg**	**Total**	**7.5 µg**	**15 µg**	**Total**
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
Seroconversion[a] or significant increase[b] day 389 [a]	80% (52-96)	86% (57-98)	83% (64-94)	80% (52-96)	71% (42-92)	76% (56-90)
Seroconversion[a] or significant increase[b] day 403 [a]	87% (60-98)	86% (57-98)	86% (68-96)	80% (52-96)	79% (49-95)	79% (60-92)
Elderly > 60 years	**N=7**	**N=10**	**N=17**	**N=7**	**N=10**	**N=17**
Seroconversion[a] or significant increase[b] day 389 [a]	43% (10-82)	50% (19-81)	47% (23-72)	43% (10-82)	30% (7-65)	35% (14-62)
Seroconversion[a] or significant increase[b] day 403[a]	57% (18-90)	80% (44-97)	71% (44-90)	43% (10-82)	60% (26-88)	53% (28-77)

Abbreviations: CI, confidence interval; PPS, per protocol set; SRH, single radial hemolysis.

[a] Seroconversion is defined as negative pre-booster vaccination serum (i.e, SRH titer ≤4mm2) and post-vaccination SRH area ≥25 mm2; [b] Significant increase is defined as at least a 50% increase in SRH area in subjects who were positive pre-booster vaccination (i.e, SRH area > 4mm2); Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 µg on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 9. Percentages of Subjects with MN Titers ≥ 40, by Age Group - PPS

	n (%) and (95%CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			**Strain H5N1 A/Vietnam (Clade 1)**		
	7.5 µg	**15 µg**	**Total**	**7.5 µg**	**15 µg**	**Total**
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 382 (pre-booster)	7% (0-32)	0% (0-23)	3% (0.087-18)	27% (8-55)	14% (2-43)	21% (8-40)
day 389	87% (60-98)	79% (49-95)	83% (64-94)	87% (60-98)	79% (49-95)	83% (64-94)
day 403	87% (60-98)	79% (49-95)	83% (64-94)	93% (68-100)	79% (49-95)	86% (68-96)
Elderly > 60 years	**N=7**	**N=10**	**N=17**	**N=7**	**N=10**	**N=17**
day 382 (pre-booster)	43% (10-82)	10% (0-45)	24% (7-50)	43% (10-82)	20% (3-56)	29% (10-56)

	n (%) and (95%CI)					
day 389	71% (29-96)	60% (26-88)	65% (38-86)	71% (29-96)	60% (26-88)	65% (38-86)
day 403	100% (59-100)	80% (44-97)	88% (64-99)	86% (42-100)	80% (44-97)	82% (57-96)

Abbreviations: CI, confidence interval; MN, microneutralization; PPS, per protocol set.

Table 10. Percentages of Subjects With at Least a 4-fold Increase in MN Titers, by Age Group - PPS

	n (%) and (95%CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	15 µg	Total	7.5 µg	15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
4-Fold Increase day 389	87% (60-98)	79% (49-95)	83% (64-94)	73% (45-92)	71% (42-92)	72% (53-87)
4-Fold Increase day 403	87% (60-98)	79% (49-95)	83% (64-94)	93% (68-100)	79% (49-95)	86% (68-96)
Elderly > 60 years	**N=7**	**N=10**	**N=17**	**N=7**	**N=10**	**N=17**
4-Fold Increase day 389	43% (10-82)	50% (19-81)	47% (23-72)	29% (4-71)	30% (7-65)	29% (10-56)
4-Fold Increase day 403	71% (29-96)	70% (35-93)	71% (44-90)	57% (18-90)	60% (26-88)	59% (33-82)

Abbreviations: CI, confidence interval; MN, microneutralization; PPS, per protocol set.

Table 11. Percentages of Subjects with SRH Area ≥ 25 mm^2, by Age Group - PPS

	n[a] (%) and (95%CI)					
	Strain H5N1 A/turkey/Turkey (Clade 2.2)			Strain H5N1 A/Vietnam (Clade 1)		
	7.5 µg	15 µg	Total	7.5 µg	15 µg	Total
Adults 18-60 years	**N=15**	**N=14**	**N=29**	**N=15**	**N=14**	**N=29**
day 382 (pre-booster)	20% (4-48)	0% (0-23)	10% (2-27)	20% (4-48)	0% (0-23)	10% (2-27)
day 389	87% (60-98)	86% (57-98)	86% (68-96)	80% (52-96)	71% (42-92)	76% (56-90)
day 403	87% (60-98)	86% (57-98)	86% (68-96)	80% (52-96)	79% (49-95)	79% (60-92)
Elderly > 60 years	**N=7**	**N=10**	**N=17**	**N=7**	**N=10**	**N=17**

	n[a] (%) and (95%CI)					
day 382 (pre-booster)	43% (10-82)	30% (7-65)	35% (14-62)	43% (10-82)	30% (7-65)	35% (14-62)
day 389	86% (42-100)	80% (44-97)	82% (57-96)	71% (29-96)	50% (19-81)	59% (33-82)
day 403	100% (59-100)	90% (55-100)	94% (71-100)	71% (29-96)	80% (44-97)	76% (50-93)

Abbreviations: CI, confidence interval; PPS, per protocol set; SRH, single radial hemolysis.

[a] n = responders (i.e, subjects who met the SRH definition of seroprotection) as part of the total number of subjects in the population N; Primary vaccination with Fluad H5N1 Vietnam 7.5 or 15 µg on study days 1 and 22, booster with Fluad H5N1 turkey/Turkey 7.5 µg on study day 382.

Table 12. Summary of Subjects with At Least One Reactogenicity Sign, by Age

Number (%) of Subjects With Solicited Reactions	
Adults 18-60 years	**N=29**
Any	21 (72)
Local	19 (66)
Systemic	10 (34)
Other	4 (14)
Elderly > 60 years	**N=18**
Any	7 (39)
Local	6 (33)
Systemic	4 (22)
Other	0

Table 13. Summary of Subjects with At Least One Reactogenicity Sign, by Age

Number (%) of Subjects With Injection Site Reactions		
		Total
Adults 18-60 years		**N=29**
Erythema (mm)	Any	1 (3)
	>50 mm	0
Induration (mm)	Any	7 (24)
	>50 mm	0
Swelling (mm)	Any	4 (14)
	>50 mm	0

Number (%) of Subjects With Injection Site Reactions		
Ecchymosis (mm)	Any	0
	>50 mm	0
Pain	Any	18 (62)
	>50 mm	0
Elderly > 60 years		**N=18**
Erythema (mm)	>50 mm	0
	Any	0
Induration (mm)	>50 mm	1 (6)
	Any	0
Swelling (mm)	>50 mm	0
	Any	0
Ecchymosis (mm)	>50 mm	0
	Any	0
Pain	>50 mm	6 (33)
	Any	0

Table 13. Summary of Systemic Reactions by Severity and Other Indicators of Reactogenicity, Adults 18 – 60 Years of Age

Number (%) of Subjects With Systemic Reactions		
		Total
Adults 18-60 years		**N=29**
Chills (mm)	Any	2 (7)
	Severe	0
Malaise (mm)	Any	1 (3)
	Severe	0
Myalgia (mm)	Any	6(21)
	Severe	0
Arthralgia (mm)	Any	3(10)
	Severe	0
Headache	Any	4 (14)
	Severe	0
Sweating	Any	0
	Severe	0
Fatigue	Any	1 (3)

Number (%) of Subjects With Systemic Reactions		
	Severe	0
Nausea	Any	0
	Severe	0
Fever (≥ 38ºC)	Yes	0
Other		
Temperature.º(C)	< 38ºC	29(100)
Stayed Home	Yes	1(3)
Analgesics Antipyretics. Medications. Used	Yes	3(10)

Table 15. Summary of Systemic Reactions by Severity and Other Indicators of Reactogenicity, Elderly > 60 Years of Age

Number (%) of Subjects with Systemic Reactions		
		Total
Elderly > 60 years		**N=18**
Chills (mm)	Any	0
	Severe	0
Malaise (mm)	Any	0
	Severe	0
Myalgia (mm)	Any	2 (11)
	Severe	0
Arthralgia (mm)	Any	1 (6)
	Severe	0
Headache	Any	1 (6)
	Severe	0
Sweating	Any	0
	Severe	0
Fatigue	Any	2 (11)
	Severe	0
Nausea	Any	1 (6)
	Severe	0
Fever (≥ 38ºC)	Yes	0
Other		

Number (%) of Subjects with Systemic Reactions		
Temperature°(C)	< 38°C	18 (100)
	≥ 40°C	0
Stayed Home	Yes	0
Analgesics Antipyretics. Medications. Used	Yes	0

Table 16. Overview of All and at Least Possibly Related Other Adverse Events by System Organ Class, Adults and Elderly

		Number (%) of Subjects with Adverse Events	
		All	At least Possibly Related
		Total	Total
		N=29	N=29
Adults 18-60 years	Any Adverse Events	2 (7)	0
	Infections & Infestations	2 (7)	0
		N=18	**N=18**
Elderly > 60 years	Any Adverse Events	1 (6)	0
	Infections & Infestations	1 (6)	0

Table 17. Summary of All and at Least Possibly Related Other Adverse Events (Preferred Term), Adults

	Preferred Term	Number (%) of Subjects with Adverse Events	
		All	At least Possibly Related
		N=29	N=29
Adults 18-60 years	Ear Infection	1 (3)	-
	Influenza	1 (3)	-
		N=18	**N=18**
Elderly > 60 years	Cystitis	1 (6)	-
	Pharyngitis	1 (6)	-

Conclusion:

At study day 382 (actually 492 to 578 days after the 2nd vaccination in V87P1), approximately 18 months, after primary vaccination with two 0.5 ml IM doses (7.5 µg or 15 µg) of aTIV-H5N1 influenza vaccine containing A/Vietnam/1194/2004-like (H5N1) influenza antigen antibodies as measured by Hemagglutination Inhibition (HI), Single Radial Hemolysis (SRH) and Microneutralization (MN) assays had almost returned to baseline values for both the A/turkey/Turkey and the A/Vietnam strains.

Administration of a heterologous booster injection of aTIV-H5N1 influenza vaccine containing A/turkey/Turkey/1/2005-like (H5N1) influenza antigen approximately 18 months after the primary vaccination resulted in an increase in all immunogenicity parameters as measured by HI, SRH and MN for both the A/turkey/Turkey and the A/Vietnam strains already at one week after the booster vaccination. This increase was sustained or further increased at 3 weeks after the booster administration. The increase after the heterologous booster injection clearly demonstrated a memory response from the previous vaccination.

In the adult group, three weeks after the booster injection, as assessed by HI, all three Committee for Medicinal Products for Human Use (formerly CPMP; CHMP) criteria were met for the A/turkey/Turkey strain in group primed with 7.5 µg aTIV-H5N1 and only two out of three CHMP criteria (GMR and seroconversion or significant increase) were fulfilled in group primed with 15 µg aTIV-H5N1, whereas all three CHMP criteria were met for the A/Vietnam strain. All three CHMP criteria as assessed by SRH were met for both strains in this age group. Between 83% and 86% of adult subjects achieved a 4-fold increase in MN titers against the A/turkey/Turkey and the A/Vietnam strains.

In the elderly group, all three CHMP criteria were met three weeks after the booster injection for both strains, as assessed by the HI and SRH assays respectively. Between 71% and 59% of elderly subjects achieved a 4-fold increase in MN titers against both strains.

The heterologous booster injection aTIV-H5N1 influenza vaccine containing A/turkey/Turkey/1/2005-like (H5N1) influenza antigen approximately 18 months after the primary vaccination was well tolerated, and the local and systemic reactions after vaccination were mostly mild or moderate in severity. During the study period, no deaths, Serious Adverse Events (SAEs) or any Adverse Events (AEs) possibly/probably related to the study vaccine were reported.

Date of Clinical Trial Report: 04 MAR 09