Sponsor:	Novartis Vaccines and Diagnostics Srl.
Investigational Product:	Fluad-H5N1 influenza vaccine containing 7.5 μg of the A/Vietnam/1194/04 (NIBRG 14) influenza antigen
Indication:	Prophylaxis of A/H5N1 avian influenza
Protocol Number:	V87P12
Protocol Title:	A Phase III, Randomized, Open-label, Single-center Study to Evaluate the Safety and Immunogenicity of a FLUAD-H5N1 Influenza Vaccine in Adult Subjects Using Four Different Vaccination Schedules
Phase of Development:	Phase III
Study Period:	
Date of first enrolment:	24 NOV 08
Date of last visit:	28 JUN 09

Methodology:

This was a prospective, randomized, open-label phase III study that was performed over a period of approximately 7 months. A total of 240 subjects aged 18 to 60 years were enrolled and randomized at a 1:1:1:1 ratio to 4 different vaccination schedules.

Vaccines were administered 1, 2, 3, or 6 weeks apart, intramuscularly (IM) into the deltoid muscle (preferably of the non-dominant arm). Blood samples were taken from all subjects before first vaccination (day 1), on the day before the second vaccination on day 7, 15, 22 or 43, and three weeks after the second vaccination.

Immunogenicity was evaluated in serum by Hemagglutination Inhibition (HI), Single Radial Hemolysis (SRH) and Micro-Neutralization (MN) assays.

The complete study period was categorized into Primary Period (from day 1 to 21 days after the second vaccination) and Follow-up period (from 21 days post second vaccination to day 202).

Subjects were observed for 30 minutes after each vaccination for any immediate reactions. All local and systemic reactions as well as body temperature/fever, events that caused the subject to stay at home due to a reaction and use of analgesic/antipyretic

medications, starting on the day of vaccination and for each of the 6 days following each vaccination were reported.

All unsolicited AEs (i.e., excluding local and systemic reactions solicited within 7 days of each vaccination), including serious adverse events, AEs necessitating a non-routine physician's visit or consultation (if medically relevant as judged by the investigator) and/or leading to withdrawal were collected between visits 1 to 3. Only SAEs and AEs necessitating a non-routine physician's visit or consultation (if medically relevant as judged by the investigator) and/or leading to withdrawal from the study were collected between visits 3 and 4 (up to day 202).

Number of Subjects (planned and analyzed):

Planned: Up to 240 subjects from 18 to 60 years of age were to be enrolled in four groups and were to receive 2 vaccinations of MF59-PanH5N1 influenza vaccine containing 7.5µg of H5N1 influenza antigen. The four vaccine groups were:

- Day1-8: 60 adults, receiving the two vaccinations 1 week apart,
- Day1-15: 60 adults, receiving the two vaccinations 2 weeks apart,
- Day1-22: 60 adults, receiving the two vaccinations 3 weeks apart,
- Day1-43: 60 adults, receiving the two vaccinations 6 weeks apart.

Analyzed: The enrollment of the subjects in each of the groups was according to the plan-with exactly 60 subjects being enrolled in each of the groups. All enrolled subjects were included in the Full Analysis Set (FAS) analysis for immunogenicity and in the Safety set.

Study Centers:

Single center in Czech Republic.

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

NCT00848029

Objectives:

Immunogenicity

To evaluate the magnitude of antibody responses to two doses of MF59-adjuvanted egg-derived pandemic monovalent A/H5N1(MF59-PanH5N1) influenza vaccine, each containing 7.5µg of A/H5N1 antigen administered 1, 2, 3, or 6 weeks apart.

In addition to testing for homologous [A/Vietnam/1194/04] antibody response, 2 treatment groups, day 1-15 and day 1-23, were also tested for heterologous response against the A/H5N1/Turkey/Turkey/05 strain.

Safety

To evaluate the safety and tolerability of two 0.5mL intramuscular (IM) injections of MF59-PanH5N1 influenza vaccine containing 7.5µg of A/H5N1 influenza antigen.

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

Two 0.5mL injections of MF59-adjuvanted egg-derived pandemic monovalent A/H5N1 (MF59-PanH5N1) FLUAD-H5N1(Lot No. 070701) influenza vaccine containing 7.5µg of A/H5N1 antigen (A/Vietnam/1194/04), administered 1, 2, 3, or 6 weeks apart IM into the deltoid muscle (preferably of the non-dominant arm). The MF59 adjuvant contained 9.75 mg squalene.

Duration of Study:

Approximately 7 months per subject.

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

There were no reference vaccines.

Statistical Methods:

There were no statistical (null) hypotheses associated with the objectives which were assessed descriptively. This study was not powered to detect statistical differences between vaccine groups.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

1. Subjects aged 18 to 60 years of age who were mentally competent and who had signed an informed consent form after having received a detailed explanation of the study protocol;
2. In good health as determined by:
   - Medical history,
   - Physical examination,
   - Clinical judgment of the Investigator;
3. Able to understand and comply with all study procedures and to complete study diaries, could be contacted, and were available for all study visits.

Informed consent was obtained for all the subjects before enrollment into the study.

Exclusion Criteria:

1. Previous receipt of any H5 vaccine;
2. Receipt of another investigational agent within four weeks, or before completion of the safety follow-up period in another study, whichever was longer, prior to enrollment and unwilling to refuse participation in another clinical study through the end of the study;
3. Experienced any acute disease or infection requiring systemic antibiotic or antiviral therapy (chronic antibiotic therapy for urinary tract prophylaxis was acceptable) within the past seven days;
4. Experienced fever (defined as axillary temperature ≥38.0°C) within three days prior to visit 1;
5. Pregnant or breastfeeding;
6. Females of childbearing potential who refused to use an acceptable method of birth control for the duration of the study. Adequate contraception was defined as hormonal (e.g., oral, injection, transdermal patch, implant, cervical ring), barrier (e.g., condom with spermicide or diaphragm with spermicide), intrauterine device (e.g., IUD), or monogamous relationship with vasectomized partner who had been vasectomized for 6 months or more prior to the subject's study entry;
7. Any serious disease, such as:
   a. cancer,
   b. Autoimmune disease (including rheumatoid arthritis),
   c. diabetes mellitus,
   d. chronic pulmonary disease,
   e. acute or progressive hepatic disease,
   f. acute or progressive renal disease;
8. Surgery planned during the study period;
9. Bleeding diathesis;
10. Hypersensitivity to eggs, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin or any other component of the study vaccine;
11. History of any neurological symptoms or signs following administration of any vaccine, or anaphylactic shock following administration of any vaccine;
12. Known or suspected impairment/alteration of immune function, for example, resulting from:
    a. Receipt of immunosuppressive therapy (any corticosteroid therapy,
    b. Receipt of immunostimulants,
    c. High risk for developing an immunocompromising disease;
13. Receipt of non-study vaccine (with the exception of post-exposure vaccination in a medical emergency, e.g hepatitis, rabies, tetanus) within three weeks prior to Visit 1 or planned vaccination within three weeks following the last study vaccination;
14. Body Mass Index above 35 kg/m^2;

15. History of (or current) drug or alcohol abuse that in the investigator's opinion would interfere with safety of the subject or the evaluation of study objectives;
16. Any condition, which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives;
17. Members of research staff and their relatives.

Criteria for Evaluation:

Immunogenicity:

- Geometric mean titers/areas (GMTs/GMAs) and geometric mean ratios (GMRs) at baseline, after the first and after the second vaccination, as determined by HI, SRH, and MN.
- Percentage of subjects achieving seroconversion[1] or significant increase[2] in antibody titer on visits 2 and 3, as measured by HI and SRH.
- Percentage of subjects achieving an HI titer ≥40/ SRH area ≥25mm^2 on visits 2 and 3.
- Percentage of subjects with MN titers ≥20, ≥40, ≥80 on visits 1, 2, and 3.
- Percentage of subjects achieving at least a four-fold rise in MN antibody titer on visits 2 and 3.

The HI and SRH results were interpreted in the context of Committee for Medicinal Products for Human Use (CHMP) criteria (CPMP/BWP/214/96).

Safety:
Percentages of subjects with at least one local reaction between 1 and 7 days after each vaccine injection.

Percentages of subjects with at least one systemic reaction between 1 and 7 days after each vaccine injection.

Percentages of subjects with at least one unsolicited adverse event between visit 1 and 3.

Numbers and percentages of subjects with serious adverse events or adverse events necessitating a physician's visit or consultation and/or leading to withdrawal from the study between day 1 and the study termination visit (day-202).

Safety was assessed in accordance with available safety data on influenza vaccines. The safety of the study vaccine was assessed in terms of percentages of subjects with reported

[1] Seroconversion is defined as negative pre-vaccination serum / post-vaccination titer ≥40 for HI (area ≥ 25 mm^2 for SRH)

[2] Significant increase in antibody titer is defined as at least a four-fold increase from non-negative pre-vaccination serum (≥ 10) for HI or a 50% increase in area for SRH.

local and systemic reactions, as well as percentages with other adverse events, including serious adverse events and/or adverse events necessitating a physician's visit and/or resulting in premature withdrawal from the study. All adverse events were summarized separately for the primary period (from day 1 to 21 days after second vaccination) and for the follow-up period (from 21 days post second vaccination to day 202). Due to the different schedules investigated in this study, the lengths of the primary and follow-up periods vary between vaccine groups.

Results:

Table 1. Time and Events

Study Visit	**1**	**2**	**3**	**4☎**
Study Day(window)	**1**	**8, 15, 22 or 43 (-1/+7)**	**29, 36, 43 or 64 (-1/+10)**	**202 (±14)**
Informed Consent	X			
Inclusion/Exclusion Criteria Assessment	X			
Medical History	X			
Physical Examination	X			
Brief Physical Evaluation		X		
Pregnancy Test	X[a]	X[a]		
Blood Draws	X	X	X	
Vaccination	X	X		
Local and Systemic Reactions (7 days post-vaccination)	X	X	X	
Adverse Events	X	X	X	X[b]
Concomitant Medications	X	X	X	X[b]
Diary Card/ Memory Aid Dispensed	X	X	X[bc]	
Diary Card/ Memory Aid Review		X	X	X
Study Termination				X

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

[b] Only Serious Adverse Events (SAEs), Adverse Events (AEs) that led to a physician's visit, AEs that led to withdrawal from the study, and concomitant medications associated with these events were recorded from visit 3 (3 weeks after second vaccination) to 4 (day-202).

[c] Memory aid dispensed on visit 3.

Table 2. Number (%) of Subjects with Study Terminations

Vaccine Schedule		Day 1-8	Day 1-15	Day 1-22	Day 1-43	Total
Enrolled		60	60	60	60	240
Completed study		59 (98%)	59 (98%)	59 (98%)	59 (98%)	236(98%)
Premature withdrawals (Primary withdrawal reason)		1 (2%)	1 (2%)	1 (2%)	1 (2%)	4 (2%)
	Withdrew consent	0	1 (2%)	0	0	1 (<1%)
	Lost to follow-up	1 (2%)	0	1 (2%)	1 (2%)	3 (1%)

Table 3. Overview of Populations Analyzed

Vaccine Schedule	Day 1-8	Day 1-15	Day 1-22	Day 1-43	Total
All Enrolled Set	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)
Exposed Set	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)
Full Analysis Set (HI)	60 (100%)	60 (100%)	60 (100%)	59 (98%)	239 (100%)
Full Analysis Set (MN)	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)
Full Analysis Set (SRH)	60 (100%)	60 (100%)	58 (97%)	60 (100%)	238 (99%)
Safety Set	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)

HI: Hemagglutination Inhibition; MN: Micro-Neutralization; SRH: Single Radial Hemolysis.

Table 4. Demography and Baseline Characteristics-Enrolled Set

		Day 1-8	Day 1-15	Day 1-22	Day 1-43	Total
		N=60	N=60	N=60	N=60	N=240
Age		32.4±9.4	33.6±9.9	32.3±8.5	33.9±9.2	33.1±9.3
Sex	Male	30 (50%)	26 (43%)	31 (52%)	31 (52%)	118 (49%)
	Female	30 (50%)	34 (57%)	29 (48%)	29 (48%)	122 (51%)
Race	Caucasian	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)
Weight (kg):		75.0±14.2	76.0±17.1	75.0±14.2	73.2±15.5	74.8±15.2
Height (cm):		173.1±9.5	174.2±10.0	174.5±9.3	173.4±9.5	173.8±9.5
BMI (kg/m²):		24.93±3.95	24.81±3.99	24.52±3.38	24.13±3.63	24.60±3.74
Females with Child Bearing Potential:		29 (48%)	31 (52%)	27 (45%)	27 (45%)	114 (48%)
Previous Influenza Vaccine:		60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)

	Day 1-8	Day 1-15	Day 1-22	Day 1-43	Total
Entry Criteria Met:	60 (100%)	60 (100%)	60 (100%)	60 (100%)	240 (100%)

Table 5. Immunogenicity analysis by HI assay using Homologous Strain [A/Vietnam/1194/04 (H5N1)] (CHMP Criteria)-FAS[a]

	Day 1-8	Day 1-15	Day 1-22	Day 1-43
	N=60	**N=60**	**N=60**	**N=59**
Geometric Mean HI titers and Geometric Mean Ratios				
Baseline (Day 1)	5.95 (5.06-6.99)	5.55 (4.72-6.52)	5.74 (4.88-6.75)	5.43 (4.61-6.39)
Post 1st vacc.	7.87 (4.99-12) N=58	26 (16-40)	24 (16-38)	14 (8.86-22) N=58
Post 1st vacc. to baseline (GMR)	1.36 (0.89-2.06) N=58	**4.65** **(3.08-7.01)**	**4.24** **(2.81-6.39)**	**2.57** **(1.69-3.9)** **N=58**
Post 2nd vacc.	46 (27-77)	118 (70-200) N=59	126 (74-214) N=58	197 (116-335) N=58
Post 2nd vacc. to baseline (GMR)	**7.73** **(4.64-13)**	**21** **(13-35)** **N=59**	**22** **(13-37)** **N=58**	**36** **(22-61)** **N=58**
Percentages of Subjects With Seroprotection HI Titer ≥ 40				
Baseline (Day 1)	3% (0-12)	2% (0.042-9)	3% (0-12)	2% (0.043-9)
Post 1st vacc.	10% (4-21)	42% (29-55)	45% (32-58)	27% (16-40)
Post 2nd vacc.	55% (42-68)	**76%** **(63-86)** **N=59**	**72%** **(59-83)**	**79%** **(67-89)** **N=58**
Percentages of Subjects With Seroconversion or Significant Increase In HI Titers				
Post 1st vacc.	7% (2-16)	40% (28-53)	**45%** **(32-58)**	27% (16-40)
Post 2nd vacc.	**53%** **(40-66)**	**76%** **(63-86)** **N=59**	**72%** **(59-83)**	**79%** **(67-89)** **N=58**

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group; **Bold** font: CHMP criteria achieved

Table 6. Immunogenicity analysis by HI assay using Heterologous Strain [A/H5N1/Turkey/Turkey/05] (CHMP Criteria) –FAS[a]

	DAY1-15	DAY1-22
	N=60	N=60
Geometric Mean HI Titers and Geometric Mean Ratios		
Baseline (Day 1)	5.12 (4.95-5.29)	5 (4.84-5.16)
Post 1st vacc.	8.17 (6.24-11)	6.83 (5.22-8.94)
Post 1stvacc. to baseline (GMR)	1.6 (1.23-2.07)	1.37 (1.05-1.77)
Post 2nd vacc.	9.05 (6.51-13) N=59	11 (8.29-16)
Post 2nd vacc. to baseline (GMR)	1.77 (1.28-2.44) N=59	2.3 (1.67-3.16)
Percentages of Subjects With Seroprotection HI Titer ≥ 40		
Baseline (Day 1)	0% (0-6)	0% (0-6)
Post 1st vacc.	12% (5-23)	10% (4-21)
Post 2nd vacc.	17% (8-29) N=59	28% (17-41)
Percentages of Subjects With Seroconversion or Significant Increase In HI Titers		
Post 1st vacc.	12% (5-23)	10% (4-21)
Post 2nd vacc.	17% (8-29) N=59	28% (17-41)

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group.

Table 7: Immunogenicity analysis by SRH assay using Homologous Strain [A/Vietnam/1194/04 (H5N1)] (CHMP Criteria) -FAS[a]

	Day 1-8	Day 1-15	Day 1-22	Day 1-43
	N=60	**N=60**	**N=58**	**N=60**
Geometric Mean SRH Areas and Geometric Mean Ratios				
Baseline (Day1)	11 (9.06-14)	14 (11-17)	11 (8.76-14)	11 (8.38-13)
Post 1st vacc.	16 (13-19)	33 (27-41) N=59	23 (19-29) N=55	23 (18-28)
Post 1st vacc. to Baseline (GMR)	1.36 (1.11-1.66)	2.5 (2.04-3.07) N=59	2.03 (1.64-2.5) N=55	2.13 (1.74-2.61)
Post 2nd vacc.	34 (30-39) N=59	45 (39-52) N=59	42 (37-49)	50 (44-57) N=58
Post 2nd vacc. to Baseline (GMR)	**2.92** **(2.29-3.72)** **N=59**	**3.26** **(2.56-4.15)** **N=59**	**3.82** **(3-4.88)**	**4.57** **(3.58-5.84)** **N=58**
Percentage of Subjects with Seroprotection SRH area (>25 mm^2)				
Baseline (Day1)	23% (13-36)	27% (16-40)	24% (14-37)	23% (13-36)
Post 1st vacc.	38% (26-52)	**85%** **(73-93)** **N=59**	67% (53-79) N=55	63% (50-75)
Post 2nd vacc.	**86%** **(75-94)** **N=59**	**98%** **(91-100)** **N=59**	**88%** **(77-95)**	**97%** **(88-100)** **N=58**
Percentage of Subjects with Seroconversion or Significant Increase in SRH Areas				
	N=60	**N=59**	**N=58**	**N=60**
Post 1st vacc.	13% (6-25)	**53%** **(39-66)**	**45%** **(32-59)** **N=55**	**43%** **(31-57)**
Post 2nd vacc.	**64%** **(51-76)** **N=59**	**75%** **(62-85)**	**71%** **(57-82)**	**90%** **(79-96)** **N=58**

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group;
Bold font: CHMP criteria achieved

Table 8. Immunogenicity analysis by SRH assay using Heterologous Strain [A/H5N1/Turkey/Turkey/05] (CHMP Criteria) -FAS[a]

	Day 1-15	**Day 1-22**
	N=60	**N=60**
Geometric Mean SRH Areas and Geometric Mean Ratios		
Baseline (Day1)	5.74 (4.98-6.62)	5.29 (4.59-6.1)
Post 1st vacc.	14 (11-17)	12 (9.37-15)
Post 1st vacc. to Baseline (GMR)	2.36 (1.85-3.01)	2.26 (1.78-2.88)
Post 2nd vacc.	25 (20-30) N=59	24 (20-29)
Post 2nd vacc. to Baseline (GMR)	**4.3** **(3.45-5.35)** **N=59**	**4.51** **(3.63-5.61)**
Percentage of Subjects with Seroprotection SRH area (>25 mm^2)		
Baseline (Day1)	7% (2-16)	3% (0-12)
Post 1st vacc.	42% (29-55)	37% (25-50)
Post 2nd vacc.	**76%** **(63-86)** **N=59**	65% (52-77)
Percentage of Subjects with Seroconversion or Significant Increase in SRH Areas		
Post 1st vacc.	35% (23-48)	33% (22-47)
Post 2nd vacc.	**69%** **(56-81)** **N=59**	**65%** **(52-77)**

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group

Bold font: achieved CHMP criteria.

Table 9. Immunogenicity analysis by MN assay using Homologous Strain [A/Vietnam/1194/04 (H5N1)]–FAS[a]

	Day 1-8	Day 1-15	Day 1-22	Day 1-43
	N=60	N=60	N=60	N=60
Geometric Mean MN titers and Geometric Mean Ratios				
Baseline (Day1)	11 (10-12)	11 (9.88-11)	10 (9.31-11)	10 (9.69-11)
Post 1st vacc.	11 (8.84-15)	25 (20-33)	21 (16-27)	18 (14-23)
Post 1st vacc. to Baseline (GMR)	1.06 (0.83-1.37)	2.39 (1.87-3.07)	2.08 (1.62-2.67)	1.71 (1.33-2.19)
Post 2nd vacc.	24 (18-32)	72 (54-96) N=59	75 (56-100)	181 (135-243) N=59
Post 2nd vacc. to Baseline (GMR)	2.22 (1.67-2.96)	6.78 (5.07-9.06) N=59	7.49 (5.62-9.98)	17 (13-23) N=59
Percentages of Subjects With MN titers ≥40				
Baseline (Day1)	3% (0-12)	2% (0.042-9)	0% (0-6)	2% (0.042-9)
Post 1st vacc.	7% (2-16)	35% (23-48)	23% (13-36)	20% (11-32)
Post 2nd vacc.	38% (26-52)	76% (63-86) N=59	73% (60-84)	90% (79-96) N=59
Percentages Of Subjects With At Least 4-Fold Increase In MN Titers				
Post 1st vacc.	3% (0-12)	33% (22-47)	23% (13-36)	20% (11-32)
Post 2nd vacc.	35% (23-48)	75% (62-85) N=59	73% (60-84)	90% (79-96) N=59

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group.

Table 10. Immunogenicity analysis by MN assay using Heterologous Strain [A/H5N1/Turkey/Turkey/05] -FAS[a]

	Day 1-15	Day 1-22
	N=60	**N=60**
Geometric Mean MN titers and Geometric Mean Ratios		
Baseline (Day1)	10 (9.91-11)	10 (9.68-10)
Post 1st vacc.	19 (15-25)	14 (11-19)
Post 1st vacc. to Baseline (GMR)	1.88 (1.47-2.42)	1.44 (1.12-1.85)
Post 2nd vacc.	27 (20-35) N=59	31 (24-40)
Post 2nd vacc. to Baseline (GMR)	2.61 (2.01-3.4) N=59	3.08 (2.37-4)
Percentages of Subjects With MN titers ≥40		
Baseline (Day1)	2% (0.042-9)	0% (0-6)
Post 1st vacc.	18% (10-30)	13% (6-25)
Post 2nd vacc.	27% (16-40) N=59	32% (20-45)
Percentages Of Subjects With At Least 4-Fold Increase In MN Titers		
Post 1st vacc.	18% (10-30)	13% (6-25)
Post 2nd vacc.	27% (16-40) N=59	32% (20-45)

[a] Blood Draw taken prior to 2nd vaccination is at different time points depending on the vaccine group.

Table 11. Number (%) of Subjects with Solicited AEs Reported 7 Days After Each Vaccination – Safety Population

	1st Vaccination				2nd Vaccination			
	Day 1-8	**Day 1-15**	**Day 1-22**	**Day 1-43**	**Day 1-8**	**Day 1-15**	**Day 1-22**	**Day 1-43**
	N=60	**N=60**	**N=60**	**N=60**	**N=60**	**N=59**	**N=60**	**N=59**
Any	49 (82)	47 (78)	49 (82)	45 (75)	25 (42)	26 (44)	34 (57)	28 (47)
Local	44 (73)	39 (65)	42 (70)	39 (65)	22 (37)	21 (36)	30 (50)	24 (41)
Systemic	26 (43)	30 (50)	26 (43)	23 (38)	16 (27)	17 (29)	15 (25)	13 (22)
Other	5 (8)	7 (12)	10 (17)	4 (7)	2 (3)	5 (8)	1 (2)	0

Table 12. Number (%) of Subjects with Solicited Local Reactions -Overall and Severe Reactions Reported 7 Days After Each Vaccination – Safety Population

	1st Vaccination				2nd Vaccination			
	Day 1-8	**Day 1-15**	**Day 1-22**	**Day 1-43**	**Day 1-8**	**Day 1-15**	**Day 1-22**	**Day 1-43**
	N=60	**N=60**	**N=60**	**N=60**	**N=60**	**N=59**	**N=60**	**N=59**
Erythema (mm)	0	0	7 (12)	7 (12)	0	2 (3)	5 (8)	3 (5)
> 50 mm	0	0	0	0	0	0	0	0
Induration (mm)	1 (2)	2 (3)	5 (8)	2 (3)	2 (3)	2 (3)	3 (5)	1 (2)
> 50 mm	0	0	0	0	0	0	0	0
Swelling (mm)	2 (3)	1 (2)	6 (10)	4 (7)	0	0	4 (7)	3 (5)
> 50 mm	0	0	0	0	0	0	0	0
Ecchymosis (mm)	0	0	4 (7)	0	0	0	1 (2)	0
> 50 mm	0	0	0	0	0	0	0	0
Pain	44 (73)	39 (65)	42 (70)	38 (63)	22 (37)	20 (34)	29 (48)	22 (37)
Severe	0	0	1(2)	0	0	0	0	1 (2)

Table 13. Number (%) of Subjects with Solicited Systemic Reactions- Overall and Severe Reactions Reported Within 7 Days after Each Vaccination: Safety Population

	1st Vaccination				2nd Vaccination			
	Day 1-8	**Day 1-15**	**Day 1-22**	**Day 1-43**	**Day 1-8**	**Day 1-15**	**Day 1-22**	**Day 1-43**
Systemic reaction	**N=60**	**N=60**	**N=60**	**N=60**	**N=60**	**N=59**	**N=60**	**N=59**
Chills	2 (3)	3 (5)	4 (7)	4 (7)	2 (3)	1 (2)	1 (2)	1 (2)
Severe	0	0	1 (2)	1 (2)	0	0	0	0
Malaise	8 (13)	3 (5)	5 (8)	3 (5)	5 (8)	3 (5)	4 (7)	3 (5)
Severe	0	0	0	0	0	0	0	0
Myalgia	6 (10)	8 (13)	16 (27)	12 (20)	4 (7)	6 (10)	7 (12)	5 (8)
Severe	0	0	1 (2)	0	0	0	0	0
Arthralgia	2 (3)	4 (7)	5 (8)	5 (8)	2 (3)	3 (5)	3 (5)	1 (2)
Severe	0	0	1(2)	0	0	0	0	0
Headache	13 (22)	10 (17)	9 (15)	10 (17)	3 (5)	5 (8)	7 (12)	6 (10)
Severe	0	0	1(2)	0	0	0	0	0
Sweating	4 (7)	3 (5)	8 (13)	7 (12)	1 (2)	3 (5)	2 (3)	2 (3)
Severe	0	0	0	1(2)	0	0	0	0
Nausea	2 (3)	0	4 (7)	4 (7)	1 (2)	1 (2)	0	3 (5)
Severe	0	0	0	0	0	0	0	0
Vomiting	0	1 (2)	1 (2)	0	1 (2)	1 (2)	0	0
Severe	0	0	0	0	0	0	0	0
Diarrhea	5 (8)	4 (7)	4 (7)	2 (3)	1 (2)	0	1 (2)	0
Severe	0	0	1 (2)	0	0	0	0	0
Fatigue	18 (30)	18 (30)	17 (28)	15 (25)	12 (20)	14 (24)	8 (13)	10 (17)
Severe	0	0	1 (2)	0	0	1 (2)	0	0
Fever (≥ 38C)	0	0	1 (2)	0	0	0	0	0
≥ 40 C	0	0	0	0	0	0	0	0
Stayed Home	0	0	1 (2)	2 (3)	1 (2)	0	1 (2)	0
Analge. Antipyr. Med.Used	5 (8)	7 (12)	10 (17)	3 (5)	1 (2)	5 (8)	0	0

Table 14. Number (%) of Subjects with Unsolicited AEs- by Reporting Period – Safety Population

		Day 1-8	Day 1-15	Day 1-22	Day 1-43	Total
Primary Period (day1 to 3 weeks post 2nd vacc.)		**N=60**	**N=60**	**N=60**	**N=60**	**N=240**
	Any AEs	6 (10)	12 (20)	11 (18)	9 (15)	38 (16)
	At least possibly related AEs	0	1 (2)	0	1 (2)	2 (1)
	Serious AEs	0	0	0	0	0
	AEs leading to discontinuation	0	0	0	0	0
Follow-up Period (3 weeks post 2nd vacc. to day 202)		**N=60**	**N=60**	**N=60**	**N=60**	**N=240**
	Any AEs	0	1 (2)	0	1 (2)	2 (1)
	At least possibly related AEs	0	0	0	0	0
	Serious AEs	0	1 (2)	0	1 (2)	2 (1)
	AEs leading to discontinuation	0	0	0	0	0

Table 15. Serious AEs after any Vaccination until Study Termination

MedDRA SOC	SAE	Day 1-8	Day 1-15	Day 1-22	Day 1-43
		N=60	**N=60**	**N=60**	**N=60**
Gastrointestinal Disorders	Dyspepsia	0	1 (2%)	0	0
Injury & poisoning	Subdural Haematoma	0	0	0	1 (2%)

Table 16. Unsolicited AEs Reported by >5% of Subjects until Study Termination – Safety Population

MedDRA SOC	Preferred Term	Day 1-8	Day 1-15	Day 1-22	Day 1-43
		N=60	**N=60**	**N=60**	**N=60**
Infections & Infestations	Pharyngitis	0	2 (3%)	6 (10%)	0

Conclusion:

Based on the pre-pandemic guideline EMEA/CHMP/VWP/263499/2006, which requires all three Committee for Medicinal Products for Human Use (CHMP) criteria to be met, two vaccinations with an interval of at least 14 days between the first and second vaccinations were necessary when assessed by both Hemagglutination Inhibition (HI) and Single Radial Hemolysis (SRH) assay against the homologous strain. Neither of the 2 treatment groups tested for heterologous response (day 1-15 and day 1–23) met any of the CHMP criteria using HI assay results after one or 2 vaccinations; using SRH testing, the day1-15 group met all 3 criteria after the second vaccination, and the day 1-23 group met 2 of 3 criteria (Geometric Mean Titer (GMT) and seroconversion). In conclusion, the interval between first and second pre-pandemic vaccinations could be reduced to two weeks.

The vaccine was safe and well tolerated with no deaths, possibly/probably related Serious Adverse Events (SAEs), and no Adverse Events (AE) led to subject withdrawal. The time interval between the first and second vaccinations did not impact the safety profile.

Date of Clinical Trial Report: 08 SEP 09