Sponsor: Novartis Vaccines and Diagnostics

Investigational Product: Optaflu®, Cell culture-derived influenza subunit vaccine for the season 2011/2012

Indication: Prophylaxis: Influenza

Protocol Number: V58_25S

Protocol Title: A Phase III Open Label, Uncontrolled, Multi Center Study to Evaluate Safety and Immunogenicity of a Surface, Antigen, Inactivated, Influenza Vaccine Produced in Mammalian Cell Culture (cTIV), Formulation 2011/2012, when administered to Adult and Elderly Subjects.

Phase of Development: Phase III

Study Period:

Date of first enrolment: 14 SEP 11

Date of last visit: 05 OCT 11

Methodology:

In this open label single treatment arm study, 126 subjects were planned to be enrolled into two groups according to age (at least 50 subjects aged 18-60 years should be evaluable; at least 50 subjects aged over 60 years should be evaluable). On day 1, the study staff queried each female of childbearing potential to determine the date of her last menstrual period and, the subject's commitment to use a birth control from day 1 up to and including the three weeks following vaccination. To be eligible for this study, all females of childbearing potential were required to have a negative urine pregnancy test to receive study vaccination. Subjects were observed for approximately 30 minutes after study vaccination on day 1 for any immediate reactions. Each subject was instructed to complete a diary card for 3 days post the day of immunization to describe local (pain, erythema, ecchymosis, swelling and induration) and systemic reactions [fever (i.e., axillary temperature ≥ 38°C), chills/shivering, malaise, headache, myalgia, arthralgia, sweating and fatigue]. Subjects were contacted by phone on day 5 (window: 0/+3) after immunization to ensure that local and systemic reaction data had been collected on the subject's Diary Card and also to determine the subject's clinical status. All adverse events were collected during days 1 to 4. All adverse events necessitating a physician's visit or consultation and/or leading to premature study discontinuation and all serious adverse events were collected throughout the trial. Subjects were informed that in the event of severe inter-current infection (i.e., any severe flu like symptoms) during the study period until day 22 (window: -1/+5), he/she had to contact the Investigator who took a nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of

viral origin. Specimens were analyzed via Quick test and RT-PCR or culture for confirmatory purposes.

Blood samples for immunogenicity assays were collected before vaccination (day 1) and 21 days after vaccination (day 22, window: -1/+5).

Number of Subjects (planned and analyzed):

Approximately 126 subjects were planned to be enrolled, of which 63 in the non-elderly adult age group (aged 18 to 60) and 63 in the elderly age group (aged 61 and older). In the non-elderly adult age group, not more than approximately half of the subjects should have been aged between 41 and 60 years. The sample size (126) allowed for up to 13 non evaluable subjects per age group (non-evaluable subjects are enclosed in the Per-Protocol Set (PPS) exclusions due to major protocol deviation as predefined in the analysis plan). Subjects who received the immunization and provided post-baseline safety data were included in the safety analyses.

In total 126 subjects were actually enrolled and included in the safety analysis, 120 subjects in the Hemagglutination Inhibition (HI) immunogenicity analysis (HI PPS) and 116 subjects in the Single Radial Hemolysis (SRH) immunogenicity analysis (SRH PPS).

Study Centers:

One center in Germany.

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

PMCID: PMC3745456; NCT01422512

Objectives:

Immunogenicity:

Primary

To evaluate the antibody response to each influenza vaccine antigen, as measured by Hemagglutination Inhibition (HI) at 21 days post immunization in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96).

Antibodies may be additionally quantified using the Single Radial Hemolysis (SRH) test for confirmation purposes (Note for Guidance on Harmonization of Requirements for Influenza Vaccines. CPMP/BWP/214/96: 12 March 1997 [23]).

Safety:

To evaluate safety of a single intramuscular (IM) injection of cTIV in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96).

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

A single 0.5 mL dose of cTIV (Lot No.: 026021A; Date of expiry-JAN 12) was supplied in prefilled syringes and was administered intramuscularly in the deltoid muscle of (preferably) the non-dominant arm.

A 0.5 mL dose of cTIV contains purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA), including 15 µg of HA of each of the three strains (A/H1N1-like strain, A/H3N2-like strain, B-like strain), recommended for inclusion in the vaccine composition for the influenza season 2011/2012 in the Northern Hemisphere.

Duration of Study:

Each subject participated approximately for 3 weeks after enrollment into the study.

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

None

Statistical Methods:

There was no statistical null hypothesis associated with the immunogenicity objective. Statistical analysis was carried out descriptively.

This study was in compliance with the sample size requirements of the current Committee for Medicinal Products for Human Use (CHMP) guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96). The main immunogenicity analyses were based on PPS.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

1. Males and females volunteers of 18 years of age or older, mentally competent, willing and able to give written informed consent prior to study entry;
2. Individuals able to comply with all the study requirements;
3. Individuals in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

Written informed consent must be obtained for all the subjects before enrollment into the study after the nature of the study had been explained.

Exclusion Criteria

1. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
2. Individuals with any serious chronic or acute disease (in the judgment of the investigator), including but not limited to:

- Medically significant Cancer (except for benign or localized skin cancer, cancer in remission for ≥ 10 years or localized prostate cancer that had been clinically stable for more than 2 years without treatment);
- Medically significant advanced congestive heart failure (ie, NYHA class III and IV);
- Chronic obstructive pulmonary disease (COPD);
- Autoimmune disease (including rheumatoid arthritis, except for Hashimoto's thyroiditis that had been clinically stable for ≥ 5 years);
- Diabetes mellitus type I;
- Poorly controlled diabetes mellitus type II;
- Advanced arteriosclerotic disease;
- History of underlying medical condition such as major congenital abnormalities requiring surgery, chronic treatment, or associated with developmental delay (eg, Down's syndrome);
- Acute or progressive hepatic disease;
- Acute or progressive renal disease;
- Severe neurological (es. Guillain–Barré syndrome) or psychiatric disorder;
- Severe asthma.

3. Individuals with history of any anaphylactic reaction and/or serious allergic reaction following a vaccination, a proven hypersensitivity to any component of the study vaccine (eg, influenza viral protein, and excipients).
4. Individuals with known or suspected (or have a high risk of developing) impairment/alteration of immune function (excluding that normally associated with advanced age) resulting, for example, from:

    - Receipt of immunosuppressive therapy (any parenteral or oral corticosteroid or cancer chemotherapy/radiotherapy) within the past 60 days and for the full length of the study;
    - Receipt of immunostimulants;
    - Receipt of parenteral immunoglobulin preparation, blood products and/or plasma derivates within the past 3 months and for the full length of the study;
    - Suspected or known Human Immunodeficiency Virus (HIV) infection or HIV-related disease;

5. Individuals with known or suspected history of drug or alcohol abuse.
6. Individuals with a bleeding diathesis or conditions associated with prolonged bleeding time that in the investigator's opinion would have interfered with the safety of the subject.
7. Female who were pregnant or nursing (breastfeeding) mothers or females of childbearing potential do not plan to use acceptable birth control measures, for the whole duration of the study. Adequate contraception was defined as hormonal (eg, oral, injection, transdermal patch, implant, cervical ring), barrier (eg, condom with spermicide or diaphragm with spermicide), intrauterine device (IUD), or monogamous relationship with vasectomized partner who had been vasectomized for 6 months or more prior to the subject's study entry.
8. Individuals who were not able to comprehend and to follow all required study procedures for the whole period of the study.
9. Individuals with history or any illness that, in the opinion of the investigator, might have interfered with the results of the study or pose additional risk to the subjects due to participation in the study.
10. Individuals Within the past 6 months, they had:
    - Had any seasonal or pandemic laboratory confirmed influenza disease;
    - Received any seasonal or pandemic influenza vaccine.
11. Individuals with any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days.
12. Individuals that had experienced fever (i.e., axillary temperature $\geq 38°C$) within the last 3 days of intended study vaccination.
13. Individuals participating in any clinical trial with another investigational product 4 weeks prior to first study visit or intended to participate in another clinical study at any time during the conduct of this study.
14. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who were planning to receive any vaccine within 4 weeks from the study vaccines.
15. Individuals who had ever received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks and for the full length of the study.
16. Individuals who were part of study personnel or close family members conducting this study.
17. Body mass index (BMI) > 35 kg/m^2.

Criteria for Evaluation:

Immunogenicity

Seroprotection rate, Geometric Mean Ratio (GMR) and rate of seroconversion or significant increase were determined by HI and SRH and assessed according to CPMP/BWP/214/96. In non-elderly adult subjects aged 18 to 60 years at least one of the assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: ie, seroprotection rate > 70%; seroconversion or significant increase rate > 40%;·post/prevaccination GMR > 2.5. In elderly subjects aged 61 years and older at least one of the following assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: ie, seroprotection rate > 60%; seroconversion or significant increase rate > 30%; post/prevaccination GMR > 2.0.

Safety

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

Results:

Table 1: Overview of Subject Populations for Immunogenicity Analysis

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=62	**N=64**	**N=126**
Population:			
Enrolled	62 (100%)	64 (100%)	126 (100%)
HI Immunogenicity (FAS)	60 (97%)	60 (94%)	120 (95%)
HI Immunogenicity (PPS)	60 (97%)	60 (94%)	120 (95%)
SRH Immunogenicity (PPS)	58 (94%)	58 (91%)	116 (92%)

Abbreviations: FAS : full analysis set; HI : hemagglutination inhibition; PPS : per-protocol set; SRH : single radial hemolysis; YOA : years of age.
Note: For immunogenicity analysis subjects were included as enrolled (ie, 2 non-elderly adults were erroneously enrolled in the elderly age group).

Table 2: Overview of Subject Populations for Safety Analysis

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=64	**N=62**	**N=126**
Population:			
Enrolled	64 (100%)	62 (100%)	126 (100%)
Exposed	64 (100%)	62 (100%)	126 (100%)
Safety	64 (100%)	62 (100%)	126 (100%)
Safety After Study day 4	64 (100%)	62 (100%)	126 (100%)

Abbreviation: YOA : years of age.
Note: For safety analyses subjects were analyzed according to their real age.

Table 3: Summary of Study Terminations - All Enrolled Set

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
Enrolled	62	64	126
Completed protocol	60 (97%)	60 (94%)	120 (95%)
Premature withdrawals	2 (3%)	4 (6%)	6 (5%)
Protocol deviations/violation	1 (2%)	2 (3%)	3 (2%)
Lost to follow-up	1 (2%)	2 (3%)	3 (2%)

Abbreviation: YOA : years of age.

Table 4: Demographic and Other Baseline Characteristics - All Enrolled Set

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=62	**N=64**	**N=126**
Age (Years):	39.7±12.0	68.5±6.0	54.3±17.3
Gender:			
Male	27 (44%)	29 (45%)	56 (44%)
Female	35 (56%)	35 (55%)	70 (56%)
Child Bearing Potential:			
No	10 (16%)	35 (55%)	45 (36%)
Yes	25 (40%)	0	25 (20%)
Not applicable	27	29	56
Pregnancy Test:			
Negative	25 (40%)	0	25 (20%)
Not Done	10 (16%)	35 (55%)	45 (36%)
Not applicable	27	29	56
Ethnic Origin:			
White, Non-Hispanic	62 (100%)	64 (100%)	126 (100%)
Weight (kg):	75.56±12.58	77.58±14.70	76.59±13.68
Height (cm):	172.2±9.6	168.7±9.3	170.4±9.5
Body Mass Index:	25.42±3.29	27.16±4.02	26.30±3.77
Prev. Seas. Flu Vac.:			
No	24 (39%)	6 (9%)	30 (24%)
Yes	38 (61%)	58 (91%)	96 (76%)
Prev. Pand. Flu Vac.:			
No	54 (87%)	58 (91%)	112 (89%)
Unknown	0	1 (2%)	1 (<1%)
Yes	8 (13%)	5 (8%)	13 (10%)
Met Entry Criteria:			
No	1 (2%)	2 (3%)	3 (2%)
Yes	61 (98%)	62 (97%)	123 (98%)

Categorical parameters: N (%), non-categorical parameters: Mean±Std.
Abbreviations: Prev. Pand. Flu Vac.: Previous pandemic influenza vaccination, non elderly adults vaccinated in 2009, elderly subjects vaccinated in 2009 and 2010 (specific date mostly unknown) Prev. Seas. Flu Vac.: Previous seasonal influenza vaccinations, non elderly adults vaccinated Oct. 2003 to Jan. 2011 (mostly in 2010), elderly subjects vaccinated Sep 2005 to Dec 2010 (mostly in 2010; Std : standard deviation; YOA : years of age.

Table 5: Vaccine Immunogenicity Assessed by HI Assay - Per Protocol Set

		18-60 YOA (N=60)							≥ 61 YOA (N=60)					
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**	
PREVACCINATION														
		n/N[1]	**%**	**n/N**	**%**	**n/N**	**%**		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
GMT[2]		17		40		36			26		87		43	
95% CI[3]		12-25		27-59		27-49			18-37		65-117		33-56	
Seroprotection rate[4]		23/60	38%	35/60	58%	35/60	58%		26/60	43%	53/60	88%	42/60	70%
95% CI		26-52		45-71		45-71			31-57		77-95		57-81	
POSTVACCINATION														
	CHMP[8]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP[8]**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate[5]		21/29	72%	12/12	100%	5/7	71%		10/15	67%	1/1	100%	2/4	50%
Significant increase[6]		20/31	65%	20/48	42%	16/53	30%		31/45	69%	15/59	25%	8/56	14%
Seroconversion rate or significant increase	**>40%**	41/60	**68%**	32/60	**53%**	21/60	35%	**>30%**	41/60	**68%**	16/60	27%	10/60	17%
95% CI		55-80		40-66		23-48			55-80		16-40		8-29	
GMT		205		264		128			167		245		81	
95% CI		137-308		201-347		99-166			115-242		184-327		64-103	
GMR[7]	**>2.5**	**12**		**6.61**		**3.54**		**>2.0**	**6.46**		**2.81**		1.89	
95% CI		7.8-18		4.24-10		2.52-4.97			4.65-8.98		2.05-3.87		1.58-2.26	
Seroprotection rate	**>70%**	52/60	**87%**	59/60	**98%**	56/60	**93%**	**>60%**	54/60	**90%**	59/60	**98%**	54/60	**90%**
95% CI		75-94		91-100		84-98			79-96		91-100		79-96	

Abbreviations: CHMP : Committee for Medicinal Products for Human Use; CI : confidence interval; GMR : geometric mean ratio; GMT : geometric mean titer; HI : hemagglutination inhibition; YOA : years of age.

Bold = CHMP criteria met; [1] n/N: responders (n) as part of number of subjects of the (sub-)population (N); [2] GMT: geometric mean titer; [3] 95% CI: 95% confidence interval; [4] Seroprotection rate: proportion of subjects with a protective titer (titer ≥ 40); [5] Seroconversion rate: proportion of subjects with antibody increase from < 10 prevaccination to ≥40 postvaccination; [6] Significant increase in antibody titers: proportion of subjects with an antibody titer of ≥10 prevaccination and at least 4-fold antibody increase postvaccination; [7] GMR = Geometric mean ratio pre/postvaccination; [8] CHMP criteria.

Table 6: Vaccine Immunogenicity Assessed by SRH Assay - Per Protocol Set

		18-60 YOA (N=58)							≥ 61 YOA (N=58)					
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**	
PREVACCINATION														
		n/N[1]	**%**	**n/N**	**%**	**n/N**	**%**		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
GMA[2]		15		13		33			20		16		38	
95% CI[3]		11-21		10-17		26-41			14-27		13-21		30-49	
Seroprotection rate[4]		24/58	41%	20/58	34%	46/58	79%		32/58	55%	21/58	36%	49/58	84%
95% CI		29-55		22-48		67-89			42-68		24-50		73-93	
POSTVACCINATION														
	CHMP[7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP[7]**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate[5]		17/21	81%	6/18	33%	6/7	86%		11/17	65%	5/11	45%	3/7	43%
Significant increase[6]		22/37	59%	24/40	60%	24/51	47%		22/41	54%	27/47	57%	10/51	20%
Seroconversion rate or significant increase	**> 40%**	39/58	**67%**	30/58	**52%**	30/58	**52%**	**> 30%**	33/58	**57%**	32/58	**55%**	13/58	22%
95% CI[3]		54-79		38-65		38-65			43-70		42-68		13-35	
GMA[2]		53		33		62			49		33		51	
95% CI[3]		44-65		25-42		54-70			41-60		26-41		42-62	
GMR[8]	**> 2.5**	**3.51**		**2.51**		1.88		**> 2.0**	**2.52**		2		1.34	
95% CI[3]		2.68-4.59		1.96-3.23		1.5-2.35			1.94-3.26		1.61-2.5		1.15-1.55	
Seroprotection rate[4]	**> 70%**	52/58	**90%**	41/58	**71%**	57/58	**98%**	**> 60%**	51/58	**88%**	44/58	**76%**	53/58	**91%**
95% CI[3]		79-96		57-82		91-100			77-95		63-86		81-97	

Abbreviations: CHMP : Committee for Medicinal Products for Human Use; CI:= confidence interval; GMA : geometric mean area; GMR : geometric mean ratio; SRH : single radial hemolysis; YOA : years of age.

Bold = CHMP criteria met;; [1]n/N: responders (n) as part of number of subjects of the (sub-)population (N); [2]GMA: geometric mean area; [3]95% CI: 95% confidence interval; [4]Seroprotection rate: proportion of subjects with a pre- or post-vaccination area ≥ 25 mm^2; [5]Seroconversion rate: proportion of subjects with negative pre-vaccination serum and a postvaccination serum area ≥ 25 mm^2; [6]Significant increase in antibody titers: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum; [7] CHMP Criteria; [8] GMR = Geometric mean ratio pre/postvaccination.

Table 7: Overview of Solicited Reactions – Safety Set[1]

	Number (%) of Subjects with Solicited Reactions		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=63	**N=62**	**N=125**
Any[2]	39 (62%)	27 (44%)	66 (53%)
Local	31 (49%)	16 (26%)	47 (38%)
Systemic	24 (38%)	16 (26%)	40 (32%)

Abbreviations: AEs : adverse events; YOA : years of age.

[1] One subject (age group 18 to 60 years) did not return the diary; this is the reason why the reactogenicity safety set included 125 subjects while the AEs safety set included 126 subjects; [2] Number and percent of subjects with one or more local and systemic reactions. Hence, number and percent of local and systemic reactions may not sum to number and percent of subjects with any reactions.

Table 8: Overview of Solicited Local Reactions (1-4 days Post-Vaccination) – Safety Set[1]

		Number (%) of Subjects with Injection Site Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=63	**N=62**	**N=125**
Ecchymosis (mm)	Any	2 (3%)	3 (5%)	5 (4%)
	>50 mm	0	0	0
Erythema (mm)	Any	3 (5%)	0	3 (2%)
	>50 mm	0	0	0
Induration (mm)	Any	5 (8%)	2 (3%)	7 (6%)
	>50 mm	0	0	0
Swelling (mm)	Any	6 (10%)	0	6 (5%)
	>50 mm	0	0	0
Pain	Any	27 (43%)	13/60 (22%)	40/123 (33%)
	Severe	0	0	0

Abbreviations: AEs : adverse events; YOA : years of age.

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

Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter <10 mm), mild (diameter 10-25 mm), moderate (diameter 26-50 mm) and severe (diameter >50 mm);

[1] One subject (age group 18 to 60 years) did not return the diary; this is the reason why the reactogenicity safety set included 125 subjects while the AEs safety set included 126 subjects.

Table 9: Overview of Solicited Systemic Reactions (1-4 days Post-Vaccination) – Safety Set[1]

		Number (%) of Subjects with Systemic Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=63	**N=62**	**N=125**
Chills/Shivering	Any	2 (3%)	2 (3%)	4 (3%)
	Severe	0	0	0
Malaise	Any	3 (5%)	3 (5%)	6 (5%)
	Severe	0	0	0
Myalgia	Any	12 (19%)	5 (8%)	17 (14%)
	Severe	0	0	0
Arthralgia	Any	4 (6%)	1 (2%)	5 (4%)
	Severe	0	0	0
Headache	Any	11 (17%)	6 (10%)	17 (14%)
	Severe	0	0	0
Sweating	Any	2 (3%)	0	2 (2%)
	Severe	0	0	0
Fatigue	Any	15 (24%)	10 (16%)	2 5(20%)
	Severe	1 (2%)	0	1 (1%)
Fever (≥ 38°C)	Yes	0	0	0

Abbreviation: YOA : years of age.

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

[1] One subject (age group 18 to 60 years) did not return the diary.

Table 10: Overview of Other AEs - Safety Set[1]

	Number (%) of Subjects with Adverse Events		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=64	**N=62**	**N=126**
Any AEs	5 (8)	8 (13)	13 (10)
At least possibly related AEs	4 (6)	5 (8)	9 (7)
Serious AEs	0	0	0
At least possibly related SAEs	0	0	0

Abbreviations: AEs : adverse events; SAEs : serious adverse events; YOA = years of age.

[1] One subject (age group 18 to 60 years) did not return the diary.

Table 11: Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term, sorted by System Organ Class - Safety Set

None Reported

Table 12: Number (Percentages) of Subjects with Unsolicited Adverse Events Reported in ≥ 5 % of Subjects by Preferred Term sorted by System Organ Class - Safety Set

None Reported

Conclusion:

In this prospective clinical trial involving 64 non-elderly adults (18 – 60 years) and 62 elderly subjects (≥ 61 years of age), immunogenicity, safety and tolerability of the trivalent subunit influenza vaccine Optaflu were investigated. The vaccine contained purified viral envelope-glycoproteins, neuraminidase and hemagglutinin of the virus strains selected for 2011/2012 according to WHO recommendations (i.e., A/California/7/09 (H1N1)-like strain; A/Perth/16/09 (H3N2)-like strain; B/Brisbane/60/08-like strain). The vaccine was injected into the deltoid muscle. Optaflu fulfilled the CHMP requirement that at least one of the CHMP criteria was met measured with HI assay for each strain in both adult and elderly subjects. For the 2 Astrains in non-elderly adults and 1 A-strain (H1N1) in the elderly subjects all three CHMP criteria were met. For B Strain in non-elderly adults and another A strain (H3N2) in the elderly subjects 2 out of 3 CHMP criteria were met (seroconversion criterion was not met). For B strain in the elderly subjects 1 out of 3 CHMP criteria was met (seroprotection criterion was met).

Overall, the incidences of solicited local and systemic reactions reported were comparable with incidences seen with other influenza vaccines and mostly similar to incidences seen in other studies with this vaccine. As expected more local and systemic reactions were reported in the non-elderly adults than in the elderly population. No subject reported a SAE and no AE led to a premature withdrawal from the study.

Thus, Optaflu, Surface, Antigen, Inactivated, Influenza Vaccine Produced in Mammalian Cell Culture, formulation 2011-2012, is well tolerated and can be considered protective, and complies with the CHMP criteria for the approval of influenza vaccines.

Date of Clinical Trial Report: **21 OCT 11**