Sponsor:	Novartis Vaccines and Diagnostics S.r.l.
Investigational Product:	Adjuvanted trivalent influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived)
Indication:	Prophylaxis: Influenza
Protocol Number:	V70_09S
Protocol Title:	A Phase II, Open Label, Uncontrolled, Multi Center Study to Evaluate Safety and Immunogenicity of FLUAD® Surface Antigen, Inactivated, Adjuvanted with MF59C.1 Influenza Vaccine, Formulation 2009-2010, when Administered to Elderly Subjects
Phase of Development:	Phase II
Study Period:	
Date of first enrolment:	08 JUN 09
Date of last visit:	30 JUN 09

Methodology:

All subjects were to receive one dose of adjuvanted subunit influenza vaccine on Day 0. Blood samples for the determination of antibody titers were drawn on Day 0 prior to vaccination and on Day 21 (-1/ +5). Subjects were observed at the clinic for 30 minutes after vaccination for any immediate reactions. Each subject was instructed to fill in a diary card for three days following vaccination to collect local (ecchymosis, erythema, induration, swelling and pain) and systemic (chills/shivering, malaise, myalgia, arthralgia, headache, sweating, fatigue and fever [i.e., axillary temperature ≥ 38°C]) reactions. Subjects were contacted by phone on Day 4 (window: 0 / +2) after vaccination 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 Day 0 to 3. All serious adverse events and/or adverse events necessitating a physician's visit or consultation and/or resulting in premature subject's withdrawal from the study were collected throughout the study. Subjects were informed that in the event of severe inter-current infection (i.e., any severe flu like symptoms) they had to contact the Investigator who would take a nasal and/or pharyngeal swab to diagnose influenza or

other respiratory infection of viral origin (via quick test and reverse transcription polymerase chain reaction (RT-PCR) or culture for confirmatory purposes).

Number of Subjects (planned and analyzed):

A total of 63 subjects (aged 65 years and above) were planned to be enrolled. This sample size allows for 13 non evaluable subjects (non evaluable subjects are excluded from the per protocol analysis due to protocol deviation).

In total 63 subjects were actually enrolled. All enrolled subjects were included in the safety analysis. 61 subjects were included in the immunogenicity analysis (per protocol [PP] set).

Study Centers:

Three study centers in Italy.

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

NCT00956761

Objectives:

Immunogenicity Objectives:

To evaluate the antibody response to each influenza vaccine antigen, as measured by Single Radial Hemolysis (SRH) at 21 days post-immunization in elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines. Antibodies maybe additionally quantified using the hemagglutination inhibition (HI) test for confirmation purposes (Note for Guidance on Harmonisation of Requirements for Influenza Vaccines. CPMP/BWP/214/96: 12 March 1997).

Safety Objectives:

To evaluate safety of a single intramuscular (IM) injection of FLUAD® in elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccine (CPMP/BWP/214/96).

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

A single 0.5 mL dose of adjuvanted trivalent influenza virus vaccine, for the Northern Hemisphere (NH) influenza season 2009/2010 was IM administered. Lot No.: 092301.

Duration of Study:

Three days enrollment, three weeks participation per subject.

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

None

Statistical Methods:

There was no statistical null hypothesis to be tested in this study. Statistical analysis was done descriptively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

Subjects eligible for enrollment into this study are male and female adults who were:

1. ≥ 65 years of age, mentally competent, willing and able to give written informed consent prior to study entry
2. able to comply with all study requirements
3. in general good health as determined by:
   - medical history
   - physical examination
   - clinical judgment of the investigator

Written informed consent had to be obtained from all the subjects before enrollment in the study after the nature of the study had been explained.

Exclusion Criteria:

Subjects were not to be enrolled into the study if at least one of the following criteria was fulfilled:

1. Any serious chronic or acute disease (in the judgment of the investigator), including but not limited to:
   a. Cancer, except for localized skin cancer;
   b. Advanced congestive heart failure;
   c. Chronic obstructive pulmonary disease (COPD);
   d. Autoimmune disease (including rheumatoid arthritis);
   e. Acute or progressive hepatic disease;

   f. Acute or progressive renal disease;
   g. Severe neurological or psychiatric disorder;
   h. Severe asthma;

2. History of any anaphylactic reaction and/or serious allergic reaction following a vaccination, a proven hypersensitivity to any component of the study vaccine (e.g., to ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin, and neomycin sulphate);
3. 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:
   a. Receipt of immunosuppressive therapy (any parental or oral cortical steroid or cancer chemotherapy/radiotherapy) within the past 60 days and for the full length of the study;
   b. Receipt of immunostimulants;
   c. Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the past 3 months and for the full length of the study;
   d. Suspected or known HIV infection or HIV-related disease;
4. Known or suspected history of drug or alcohol abuse;
5. Bleeding diathesis or conditions associated with prolonged bleeding time that in the investigator's opinion would have been interfered with the safety of the subject;
6. Within the past 12 months, they had:
   - received more than one injection of influenza vaccine;
7. Within the past 6 months, they had:
   - had laboratory confirmed influenza disease;
   - received influenza vaccine;
8. Within the past 4 weeks they had received:
   - another vaccine;
   - any investigational agent;
9. Any acute or chronic infection requiring systemic antibiotic treatment or antiviral therapy within the last 7 days;
10. Fever (i.e. axillary temperature $\geq$38.0ºC) within the last 3 days;
11. Simultaneous participation in another clinical study;

12. Any condition, which, in the opinion of the investigator, could interfere with the evaluation of the study objectives;

13. Severely obese with Body Mass Index (BMI) > 35;

Site personnel involved in evaluation of safety and their immediate relatives were excluded from participation.

Criteria for Evaluation:

Immunogenicity:

Immunogenicity analyses were performed by SRH assay and assessed according to CPMP/BWP/214/96. In elderly subjects aged 65 years and over at least one of the following criteria was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 60%; seroconversion or significant increase rate > 30%; post/pre-vaccination geometric mean ratio (GMR) > 2.0.

Safety

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

The incidence of local reactions and systemic reactions (Days 0 to 3) was summarized by maximal severity.

The incidence of adverse events (including local and systemic reactions with a duration beyond Day 3 post vaccination) between Day 0 and the study termination visit was summarized by low level term and system organ class (SOC).

Table 1 Time and Events

	Visit 1 Day 0	☎ Day 4 (0/+2)	Visit 2 Day 21 (-1/+5)
Informed consent	**X**		
Inclusion/Exclusion criteria	**X** [1]		
Medical History	**X** [1]		
Brief physical examination	**X**		**X**
Concomitant medication	**X**	**X**	**X**
Pre-vaccination temperature	**X**		
Blood draw	**X** [1]		**X**
Vaccination	**X**		
Diary card dispensing	**X**		
Local and systemic reaction reporting	**X**	**X**	**X**
Adverse event reporting	**X**	**X**	**X**
Follow-up telephone call		**X**	
Diary card collected and/or reviewed [2]		**X**	**X**
Study Termination			**X**

[1] Before vaccination.

[2] Diary card review will be performed over the phone for Day 4, and at Day 21 clinic visits. Diaries will be returned at Day 21 clinic visit.

Results:

Table 2 Overview of Subjects Population

	Number (%) of Subjects
	FLUAD N=63
Population:	
Enrolled	63 (100%)
Immunogenicity (FAS)	63 (100%)
Immunogenicity (PP)	61 (97%)
Exposed	63 (100%)
Safety	63 (100%)

FAS = full analysis set; PP = per protocol.

Table 3 Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects
	FLUAD N=63
Enrolled	63 (100%)
Completed study	63 (100%)

Table 4 Demographic and Other Baseline Characteristics- All enrolled set

	FLUAD N=63
Age (YOA):	72.9±6.0
Gender:	
Male	36 (57%)
Female	27 (43%)
Ethnic Origin:	
Caucasian	63 (100%)
Weight (kg):	74.63±11.83
Height (cm):	164.4±7.1
Body Mass Index:	27.5±3.7
Previous Influenza Vaccination:	
Unknown	1 (2%)
Yes	62 (98%)
Met Entry Criteria:	
No	1 (2%)
Yes	62 (98%)

YOA = years of age.

Table 5 Vaccine Immunogenicity assessed by SRH assay (Per-Protocol Population)

		Elderly (≥65 YOA) N=61					
Strains		**A/H1N1**		**A/H3N2**		**B**	
PRE-VACCINATION							
		n/N[1]	%	n/N[1]	%	n/N[1]	%
GMA[2]		30		28		32	
95% CI[3]		24-37		24-33		26-40	
Seroprotection rate[4]		49/61	80%	46/61	75%	46/61	75%
95% CI[3]		68%-89%		63%-86%		63%-86%	
POST-VACCINATION							
	CHMP Requirements	n/N[1]	%	n/N[1]	%	n/N[1]	%
Seroconversion rate [5]		4/7	57%	3/3	100%	5/6	83%
Significant increase [6]		22/54	41%	25/58	43%	21/55	38%
Seroconversion or significant increase [7]	**> 30%**	26/61	**43%**	28/61	**46%**	26/61	**43%**
95% CI [3]		30%-56%		33%-59%		30%-56%	
GMA[2]		47		43		51	
95% CI [3]		40-54		39-47		46-57	
Geometric mean increase	**> 2**	1.55		1.53		1.59	
95% CI [3]		1.33-1.81		1.31-1.79		1.36-1.87	
Seroprotection rate[4]	**> 60%**	57/61	**93%**	57/61	**93%**	60/61	**98%**
95% CI [3]		84%-98%		84%-98%		91%-100%	

YOA: years of age; CHMP: Committee for Medicinal Products for Human Use.

[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 post-vaccination serum area ≥ 25 mm^2. [6] Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum. [7] Seroconversion or significant increase: proportion of subjects with either seroconversion or significant increase.

Table 6 CHMP criteria met by SRH Assay

Viral Strain		A/H1N1	A/H3N2	B
≥ 65 YOA	Seroprotection	+	+	+
	Geometric mean increase	-	-	-
	Seroconversion or significant increase	+	+	+

CHMP: Committee for Medicinal Products for Human Use; "+" CHMP criteria met: "-" CHMP criteria not met; YOA = years of age

Table 7 Overview of Solicited Adverse Events - Safety Set

	Number (%) of Subjects With Solicited Reactions
	FLUAD N=63
Any	20 (32)
Local	18 (29)
Systemic	5 (8)

[1] 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 Adverse Events (0-3 Days Post-Vaccination)- Safety Set

		Number (%) of Subjects With Injection Site Reactions
		FLUAD N=63
Ecchymosis (mm)	Any	2 (3)
	> 50 mm	0
Erythema (mm)	Any	8 (13)
	> 50 mm	2 (3)
Induration (mm)	Any	3 (5)
	> 50 mm	2 (3)
Swelling (mm)	Any	6 (10)
	> 50 mm	2 (3)
Pain	Any	9 (14)
	Severe	1 (2)

Note: The number (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).

Table 9 Overview of Solicited Systemic Adverse Events (0-3 Days Post-Vaccination) - Safety Set

		Number (%) of Subjects With Systemic Reactions
		FLUAD N=63
Chills/Shivering	Any	1 (2)
	Severe	0
Malaise	Any	1 (2)
	Severe	0
Myalgia	Any	0
	Severe	0
Arthralgia	Any	1 (2)
	Severe	0
Headache	Any	5 (8)
	Severe	1 (2)
Sweating	Any	0
	Severe	0
Fatigue	Any	1 (2)
	Severe	0
Fever (Temp. ≥ 38°C)	Yes	0

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

Table 10 Overview of Unsolicited Adverse Events - Safety Set

	Number (%) of Subjects with Adverse Events
	FLUAD N=63
Any AEs	2 (3)
At least possibly related AEs	2 (3)
Serious AEs	0
At least possibly related SAEs	0
AEs leading to discontinuation	0
Death	0

Table 11 **Serious Adverse Events by Preferred Term, sorted by System Organ Class**

None reported

Table 12 **Other Adverse Events Reported in > 5 % of Subjects by Preferred Term sorted by System Organ Class**

None reported

Conclusion:

In conclusion, the 2009/2010 adjuvanted trivalent influenza virus vaccine complies with the CHMP criteria for approval of influenza vaccines, showing a very good immunogenicity, tolerability and safety profile in the elderly.

Date of Clinical Trial Report: 09 JUL 09