Sponsor:	Novartis Vaccines and Diagnostics S.r.l.
Investigational Product:	aTIV, Adjuvanted trivalent influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived)
Indication:	Prophylaxis: Influenza
Protocol Number:	V70P7S
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 2008-2009, when Administered to Elderly Subjects
Phase of Development:	Phase II

Study Period:

Date of first enrolment:	20 JUN 08
Date of last visit:	14 JUL 08

Methodology:

All subjects received a single injection 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. All subjects were instructed to fill in a diary card for three days following vaccination to collect local (ecchymosis, erythema, induration, swelling and pain at the injection site) 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 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 (solicited and unsolicited) 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 during the study period 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.

Number of Subjects (planned and analyzed):

A total of 63 subjects (aged 65 years and above) are to be enrolled. This sample size allows for 13 non evaluable subjects.

In total 64 subjects were actually enrolled. All enrolled subjects were included in the safety and immunogenicity analysis (per protocol [PP] set).

Study Centers:

The study was conducted in three study centers in Italy.

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

NCT00734734.

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 (≥65 years) in compliance with the requirements of the current European union (EU) recommendations for clinical trials related to yearly licensing of influenza vaccines. (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) dose of aTIV vaccine in elderly subjects (≥65 years) 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:

aTIV vaccine, for the Northern Hemisphere (NH) influenza season 2008/2009 was IM administered. Lot No.: Y52P13H1.

Duration of Study:

Approximately 4 weeks (approximately 1 week enrollment, 3 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 were male and female elderly volunteers who were:

1. ≥ 65 years of age, mentally competent, willing and able to give informed consent prior to study entry;
2. able to comply with all study requirements; and
3. in good health as determined by: medical history, physical examination and 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 was explained.

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

1. They had 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. They had 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. They had a 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 parenteral or oral corticosteroid 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 derivates within the past 3 months and for the full length of the study;
   d. suspected or known HIV infection or HIV-related disease;
4. They had a known or suspected history of drug or alcohol abuse;
5. They had a bleeding diathesis or condition associated with prolonged bleeding time that in the investigator's opinion would interfere with the safety of the subject;
6. Within the past 12 months, they have received more than one injection of influenza vaccine;
7. Within the past 6 months, they have:
   a. had laboratory confirmed influenza disease;
   b. received influenza vaccine;
8. Within the past 4 weeks they have received:
   a. another vaccine;
   b. any investigational agent;
9. They had any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days;
10. They had experienced an acute exacerbation of a COPD within the past 14 days;
11. They had experienced fever (i.e., axillary temperature $\geq 38°C$) within the last 3 days;
12. They were taking part in another clinical study;
13. They had any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives;
14. They were severely obese with Body Mass Index (BMI) > 35

Criteria for Evaluation:

Immunogenicity

Immunogenicity analyses were performed by means of SRH assay.

For each of the three virus strains, at least one of the following criteria had to be met, according to CPMP/BWP/214/96 guidance in subjects aged 65 years and over, approximately 3 weeks after vaccination:

- number of seroconversions or significant increases in antibody titer > 30%
- mean geometric increase >2.0
- percentage of subjects achieving an SRH area $\geq$25 mm^2 >60%

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 preferred term and system organ class (SOC).

Results:

Table 1. Population Analyzed - All Enrolled Population

	Number (%) of Subjects
Population	**aTIV**
Enrolled	64 (100%)
Immunogenicity (FAS)	64 (100%)
Immunogenicity (PP)	64 (100%)
Safety	64 (100%)

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

Table 2. Summary of Study Terminations - All Enrolled Population

	Number of (%) of Subjects
Primary Withdrawal Reason	**aTIV**
Total Number Of Subjects Enrolled	64 (100%)
Completed	64 (100%)
Completed protocol	64 (100%)

Table 3. Demography and Baseline Characteristics - All Enrolled Population

	Number (%) of Subjects
	aTIV N=64
Age (Years)	73.1±4.8
Sex :	
Male	32 (50)
Female	32 (50)
Race :	
Caucasian	64 (100%)
Weight (kg) :	71.85±11.06
Height (cm) :	164.3±5.4

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

Table 4. Percentages of Subjects with SRH Area ≥ 25mm^2 - Per Protocol Set

		Percentage (%) of Subjects and (95% CI)
Strain	**Timepoint**	**aTIV N=64**
H1N1	Day 0	61 % (48-73)
	Day 21	89 % (79-95)
H3N2	Day 0	23 % (14-36)
	Day 21	75 % (63-85)
B	Day 0	42 % (30-55)
	Day 21	80 % (68-89)

Strains: A/Brisbane/59/2007-like (H1N1); A/Brisbane/10/2007-like (H3N2); B/Florida/4/2006-like.
Abbreviation: SRH = single radial hemolysis.

Table 5. Percentages of Subjects Seroconversion or Significant Increase in SRH Areas - Per Protocol Set

		Percentage (%) of Subjects and 95% CI
Strain	**Timepoint**	**aTIV N=64**
H1N1	Day 21	38 % (26-50)
H3N2	Day 21	55 % (42-67)
B	Day 21	42 % (30-55)

Abbreviation: SRH = single radial hemolysis.

Table 6. Geometric Mean SRH Areas and Geometric Mean Ratios - Per Protocol Set

		Number and 95% CI
Strain	**Timepoint**	**aTIV N=64**
GMA (H1N1)	Day 0	21 (16-27)
	Day 21	39 (33-47)
GMA (H3N2)	Day 0	8.32 (6.4-11)
	Day 21	31 (24-41)
GMA (B)	Day 0	13 (9.88-18)
	Day 21	31 (25-40)
GMR (H1N1)	Day 21/ Day 0	1.87 (1.5-2.33)
GMR (H3N2)	Day 21/ Day 0	3.74 (2.73-5.11)
GMR (B)	Day 21/ Day 0	2.38 (1.81-3.13)

Abbreviation: GMA = geometric mean area, GMR = geometric mean ratio, SRH = single radial hemolysis.

Table 7. Overview of Solicited Adverse Events - Safety Population

	Number (%) of Subjects with Solicited Reactions
	aTIV N=64
Any Reaction	18 (28)
Local Reaction	18 (28)
Systemic Reaction	2 (3)

Table 8. Overview of Local Reactions (0-3 Days Post-Vaccination) – Safety Population

		Number (%) of Subjects with Injection Site Reactions
		aTIV N=64
Ecchymosis (mm)	Any	1 (2)
	> 50 mm	0
Erythema (mm)	Any	10 (16)
	> 50 mm	1 (2)
Induration (mm)	Any	2 (3)
	> 50 mm	0
Swelling (mm)	Any	1 (2)
	> 50 mm	0
Pain	Any	11 (17)
	Severe	0

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 <10mm), mild (diameter 10-25mm), moderate (diameter 26-50mm) and severe (diameter >50mm)

Table 9. Overview of Systemic Reactions (0-3 Days Post-Vaccination) – Safety Population

		Number (%) of Subjects with Systemic Reactions
		aTIV N=64
Chills Shivering	Any	0
	Severe	0
Malaise	Any	0
	Severe	0
Myalgia	Any	1 (2)
	Severe	0
Arthralgia	Any	0
	Severe	0
Headache	Any	2 (3)
	Severe	0
Sweating	Any	1 (2)
	Severe	0
Fatigue	Any	2 (3)
	Severe	0
Fever (Temperature ≥ 38°C)	Any	0
	≥ 38°C	0

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

Table 10. Overview of Unsolicited AEs - Safety Population

	Number (%) of Subjects with Adverse Event
	aTIV N=64
Any AE	4 (6)
At least possibly related AE	4 (6)
Serious AEs	0
At least possibly related SAEs	0
AEs leading to discontinuation	0
Death	0

Abbreviations: AE = adverse event; SAE = serious adverse event.

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 2008/2009 Adjuvanted trivalent influenza virus vaccine has a very good immunogenicity and safety profile and complies with the Committee for Medicinal Products for Human Use (CHMP) criteria for approval of influenza vaccines.

Date of Clinical Trial Report: 21 JUL 08