Sponsor:	Novartis Vaccines and Diagnostics
Investigational Product:	MF59-eTIV-Adjuvanted trivalent influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived)
Indication:	Prophylaxis: Influenza
Protocol Number:	V70_32S
Protocol Title:	A Phase II Open Label, Uncontrolled, Multi-Center Study to Evaluate Safety and Immunogenicity of a Surface Antigen, Inactivated, Adjuvanted with MF59C.1 Influenza Vaccine (Fluad®) Formulation 2011/2012, when administered to elderly subjects.
Phase of Development:	Phase II
Study Period:	
Date of first enrolment:	16 MAY 11
Date of last visit:	08 JUN 11

Methodology:

In this open label single treatment arm study, 63 subjects were enrolled. 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 were 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 reverse transcriptase polymerase chain reaction (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 63 subjects (aged 65 years and older) were planned to be enrolled. This sample size allowed for up to 13 non-evaluable subjects (non-evaluable subjects were excluded from the per protocol set (PPS) due to 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 63 subjects were actually enrolled. All enrolled subjects were included in the safety analysis. Sixty-two subjects were included in the immunogenicity analysis PPS.

Study Centers:

Six centers in Italy

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

Objectives:

Immunogenicity:

Primary

To evaluate the antibody response to each influenza vaccine antigen, as measured by Single Radial Hemolysis (SRH) at 21 days post-immunization in compliance with the requirements of the 1997 EU recommendations for clinical trials related to yearly licensing of influenza vaccines.

Antibodies may be additionally quantified using the hemagglutination inhibition (HI) test for confirmation purposes (Note for Guidance on Harmonization of Requirements for Influenza Vaccines, CPMP/BWP/214/96: 12 March 1997).

Safety:

To evaluate the safety of a single intramuscular (IM) injection of MF59-eTIV in elderly subjects in compliance with the requirements of the 1997 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 the study vaccine 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 MF59-eTIV (Lot No.: 116422A; expiry date-JAN 12) contained 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. Immunogenicity analyses were based on the PPS.

This study was in compliance with the sample size requirements of the 1997 CHMP guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

1. Males and females volunteers of 65 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 was 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:
    a) Medically significant cancer (except for benign or localized skin cancer, cancer in remission for ≥10 years or localized prostate cancer that has been clinically stable for more than 2 years without treatment);
    b) Medically significant advanced congestive heart failure (ie. (ie, New York Heart Association [NYHA] class III and IV);
    c) Chronic obstructive pulmonary disease (COPD);
    d) Autoimmune disease (including rheumatoid arthritis, except for Hashimoto's thyroiditis that has been clinically stable for ≥ 5 years);
    e) Diabetes mellitus type I;
    f) Poorly controlled diabetes mellitus type II;
    g) Advanced arteriosclerotic disease;

h) History of underlying medical condition such as major congenital abnormalities requiring surgery, chronic treatment, or associated with developmental delay (e.g., Down's syndrome);

i) Acute or progressive hepatic disease;

j) Acute or progressive renal disease;

k) Severe neurological (eg. Guillain–Barré syndrome) or psychiatric disorder;

l) 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 (e.g. to eggs or eggs product as well as ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin and neomycin sulphate).
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:

   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 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 interfere with the safety of the subject
7. Individuals who were not able to comprehend and to follow all required study procedures for the whole period of the study.
8. Individuals within the past 6 months, they had:

   a) Had any seasonal or pandemic laboratory confirmed influenza disease;

   b) Received any seasonal or pandemic influenza vaccine.

9. Individuals with any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days.
10. Individuals that had experienced fever (i.e., axillary temperature $\geq$ 38°C) within the last 3 days of intended study vaccination.

11. Individuals with history of any illness that, in the opinion of the investigator, might have interfered with the results of the study or pose additional risk to the subject due to participation in the study.
12. 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.
13. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who are planning to receive any vaccine within 4 weeks from the study vaccines.
14. 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.
15. Individuals who were part of study personnel or close family members conducting this study.
16. Body mass index (BMI) > 35 kg/m^2

Criteria for Evaluation:

Immunogenicity analyses were performed by SRH and assessed according to CPMP/BWP/214/96. In elderly subjects aged 65 years and older 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

Results:

Table 1: Overview of Subject Populations

	MF59-eTIV N=63
Population:	
Enrolled	63(100%)
Immunogenicity (FAS)	62(98%)
Immunogenicity (PPS)	62(98%)
Exposed	63(100%)
Safety	63(100%)
Safety After Study Day 4	63(100%)

Abbreviations: FAS=full analysis set; PPS=per-protocol set

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects
	MF59-eTIV
	N=63
Enrolled	63
Completed study	62 (98%)
Premature withdrawals	1 (2%)
Unable to classify[1]	1 (2%)

[1] One subject could not come to visit 3 due to personal problems

Table 3: Demographic and Other Baseline Characteristics - All Enrolled Subjects

	MF59-eTIV N=63
Age (Yrs):	73.2±5.2
Gender:	
Male	32(51%)
Female	31(49%)
Ethnic Origin:	
White, Non-Hispanic	63(100%)
Weight (kg):	75.03±11.95
Height (cm):	166.4±6.4
Body Mass Index:	27.04±3.78
Prev. Seasonal Influenza Vaccination:	
No	1(2%)
Unknown	1(2%)
Yes[1]	61(97%)
Prev. Pandemic Influenza Vaccination:	
No	38(60%)
Unknown	5(8%)
Yes[2]	20(32%)
Type of Prev. Pandemic Influenza Vaccination:	
Focetria[2]	20(32%)
Not Available	43
Met Entry Criteria:	
Yes	63(100%)

Categorical parameters: N(%), non-categorical parameters: Mean±Std.
[1]All vaccinated June to November 2010; [2]All vaccinated June to November 2009.

Table 4: Vaccine Immunogenicity Assessed by SRH assay (Per-Protocol Set)

	Elderly (≥65 YOA) N=62						
Strains		**A/H1N1**		**A/H3N2**		**B**	
PRE-VACCINATION							
		n/N[1]	%	n/N[1]	%	n/N[1]	%
GMA[2]		14		13		35	
95% CI[3]		11-17		11-15		29-42	
Seroprotection rate[4]		18/62	29%	10/62	16%	51/62	82%
95% CI[3]		18-42		8-28		70-91	
POST-VACCINATION							
	CHMP Requirements						
Seroconversion rate [5]		9/12	75%	4/10	40%	3/4	75%
Significant increase [6]		34/50	68%	27/52	52%	13/58	22%
Seroconversion or significant increase [7]	**> 30%**	43/62	**69%**	31/62	**50%**	16/62	26%
95% CI [3]		56-80		37-63		16-38	
GMA[2]		35		24		48	
95% CI [3]		31-40		21-27		42-55	
Geometric mean increase	**> 2**	**2.54**		1.9		1.36	
95% CI [3]		2.1-3.07		1.63-2.2		1.21-1.53	
Seroprotection rate[4]	**> 60%**	55/62	**89%**	43/62	**69%**	58/62	**94%**
95% CI [3]		78-95		56-80		84-98	

YOA = years of age
[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 $\geq$ 25 mm^2; [5]Seroconversion rate: proportion of subjects with negative pre-vaccination serum (SRH area < 4mm^2) and a post-vaccination serum area $\geq$ 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 5: Overview of Solicited Reactions

	Number (%) of Subjects With Solicited Reactions
	MF59-eTIV N=62[1]
Any[2]	24(39)
Local	23(37)
Systemic	9(15)

[1] One subject communicated in the compliance visit that she had no reaction after vaccination, but she has not returned the diary and was excluded from reactogenicity analysis;

[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 6: Overview of Solicited Local Reactions (1-4 Days Post-Vaccination)

		Number (%) of Subjects With Injection Site Reactions
		MF59-eTIV N=62
Ecchymosis (mm)	Any	3(5)
	>50 mm	0
Erythema (mm)	Any	7(11)
	>50 mm	3(5)
Induration (mm)	Any	4(6)
	>50 mm	2(3)
Swelling (mm)	Any	7(11)
	>50 mm	1(2)
Pain	Any	21(34)
	Severe	0

Note: The numbers (N) in the header is the total number of subjects with documented reactions. One subject communicated in the compliance visit that she had no reaction after vaccination, but she has not returned the diary and was excluded from reactogenicity analysis;

Categorization of erythema, swelling, ecchymosis and induration: none (diameter <10mm), mild (diameter 10-25mm), moderate (diameter 26-50mm) and severe (diameter >50mm).

Table 7: Overview of Solicited Systemic Reactions (1-4 Days Post-Vaccination)

		Number (%) of Subjects With Systemic Reactions
		MF59-eTIV N=62
Systemic		
Chills/Shivering	Any	4(6)
	Severe	0
Malaise	Any	3(5)
	Severe	0
Myalgia	Any	6(10)
	Severe	0
Arthralgia	Any	4(6)
	Severe	0
Headache	Any	4(6)
	Severe	0
Sweating	Any	1(2)
	Severe	0
Fatigue	Any	2(3)
	Severe	0
Fever (≥ 38°C)	Yes	0/N=61

Note: The numbers (N) in the header is the total number of subjects with documented reactions. One subject communicated in the compliance visit that she had no reaction after vaccination, but she has not returned the diary and was excluded from reactogenicity analysis. Further 1 subject has not provided data for body temperature.

Table 8: Overview of Other AEs

	Number (%) of Subjects with Adverse Events
	MF59-eTIV N=63
Any AEs	6 (10)
At least possibly related AEs	5 (8)
Serious AEs	0
At least possibly related SAEs	0
AEs leading to discontinuation	0
Death	0

Abbreviations: AEs = adverse events; SAEs = serious adverse events

Table 9: Serious Adverse events by Preferred Term sorted by System Organ Class

None Reported

Table 10: Unsolicited AEs Reported by >5% of Subjects by Decreasing Frequency Sorted By System Organ Class

None Reported

Conclusion:

In conclusion, MF59-eTIV 2011/2012 NH formulation is immunogenic and has a good tolerability and safety profile and complies with the CHMP criteria for approval of influenza vaccines.

Date of Clinical Trial Report: 17 JUN 11