Sponsor: Novartis Vaccines and Diagnostics S.r.l.

Investigational Product: Adjuvanted trivalent influenza virus vaccine (surface antigen, inactivated, adjuvanted with MF59C.1, egg-derived) (FLUAD (aTIV))

Indication: Prophylaxis: Influenza

Protocol Number: V70P4

Protocol Title: A Phase II, Open Label, Uncontrolled, Multi-Center Study to support annual strain update and to Evaluate Safety and Immunogenicity of FLUAD Surface Antigen, Inactivated, (Adjuvanted with MF59C.1) Influenza Vaccine, Formulation 2007 2008, when Administered to Subjects aged 18-64 years affected by chronic diseases

Phase of Development: Phase II

Study Period:

Date of first enrolment: 18 JUN 07

Date of last visit: 18 JUL 07

Methodology:

This trial was designed as a phase II, open-label, uncontrolled, multi-center study.

The subjects participating in the study were admitted to the trial on the basis of their medical history and of a physical examination in order to ensure conformity with the protocol inclusion/exclusion criteria. Vaccine was administered intramuscularly, preferably in the deltoid muscle of the non dominant arm.

Blood samples (approximately 10 mL) were taken from each participant immediately before immunization (Day 0) and about 21 days (range = 20-24) after vaccination. The sera obtained from these samples were stored at ≤-18° C until the time of antibody assay.

The study enrolled 52 subjects aged 18-64 years, thereby exceeding the 50-subject sample specified by the protocol and by the European requirements.

The subjects were kept under observation for 30 minutes after vaccination for any immediate reactions; in addition, subjects received instructions on self-monitoring of local and systemic reactions (i.e., pain at injection site, erythema, ecchymosis, swelling and induration – measured using the ruler included in diary card – as well as occurrence of fever (i.e. axillary temperature ≥38°C), chills, malaise, headache, myalgia, arthralgia, sweating and fatigue) during the 3 days following vaccination. Any reactions and daily measurements of axillary temperature during that period were recorded in a subject diary provided by the study staff. The subjects were also contacted by telephone 4 days after immunization to ascertain temperature measurements and any symptoms recorded in the diaries.

Number of Subjects (planned and analyzed):

After evaluation of protocol inclusion/exclusion criteria, 52 subjects were enrolled (with only one subject who did not meet all inclusion criteria).

Study Centers: 2 centers in Italy.

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

NCT00522067

Objectives:

- To evaluate the antibody response to each influenza vaccine antigen, as measured by Single Radial Hemolysis (SRH) at 21 days post-vaccination in at risk adult subjects in compliance with the requirements of the current EU recommendations for the evaluation of the immunogenicity for a new formulation of a licensed flu vaccine (CPMP/BWP/214/96).
- To evaluate the safety of the administration of a single intramuscular (IM) injection of aTIV in at risk adult subjects.

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

The Novartis adjuvanted subunit influenza vaccine, aTIV (lot no. 078301A) is a suspension containing highly purified surface antigens obtained from A and B influenza viruses cultivated in embryonate chicken eggs and inactivated with formaldehyde.

A single 0.5 mL dose of aTIV contained 45 μg of viral hemagglutinin, composed of 15 μg of the three influenza antigens:

- A(H1N1) strain: IVR-145 (Solomon Island/3/2006 - like strain)
- A(H3N2) strain: NYMC X-161B (A/Wisconsin/67/2005-like strain)
- B strain: (B/Malaysia/2506/2004-like strain)

in accordance with the recommendations of the World Health Organization, the EU and the national Regulatory Agencies for the 2007/2008 season.

The antigen content was standardized in micrograms of viral hemagglutinin to allow comparison with the reference preparations of the WHO.

The vaccine is a milky liquid, and was packaged in ready to use, single dose syringes.

The vaccine was administered intramuscularly (IM), preferably in the deltoid muscle of non dominant arm.

Duration of Study:

The duration of the whole study was one month.

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

None

Statistical Methods:

Only subjects who contributed evaluable serum samples both before and at 21 days after immunization (acceptable time interval 20-24 days) were to be included in the immunogenicity analyses.

For each vaccine antigen, geometric mean areas were calculated by exponentiating (base 10) the mean of the log-transformed (base 10) titers. Day 21 to day 0 geometric mean ratios of areas were computed as the geometric mean of the ratios of the day 21 area to the day 0 area of each subject. Percentages of subjects with seroconversion, with significant increase and protected were also computed separately for each vaccine antigen.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

The study population consisted of healthy male and female adults volunteers who were 18-64 years of age, mentally competent, willing and able to give informed consent prior to study entry and suffering from at least one of the following chronic diseases:

- hypertension
- hearth diseases
- chronic obstructive pulmonary disease (COPD) or asthma

- hepatic or renal insufficiency
- arteriosclerotic disease or insulin dependent diabetes mellitus

Exclusion criteria:

Individuals were not included in the study if:

- They had hypersensitivity to ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin and neomycin sulphate or any other component of the vaccine;
- They had a history of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine;
- They had a known or suspected impairment/ alteration of immune function;
- Women who were pregnant, or were breast-feeding or were able to bear children but not willing to practice acceptable contraception for the duration of the trial (21 days);
- They had any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives;
- They received one or more influenza vaccine within the past 6 or 12 months respectively or had a laboratory confirmed influenza disease within the past 6 months or another vaccine within the past 4 weeks.

Criteria for Evaluation:

Measurement of antibody titers was performed using the single radial hemolysis (SRH) assay.

For each of the three virus strains, at least one of the following criteria had to be met in subjects aged between 18 and 64[1] years, approximately 3 weeks after vaccination:

- number of seroconversions or significant increases in antibody titer > 40%
- mean geometric increase >2.5
- percentage of subjects achieving an SRH area $\geq$25 mm^2 >70%

[1]CHMP criteria, reported in CPMP/BWP/214/96 Guidance, issued 12 March 1997, are defined for age group 18-60 years. It was decided to follow the conservative approach and to apply those criteria to all study population (actually aged 18-64 years).

[1]

SRH results were to be considered negative when < 4 mm^2. For the purposes of analyses, any negative SRH result was expressed as 3.997 mm^2

Results:

Table 1: Overview of Subject Populations

	Number (%) Subjects
	aTIV (N = 52)
Enrolled	52(100%)
Immunogenicity – (ITT)	52(100%)
Immunogenicity – (PP)	51(98%)
Safety	52(100%)

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) Subjects
	aTIV
Total Number of Subjects Enrolled	52
Completed	52(100%)
Completed Protocol	52(100%)

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

	aTIV (N = 52)
Age (Years)	54.6 ± 8.3
Sex:	
Male	21(40%)
Female	31(60%)
Race	
Caucasian	52(100%)
Met Protocol Criteria	
Yes	51(98%)
No	1(2%)
Criteria Violation Specification	
Diabetes Mellitus Not Insulin Dependent	1(2%)
Previous Influenza Vaccination	
Yes	35(67%)
No	16(31%)
Unknown	1(2%)
Hypertension:	
Yes	39 (75%)
No	13 (25%)
Congestive Heart Failure:	
Yes	7 (13%)
No	45 (87%)
COPD or Asthma:	
Yes	6 (12%)
No	46 (88%)
Hepatic or Renal Insuf:	1 (2%)
Yes	51 (98%)
No	
Arteriosclerosis or Diabetes Mellitus:	
Yes	3 (6%)
No	49 (94%)

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

Table 4-Vaccine Immunogenicity at Day 21 for Subjects Aged 18-64 Years

		Adults (18-64 years) N = 51					
Strains		**A/(H1N1)**		**A/(H3N2)**		**B**	
PREVACCINATION							
		n/N[1]	%	n/N[1]	%	n/N[1]	%
GMA[2]		15		12		16	
95% CI[3]		11-21		8.15-16		12-22	
Seroprotection Rate[4]		24/51	47	19/51	37	28/51	55
95% CI[3]		33-62		24-52		40-69	
POSTVACCINATION							
	Requirements	n/N[1]	%	n/N[1]	%	n/N[1]	%
Seroconversion Rate[5]		16/19	84	28/28	100	14/20	70
Significant Increase[6] in Antibody titre		17/32	53	10/23	43	15/31	48
Seroconversion or Significant Increase[7]	> 40%	33/51	65	38/51	75	29/51	57
95% CI[3]		50-78		60-86		42-71	
GMA		47		64		41	
95% CI[3]		39-57		60-69		32-53	
Mean GMA Increase	> 2.5	3.08		5.56		2.56	
95% CI[3]		2.26-4.21		3.95-7.82		1.89-3.47	
Seroprotection Rate[4]	> 70%	46/51	90	51/51	100	44/51	86
95% CI[3]		79-97		93-100		74-94	

[1]n/N: responders (n) as part of number of subjects of the (sub) population (N), i.e. seroconversion or significant increase

[2]GMA: geometric mean area

[3]95% CI: 95% confidence interval

[4]Seroprotection rate: proportion of subjects with a protective titer pre- or postvaccination = SRH-test ≥ 25 mm^2

[5]Seroconversion rate: proportion of subjects with antibody increase from prevaccination (seronegative) to postvaccination area $\geq 25mm^2$

[6]Significant increase: proportion of subjects with a significant increase in antibody titer, i.e. at least a 50% increase in area

[7]Seroconversion rate or significant increase: proportion of subjects with either seroconversion or significant increase in antibody titer

Table 5: Overview of Solicited Reactions (0-3 Days Post vaccination)

	Number (%) of Subjects
	aTIV (N = 52)
Any	19(37%)
Local	16(31%)
Systemic	15(29%)

Table 6 - Local and Systemic Reactions After the Administration of aTIV in Subjects Aged 18-64 Years (0-3 Days Post vaccination)

	18-64 years N = 52	
	n	%
Local reactions	16	31
Pain	13	25
Erythema	4	8
Ecchymosis	1	2
Swelling	1	2
Induration	1	2
Systemic Reactions	15	29
Fever (Temp ≥ 38°C)	2	4
Chills	1	2
Malaise	4	8
Headache	4	8
Myalgia	9	17
Arthralgia	5	10
Sweating	5	10
Fatigue	7	13

Table 7: Overview of Unsolicited AEs

None reported

Table 8: Serious Adverse Events by Preferred Term Sorted by System Organ Class

None reported

Table 9: Unsolicited AEs Reported by ≥ 5% of Subjects by Preferred Term Sorted by System Organ Class

None reported

Conclusion:

The 2007/2008 aTIV adjuvanted influenza vaccine had a very good immunogenicity, a good safety profile and complies with CHMP criteria for approval of influenza vaccines.

Date of Clinical Trial Report: 27 JUL 07