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: V70P5S

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 2007-2008, when Administered to Elderly Subjects

Phase of Development: Phase II

Study Period:

Date of first enrolment: 18 JUN 2007
Date of last visit: 11 JUL 2007

Methodology:

This trial was designed as a phase II, open-label, uncontrolled, multi-center study. The study protocol was approved by the Ethics Committees of Università degli Studi di Siena, Università degli Studi "G. D'Annunzio", Chieti, and of Azienda Sanitaria Locale Lanciano-Vasto.
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.
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 56 subjects aged 65 years and over. 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 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. Statistical analyses of the results were performed using the SAS® version 9.1 (SAS Institute, Cary, NC) software.

Number of Subjects (planned and analyzed):

The study enrolled 56 subjects aged 65 years and over, thereby exceeding the 50-subject sample specified by the protocol and by the European requirements.

Study Centers: One center in Italy (3 planned)

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

NCT00522236

Objectives:

- To evaluate the antibody response to each influenza vaccine antigen, as measured by single radial hemolysis (SRH) at 21 days post-vaccination in elderly subjects (≥ 65 years) 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 vaccine (formulation 2007/2008) in elderly subjects (≥ 65 years).

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

A single 0.5 mL dose of aTIV (lot no. 078301; Expiry date: Apr 2008) is a suspension containing highly purified surface antigens obtained from A and B influenza viruses cultivated in embryonate chicken eggs and inactivated with formaldehyde. The vaccine is adjuvanted with MF59C.1 adjuvant emulsion to potentiate its immunogenicity. 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 (WHO), 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. Vaccine was administered intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

Duration of Study: 3 weeks.

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

Not applicable.

Statistical Methods:

Only subjects who contributed evaluable serum samples both before immunization and at 21 days after immunization (acceptable time interval 20-24 days) were 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, significant increase or protected) were also computed separately for each vaccine antigen. Statistical analyses of the results were performed using the SAS® version 9.1 (SAS Institute, Cary, NC) software.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria
Subjects eligible for enrollment into this study are male and female adult volunteers who are:

1. 65 years of age or older, mentally competent, willing and able to give written informed consent prior to study entry;
2. Able to comply with all the study requirements;
3. In general good health as determined by:
    - •Medical history;
    - •Physical examination;
    - •Clinical judgment of the investigator;

Informed consent must be obtained for all the subjects before enrollment into the study.

Exclusion Criteria
Individuals are not to be enrolled into the study if:

1. They have any serious disease such as:
    - •Cancer (leukemia, lymphomas, neoplasm) except for benign or localized skin cancer and non-metastatic prostate cancer not presently treated with chemotherapy;
    - •Autoimmune disease (including rheumatoid arthritis);
    - •Advanced arteriosclerotic disease or insulin dependent diabetes mellitus;
    - •Chronic obstructive pulmonary disease (COPD) that requires oxygen therapy;
    - •Acute or progressive hepatic disease;
    - •Acute or progressive renal disease;
    - •Congestive heart failure;
2. They are hypersensitive to ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin and neomycin sulphate or any other component of the vaccine;
3. They have a history of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine;

4. They have 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:
    - •Receipt of immunosuppressive therapy (any parenteral or oral cortical steroid 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 HIV infection or HIV-related disease;
5. They have a known or suspected history of drug or alcohol abuse;
6. They have 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. Within the past 12 months, they have:
    - •Received more than one injection of influenza vaccine;
8. Within the past 6 months, they have:
    - • had laboratory confirmed influenza disease;
    - • received influenza vaccine,
9. Within the past 4 weeks they have received:
    - •Another vaccine;
    - •Any investigational agent;
10. Within the past 7 days, they have experienced:
    - •Any acute disease;
    - •Infections requiring systemic antibiotic or antiviral therapy (chronic antibiotic therapy for urinary tract prophylaxis is acceptable);
11. They have experienced an acute exacerbation of a COPD (chronic obstructive pulmonary disease) within the past 14 days;
12. Within the past 3 days, they have experienced:
    - •Fever (i.e., axillary temperature ≥ 38°C);
13. They are taking part in another clinical study;
14. They have any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objective.

Criteria for Evaluation:

For each of the three virus strains, at least one of the following criteria had to be met 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 ≥25 mm^2 >60%

Results:

Table 1: Overview of Subject Populations

	aTIV N=56
Population:	
Enrolled	56 (100%)
Immunogenicity (ITT)	56 (100%)
Immunogenicity (PP)	56 (100%)
Safety	56 (100%)

Abbreviations: ITT = intent to treat; PP = per protocol.

Table 2: Summary of Study Terminations - All Enrolled Set

	Number of Subjects (% of Total)
Primary Withdrawal Reason	**aTIV**
Total number of subjects Enrolled	56
Completed	56 (100%)
Completed protocol	56 (100%)

Table 3: Summary of Demography - All Enrolled Set

	aTIV N=56
Age (yrs):	
Mean	74.1
Standard deviation	7.2
Sex:	
Male	30 (54%)
Female	26 (46%)
Ethnic Origin:	
Caucasian	56 (100%)
Weight (kg):	
Mean	73.5
Standard deviation	12.1
Height (cm):	
Mean	163.7
Std. Dev.	6.8
Previous influenza vaccine:	
No	4 (7%)
Yes	49 (88%)
Met entry criteria:	
Yes	56 (100%)

Table 4: Vaccine Immunogenicity Assessed by SRH Assay at Day 21 for Subjects Aged 65 Years and Over

		Elderly (≥65 years) N=56					
Strains		**A/H1N1**		**A/H3N2**		**B**	
PREVACCINATION							
		n/N	**%**	**n/N**	**%**	**n/N**	**%**
GMT[2]		27		20		39	
95% CI[3]		21-34		15-27		32-48	
Seroprotection rate[4]		39/56	70%	32/56	57%	48/56	86%
95% CI		56-81		43-70		74-94	
POSTVACCINATION							
	CHMP	**n/N** [1]	**%**	**n/N** [1]	**%**	**n/N** [1]	**%**
Seroconversion rate[5]		5/8	63%	16/16	100%	3/4	75%
Significant increase in antibody titers[6]		18/48	38%	23/40	58%	16/52	31%
Seroconversion rate or significant increase[7]	**>30%**	23/56	**41%**	39/56	**70%**	19/56	**34%**
95% CI		28-55		56-81		22-48	
GMT		46		65		57	
95% CI		38-55		60-71		51-65	
Mean GMT Increase	**>2**	1.72		**3.3**		1.45	
95% CI		1.41-2.11		2.41-4.5		1.23-1.72	
Seroprotection rate	**>60%**	51/56	**91%**	55/56	**98%**	55/56	**98%**
95% CI		80-97		90-100		90-100	

Bold = Committee for Medicinal Products for Human Use (CHMP) criterion 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 pre- or post-vaccination = single radial hemolysis (SRH) test ≥25 mm^2.

[5] Seroconversion: proportion of subjects with antibody increase from prevaccination (seronegative) to postvaccination area ≥ 25 mm^2.

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

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

Table 5: Overview of Solicited Reactions

	Number (%) of Subjects With Solicited Reactions
	aTIV
	N=56
Any	13(23%)
Local	11(20%)
Systemic	12(21%)

Table 6: Local and Systemic Reactions after the Administration of aTIV in Subjects Aged 65 years and over

	Number (%) of Subjects With Injection Site Reactions
	≥65 years
	N=56
Local Reactions	11(20%)
Pain	10 (18%)
Erythema (mm)	3 (5%)
Ecchymosis (mm)	2 (4%)
Swelling (mm)	2 (4%)
Induration (mm)	2 (4%)
Systemic Reactions	12 (21%)
Fever (≥ 38°C)	0
Chills	2 (4%)
Malaise	5 (9%)
Headache	7 (13%)
Myalgia	5 (9%)
Arthralgia	4 (7%)
Sweating	3 (5%)
Fatigue	7 (13%)

Table 7: Overview of Other AEs

	Number (%) of Subjects With Adverse Events
	aTIV
	N=56
Any AEs	1 (2%)
At least possibly related AEs	1 (2%)
Serious AEs	0
At least possibly related SAEs	0
AEs leading to discontinuation	0
Death	0

Abbreviations: AEs = adverse events; SAE = serious adverse events.

Table 8: Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term sorted by System Organ Class

None reported.

Table 9: Number (Percentages) of Subjects with Unsolicited Adverse Events Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class

None reported.

Conclusion:

The results of the present study enable us to draw the following conclusions:
For the A/H1N1 and B antigens two criteria were met (ie, the proportion of subjects with seroconversion was >30% and the proportion of subjects with a SRH area $\geq$ 25 mm^2 was > 60%). For the A/H3N2 antigen all three criteria were met (i.e., the proportion of subjects with seroconversion was >30%, the mean GMT increase was >2 and the proportion of subjects with a SRH area $\geq$ 25 mm^2 was > 60%).
With regard to side effects, we can conclude the following:

1. The incidence of pain at the injection site (18%) was lower than that seen in previous studies and the incidence of other local reactions (4-5%) was consistent with that seen in previous studies.
2. Systemic reactions were infrequent and their incidence (range 0% to 13%) was similar to that previously observed.
3. Most of reactions were mild or moderate and all resolved shortly after immunization.

We can therefore conclude that the 2007/2008 aTIV adjuvanted influenza vaccine has a very good immunogenicity and safety profile and complies with Committee for Medicinal Products for Human Use (CHMP) criteria for approval of influenza vaccines.

Date of Clinical Trial Report: 19 JUL 07