Sponsor: Novartis Vaccines and Diagnostics GmbH & Co. KG

Investigational Product: FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur]

Indication: Prophylaxis: Influenza

Protocol Number: V78_07S

Protocol Title: A Phase II, single center, uncontrolled, open label study to evaluate safety and immunogenicity of FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur], Formulation 2009/2010, when Administered to Adult and Elderly Subjects

Phase of Development: Phase II

Study Period:

Date of first enrolment: 06 JUL 09

Date of last visit: 30 JUL 09

Methodology:

All subjects were to receive one dose of 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). Urine pregnancy tests were performed before vaccination on all females of childbearing potential and only subjects with negative result received study vaccination. Each female was queried in private by study staff to determine if the subject was sexually active, the date of her last menstrual period and the subject's commitment to use a reliable birth control method for the complete duration of the Trial. Subjects were observed for 30 minutes 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 (+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 (solicited and unsolicited) were collected during Day 0 to 3. All serious adverse events and/or adverse events necessitating a physician's visit 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 RT-PCR or culture for confirmatory purposes).

Number of Subjects (planned and analyzed):

A total of 126 subjects were planned to be enrolled, of which 63 in the non-elderly adult age group (age 18 to 60) and 63 in the elderly age group (age 61 and above). This sample size allowed for 13 non evaluable subjects (non evaluable subjects are excluded from the per protocol analysis due to major protocol deviation). In the non-elderly adult age group, no more than approximately half of the subjects should have been aged between 41 and 60 years.

In total 139 subjects were actually enrolled, 135 subjects were included in the safety analysis and 131 subjects in the immunogenicity analysis (per protocol set).

Study Centers:

One center in United Kingdom.

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

NCT00956449

Objectives:

Immunogenicity Objectives: To evaluate the antibody response to each influenza vaccine antigen, as measured by hemagglutination inhibition (HI) test on Day 0 and on Day 21, i.e., 21 days after vaccination in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96). Antibodies may be additionally quantified using the Single Radial Hemolysis (SRH) 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 IM (intramuscular) dose of the subunit vaccine Fluvirin in non-elderly adult and elderly subjects in compliance with the requirements of the current 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 0.5mL dose of Fluvirin (Lot No.: 97773), influenza subunit vaccine for the Northern Hemisphere (NH) influenza season 2009/2010 was administered IM. Each dose

contained 15 µg each of Influenza A/Brisbane/59/2007 (H1N1)-like virus; Influenza A/Brisbane/10/2007 (H3N2)-like virus; Influenza B/Brisbane/60/2008-like virus.

Duration of Study:

25 days (5 days enrollment, approximately 21days per subject).

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

None

Statistical Methods:

There was no statistical null hypothesis 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. ≥ 18 years of age, mentally competent, willing and able to give informed consent prior to study entry
2. Able to comply with all study requirements
3. In good health as determined by:
    a. Medical history
    b. Physical examination
    c. Clinical judgment of the investigator
4. 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 eggs, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin).

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. Women who were pregnant or woman of childbearing potential unwilling to practice acceptable contraception for the duration of the study (21 days). Female who were pregnant or nursing (breastfeeding) mothers of females of childbearing age who did not plan to use acceptable birth control measures, for the duration of the study. Adequate contraception was defined as hormonal (oral, injection, transdermal patch, implant, cervical ring), barrier (condom or diaphragm), intrauterine device (IUD) or monogamous relationship with vasectomized partner who were vasectomized for 6 months or more prior to the subject's study entry.

7. Influenza immunization or laboratory confirmed influenza within the last 6 months and more than one influenza immunization within the past 12 months

8. Within the past 4 weeks they had received:

a. Another vaccine

b. 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 ≥ 38.0°C) within the last 3 days
11. Simultaneous participation in another clinical study
12. Any condition, which, in the opinion of the investigator, might prevent the subject from participation or interfere with the evaluation of the study objectives.
13. Severely obese with Body Mass Index (BMI) > 35
14. Site personnel involved in evaluation of safety and their immediate relatives are excluded from participation.

Criteria for Evaluation:

Immunogenicity:

Seroprotection rate, GMR and seroconversion rate were determined by HI and assessed according to CPMP/BWP/214/96. In adult subjects aged 18 to 60 years at least one of the assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 70%; seroconversion or significant increase rate > 40%;·post-/pre-vaccination GMR > 2.5**.** In elderly subjects aged 61 years and over at least one of the following assessments 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 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 and by age group.
The incidence of adverse events (including local and systemic reactions with duration beyond Day 3 post vaccination) between Day 0 and the study termination visit was summarized by each age group and by preferred term and system organ class (SOC).

Results:

Table 1 Overview of Subjects Population

	18-60 years N=70	≥ 61 years N=69	TOTAL N=139
Population:			
Enrolled	70(100%)	69(100%)	139(100%)
Immunogenicity (FAS)	68(97%)	67(97%)	135(97%)
Immunogenicity (PP)	65(93%)	66(96%)	131(94%)
Exposed	68(97%)	67(97%)	135(97%)
Safety	68(97%)	67(97%)	135(97%)

Table 2 Summary of Study Terminations – All Enrolled Set

	Number (%) of Subjects		
	18-60 years	≥ 61 years	TOTAL
Enrolled	70	69	139
Completed protocol	66 (94%)	65 (94%)	131 (94%)
Premature withdrawals	4 (6%)	4 (6%)	8 (6%)
Lost to follow-up	2 (3%)	1 (1%)	3 (2%)
Protocol deviations/violation	1 (1%)	2 (3%)	3 (2%)
Unable to classify	1 (1%)	1 (1%)	2 (1%)

Table 3 Demographic and Other Baseline Characteristics - All Enrolled Subjects

	18-60 years N=70	≥ 61 years N=69	TOTAL N=139
Age (Yrs):	43.5±13.8	70.0±6.2	56.6±17.1
Gender:			
Male	25(36%)	38(55%)	63(45%)
Female	45(64%)	31(45%)	76(55%)
Ethnic Origin:			
Caucasian	69(99%)	69(100%)	138(99%)
Not done	1(1%)	0	1(<1%)
Weight (kg):	73.11±13.37 (N=69)	78.93±15.02	76.02±14.47 (N=138)
Height (cm):	168.9±9.5 (N=69)	170.2±10.1	169.5±9.8 (N=138)
Body Mass Index:	25.629±4.230 (N=69)	27.197±4.399	26.413±4.371 (N=138)
Child Bear. Pot.:			
No	21(30%)	31(45%)	52(37%)
Yes	24(34%)	0	24(17%)
Not applicable (male)	25	38	63
Pregnancy Test:			
Negative	24(34%)	0	24(17%)
Not Applicable	21(30%)	31(45%)	52(37%)
Not applicable (male)	25	38	63
Prev. Influ. Vac.:			
No	17(24%)	2(3%)	19(14%)
Unknown	3(4%)	0	3(2%)
Yes	50(71%)	67(97%)	117(84%)
Met Entry Criteria:			
No	2(3%)	1(1%)	3(2%)
Yes	68(97%)	68(99%)	136(98%)

Table 4 Immunogenicity results assessed by HI Assay on Day 21

		18 – 60 years	**≥ 61 years**
	Number of subjects	N=65	N=66
A/Brisbane/59/2007 (H1N1)-like strain	GMT[1]	174	73
	Geometric mean increase	**6.57**	**2.49**
	Seroprotection rate [2]	**97%**	**83%**
	Seroconversion or significant increase [3]	**54%**	26%
A/Brisbane/10/2007 (H3N2)-like strain	GMT[1]	329	246
	Geometric mean increase	**8.09**	**4.24**
	Seroprotection rate [2]	**98%**	**91%**
	Seroconversion or significant increase [3]	**68%**	**48%**
B/Brisbane/60/2008-like strain	GMT[1]	86	48
	Geometric mean increase	**4.72**	**2.29**
	Seroprotection rate [2]	**89%**	**67%**
	Seroconversion or significant increase [3]	**51%**	20%

Bold = CHMP criteria met. [1] GMT=Geometric mean titer; [2] Seroprotection rate: proportion of subjects with a protective titer (titer ≥ 40). [3] Seroconversion or significant increase: proportion of subjects with either seroconversion or significant increase. Seroconversion: proportion of subjects with antibody increase from < 10 prevaccination to ≥ 40 post-vaccination. Significant increase: proportion of subjects with an antibody titer of ≥10 prevaccination and ≥4-fold antibody increase postvaccination.

Table 5 CHMP criteria met by HI Assay (Non-Elderly Adults 18 - 60 and Elderly Subjects ≥ 61 Years)

Viral Strain		A/H1N1	A/H3N2	B
18 – 60 years	Seroprotection	+	+	+
	Geometric mean increase	+	+	+
	Seroconversion or significant increase	+	+	+
≥ 61 years	Seroprotection	+	+	+
	Geometric mean increase	+	+	+
	Seroconversion or significant increase	-	+	-

"+" CHMP criteria met: "-" CHMP criteria not met

Table 6 Overview of Solicited Reactions

	Number (%) of Subjects With Solicited Reactions		
	18-60 years N=66	≥ 61 years N=65	TOTAL N=131 [2]
Any [1]	34(52)	11(17)	45(34)
Local	24(36)	5(8)	29(22)
Systemic	23(35)	9(14)	32(24)

[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.

[2] Four subjects out of the 135 did not return any diary card (excluded from reactogenicity population), but were included in the safety population of AEs.

Table 7 Overview of Solicited Local Reactions (0-3 Days Post-vaccination)

		Number (%) of Subjects With Injection Site Reactions		
		18-60 years	**≥ 61 years**	**TOTAL**
		N=66	**N=65**	**N=131** [1]
Ecchymosis (mm)	Any	1(2)	1(2)	2(2)
	> 50 mm	0	0	0
Erythema (mm)	Any	5(8)	0	5(4)
	> 50 mm	1(2)	0	1(1)
Induration (mm)	Any	4(6)	0	4(3)
	> 50 mm	1(2)	0	1(1)
Swelling (mm)	Any	4(6)	0	4(3)
	> 50 mm	2(3)	0	2(2)
Pain	Any	20(30)	5/64(8) [2]	25/130(19)
	Severe	0	0	0

Note: The numbers (N) in the header is the total number of subjects in the safety set.

Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter <10mm), mild (diameter 10-25mm), moderate (diameter 26-50mm) and severe (diameter >50mm)

[1] Four subjects out of 135 did not return any diary card (excluded from reactogenicity population), but were included in the safety population of AEs.

[2] By mistake subject 01/157 was not included in the reactogenicity data set for pain. Please note that the subject did not report pain. The 8% of pain reported is therefore confirmed

Table 8 Overview of Solicited Systemic Reactions (0-3 Days Post-vaccination)

		Number (%) of Subjects With Systemic Reactions		
		18-60 years	**≥ 61 years**	**TOTAL**
		N=66	**N=65**	**N=131 [1]**
Chills / Shivering	Any	3(5)	0	3(2)
	Severe	1(2)	0	1(1)
Malaise	Any	6(9)	1(2)	7(5)
	Severe	1(2)	0	1(1)
Myalgia	Any	9(14)	3(5)	12(9)
	Severe	1(2)	0	1(1)
Arthralgia	Any	2(3)	1(2)	3(2)
	Severe	1(2)	0	1(1)
Headache	Any	13(20)	4(6)	17(13)
	Severe	1(2)	0	1(1)
Sweating	Any	4(6)	0	4(3)
	Severe	0	0	0
Fatigue	Any	12(18)	3(5)	15(11)
	Severe	1(2)	0	1(1)
Fever (Temp. ≥ 38C)	Yes	0	0	0

Note: The numbers (N) in the header is the total number of subjects in the safety set.[1] Four subjects out of 135 did not return any diary card (excluded from reactogenicity population), but were included in the safety population of AEs

Table 9 Overview of Unsolicited AEs

	Number (%) of Subjects with Adverse Events		
	18-60 years	**≥ 61 years**	**TOTAL**
	N=68	**N=67**	**N=135**
Any AEs	14 (21)	9 (13)	23 (17)
At least possibly related AEs	4 (6)	1 (1)	5 (4)
Serious AEs	0	1 (1)	1 (1)
At least possibly related SAEs	0	0	0
AEs leading to discontinuation	0	0	0
Death	0	0	0

Table 10 Number (Percentages) of Subjects With Serious Adverse events by Preferred Term sorted by System Organ Class

	Number (%) of Subjects [1]		
MedDRA System Organ Class	**18-60 years**	**≥ 61 years**	**TOTAL**
MedDRA Preferred Term	**N=68**	**N=67**	**N=135**
Any Serious Adverse Event	0	1 (1%)	1 (1%)
Injury & Poisoning			
Fall	0	1 (1%)	1 (1%)

[1]Number and percent of subjects with one or more events (as reported on Adverse Events form) that map to each MedDRA system organ class or MedDRA preferred term. Hence, MedDRA preferred term counts may not sum to MedDRA system organ class counts, and MedDRA system organ class counts may not sum to overall counts.

Table 11 Number (Percentages) of Subjects With Unsolicited AEs Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class

None Reported

Conclusion:

FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur], formulation 2009-2010, was well tolerated and can be considered protective, and complies with the CHMP criteria for the approval of influenza vaccines.

Date of Clinical Trial Report: 10 AUG 09