Sponsor: Novartis Vaccines and Diagnostics S.r.l

Investigational Product: Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)

Indication: Prophylaxis: Influenza

Protocol Number: V71_10S

Protocol Title: A Phase II, Open Label, Uncontrolled, Multi Center Study to Evaluate Safety and Immunogenicity of AGRIPPAL® S1 Surface Antigen, Inactivated, Influenza Vaccine, Formulation 2009-2010, when Administered to Non-Elderly Adult and Elderly Subjects

Phase of Development: II

Study Period:

Date of first enrolment: 08 JUN 09

Date of last visit: 06 JUL 09

Methodology:

All subjects received 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 at the clinic for 30 minutes after vaccination for any immediate reactions. Each subject was instructed to fill in a diary card for three days following vaccination to collect local (ecchymosis, erythema, induration, swelling and pain) 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 (window: 0 / +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 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 (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, 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.

A total of 130 subjects were actually enrolled. Of this total, 129 subjects were included in the safety analysis and 126 subjects in the immunogenicity analysis (Per Protocol [PP] set).

Study Centers:

Three study centers in Italy**.**

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

NCT00918268

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 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. Antibodies maybe additionally quantified using the hemagglutination inhibition (HI) 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 intramuscular (IM) injection of AGRIPPAL S1 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 vaccine (CPMP/BWP/214/96).

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

0.5 mL of the subunit trivalent influenza virus vaccine for the Northern Hemisphere (NH) influenza season 2009/2010, was presented in a prefilled syringe (Lot No: 095001; Date of expiry-APR10) contained: 15 µg each of Influenza A/Brisbane/59/2007 (H1N1)-like virus; Influenza A/Brisbane/10/2007 (H3N2)-like virus and Influenza B/Brisbane/60/2008-like virus. The vaccine was administered by intra muscular route.

Duration of Study:

Approx. 4 weeks (approx. 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 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 written 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

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 ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin, and neomycin sulphate);
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. Female who were pregnant or nursing (breastfeeding) mothers or females of childbearing age did not plan to use acceptable birth control measures, for the duration of the study. Adequate contraception was defined as hormonal (e.g., oral, injection, transdermal patch, implant, cervical ring), barrier (e.g., condom or diaphragm), intrauterine device (IUD), or monogamous relationship with vasectomized partner who had been vasectomized for 6 months or more prior to the subject's study entry;
7. Within the past 12 months, they had:
   a. Received more than one injection of influenza vaccine;
8. Within the past 6 months, they had:
   a. Had laboratory confirmed influenza disease;
   b. Received influenza vaccine;
9. Within the past 4 weeks they had received:
   a. Another vaccine;
   b. Any investigational agent;
10. Any acute or chronic infection requiring systemic antibiotic treatment or antiviral therapy within the last 7 days;
11. Fever (i.e. axillary temperature ≥ 38.0°C) within the last 3 days;
12. Simultaneous participation in another clinical study;

13. Any condition, which, in the opinion of the investigator, might interfere with the evaluation of the study objectives;

14. Severely obese with Body Mass Index (BMI) > 35;

15. Site personnel involved in evaluation of safety and their immediate relatives were excluded from participation.

Criteria for Evaluation:

Immunogenicity

Immunogenicity analyses were performed by SRH assay and assessed according to CPMP/BWP/214/96. In non-elderly 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 Geometric Mean Ratio (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).

Table 1: Time and Events

	Visit 1 Day 0	☎ Day 4 (0/+2)	Visit 2 Day 21 (-1/+5)
Informed consent	**X**		
Inclusion/Exclusion criteria	**X** [1]		
Medical History	**X** [1]		
Brief physical examination	**X**		**X**
Pregnancy Test	**X** [1]		
Concomitant Medication	**X**	**X**	**X**
Pre-vaccination temperature	**X**		
Blood draw	**X** [1]		**X**
Vaccination	**X**		
Diary card dispensing	**X**		
Local and systemic reaction reporting	**X**	**X**	**X**
Adverse event reporting	**X**	**X**	**X**
Follow up telephone call		**X**	
Diary card collected and/or reviewed [2]		**X**	**X**
Study Termination			**X**

[1] Before vaccination

[2] Diary card review was performed over the phone for Day 4 and at Day 21 visits. Diaries were returned at Day 21 clinic visit.

Results:

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=65	**N=65**	**N=130**
Enrolled	65	65	130
Completed study	64 (98%)	65 (100%)	129 (99%)
Premature withdrawals	1 (2%)	0	1 (<1%)
Lost to follow-up	1 (2%)	0	1 (<1%)

YOA = years of age

Table 3: Overview of Subjects Population

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=65	**N=65**	**N=130**
Population:			
Enrolled	65(100%)	65(100%)	130(100%)
Exposed	65(100%)	65(100%)	130(100%)
Immunogenicity (FAS)	65(100%)	65(100%)	130(100%)
Immunogenicity (PP)	61(94%)	65(100%)	126(97%)
Safety	64(98%)	65(100%)	129(99%)

YOA = years of age

Table 4: Demographic and Other Baseline Characteristics - All Enrolled Subjects

	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=65	**N=65**	**N=130**
Age (YOA):	45.9±10.7	69.5±7.2	57.7±14.9
Gender:			
Male	23(35%)	28(43%)	51(39%)
Female	42(65%)	37(57%)	79(61%)
Ethnic Origin:			
Caucasian	65(100%)	65(100%)	130(100%)
Weight (kg):	73.29±13.16	74.39±12.65	73.84±12.87
Height (cm):	166.6±8.3	164.7±7.9	165.6±8.1
Body Mass Index:	26.342±3.884	27.322±3.673	26.832±3.797
Prev. Influ. Vac.:			
No	12(18%)	5(8%)	17(13%)
Unknown	1(2%)	0	1(<1%)
Yes	52(80%)	60(92%)	112(86%)
Met Entry Criteria:			
No	2(3%)	0	2(2%)
Yes	63(97%)	65(100%)	128(98%)

YOA = years of age

Table 5: Vaccine Immunogenicity Assessed by SRH Assay (Per-Protocol Set)

		18-60 YOA (N=61)							≥ 61 YOA (N=65)						
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**		
PREVACCINATION															
		n/N	**%**	**n/N**	**%**	**n/N**	**%**		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
GMA [2]		41		30		32			29		28		45		
95% CI [3]		36-48		27-34		25-40			25-35		25-30		39-53		
Seroprotection rate [4]		55/61	90%	47/61	77%	46/61	75%		43/65	66%	41/65	63%	56/65	86%	
95% CI		80-96		65-87		63-86			53-77		50-75		75-93		
POSTVACCINATION															
	CHMP [7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP** [7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
Seroconversion rate [5]		2/2	100%	1/1	100%	8/8	100%		2/4	50%	0/0	0	2/2	100%	
Significant increase in antibody titers [6]		15/59	25%	13/60	22%	18/53	34%		20/61	33%	18/65	28%	13/63	21%	
Seroconversion rate or significant increase	**>40%**	17/61	28%	14/61	23%	26/61	**43%**	**>30%**	22/65	**34%**	18/65	28%	15/65	23%	
95% CI [3]		17-41		13-35		30-56			23-47		17-40		14-35		
GMA [2]		56		37		59			40		33		58		
95% CI [3]		52-61		35-40		54-65			34-46		30-36		53-64		
GM Increase [8]	**>2.5**	1.35		1.24		1.88		**>2.0**	1.35		1.21		1.29		
95% CI [3]		1.18-1.55		1.14-1.35		1.48-2.38			1.19-1.52		1.13-1.28		1.15-1.45		
Seroprotection rate [4]	**>70%**	60/61	**98%**	59/61	**97%**	60/61	**98%**	**>60%**	57/65	**88%**	55/65	**85%**	62/65	**95%**	
95% CI [3]		91-100		89-100		91-100			77-95		74-92		87-99		

Bold = Committee for Medicinal Products for Human Use (CHMP) criteria met; 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 ≥ 25 mm^2; [5]Seroconversion rate: proportion of subjects with negative pre-vaccination serum and a postvaccination serum area ≥ 25 mm^2; [6]Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum; [7]CHMP Criteria; [8] GM increase = Geometric mean increase

Table 6: Overview of Solicited Reactions

Number (%) of Subjects With Solicited Reactions			
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=64	**N=65**	**N=129**
Any [1]	29(45)	19(29)	48(37)
Local	25(39)	14(22)	39(30)
Systemic	15(23)	12(18)	27(21)

YOA = years of age

[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.

Table 7: Summary of Solicited Local Reactions (0-3 Days Post-Vaccination)

		Number (%) of Subjects With Injection Site Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=64	**N=65**	**N=129**
Ecchymosis (mm)	Any	4(6)	4(6)	8(6)
	> 50 mm	0	0	0
Erythema (mm)	Any	8(13)	10(15)	18(14)
	> 50 mm	0	0	0
Induration (mm)	Any	8(13)	8(12)	16(12)
	> 50 mm	0	0	0
Swelling (mm)	Any	4(6)	5(8)	9(7)
	> 50 mm	0	0	0
Pain	Any	21(33)	6(9)	27(21)
	Severe	1(2)	0	1(1)

YOA = years of age;

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

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

Table 8: Summary of Solicited Systemic Reactions (0-3 Days Post-Vaccination)

		Number (%) of Subjects With Systemic Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=64	**N=65**	**N=129**
Chills Shivering	Any	3(5)	2(3)	5(4)
	Severe	0	0	0
Malaise	Any	4(6)	3(5)	7(5)
	Severe	1(2)	0	1(1)
Myalgia	Any	9(14)	6(9)	15(12)
	Severe	2(3)	0	2(2)
Arthralgia	Any	3(5)	5(8)	8(6)
	Severe	1(2)	0	1(1)
Headache	Any	8(13)	3(5)	11(9)
	Severe	1(2)	0	1(1)
Sweating	Any	3(5)	7(11)	10(8)
	Severe	0	1(2)	1(1)
Fatigue	Any	5(8)	2(3)	7(5)
	Severe	1(2)	0	1(1)
Fever (Temp. ≥ 38C)	Yes	0	0	0

YOA = years of age;
Note: The numbers (N) in the header is the total number of subjects with documented reactions

Table 9: Overview of Unsolicited AEs

	Number (%) of Subjects with Adverse Events		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=64	**N=65**	**N=129**
Any AEs	6 (9)	4 (6)	10 (8)
At least possibly related AEs	5 (8)	3 (5)	8 (6)
Serious AEs	0	0	0
At least possibly related SAEs	0	0	0
AEs leading to discontinuation	0	0	0
Death	0	0	0

YOA = years of age;

Table 10: Serious Adverse events by Preferred Term sorted by System Organ Class

None Reported

Table 11: Unsolicited AEs Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class

None Reported

Conclusion:

In conclusion, the 2009/2010 AGRIPPAL S1 influenza vaccine provides a good immunogenicity, tolerability and safety profile in non-elderly adults and elderly subjects and complies with the CHMP criteria for approval of influenza vaccines.

Date of Clinical Trial Report: **13 JUL 09**