Sponsor: Novartis Vaccines and Diagnostics

Investigational Product: eTIV_a, Surface Antigen Inactived, Influenza Vaccine, Formulation 2010-2011

Indication: Prophylaxis: Influenza

Protocol Number: V71_19S

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 2010-2011, when Administered to Non-Elderly Adult and Elderly Subjects .

Phase of Development: Phase II

Study Period:

Date of first enrolment: 14 JUN 10

Date of last visit: 12 JUL 10

Methodology:

In this open label study, subjects were enrolled into two groups according to age (at least 50 subjects aged 18 to 60 years; at least 50 subjects aged over 60 years). Prior to vaccination on Day 1 (Visit 1), the study staff queried each female of childbearing potential to determine the date of her last menstrual period and, the subject's commitment to use a birth control from Day 1 up to and including the three weeks following vaccination. To be eligible for this study, all females of childbearing potential were required to have a negative urine pregnancy test to receive study vaccination. Blood samples, approx. 10 mL, for the determination of antibody titers were drawn on Day 1 prior to vaccination and on Day 22 (-1/+5 days) (end of individual study participation).

After immunization on Day 1, subjects were observed for approximately 30 minutes for any immediate reactions. Each subject was instructed to complete a diary card for three more days following immunization to collect local (ecchymosis, erythema, induration, swelling and pain at the injection site) and systemic reactions (chills/shivering, malaise, myalgia, arthralgia, headache, sweating, fatigue and fever [i.e., axillary temperature ≥ 38°C]). Subjects were contacted by phone on Day 5 (window: 0/+2) after immunization to ensure that local and systemic reaction data were 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 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 was to take nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of viral origin. For confirmatory purpose specimens were planned to be analyzed via Quick test and Real Time – Polymerase Chain Reaction (RT-PCR) or culture.

Number of Subjects (planned and analyzed):

Approximately 126 subjects were planned to be enrolled, of which 63 in the non-elderly adult age group (aged 18 to 60) and 63 in the elderly age group (aged 61 and older). In the non-elderly adult age group, not more than approximately half of the subjects should had been aged between 41 and 60 years. The sample size (126) allowed for up to 13 non evaluable subjects per age group (non-evaluable subjects were enclosed in the per protocol set exclusions due to protocol deviation as predefined in the analysis plan).

In total 138 subjects were actually enrolled and included in the safety analysis and 131 subjects in the immunogenicity analysis (per protocol set).

Study Centers:

Six centers in Italy.

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

NCT01151059

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 non-elderly adult and elderly subjects in compliance with the requirements of the current European Union (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 safety of a single IM (intramuscular) dose of eTIV_a 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:

eTIV_a subunit vaccine (Lot No.:106501A; Date of expiry 27 APR 2011) for the Northern Hemisphere (NH) influenza season 2010/2011. The vaccine was administered IM.

Duration of Study:

Each subject participated approximately for 3 weeks after enrolment into the study.

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

None

Statistical Methods:

There is no statistical null hypothesis associated with the immunogenicity objective. Statistical analysis was carried out descriptively.

This study was in compliance with the sample size requirements of the current Committee for Medical Products for Human use (CHMP) guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

1. Male and female volunteers of 18 years of age and older, mentally competent, were 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 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, could 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. 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;
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 entire duration 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 entire duration 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 could interfere with the safety of the subject;
7. Females who were pregnant or nursing (breastfeeding) mothers or 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 (e.g., oral, injection, transdermal patch, implant, cervical ring), barrier (e.g., condom with spermicide or diaphragm with spermicide), 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;

8. Individuals who were not able to comprehend and to follow all required study procedures for the whole period of the study;
9. Individuals that within the past 6 months :
   a. had laboratory confirmed seasonal or pandemic influenza disease;
   b. received seasonal or pandemic influenza vaccine;
10. Individuals with any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days;
11. Individuals that experienced fever (i.e., axillary temperature ≥ 38°C) within 3 days before the intended study vaccination;
12. Individuals with history or any illness that, in the opinion of the investigator, could interfere with the results of the study or pose additional risk to the subjects due to participation in the study;
13. Individuals who participated in any clinical trial with another investigational product 4 weeks prior to first study visit or intent to participate in another clinical study at any time during the conduct of this study;
14. Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who were planning to receive any vaccine within 4 weeks following receipt of the study vaccine;
15. Individuals who received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks and for the entire duration of the study;
16. Individuals who were part of study personnel or close family members conducting this study;
17. Body Mass Index (BMI) > 35 kg/m^2.

Criteria for Evaluation:

Seroprotection rate, Geometric Mean Ratio (GMR) and rate of seroconversion or significant increase were determined by SRH 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 older 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.

Results:

Table 1: Overview of Subject Populations Analyzed – All Enrolled Subjects

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=62**	**N=138**
Population:			
Enrolled	76 (100%)	62 (100%)	138 (100%)
Immunogenicity (FAS)	73 (96%)	60 (97%)	133 (96%)
Immunogenicity (PPS)	72 (95%)	59 (95%)	131 (95%)
Exposed	76 (100%)	62 (100%)	138 (100%)
Safety	76 (100%)	62 (100%)	138 (100%)
Safety After Study Day 4	76 (100%)	62 (100%)	138 (100%)

YOA = years of age; FAS=Full Analysis Set, PPS= Per Protocol Set.

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=62**	**N=138**
Enrolled	76	62	138
Completed study	73 (96%)	60 (97%)	133 (96%)
Premature withdrawals	3 (4%)	2 (3%)	5 (4%)
Lost to follow-up	3 (4%)	2 (3%)	5 (4%)

YOA = years of age.

Table 3: Demography and Other Baseline Characteristics – All Enrolled Subjects

	18-60 YOA N=76	≥ 61 YOA N=62	TOTAL N=138
Age (Years):	43.8±11.5	68.4±5.5	54.8±15.4
Gender:			
Male	23 (30%)	32 (52%)	55 (40%)
Female	53 (70%)	30 (48%)	83 (60%)
Child Bearing Potential:			
No	17 (22%)	31 (50%)	48 (35%)
Yes	36 (47%)	0	36 (26%)
Not Available	23	31	54
Pregnancy Test:			
Negative	36 (47%)	0	36 (26%)
Not Applicable	17 (22%)	31 (50%)	48 (35%)
Not Available	23	31	54
Ethnic Origin:			
Caucasian	75 (99%)	62 (100%)	137 (99%)
Hispanic	1 (1%)	0	1 (<1%)
Weight (kg):	68.36±13.38	74.19±12.87	70.97±13.42
Height (cm):	166.5±8.8	165.3±7.0	166.0±8.1
Body Mass Index:	24.54±3.68	27.03±3.74	25.66±3.90
Previous Seasonal Influenza vaccination:			
No	23 (30%)	4 (6%)	27 (20%)
Unknown	1 (1%)	0	1 (<1%)
Yes	52 (68%)	58 (94%)	110 (80%)
Previous Pandemic Influenza vaccination:			
No	43 (57%)	31 (50%)	74 (54%)
Unknown	1 (1%)	2 (3%)	3 (2%)
Yes	32 (42%)	29 (47%)	61 (44%)
Met Entry Criteria:			
Yes	76 (100%)	62 (100%)	138 (100%)

Categorical parameters: N (%), non-categorical parameters: Mean±Standard deviation.
YOA = years of age.

Table 4: Vaccine Immunogenicity Assessed By SRH Assay - Per Protocol Set

		18-60 YOA (N=72)							≥ 61 YOA (N=59)					
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]		22		18		34			27		17		35	
95% CI[3]		19-26		17-20		30-38			22-32		15-20		31-39	
Seroprotection rate[4]		33/72	46%	11/72	15%	54/72	75%		32/59	54%	12/59	20%	46/59	78%
95% CI		34-58		8-26		63-84			41-67		11-33		65-88	
POSTVACCINATION														
	CHMP[7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP**[7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate[5]		1/2	50%	0/1	0	1/1	100%		0/1	0	1/2	50%	0/0	0
Significant increase in antibody titers[6]		43/70	61%	36/71	51%	29/71	41%		31/58	53%	35/57	61%	19/59	32%
Seroconversion rate or significant increase	**> 40%**	44/72	**61%**	36/72	**50%**	30/72	**42%**	**> 30%**	31/59	**53%**	36/59	**61%**	19/59	**32%**
95% CI[3]		49-72		38-62		30-54			39-66		47-73		21-46	
GMA[2]		44		28		49			45		30		45	
95% CI[3]		40-50		26-31		46-53			39-51		27-34		42-49	
GM Increase[8]	**> 2.5**	1.97		1.56		1.44		**> 2.0**	1.69		1.77		1.3	
95% CI[3]		1.71-2.26		1.42-1.7		1.31-1.59			1.47-1.93		1.57-1.99		1.21-1.4	
Seroprotection rate[4]	**> 70%**	66/72	**92%**	54/72	**75%**	70/72	**97%**	**> 60%**	54/59	**92%**	44/59	**75%**	57/59	**97%**
95% CI[3]		83-97		63-84		90-100			81-97		62-85		88-100	

Bold = 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 5: Overview of Solicited Reactions – Safety Set

	Number (%) of Subjects With Solicited Reactions		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=73	**N=60**	**N=133**
Any[1]	47 (64)	12 (20)	59 (44)
Local	41 (56)	11 (18)	52 (39)
Systemic	22 (30)	6 (10)	28 (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. Five subjects have not provided any information about reactogenicity.

Table 6: Overview of Local Reactions (1-4 Days Post-Vaccination) – Safety Set

		Number (%) of Subjects With Injection Site Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=73	**N=60**	**N=133**
Ecchymosis (mm)	Any	1 (1)	4 (7)	5 (4)
	>50 mm	0	0	0
Erythema (mm)	Any	10 (14)	2 (3)	12 (9)
	>50 mm	0	0	0
Induration (mm)	Any	10 (14)	2 (3)	12 (9)
	>50 mm	0	0	0
Swelling (mm)	Any	8 (11)	1 (2)	9 (7)
	>50 mm	0	0	0
Pain	Any	38 (52)	8 (13)	46 (35)
	Severe	0	0	0

YOA = years of age.

Note: The numbers (N) in the header is the total number of subjects with documented reactions. Five subjects have not provided any information about reactogenicity.

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

		Number (%) of Subjects With Systemic Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=73	**N=60**	**N=133**
Chills/ Shivering	Any	2 (3)	0	2 (2)
	Severe	0	0	0
Malaise	Any	6 (8)	2 (3)	8 (6)
	Severe	0	0	0
Myalgia	Any	13 (18)	3 (5)	16 (12)
	Severe	0	0	0
Arthralgia	Any	3 (4)	1 (2)	4 (3)
	Severe	0	0	0
Headache	Any	4 (5)	1 (2)	5 (4)
	Severe	0	0	0
Sweating	Any	5 (7)	4 (7)	9 (7)
	Severe	0	0	0
Fatigue	Any	9 (12)	4 (7)	13 (10)
	Severe	0	0	0
Fever (≥ 38°C)	Yes	1 (1)	0/59	1/132 (1)

YOA = years of age.

Note: The numbers (N) in the header is the total number of subjects with documented reactions. Five subjects have not provided any information about reactogenicity. Additionally one elderly subject has not provided data for body temperature.

Table 8: Overview of Unsolicited AEs – Safety Set

	Number (%) of Subjects with Adverse Events		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=62**	**N=138**
Any AEs	11 (14)	4 (6)	15 (11)
At least possibly related AEs	5 (7)	2 (3)	7 (5)
Serious AEs	0	1 (2)	1 (1)
At least possibly related SAEs	0	0	0
AEs leading to discontinuation	0	0	0
Death	0	0	0

YOA = years of age; AEs = adverse events.

Table 9: Serious Adverse Events by Preferred Term Sorted by System Organ Class – Safety Set

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=62**	**N=138**
Ear & Labyrinth Disorders			
Vertigo	0	1 (2%)	1 (1%)

YOA = years of age.

Table 10: Unsolicited AEs Reported by ≥ 5% of Subjects by Preferred Term Sorted by System Organ Class - – Safety Set

None reported.

Conclusion:

The 2010/2011 eTIV_a (Surface Antigen Inactived, Influenza Vaccine, Formulation 2010-2011) vaccine formulation has a good immunogenicity, tolerability and safety profile and complies with the Committee for Medical Products for Human use CHMP criteria for the approval of influenza vaccines.

Date of Clinical Trial Report: 21 JUL 10