Sponsor:	Novartis Vaccines and Diagnostics
Investigational Product:	Agrippal® S1 Surface Antigen, Inactivated, Influenza Vaccine, Formulation 2010-2011
Indication:	Prophylaxis: Influenza
Protocol Number:	V71_27S
Protocol Title:	A Phase II Open Label, Uncontrolled, Multi Center Study to Evaluate Safety and Immunogenicity of a Surface, Antigen, Inactivated, Influenza Vaccine (Agrippal®), Formulation 2011/2012, when Administered to adult and elderly subjects.
Phase of Development:	Phase II
Study Period:	
Date of first enrolment:	16 MAY 11
Date of last visit:	13 JUN 11

Methodology:

In this open label single treatment arm study, 126 subjects were planned to be enrolled into two groups according to age (at least 50 subjects aged 18-60 years should be evaluable; at least 50 subjects aged over 60 years should be evaluable). On Day 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. Subjects were observed for approximately 30 minutes after study vaccination on Day 1 for any immediate reactions. Each subject was instructed to complete a diary card for 3 days post the day of immunization to describe local (pain, erythema, ecchymosis, swelling and induration) and systemic reactions [fever (i.e., axillary temperature $\geq$ 38°C), chills/shivering, malaise, headache, myalgia,arthralgia, sweating and fatigue]. Subjects were contacted by phone on Day 5 (window:0/+3) after immunization 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 Days 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 took a nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of

viral origin. Specimens were analyzed via Quick test and RT-PCR or culture for confirmatory purposes.

Blood samples for immunogenicity assays were collected before vaccination (Day 1) and 21 days after vaccination (Day 22, window: -1/+5).

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 have 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 are excluded from the Per Protocol Set due to major protocol deviation as predefined in the analysis plan). Subjects who received the immunization and provided post-baseline safety data were included in the safety analyses.

In total 125 subjects were actually enrolled, 123 subjects were included in immunogenicity analyses and 124 subjects were included in safety analyses.

Study Centers:

Six study centers in Italy.

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

NCT01357265

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 (at the time) current 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 intramuscular (IM) injection of Agrippal in non-elderly adult and elderly subjects in compliance with the requirements of the (at the time) 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 0.5 mL dose of Agrippal was supplied in prefilled syringes and was administered intramuscularly in the deltoid muscle of (preferably) the non dominant arm.

A 0.5 mL dose of Agrippal contains purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA), including 15 µg of HA of each of the three strains (A/H1N1-like strain, A/H3N2-like strain, B-like strain), recommended for inclusion in the vaccine composition for the influenza season 2011/2012 in the Northern Hemisphere.Lot No.:110702A.

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 was 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 (at the time) current CHMP guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96). The main immunogenicity analyses were based on PPS.

Diagnosis and Main Criteria for Inclusion and Exclusion: The study population consisted of healthy male and female adults who are ≥ 18 years of age, mentally competent, willing and able to give informed consent prior to study entry. They were eligible if they did not receive any seasonal or pandemic influenza vaccine or did not have a laboratory confirmed seasonal or pandemic influenza disease within the past 6 months.

Criteria for Evaluation:

Seroprotection rate, 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

	Number (%) of Research Participants		
	18-60 YOA N=66	**≥ 61 YOA N=59**	**TOTAL N=125**
Enrolled	66	59	125
Immunogenicity (FAS)	64 (97%)	59 (100%)	123 (98%)
Immunogenicity (PPS)	64 (97%)	59 (100%)	123 (98%)
Exposed	65 (98%)	59 (100%)	124 (99%)
Safety	65 (98%)	59 (100%)	124 (99%)
Safety After Study Day 4	65 (98%)	59 (100%)	124 (99%)

Abbreviations: FAS = full analysis set; PPS = per protocol set; YOA = years of age

Table: 2 Summary of Study Terminations - Enrolled Population

	Number (%) of Research Participants		
	18-60 YOA N=66	**≥ 61 YOA N=59**	**TOTAL N=125**
Total number of subjects enrolled	66	59	125
Missing primary reason	1 (2%)	0	1 (1%)
Completed	64 (97%)	59 (100%)	123 (98%)
Completed protocol	64 (97%)	59 (100%)	123 (98%)
Premature withdrawal	1 (2%)	0	1 (1%)
Unable to classify	1 (2%)	0	1 (1%)

YOA = years of age

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

	Number (%) of Research Participants		
	18-60 YOA N=66	**≥ 61 YOA N=59**	**TOTAL N=125**
Age (Years)	39.8 ± 12.1	68.2 ± 7.2	53.2 ± 17.4
Gender			
Male	25 (38%)	26 (44%)	51 (41%)
Female	41 (62%)	33 (56%)	74 (59%)
Child Bearing Potential			
Yes	33 (50%)	0	33 (26%)
No	8 (12%)	33 (56%)	41 (33%)
Not Available	25	26	51
Pregnancy Test			
Not applicable	[a]1 (2%)	0	1 (<1%)
Negative	33(50%)	0	33(26%)
Not Done	6 (9%)	33 (56%)	39 (31%)
Not Available	26	26	52
Ethnic Origin:			
White, Non-Hispanic	65 (98%)	59 (100%)	124 (99%)
Other	1 (2%)	0	1 (<1%)
Weight (kg)	65.66 ± 11.81	72.75 ± 12.52	69.01 ± 12.62
Height (cm)	167.8 ± 7.8	164.8 ± 6.5	166.4 ± 7.3
Body Mass Index	23.28 ± 3.60	26.69 ± 3.68	24.89 ± 4.00
Previous Seasonal Vaccination			
Yes	47 (71%)	54 (92%)	101 (81%)
No	19 (29%)	4 (7%)	23 (18%)
Unknown	0	1 (2%)	1 (<1%)
Previous Pandemic Vaccination			
Yes	23 (38%)	13 (22%)	38 (30%)
No	40 (61%)	39 (66%)	79 (63%)
Unknown	1 (2%)	7 (12%)	8 (6%)
Previous Pandemic Vaccination Type			
Focetria	25 (38%)	13 (22%)	38 (30%)
Not Available	41	46	87
Met Entry Criteria	65 (98%)	59 (100%)	124 (99%)

[a]: subject 50/007 had a surgical menopause

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

Table: 4 Vaccine Immunogenicity Assessed by SRH Assay - Per Protocol Population

		18-60 Years of age (N=64)						≥ 61 Years of age (N=59)					
Strains		**A/(H1N1)**		**A/(H3N2)**		**B**			**A/(H1N1)**		**A/(H3N2)**		**B**	
PREVACCINATION														
		n/N[1]	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**		**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**
GMA			22		16		35			14		17		44
95% CI			17 - 28		14 - 19		29 - 43			11 - 17		14 - 20		38 - 50
Seroprotection rate		36/64	56%	18/64	28%	50/64	78%		20/59	34%	20/59	34%	54/59	92%
95% CI			43%-69%		18%-41%		66%-87%			22%-47%		22%-47%		81%-97%
POSTVACCINATION														
	CHMP	**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**	**CHMP**	**n/N[1]**	**%**	**n/N[1]**	**%**	**n/N[1]**	**%**
[2]Seroconversion rate		8/11	73%	2/3	67%	5/6	83%		5/12	42%	4/5	80%	1/1	100%
[3]Significant increase in SRH area		25/53	47%	31/61	51%	16/58	28%		32/47	68%	26/54	48%	9/58	16%
Seroconversion rate or significant increase	>40%	33/64	**52%**	33/64	**52%**	21/64	33%	>30%	37/59	**63%**	30/59	**51%**	10/59	17%
95% CI			39%-64%		39%-64%		22%-46%			49%-75%		37%-64%		8%-29%
GMA			45		28		54			31		27		56
95% CI			38-53		25-30		49-61			26-38		24-31		52-60
Geometric Mean Increase	>2.5		2.03		1.72		1.55	>2		**2.29**		1.6		1.28
95% CI			1.63 - 2.52		1.5 - 1.97		1.29 - 1.85			1.9 - 2.75		1.4 - 1.83		1.13 - 1.44
Seroprotection rate	>70%	61/64	**95%**	52/64	**81%**	63/64	**98%**	>70%	46/59	**78%**	47/59	**80%**	59/59	**100%**
95% CI			87%-99%		70%-90%		92%-100%			65%-88%		67%-89%		94%-100%

Bold = CHMP criteria met; Abbreviations: CI = confidence interval; GMA – geometric mean area; CHMP -

[1]n/N: responders (n) as part of number of total number of subjects (N);

[2]Seroconversion rate: proportion of subjects with negative pre-vaccination serum (SRH area < 4mm^2) and a post-vaccination serum area ≥ 25 mm^2;

[3]Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum.

Table: 5 Immunogenicity results assessed by SRH Assay on Day 22 – PPS

		Number (%) of Research Participants	
	Number of subjects	**18-60 YOA N=64**	**≥ 61 YOA N=59**
A/California/7/2009 (H1N1)-like strain	GMA [1]	45 (38-53)	31 (26-38)
	Geometric mean increase	2.03 (1.63-2.52)	**2.29 (1.9-2.75)**
	Seroprotection rates [2]	**95% (87%-99%)**	**78% (65%-88%)**
	Seroconversion or significant increase [3]	**52% (39%-64%)**	**63% (49%-75%)**
A/Perth/16/2009 (H3N2)- like strain	GMA [1]	28 (25-30)	27 (24-31)
	Geometric mean increase	1.72 (1.5-1.97)	1.6 (1.4-1.83)
	Seroprotection rates [2]	**81% (70%-90%)**	**80% (67%-89%)**
	Seroconversion or significant increase [3]	**52% (39%-64%)**	**51% (37%-64%)**
B/Brisbane/60/ 2008-like strain	GMA [1]	54 (49-61)	56 (52-60)
	Geometric mean increase	1.55 (1.29-1.85)	1.28 (1.13-1.44)
	Seroprotection rates [2]	**98% (92%-100%)**	**100% (94%- 100%)**
	Seroconversion or significant increase [3]	33% (22%-46%)	17% (8%-29%)

Bold = CHMP criteria met;

[1]GMA=Geometric mean area;

[2]Seroprotection rate: proportion of subjects with a post-vaccination area ≥ 25 mm^2;

[3]Seroconversion or significant increase: proportion of subjects with either seroconversion or significant increase. Seroconversion: proportion of subjects with negative pre-vaccination serum and a post-vaccination serum area ≥ 25 mm^2.

Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum.

Table: 6 Overview of Solicited Reactions - Safety set

	Number (%) of Subjects With Solicited Reactions		
	18-60 YOA [a] **N=64**	**≥ 61 YOA N=59**	**TOTAL N=123**
Any	46 (72%)	16 (27%)	62 (50%)
Local	35 (55%)	13 (22%)	48 (39%)
Systemic	26 (41%)	5 (8%)	31 (25%)

Abbreviation: YOA= years of age

[a]: Subject 20/008 was excluded from the reactogenicity analyses in 18 to 60 years age group, as the subject did not have visit-3 so diary card was not collected.

Table: 7 Percentage of Subjects Reporting Solicited Local Reactions (1-4 Days Post-Vaccination) - Safety set

		Number (%) of Subjects With Injection Site Reactions		
		18-60 Years N=64[a]	**≥ 61 Years N=59**	**TOTAL N=123**
Ecchymosis	Any	2 (3%)	1 (2%)	3 (2%)
	>50 mm	0	0	0
Erythema (mm)	Any	5 (8%)	3 (5%)	8 (7%)
	>50 mm	1 (2%)	1 (2%)	2 (2%)
Induration	Any	6 (9%)	4 (7%)	10 (8%)
	>50 mm	0	1 (2%)	1 (1%)
Swelling (mm)	Any	3 (5%)	3 (5%)	6 (5%)
	>50 mm	0	1 (2%)	1 (1%)
Pain	Any	33 (52%)	9 (15%)	42 (34%)
	Severe	0	0	0

a: Subject 20/008 was excluded from the reactogenicity analyses in 18 to 60 years age group, as the subject did not have visit-3 so diary card was not collected.

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

Table: 8 Percentage of Subjects Reporting Solicited Systemic Reactions (1-4 Days Post-Vaccination) - Safety set

		Number (%) of Subjects With Systemic Reactions		
Systemic		**18-60 YOA N=64[a]**	**≥ 61 YOA N=59**	**TOTAL N=123**
Chills/ Shivering	Any	5 (8%)	2 (3%)	7 (6%)
	Severe	0	0	0
Malaise	Any	5 (8%)	2 (3%)	7 (6%)
	Severe	0	0	0
Myalgia	Any	9 (14%)	2 (3%)	11 (9%)
	Severe	0	0	0
Arthralgia	Any	7 (11%)	2 (3%)	9 (7%)
	Severe	0	0	0
Headache	Any	12 (19%)	2 (3%)	14 (11%)
	Severe	1 (2%)	0	1 (1%)
Sweating	Any	3 (5%)	2 (3%)	5 (4%)
	Severe	0	0	0
Fatigue	Any	12 (19%)	2 (3%)	14 (11%)
	Severe	0	0	0
Fever (≥ 38°C)		0	0	0
Other- Body Temp.	≥ 40°C	0	0	0

[a]: Subject 20/008 was excluded from the reactogenicity analyses in 18 to 60 years age group, as the subject did not have visit-3 so diary card was not collected.

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

Table: 9 Overview of Unsolicited AEs- Safety set

	Number (%) of Subjects with Adverse Events		
	18-60 Years	**≥ 61 Years**	**TOTAL**
	N=65	**N=59**	**N=124**
Any AEs	10 (15%)	4 (7%)	14 (11%)
At least possibly related AEs	5 (8%)	2 (3%)	7 (6%)
Serious AEs	0	0	0
At least possibly related SAEs	0	0	0
AEs leading premature withdrawal	0	0	0
Deaths	0	0	0

Abbreviations: AEs= adverse events, SAEs= serious adverse events

Table: 10 **Number (Percentages) of Subjects with Unsolicited Adverse Events Reported in > 5% of Subjects by Preferred Term sorted by System Organ Class - Safety Population**

None reported

Table: 11 **Number (Percentages) of Subjects with Unsolicited Adverse Events Reported in > 5% of Subjects by Preferred Term sorted by System Organ Class - Safety Population**

None reported

Conclusion:

In conclusion, the 2011/2012 Agrippal vaccine formulation has a good immunogenicity, tolerability and safety profile and complies with the CHMP criteria for the approval of influenza vaccines.

Date of Clinical Trial Report: **24 JUN 11**