Sponsor:	Novartis Vaccines and Diagnostics GmbH & Co. KG
Investigational Product:	Split-eTIV, Trivalent influenza virus vaccine (split virion, inactivated, egg-derived)
Indication:	Prophylaxis: Influenza
Protocol Number:	V44_13S
Protocol Title:	A Phase III, multicenter, uncontrolled, open-label study to evaluate safety and immunogenicity of Begrivac®, preservative free, inactivated split influenza vaccine, using the strain composition 2009/2010, when administered to adult and elderly subjects
Phase of Development:	Phase III
Study Period:	
Date of first enrolment:	03 JUN 09
Date of last visit:	24 JUN 09

Methodology:

All subjects were to receive one dose of split 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 (AEs; solicited and unsolicited) were collected during Day 0 to 3. All serious adverse events and/or AEs 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).

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 protocol deviation). In the non-elderly adult age group, no more than approximately half of the subjects were to be aged between 41 and 60 years.

In total 154 subjects were actually enrolled; 153 subjects were included in the safety analysis and 152 subjects in the immunogenicity analysis (per protocol set).

Study Centers:

Three centers in Germany.

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

NCT00945841

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 split influenza vaccine Begrivac®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:

0.5 mL of the Split-eTIV, influenza vaccine (Lot No.: 201110A ; Date of expiry-04/2010) for the Northern Hemisphere (NH) influenza season 2009/2010 contained: 15 µg each of hemagglutinin (HA) antigen from Influenza A/Brisbane/59/2007 (H1N1)-like virus;

Influenza A/Brisbane/10/2007 (H3N2)-like virus and Influenza B/Brisbane/60/2008-like virus, and was administered into the deltoid region of the (preferably) non-dominant arm.

Duration of Study:

23 Days (up to 2 days enrollment, 21 days participation per subject)

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

None

Statistical Methods:

There was no statistical null hypothesis to be 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 were 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:

- Medical history
- Physical examination
- Clinical judgment of the investigator

Written informed consent had to be obtained from each of 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, 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 are pregnant or nursing (breastfeeding) mothers or females of childbearing age who do 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:

- Another vaccine
- 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, geometric mean ratio (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).

Table 1 Time and Events

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

* Collect diary card and reconcile with the data on the “Local and Systemic Reactions” CRF collected at the Day 4 phone call

Results:

Table 2 Overview of Subject Populations

	Number (%) of subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=83	**N=71**	**N=154**
Population:			
Enrolled	83 (100%)	71 (100%)	154 (100%)
Immunogenicity (FAS)	83 (100%)	71 (100%)	154 (100%)
Immunogenicity (PP)	82 (99%)	70 (99%)	152 (99%)
Exposed	83 (100%)	71 (100%)	154 (100%)
Safety	82 (99%)	71 (100%)	153 (99%)

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

Table 3 Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
Enrolled	83	71	154
Completed study	82 (99%)	71 (100%)	153 (99%)
Premature withdrawals	1 (1%)	0	1 (<1%)
Lost to follow-up	1 (1%)	0	1 (<1%)

YOA = years of age

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

	18-60 YOA	≥ 61 YOA	TOTAL
	N=83	N=71	N=154
Age (years):	41.4±11.5	67.5±3.4	53.4±15.7
Gender:			
Male	37 (45%)	40 (56%)	77 (50%)
Female	46 (55%)	31 (44%)	77 (50%)
Race:			
Asian	0	1 (1%)	1 (<1%)
Caucasian	83 (100%)	70 (99%)	153 (99%)
Weight (kg):	75.31±14.28	77.19±12.07	76.18±13.30
Height (cm):	173.9±9.9	171.7±8.9	172.9±9.5
Body Mass Index:	24.805±3.545	26.144±3.305	25.422±3.490
Child Bearing Potential:			
N/A	37 (45%)	40 (56%)	77 (50%)
No	9 (11%)	31 (44%)	40 (26%)
Yes	37 (45%)	0	37 (24%)
Pregnancy Test:			
Negative	37 (45%)	0	37 (24%)
Not Available	46	71	117
Previous Influenza Vaccine:			
No	38 (46%)	9 (13%)	47 (31%)
Unknown	1 (1%)	0	1 (<1%)
Yes	44 (53%)	62 (87%)	106 (69%)
Met Entry Criteria:			
No	0	1 (1%)	1 (<1%)
Yes	83 (100%)	70 (99%)	153 (99%)

YOA = years of age

Table 5 Vaccine Immunogenicity Assessed by HI Assay - Per Protocol Population

		18-60 YOA (N=82)							≥ 61 YOA (N=70)					
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**	
PREVACCINATION														
		n/N	**%**	**n/N**	**%**	**n/N**	**%**		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
GMT [2]		16		25		15			26		54		19	
95% CI [3]		12-21		18-35		12-20			20-35		38-77		15-25	
Seroprotection rate [4]		22/82	27%	38/82	46%	23/82	28%		35/70	50%	47/70	67%	21/70	30%
95% CI		18-38		35-58		19-39			38-62		55-78		20-42	
POSTVACCINATION														
	CHMP [7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP** [7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate [5]		33/34	97%	21/23	91%	25/27	93%		6/13	46%	5/8	63%	5/14	36%
Significant increase in antibody titers [6]		31/48	65%	46/59	78%	28/55	51%		11/57	19%	21/62	34%	15/56	27%
Seroconversion rate or significant increase	**>40%**	64/82	**78%**	67/82	**82%**	53/82	**65%**	**>30%**	17/70	24%	26/70	**37%**	20/70	29%
95% CI		68-86		72-89		53-75			15-36		26-50		18-41	
GMT		232		376		125			71		172		51	
95% CI		174-309		287-491		100-156			55-91		127-231		38-67	
GM Increase [8]	**>2.5**	**15**		**15**		**8.14**		**>2.0**	**2.68**		**3.17**		**2.61**	
95% CI		10-21		11-21		5.92-11			2.07-3.47		2.42-4.15		2.04-3.34	
Seroprotection rate	**>70%**	79/82	**96%**	80/82	**98%**	77/82	**94%**	**>60%**	53/70	**76%**	63/70	**90%**	47/70	**67%**
95% CI		90-99		91-100		86-98			64-85		80-96		55-78	

Bold = CHMP criteria met. HI = hemagglutination inhibition; YOA = years of age.[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 (titer ≥ 40). [5] Seroconversion rate: proportion of subjects with antibody increase from < 10 pre-vaccination to ≥ 40 post-vaccination. [6] Significant increase: proportion of subjects with an antibody titer of ≥10 pre-vaccination and 4-fold antibody increase post-vaccination. [7] CHMP criteria. [8] GM increase = Geometric mean increase.

Table 6 Overview of Solicited Adverse Events – Safety Set

	Number (%) of Subjects With at Least One Solicited Reaction		
	18-60 YOA N=82	**≥ 61 YOA N=71**	**TOTAL N=153**
Any [1]	49(60)	24(34)	73(48)
Local	41(50)	15(21)	56(37)
Systemic	34(41)	17(24)	51(33)

Abbreviation: 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 Overview of Solicited Local Adverse Events (0-3 Days Post-Vaccination) – Safety Set

		Number (%) of Subjects With Injection Site Reactions		
		18-60 YOA N=82	**≥ 61 YOA N=71**	**TOTAL N=153**
Ecchymosis (mm)	Any	2(2)	1(1)	3(2)
	> 50 mm	0	0	0
Erythema (mm)	Any	1(1)	3(4)	4(3)
	> 50 mm	0	0	0
Induration (mm)	Any	4(5)	1(1)	5(3)
	> 50 mm	0	0	0
Swelling (mm)	Any	2(2)	2(3)	4(3)
	> 50 mm	0	0	0
Pain	Any	39(48)	14(20)	53(35)
	Severe	0	0	0

Abbreviation: YOA = years of age.
Note: 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 Overview of Solicited Systemic Adverse Events (0-3 Days Post-Vaccination) – Safety Set

		Number (%) of Subjects With Systemic Reactions		
		18-60 YOA N=82	**≥ 61 YOA N=71**	**TOTAL N=153**
Chills/Shivering	Any	5(6)	0	5(3)
	Severe	1(1)	0	1(1)
Malaise	Any	11(13)	2(3)	13(8)
	Severe	1(1)	0	1(1)
Myalgia	Any	15(18)	5(7)	20(13)
	Severe	0	0	0
Arthralgia	Any	3(4)	3(4)	6(4)
	Severe	0	0	0
Headache	Any	18(22)	5(7)	23(15)
	Severe	0	0	0
Sweating	Any	5(6)	1(1)	6(4)
	Severe	1(1)	0	1(1)
Fatigue	Any	18(22)	9(13)	27(18)
	Severe	0	0	0
Fever (≥ 38°C)	Yes	1(1)	0	1(1)

Abbreviation: YOA = years of age.

Table 9 Overview of Unsolicited Adverse Events – Safety Set

	Number (%) of Subjects With AEs		
	18-60 YOA N=82	**≥ 61 YOA N=71**	**TOTAL N=153**
Any AEs	19 (23)	6 (8)	25 (16)
At least possibly related AEs	8 (10)	4 (6)	12 (8)
SAEs	0	0	0
At least possibly related SAEs	0	0	0

	Number (%) of Subjects With AEs		
AEs leading to discontinuation	0	0	0
Death	0	0	0

Abbreviations: AEs = adverse events; SAEs = serious adverse events; YOA = years of age.

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

None reported.

Table 11 Other Adverse Events Reported in > 5 % of Subjects by Preferred Term sorted by System Organ Class

None Reported.

Conclusion:

Both adult and elderly subjects met at least one of the CPMP/BWP/214/96 criteria for each influenza strain and the safety profile was as expected for preservative- free inactivated trivalent split influenza vaccines. Split-eTIV 2009/2010 / suspension for injection / Influenza vaccine (split virion, inactivated) can be considered as protective and safe.

Date of Clinical Trial Report: 01 JUL 09