Sponsor: Novartis Vaccines and Diagnostics GmbH& Co. KG, Postfach 1630, 35006 Marburg, Germany[1]

Investigational Product: Begrivac 2008/2009, preservative free, inactivated split influenza vaccine

Indication: Prophylaxis: Influenza

Protocol Number: V44P12S

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 2008/2009, when administered to adult and elderly subjects.

Phase of Development: Phase III

Study Period:

Date of first enrolment: 30 JUN 08
Date of last visit: 21 JUL 08

Methodology: All subjects were to receive a single injection 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 those with negative result received study vaccination. 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 (±1) 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 during the study period 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.

[1] Novartis Vaccines and Diagnostics GmbH

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. 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 135 subjects were actually enrolled, 131 subjects were included in the safety analysis and 127 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:

NCT00735410

Objectives:

Immunogenicity Objectives: To evaluate the antibody response to each influenza vaccine antigen, as measured by haemagglutination 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 vaccine (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 intramuscular (IM) dose of the Begrivac influenza vaccine Split-eTIV 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: Each 0.5 mL of the influenza split vaccine (Lot No.: 174011A) for the Northern Hemisphere (NH) influenza season 2008/2009 contained ≥15 µg each of Influenza A/Brisbane/59/2007 (H1N1)-like virus, Influenza A/Brisbane/10/2007 (H3N2)-like virus and Influenza B/Florida/4/2006-like virus .The vaccine was administered IM.

Duration of Study:

23 Days (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 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. Available for all the visits scheduled in the study and 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 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 (in the judgment of the investigator) disease, 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)
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, 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 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 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 a duration beyond Day 3 postvaccination) 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 Subject Populations

	18-60 YOA N=67	≥ 61 YOA N=68	TOTAL N=135
Population:			
Enrolled	67 (100%)	68 (100%)	135 (100%)
Immunogenicity (FAS)	66 (99%)	68 (100%)	134 (99%)
Immunogenicity (PP)	62 (93%)	65 (96%)	127 (94%)
Safety	64 (96%)	67 (99%)	131 (97%)

YOA = years of age

Table 2: Summary of Study Terminations - All Enrolled Set

	Number Of Subjects (% Of Total)		
Primary Withdrawal Reason	**18-60 YOA**	**≥ 61 YOA**	**TOTAL**
Total Number Of Subjects Enrolled	67	68	135
Completed	63 (94%)	67 (99%)	130 (96%)
Completed Protocol	63 (94%)	67 (99%)	130 (96%)
Premature Withdrawal	4 (6%)	1 (1%)	5 (4%)
Death	0	0	0
Adverse Event	1 (1%)	0	1 (< 1%)
Lost To Follow-Up	1 (1%)	1 (1%)	2 (1%)
Protocol Deviation/Violation	1 (1%)	0	1 (< 1%)
Unable To Classify	1 (1%)	0	1 (< 1%)

YOA = years of age

Table 3: Summary of Demography - All Enrolled Set

	18-60 Y[a]- N=67	≥ 61 Y-[b] N=68	TOTAL N=135
Age (Yrs):			
Mean	39.3	66.9	53.2
Std. Dev.	11.8	4.7	16.5
Sex:			
Male	32 (48%)	32 (47%)	64 (47%)
Female	35 (52%)	36 (53%)	71 (53%)

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years

Table 4: Vaccine Immunogenicity Assessed by HI Assay Using Egg-Derived Test Antigens

	18-60 Y-[a] (N=62)							≥ 61 Y[b] (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**	**%**
Seroprotection rate [2]		27/62	44%	10/62	16%	8/62	13%		35/65	54%	28/65	43%	8/65	12%
95% CI		31-57		8-28		6-24			41-66		31-56		5-23	
POSTVACCINATION														
	CHMP [8]	**n/N** [1]	**%**	**n/N** [1]	**%**	**n/N** [1]	**%**	**CHMP** [4]	**n/N** [1]	**%**	**n/N** [1]	**%**	**n/N** [1]	**%**
Seroconversion rate or significant increase [3]	**>40%**	40/62	**65%**	54/62	**87%**	29/62	**47%**	**>30%**	16/65	25%	48/65	**74%**	14/65	22%
95% CI		51-76		76-94		34-60			15-37		61-84		12-33	
Mean GMT Increase	**>2.5**	**8.32**		**19**		**4.11**		**>2.0**	**2.45**		**7.92**		**2.36**	
95% CI		5.5-13		13-28		3.02-5.6			1.91-3.13		5.72-11		1.84-3.02	
Seroprotection rate	**>70%**	61/62	**98%**	59/62	**95%**	41/62	66%	**>60%**	51/65	**78%**	58/65	**89%**	28/65	43%
95% CI		91-100		87-99		53-78			67-88		79-96		31-56	

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years;
[1] n/N: responders (n) as part of number of subjects of the (sub-)population (N).
[2] Seroprotection rate: proportion of subjects with a protective titer pre- or post-vaccination (titer ≥ 40).
[3] Seroconversion rate: proportion of subjects with either seroconversion or significant increase [4] CHMP criteria

Table 5: Overview of Solicited Reactions

	Number (%) of Subjects With Solicited Reactions		
	18-60 Y[a]	**≥ 61 Y[b]**	**TOTAL [1]**
	N=63	**N=67**	**N=130**
Any	34(54)	24(36)	58(45)
Local	28(44)	13(19)	41(32)
Systemic	17(27)	19(28)	36(28)

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years;
[1] One subject did not return any diary card (excluded from reactogenicity population).
The subject is included in the safety population of AEs.

Table 6: Overview of Local Reactions (0-3 Days Post-Vaccination)

		Number (%) of Subjects With Injection Site Reactions		
		18-60 Y[a]	**≥ 61 Y[b]**	**TOTAL [1]**
		N=62	**N=67**	**N=129**
Ecchymosis (mm)	Any	2(3)	0	2(2)
	> 50 mm	0	0	0
Erythema (mm)	Any	3(5)	0	3(2)
	> 50 mm	0	0	0
Induration (mm)	Any	4(6)	0	4(3)
	> 50 mm	1(2)	0	1(1)
Swelling (mm)	Any	2(3)	1(1)	3(2)
	> 50 mm	0	0	0
Pain	Any	25(40)	13(19)	38(29)
	Severe	0	0	0

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years;
Note: The numbers (N) in the header is the total number of subjects with documented reactions in the diary card (including 0).

Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter <10mm), mild (diameter 10-25mm), moderate (diameter 26-50mm) and severe (diameter >50mm)
[1] One subject did not return any diary card (excluded from reactogenicity population).

Diary card of one subject showed missing values or "not done" only (excluded from this local and systemic reactions analyses). Both subjects are included in the safety population of AEs.

Table 7: Overview of Systemic Reactions (0-3 Days Post-Vaccination)

		Number (%) of Subjects With Systemic Reactions		
		18-60 Y[a]	**≥ 61 Y[b]**	**TOTAL [1]**
		N=62	**N=67**	**N=129**
Chills/Shivering	Any	0	0	0
	Severe	0	0	0
Malaise	Any	3(5)	3(4)	6(5)
	Severe	0	0	0
Myalgia	Any	6(10)	4(6)	10(8)
	Severe	0	0	0
Arthralgia	Any	0	3(4)	3(2)
	Severe	0	0	0
Headache	Any	9(15)	7(10)	16(12)
	Severe	0	0	0
Sweating	Any	1(2)	3(4)	4(3)
	Severe	0	0	0
Fatigue	Any	10(16)	15(22)	25(19)
	Severe	0	0	0
Fever (≥ 38°C)	Yes	0	0	0

Note: The numbers (N) in the header is the total number of subjects with documented reactions in the diary card (including 0).

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years;

[1] One subject did not return any diary card (excluded from reactogenicity analyses).

Diary card of one subject showed missing values or "not done" only (excluded from this local and systemic reactions analyses). Both subjects are included in the safety population of AEs.

Table 8: Overview of Other AEs

	Number (%) of Subjects with Adverse Events		
	18-60 Y[a] N=64	≥ 61 Y[b] N=67	TOTAL N=131
Any AEs	13 (20)	7 (10)	20 (15)
At least possibly related AEs	5 (8)	2 (3)	7 (5)
Serious AEs	1 (2)	0	1 (1)
At least possibly related SAEs	0	0	0
AEs leading to discontinuation	1 (2)	0	1 (1)
Death	0	0	0

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years

Table 9: Serious Adverse events by Preferred Term sorted by System Organ Class

MedDRA System Organ Class / MedDRA Preferred Term	Number % Of Subjects [1]		
	18-60 Y[a] N=64	≥ 61 Y[b] N=67	Total N=131
Any Serious Adverse Event	1 (2%)	0	1 (1%)
Injury & Poisoning			
Tendon Injury	1 (2%)	0	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. [a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years

Table 10: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term sorted by System Organ Class.

None Reported

Conclusion:

Considering that 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, Begrivac® 2008/2009 / suspension for injection / Influenza vaccine (split virion, inactivated) can be considered as protective and safe.

Date of Clinical Trial Report: **25 JUL 08**