Sponsor: Novartis Vaccines and Diagnostics GmbH & Co. KG

Investigational Product: Preservative free inactivated trivalent split influenza vaccine Begrivac® 2007/2008

Indication: Prophylaxis: Influenza

Protocol Number: V44PllS

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 2007/2008 when administered to adult and elderly subjects.

Phase of Development: Phase III

Study Period:

Date of first enrolment: 18 JUN 07

Date of last visit: 10 JUL 07

Methodology:

This was a phase III, uncontrolled, open label study. All volunteers were to receive a single dose of 0.5 mL split influenza vaccine into the deltoid muscle of the non-dominant arm on Day 0. Blood samples, approx. 20 mL, for the determination of antibody titers were drawn on Day 0 prior to vaccination and on Day 21± 1.

The vaccine contained inactivated split virus strains selected for 2007/2008 according to WHO recommendations, namely A/ Solomon Islands/3/2006-like (H1N1), A/Wisconsin/67/2005-like (H3N2), and B/Malaysia/2506/2004 –like (B). For the A/Solomon Islands/3/2006-like strain, the strain A/Solomon Island/3/2006 Reass. IVR-145, for the A/Wisconsin/67/2005-like strain, the strain A/Wisconsin/67/2005, NYMC X161B and for the B/Malaysia/2506/2004 -like strain, the strain B/Malaysia/2506/2004 were used for vaccine production, respectively.

Subjects were observed for 30 minutes for any immediate reactions. All subjects were instructed to fill in a diary card for three days following immunization 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. All adverse events 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, he/she had to contact the Investigator who would take a nasal and/or pharyngeal

swab for the further diagnostics, i.e. to determine the diagnosis of influenza or any other respiratory infection of viral origin.

Number of Subjects (planned and analyzed):

According to the CHMP requirements (CPMP/BWP/214/96) for seasonal influenza vaccine trials at least 100 subjects had to be included into the study (at least 50 subjects in each age group, 18-60 years and 61 years or over, respectively). To adjust for potential drop-outs, overall 120 subjects were planned to be enrolled.

Subjects who received the immunization were included in the safety analyses. Subjects who provided evaluable blood samples at Days 0 and 21 were included in the immunogenicity analyses.

127 subjects were enrolled, 125 subjects were included in the safety analysis and 121 subjects in the immunogenicity analysis (per protocol set).

Study Centers:

Two centers in Germany.

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

NCT00498303

Objectives:

Immunogenicity Objectives

To evaluate the antibody response to each influenza vaccine antigen, as measured by haemagglutination inhibition (HI) testing on Day 0 and on Day 21, i.e., 21 days after vaccination in non-elderly and elderly subjects, in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccine (CHMP/BWP/214/96).

Safety Objectives

To evaluate safety of a single IM (intramuscular) dose of the split influenza vaccine Begrivac® in non-elderly and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccine (CHMP/BWP/214/96).

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

Begrivac® 2007/2008: Preservative free inactivated trivalent split influenza vaccine
Lot Number.: 155011A
Single dose of 0.5 mL suspension for IM injection.

Duration of Study:

23 Days (2 days enrollment, 21 days 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

1. Subjects eligible for enrollment into this study were male and female adults who were ≥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 is fulfilled:

1. Any serious chronic or acute disease such as:
   - Cancer (leukemia, lymphomas, neoplasm), except for benign or localized skin cancer and non-metastatic prostate cancer not presently treated with chemotherapy
   - Congestive heart failure
   - Advanced arteriosclerotic disease
   - Chronic obstructive pulmonary disease (COPD) requiring oxygen therapy and/or acute exacerbation of a COPD within the last 14 days.
   - Autoimmune disease (including rheumatoid arthritis), if under immunosuppressive therapy
   - Insulin dependent diabetes mellitus
   - Acute or progressive hepatic disease
   - Acute or progressive renal disease

- Severe neurological or psychiatric disorder

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:

- Receipt of immunosuppressive therapy (chronic therapy with immunosuppressive drugs, any parenteral or oral corticosteroid (substitution dose in case of absence of suprarenal function allowed) or cancer chemotherapy/radiotherapy) within the last 2 months and for the full length of the study,
- Receipt of immunostimulants,
- Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within the past 3 months and for the full length of the study,
- Suspected or known HIV infection or HIV-related disease.

4. Known or suspected history of drug or alcohol abuse.
5. Bleeding diathesis or receipt of anticoagulants of the coumarin type.
6. Women who are pregnant or woman of childbearing potential unwilling to practice acceptable contraception for the duration of the study (21 days).
7. Influenza vaccination or laboratory confirmed influenza within the last 6 months and more than one influenza vaccination within the past 12 months
8. Immunization with any other vaccine and/or any investigational vaccine four weeks prior to study start.
9. Any significant acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days.
10. Fever (i.e. body temperature ≥38.0°C) within the past 3 days prior to study entry.
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.

Criteria for Evaluation:

lmmunogenicity

Influenza antibody levels in serum measured by HI test on Days 0 and 21. Any HI result <10 (undetectable) shall be expressed as 5 for purposes of calculation.
Separately in each age group the following measures will be investigated: First, for each visit the number and proportion of subjects with a titre of antibodies of at least 40 (as measured by HI test) and the geometric means of titres (GMTs) will be determined. Second, the number and percentage of subjects with seroconversion or significant

increase of titer as well as the mean geometric increase (GMT ratio) will be calculated from these data.

Safety

Incidences of local reactions (Days 0 to 3) including ecchymosis, erythema, induration, swelling and pain at the injection site) summarized by maximal severity and by age group.

Incidences of systemic reactions (Days 0 to 3) including chills/shivering, malaise, myalgia, arthralgia, headache, sweating, fatigue and fever summarized by maximal severity and by age group.

Incidences of adverse events (including local and systemic reactions with a duration beyond Day 3 post immunization) between Day 0 and study termination visit (Day 21, (±1) summarized by each age group and by preferred term and system organ class (SOC).

Results:

Table 1 Number (%) of Subjects Analyzed for Safety – As Treated

Analysis Set	18-60 yrs	≥61 yrs	Total
	N = 65	N = 62	N = 127
Population Total			
All Enrolled Set	65 (100%)	62 (100%)	127 (100%)
Safety Set	65 (100%)	60 (97%)	125 (98%)
Full Analysis Set	65 (100%)	60 (97%)	125 (98%)
Per Protocol Set	63 (97%)	58 (94%)	121 (95%)

Table 2 Number (%) of Subjects Analyzed for Safety – As Treated

Analysis Set	18-60 yrs	≥61 yrs	Total
	N = 65	N = 62	N = 127
Total Number Of Subjects Enrolled	65	62	127
Completed	64 (98%)	60 (97%)	124 (98%)
Completed Protocol	64 (98%)	60 (97%)	124 (98%)
Premature Withdrawal	1 (2%)	2 (3%)	3 (2%)
AE Or Death	1 (2%)	0	1 (<1%)
Protocol Deviation/Violation	0	2 (3%)	2 (2%)

Table 3 Demographic and Other Baseline Characteristics - All Enrolled Set

	18-60 Years	≥ 61 Years	Total
	N = 65	N = 62	N = 127
Age (years):	40.0 ± 11.4	66.8 ± 4.6	53.1 ± 16
Sex			
Male	31 (48%)	34 (55%)	65 (51%)
Female	34 (52%)	28 (45%)	62 (49%)
Race			
Asian	0	1 (2%)	1 (<1%)
Black	1 (2%)	0	1 (<1%)
Caucasian	64 (98%)	61 (98%)	125 (98%)
Weight (kg)	78.88 ± 14.69	77.89 ± 13.05	78.39 ± 13.87
Height (cm)	173.7 ± 8.6	171.8 ± 8.9	172.8 ± 8.8
Previous. Infl. Vaccine			
Yes	24 (37%)	53 (85%)	77 (61%)
No	41 (63%)	8 (13%)	49 (39%)
Unknown	0	1 (2%)	1 (<1%)
Met entry criteria			
Yes	63 (97%)	58 (94%)	121(95%)
No	2 (3%)	4 (6%)	6 (5%)

Table 4 Immunogenicity results

	Adults (18-60 years) N = 63						Elderly (≥6l years) N = 58					
Strains	A/Solomon lslands/3/2006 (H1N1)		A/Wisconsin/ 67/2005 (H3N2)		B/Malaysia/ 2506/2004		A/Solomon lslands/3/2006 (H1N1)		A/Wisconsin/ 67/2005 (H3N2)		B/Malaysia/ 2506/2004	
Prevaccination	**n/N[1]**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
[2]GMT	13		26		9.36		15		37		13	
[4]95% CI	10 – 18		19 - 36		7.29 - 12		12 - 19		27 - 52		10 - 17	
[5]Seroprotection rate	17/63	27%	28/63	44	10/63	16%	19/58	33%	34/5	59	11/58	19
95% CI	17%-40%		32%-58%		8%-27%		21%-46%		45%-71%		10%-31%	
Postvaccination	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
[5]Seroconversion rate	21/26	81%	13/14	93%	31/38	82%	12/16	75%	6/7	86%	12/20	60%
[6]Significant increase in antibody titer	28/37	76%	27/49	55%	10/25	40%	16/42	38%	15/51	29%	5/38	13%
[7]Seroconversion rate or significant increase	49/63	**78%**	40/63	**63%**	41/63	**65%**	28/58	**48%**	21/58	**36%**	17/58	29%
95% CI	66%-87%		50%-75%		52%-77%		35%-62%		24%-50%		18%-43%	
GMT	179		169		73		74		133		33	
95% CI	131-243		132-216		55-97		55-99		101-175		25-43	
Mean GMT increase	**13**		**6.42**		**7.82**		**4.99**		**3.55**		**2.47**	
95% CI	9.11 - 19		4.62 - 8.92		5.45 - 11		3.43 - 7.26		2.43 - 5.19		1.86 - 3.28	
Seroprotection rate	57/63	**90%**	62/63	**98%**	54/63	**86%**	50/58	**86%**	53/58	**91%**	34/58	**59%**
95% CI	80%-96%		91%-100%		75%-93%		75%-94%		81%-97%		45%-71%	

CHMP requirements (bold in the table): Seroconversion rate or significant increase Adults > 40%,, Elderly> 30%;

Mean GMT increase (i.e. GMT ratio= GMR) Adults> 2.5, Elderly> 2; Seroprotection rate Adults> 70%, Elderly> 60%; Figures arc bold, when the respective CHMP criterion is met.

[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 (≥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]Seroconversion rate or significant increase: proportion to subjects with either seroconversion or significant increase

Table 5 Reactogenicity (0-3 days post vaccination)- Safety Set

	Adults 18-60 years of age		Elderly ≥61 years of	
	N = 65		N = 60	
	n	%	n	%
Local reactions				
Redness/Erythema	2	3	2	3
Swelling	2	3	2	3
Pain	25	38	13	22
Ecchymosis	2	3	2	3
Induration	2	3	2	3
Systemic reactions				
Fever (temp. ≥ 38°C)[1]	0	0	0	0
Malaise	5	8	4	7
Fatigue	13	20	15	25
Headache	8	12	8	13
Sweating	5	8	4	7
Myalgia	5	8	6	10
Arthralgia	4	6	4	7
Chills	0	0	0	0
Total number of reports	73		62	
Subjects with any local reaction	27	42	15	25
Subjects with any systemic reaction	20	31	20	33
Subjects with any reaction	35	54	26	43

[1] for fever (temp. ≥ 38°C), the safety population consisted of N = 65 (adult group) and N = 60 (elderly group).

Table 6 Overview of Unsolicited Events

	Adults 18-60 years of age		Elderly ≥61 years of age		Total	
	N = 65		N = 60		N = 125	
	n	%	n	%	n	%
Any AE	21	32	8	13	29	23
At Least Possibly Related AEs	8	12	1	2	9	7
Any SAE	0	0	0	0	0	0
At Least Possibly Related SAEs	0	0	0	0	0	0
Adverse Events Leading to Premature Withdrawal	1	2	0	0	1	1

Table 7 Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term, sorted by System Organ Class

None reported

Table 8 Number (Percentages) of Subjects with Unsolicited Adverse Events Reported in > 5 % of Subjects by Preferred Term sorted by System Organ Class

None reported

Conclusion:

In a prospective clinical trial involving 63 younger adults (18- 60 years) and 58 elderly (≥61 years of age) subjects, immunogenicity, safety and tolerability of the preservative free inactivated trivalent split influenza vaccine Begrivac® 2007/2008 were investigated. The vaccine contained inactivated split virus strains selected for 2007/2008 according to WHO recommendations, namely A/ Solomon Islands/3/2006-like, A/Wisconsin/67/2005-like, and B/Malaysia/2506/2004 -like. For the A/Solomon Islands/3/2006-like strain, the strain A/Solomon Island/3/2006 Reass. IVR-145, for the A/Wisconsin/67/2005-like strain, the strain A/Wisconsin/67/2005, NYMC X161B and for the B/Malaysia/2506/2004 -like strain, the strain B/Malaysia/2506/2004 were used for vaccine production, respectively. The vaccine was injected into the deltoid muscle. Immunogenicity was assessed with respect to each strain on Days 0 and 21 post vaccination by hemagglutination-inhibition assay (HI) testing. Titers of 40 or more are regarded as protective. The evaluation of immunogenicity was based on 121 vaccinated subjects.

For all strains at least one of the EMA/CHMP requirements on influenza vaccines is fulfilled by the new preservative free inactivated trivalent split influenza vaccine Begrivac® 2007/2008. Whereas for the strain B/Malaysia/2506/2004 all three requirements are fulfilled for the age group 18-60 years, for the elderly group only the criterion geometric mean increase > 2.0 is fulfilled with 2.47. The percentages of subjects with seroconversion and significant increase and seroprotection were just below the percentages required by CHMP criteria. For both age groups the pre- vaccination GMTs for the strain B/Malaysia/2506/2004 were very low.

The most common reactions were injection site pain (30%, 38/125 vaccines), followed by fatigue (22%, 28/125 vaccines) and headache (13%, 16/125 vaccines). All other reactions were reported in a frequency of less than 10%. Only in one subject, swelling with >50mm in diameter was reported on day one and two, which was resolved on day 4. No case of body temperature of ≥38°C was reported at any time.

A total of 29 /125 (23%) subjects reported unsolicited adverse events, irrespective of relationship to vaccination. Most of the AEs were unrelated to study vaccine and were mild and moderate in intensity. In 4 subjects severe AEs were reported, none of which were related to the vaccine. No Serious Adverse Events (SAEs) occurred. One adverse event, which was not related to the vaccine, led to a premature withdrawal from the study.

In conclusion, Begrivac 2007/2008 can be regarded as protective and safe.

Date of Clinical Trial Report: 17 JUL 07