Sponsor: Chiron Behring GmbH & Co KG

Investigational Product: SplitTIVb -trivalent influenza virus vaccine (split virion, inactivated, egg-derived)

Indication: Prophylaxis: Influenza

Protocol Number: V44P10S

Protocol Title: A Phase Ill, Multicenter, Uncontrolled, Open-label study to evaluate Safety and Immunogenicity of Begrivac®, preservative free inactivated Split Influenza Vaccine, using the Strain Composition 2006/2007 when administered to Non-elderly Adult and Elderly Subjects

Phase of Development: Phase III

Study Period:

Date of first enrolment: 13 JUL 06
Date of last visit: 04 AUG 06

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 for the determination of antibodies titers, were drawn on Day 0 prior to vaccination and on Day 21 ± 1.
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 (pain at the injection site, erythema, ecchymosis, swelling and induration) and systemic (fever [i.e., axillary temperature > 38°C], chills/shivering, malaise, headache, myalgia, arthralgia, sweating and fatigue) 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, he/she had to contact the Investigator who was to take a nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of viral origin.

Number of Subjects (planned and analyzed):

According to the Committee for Medicinal Products for Human Use (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). With a drop-out rate of 20% overall 125 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.

Study Centers: Two centers in Germany.

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

NCT00354016

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 and elderly subjects in compliance with the requirements of the current EU recommendations for the evaluation of the immunogenicity for a new formulation of a licensed flu vaccine (CPMP/BWP/214/96).
Safety Objectives
To evaluate safety of a single 1M dose of the split influenza vaccine SplitTIVb in nonelderly and elderly subjects.

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

SplitTIVb: Preservative free inactivated trivalent split influenza vaccine Lot No.: 138011A and Expiry date: 31 May 2007 0.5 mL suspension for IM injection.

Duration of Study: 22 days, 21 days for a single subject (vaccination on Day 0).

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

Not applicable.

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. 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.

4. Informed consent had to be obtained from all the subjects before enrollment in the study after the nature of the study was explained.

Exclusion criteria:
Subjects were not enrolled into the study if at least one of the following criteria was fulfilled:
1. They had any serious chronic disease such as:
    - a. cancer (leukemia, lymphomas, neoplasm), except for benign or localized skin cancer and non metastatic prostate cancer not presently treated with chemotherapy,
    - b. congestive heart failure,
    - c. advanced arteriosclerotic disease,
    - d. chronic obstructive pulmonary disease (COPD) requiring oxygen therapy,
    - e. autoimmune disease (including rheumatoid arthritis),
    - f. insulin dependent diabetes mellitus,
    - g. acute or progressive hepatic disease,
    - h. acute or progressive renal disease.

2. They had a history of any anaphylaxis, serious vaccine reactions, arc hypersensitive to ovalbumin, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin or any other component of the vaccine.
3. They had a history of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine.
4. They had a 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 last 2 months 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 human immunodeficiency virus (HIV) infection or HlV-related disease.
5. They had a known or suspected history of drug or alcohol abuse.
6. They had a bleeding diathesis or receive anticoagulants of the coumarin type.
7. Women who were pregnant or who could become pregnant during the study but were not willing to practice acceptable contraception for the duration of the study (21 days).
8. Within the past 12 months, they received more than one injection of influenza vaccine.
9. Within the last 6 months they

- a. had laboratory confined influenza disease,
- b. were vaccinated against influenza.

10. Within the last 4 weeks they received
    - a. another vaccine,
    - b. any investigational agent.
11. They experienced significant acute or chronic infections requiring systen1ic antibiotic treatment or antiviral therapy within the last 7 days.
12. They experienced an acute exacerbation of a COPD within the last 14 days.
13. They experienced fever (i.e. body temperature 38.0°C) within the past 3 days.
14. They took part in another clinical study.
15. They had any condition, which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Criteria for Evaluation:

Immunogenicity
Influenza antibody levels in serum measured by HI test on Days 0 and 21.
The percentage of subjects with seroconversion or significant increase, the mean geometric increase and the percentage of subjects with a titer of at least 40 (as measured by HI test), separately by each age group, were calculated.
Safety
Number and percentage of subjects with at least one local reaction between Day 0 and Day 3 after vaccine injection.
Number and percentage of subjects with at least one systemic reaction between Day 0 and Day 3 after vaccine injection.
Number and percentage of subjects with at least one adverse event between Day 0 and the study termination visit (Day 21, window: 20-22).

Results:

Table 1: Overview of Subject Populations - All Enrolled Set

	Number (%) of Subjects	
	18-60 YOA N=71	**≥ 61 YOA N=59**
Population:		
Enrolled	71 (100%)	59 (100%)
PPS	69 (97%)	59 (100%)
Safety	70 (99%)	59 (100%)

Abbreviations: PPS = per protocol set; YOA = years of age.

Table 2: Summary of Study Terminations - All Enrolled Set

	Number (%)of Subjects	
Primary Withdrawal Reason	**18-60 YOA**	**≥ 61 YOA**
Total Number of Subjects Enrolled	71	59
Completed	70 (99%)	59 (100%)
Completed Protocol	70 (99%)	59 (100%)
Premature Withdrawal	1 (1%)	0
Protocol Deviation/Violation	1 (1%)	0

Abbreviation: YOA = years of age.

Table 3: Summary of Demography - All Enrolled Set

	18-60 YOA[a] N=71	≥ 61 YOA[b] N=59
Age (Years):		
Mean	39.2	66.6
Std. Dev.	10.7	4.4
Sex:		
Male	28 (39%)	36 (61%)
Female	43 (61%)	23 (39%)
Ethnic Origin:		
Asian	1 (1%)	0
Caucasian	70 (99%)	59 (100%)
Weight (kg):		
Mean	76.71	81.86
Std. Dev.	15.74	12.69
Height (cm):		
Mean	172.8	171.9
Std. Dev.	8.8	9.0
Previous Influenza Vaccination:		
No	39 (55%)	10 (17%)
Yes	32 (45%)	49 (83%)
Met Entry Criteria:		
Yes	71 (100%)	59 (100%)

Abbreviations: Std. Dev. = Standard Deviation; YOA = years of age.
[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years

Table 4: Vaccine Immunogenicity Assessed by HI Assay at Day 0 and Day 21 for Subjects Aged 18-60 years and Aged 61 Years and Over – Per Protocol Set

	Adults (18-60 YOA[a]) N=69							Elderly (≥ 61 YOA[b]) N=59						
Strains		**A(H1N1)**		**A(H3N2)**		**B**			**A(H1N1)**		**A(H3N2)**		**B**	
PREVACCINATION														
		n/N[1]	**%**	**n/N**	**%**	**n/N**	**%**		**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
GMT [2]		16		20		10			19		34		12	
95% CI [3]		12-21		15-26		8.42-12			15-23		24-48		9.25-14	
Seroprotection rate [4]		23/69	33%	26/69	38%	10/69	14%		19/59	32%	33/59	56%	11/59	19%
95% CI		12-46		26-50		7-25			21-46		42-69		10-31	
POSTVACCINATION														
	CHMP	**n/N** [1]	**%**	**n/N** [1]	**%**	**n/N** [1]	**%**	**CHMP**	**n/N** [1]	**%**	**n/N** [1]	**%**	**n/N** [1]	**%**
Seroconversion rate [5]		20/23	87%	11/14	79%	25/30	83%		7/9	78%	4/9	44%	13/23	57%
Significant increase in antibody titers [6]		20/46	43%	36/55	65%	25/39	64%		8/50	16%	23/50	46%	14/36	39%
Seroconversion rate or significant increase [7]	**>40%**	40/69	**58%**	47/69	**68%**	50/69	**72%**	**>30%**	15/59	25%	27/59	**46%**	27/59	**46%**
95% CI		45-70		56-79		60-83			15-38		33-59		33-59	
GMT		93		137		85			45		135		46	
95% CI		75-116		109-172		67-106			36-56		102-179		36-59	

Mean GMT Increase	**>2.5**	**5.71**		**7.02**		**8.29**		**>2.0**	**2.44**		**3.98**		**3.98**	
95% CI		4.11-7.94		5.13-9.62		6.20-11			1.86-3.21		2.91-5.42		3.01-5.26	
Seroprotection rate	**>70%**	63/69	**91%**	65/69	**94%**	61/69	**88%**	**>60%**	41/59	**69%**	53/59	**90%**	39/59	**66%**
95% CI		82-97		86-98		78-95			56-81		79-96		53-78	

Abbreviations: CHMP = committee for medicinal products for human use; HI = hemagglutination inhibition; YOA = years of age.
[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) ie seroconversion or significant increase.
[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: 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: proportion of subjects with either seroconversion or significant increase.
Bold = CHMP Criterion Passed.

Table 5: Overview of Solicited Reactions – Safety Set

	Number (%) of Subjects With Solicited Reactions	
	18-60 YOA[a]	**≥ 61 YOA[b]**
	N=70	**N=59**
Any	41 (59%)	26 (44%)
Local	35 (50%)	18 (31%)
Systemic	20 (29%)	18 (31%)

Abbreviation: YOA = years of age.
[a]≥ 18 years to ≤ 60 years; [b] ≥ 61 years.

Table 6: Local and Systemic Reactions After the Administration of SplitTIVb in Subjects aged 18 to 60 Years and 61 Years and Over – Safety Set

	Number (%) of Subjects With Injection Site Reactions	
	18-60 YOA[a]	**≥ 61 YOA[b]**
	N=70	**N=59**
Local Reactions		
Pain	33 (47%)	15 (25%)
Redness/Erythema (mm)	1 (1%)	1 (2%)
Ecchymosis (mm)	2 (3%)	2 (3%)
Swelling (mm)	4 (6%)	4 (7%)
Induration (mm)	8 (11%)	1 (2%)
Systemic Reactions		
Fever (≥ 38°C)*	0	0
Chills	0	0
Malaise	3 (4%)	2 (3%)
Headache	12 (17%)	8 (14%)
Myalgia	5 (7%)	4 (7%)
Arthralgia	2 (3%)	1 (2%)
Sweating	2 (3%)	3 (5%)
Fatigue	13 (19%)	12 (20%)

Abbreviation: YOA = years of age.

[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years;* for fever (temp. 2" 38°C), the safety population consisted of N =58 (adult group) and N = 45 (elderly group).

Table 7: Overview of Other AEs – Safety Set

	Number (%) of Subjects with AEs	
	18-60 YOA[a]	**≥ 61 YOA[b]**
	N=70	**N=59**
Any AEs	14 (20%)	6 (10%)
At least possibly related AEs	5 (7%)	3 (5%)
SAEs	0	0
At least possibly related SAEs	0	0
AEs leading to discontinuation	0	0
Death	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event; YOA = years of age.
[a] ≥ 18 years to ≤ 60 years; [b] ≥ 61 years

Table 8: Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term sorted by System Organ Class – Safety Set
None Reported

Table 9: Number (Percentages) of Subjects with Unsolicited Adverse Events Reported by > 5% of Subjects by Preferred Term sorted by System Organ – Safety Set

None Reported

Conclusion:

Considering the immunogenicity and safety results the preservative free inactivated trivalent split influenza vaccine SplitTIVb 2006/2007 can be considered as protective and safe.

Date of Clinical Trial Report: 10 AUG 06