Investigational Product:	eTIV_f
Indication:	Prophylaxis: Influenza
Sponsor:	Novartis Vaccines and Diagnostics
Date of the CSR:	09 AUG 10

Title of Study: A Phase III, multicenter, uncontrolled, open label study to evaluate safety and immunogenicity of eTIV_f , when administered to adult and elderly subjects.

Protocol Number: V78_08S

Study Centers: One center in Germany (the required number of subjects were enrolled in one center).

Publication (reference): None.

Study Period:	**Phase of Development:** Phase III
Date of first enrollment: 05 JUL 10 Date of last visit: 27 JUL 10	

Objectives:

Immunogenicity:

Primary

To evaluate the antibody response to each influenza vaccine antigen, as measured by Hemagglutination Inhibition (HI) at 21 days post immunization 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 Harmonization of Requirements for Influenza Vaccines. CPMP/BWP/214/96: 12 March 1997).

Safety:

To evaluate safety of a single IM (intramuscular) dose of the subunit influenza vaccine eTIV_f 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).

Methodology:

All volunteers received a single 0.5 mL dose of eTIV_f into the deltoid muscle of (preferably) the non-dominant arm on day 1. Prior to vaccination on day 1 (Visit 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. Blood samples, approx. 10 mL, for the determination of antibody titers were drawn on day 1 prior to vaccination and on day 22 (-1/+5 days) (end of individual study participation).

Subjects were contacted by phone on day 5 (+2) after immunization to ensure that local and systemic reaction data were collected on the Subject's Diary Card and also to determine the subject's clinical status.

After immunization, subjects were observed for approximately 30 minutes for any immediate reactions. Each subject was instructed to complete a diary card for on the immunization day and three days thereafter 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 (solicited and unsolicited) were collected during day 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.

Serology testing were performed by HI test and by SRH test.

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, he/she had to contact the Investigator who would take a nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of viral origin. For confirmatory purposes, specimens were planned to be analyzed via Quick test and RT-PCR or culture.

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.

In total 144 subjects were actually enrolled, all of the 144 subjects were included in the safety analysis and 136 subjects in the immunogenicity analysis (per protocol set)

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

Male and female volunteers of 18 years of age and older, mentally competent, willing and able to give written informed consent prior to study entry;

Individuals able to comply with all the study requirements;

Individuals in good health as determined by medical history, physical examination and clinical judgment of the investigator.

Written informed consent was obtained for all the subjects before enrollment into the study after the nature of the study had been explained.

Exclusion Criteria

Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study;

Individuals with 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;

Individuals with 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, polymyxin, neomycin);

Individuals with 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 past 60 days and for the entire duration of the study;

b. receipt of immunostimulants;

c. receipt of parenteral immunoglobulin preparation, blood products and/or plasma derivates within the past 3 months and for the entire duration of the study;

d. suspected or known HIV infection or HIV-related disease;

Individuals with known or suspected history of drug or alcohol abuse;

Individuals with a bleeding diathesis or conditions associated with prolonged bleeding time that in the investigator's opinion would interfere with the safety of the subject;

Females 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 is defined as hormonal (e.g., oral, injection, transdermal patch, implant, cervical ring), barrier (e.g., condom with spermicide or diaphragm with spermicide), intrauterine device (IUD), or monogamous relationship with vasectomized partner who has been vasectomized for 6 months or more prior to the subject's study entry;

Individuals who are not able to comprehend and to follow all required study procedures for the whole period of the study;

Individuals that within the past 12 months have received more than one injection of influenza vaccine;

Individuals that within the past 6 months have:

a. had laboratory confirmed seasonal or pandemic influenza disease;

b. received seasonal or pandemic influenza vaccine;

Individuals with any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days;

Individuals that have experienced fever (i.e., axillary temperature $\geq 38°C$) within 3 days before the intended study vaccination;

Individuals participating in any clinical trial with another investigational product 4 weeks prior to first study visit or intent to participate in another clinical study at any time during the conduct of this study;

Individuals who received any other vaccines within 4 weeks prior to enrollment in this study or who are planning to receive any vaccine within 4 weeks following receipt of the study vaccine;

Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks and for the entire duration of the study

Individuals who are part of study personnel or close family members conducting this study;

Individuals with history or any illness that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subjects due to participation in the study;

BMI > 35 kg/m^2.

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

A single 0.5mL dose of eTIV_f (Lot No.: 112078, expiry date: 02 August 2010), influenza subunit vaccine for the Northern Hemisphere (NH) influenza season 2010/2011. The vaccine was administered IM.

Duration of Study:

Each subject participated approximately for 3 weeks after enrolment into the study

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

None.

Criteria for Evaluation:

Seroprotection rate, GMR and rate of seroconversion or significant increase were determined by HI and SRH and assessed according to CPMP/BWP/214/96. In non-elderly 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

Statistical Methods:

There was no statistical null hypothesis associated with the immunogenicity objective. Statistical analysis was carried out descriptively.

This study is in compliance with the sample size requirements of the current CHMP guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96).

Table 1: Time and Events

Study Periods	Vaccination	Post-Vaccination	
Clinic Visit (Yes/No)[a]	Yes	No	Yes
Study Day	1	5	22
Study Visit Window	n/a	0/+2	-1/+5
ICF	x		
Exclusion/Inclusion	x[b]		
Medical history	x[b]		
Physical examination[c]	x		x
Pregnancy test[b] [urine beta-human chorionic gonadotropin (ß-hCG) test]	x		
Investigational vaccine administered	x		
Serology Blood draw (10mL)	x[b]		x
Diary Card Dispensed [d]	x		
Diary Card Collected and/or Reviewed [d]		x	x
Assess Local/Systemic Reactions[e]	x	x	x
Assess AEs and SAEs [f]	x	x	x
Concomitant medications	x	x	x
Study Termination			x

[a] Clinic visit "no" refers to telephone contact only with subject.
[b] Performed prior to vaccination.
[c] Physical examination were performed by a qualified health professional designated within the Site Responsibility Delegation Log. Brief physical exam was performed at study day 1 and 22. Physical examination of injection site and complaint-focused physical examination were performed at visits on day 1 and 22.
[d] Diary card review was performed over the phone for day 5 and at day 22 clinic visit. Diaries were returned at day 22 clinic visit.
[e] Data on local and systemic reactions were observed by the study personnel for all subjects for approximately 30 minutes after vaccination. Subjects recorded local and systemic reactions on the diary card daily for 3 days after study vaccination (study days 1-4).
[f] During for three days post immunization (study days 1-4) all adverse events were collected. Thereafter, only 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.

Results:

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Number (%) of Subjects		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
Enrolled	76	68	144
Completed protocol	75 (99%)	65 (96%)	140 (97%)
Premature withdrawals	1 (1%)	3 (4%)	4 (3%)
Protocol deviations/violation	1 (1%)	2 (3%)	3 (2%)
Unable to classify	0	1 (1%)	1 (<1%)

YOA = years of age

Table 3: Overview of Subject Populations

	18-60 YOA N=76	**≥ 61 YOA N=68**	**TOTAL N=144**
Population:			
Enrolled	76(100%)	68(100%)	144(100%)
Immunogenicity (FAS)	76(100%)	67(99%)	143(99%)
Immunogenicity (PPS)	75(99%)	61(90%)	136(94%)
Exposed	76(100%)	68(100%)	144(100%)
Safety	76(100%)	68(100%)	144(100%)
Safety After Study Day 4	76(100%)	68(100%)	144(100%)

YOA = years of age

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

	18-60 YOA N=76	≥ 61 YOA N=68	TOTAL N=144
Age (Yrs):	28.2±9.8	66.9±4.6	46.5±20.9
Gender:			
Male	37(49%)	28(41%)	65(45%)
Female	39(51%)	40(59%)	79(55%)
Child Bear. Pot.:			
No	5(7%)	41(60%)	46(32%)
Yes	34(45%)	0	34(24%)
Not Available	37	27	64
Pregnancy Test:			
Negative	34(45%)	0	34(24%)
Not Applicable	5(7%)	41(60%)	46(32%)
Not Available	37	27	64
Ethnic Origin:			
Caucasian	76(100%)	68(100%)	144(100%)
Weight (kg):	74.59±13.62	77.65±14.99	76.04±14.32
Height (cm):	173.9±9.6	169.8±8.8	172.0±9.4
Body Mass Index:	24.59±3.72	26.86±4.21	25.66±4.10
Prev. Seas. Vac.:			
No	30(39%)	15(22%)	45(31%)
Unknown	12(16%)	1(1%)	13(9%)
Yes	34(45%)	52(76%)	86(60%)
Prev. Pand. Vac.:			
No	73(96%)	65(96%)	138(96%)
Yes	3(4%)	3(4%)	6(4%)
Met Entry Criteria:			
No	1(1%)	2(3%)	3(2%)
Yes	75(99%)	66(97%)	141(98%)

Categorical parameters: N(%), non-categorical parameters: Mean±Std; YOA = years of age

Table 5: Vaccine Immunogenicity Assessed by HI Assay - Per Protocol Set

	18-60 YOA (N=75)						≥ 61 YOA (N=61)					
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]		29		35		12			14		47		21	
95% CI[3]		20-44		25-49		9.37-15			11-18		32-69		15-28	
Seroprotection rate[4]		29/75	39%	36/75	48%	13/75	17%		7/61	11%	37/61	61%	23/61	38%
95% CI		28-51		36-60		10-28			5-22		47-73		26-51	
POSTVACCINATION														
	CHMP[8]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP[8]**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate[5]		25/27	93%	12/12	100%	21/34	62%		14/21	67%	9/9	100%	3/15	20%
Significant increase in antibody titres[6]		37/48	77%	48/63	76%	10/41	24%		24/40	60%	33/52	63%	3/46	7%
Seroconversion rate or significant increase	**>40%**	62/75	**83%**	60/75	**80%**	31/75	**41%**	**>30%**	38/61	**62%**	42/61	**69%**	6/61	10%
95% CI		72-90		69-88		30-53			49-74		56-80		4-20	
GMT		749		411		46			122		367		33	
95% CI		522-1075		312-541		37-58			79-188		277-486		24-44	
GM Increase[7]	**>2.5**	**25**		**12**		**3.89**		**<2.0**	**8.43**		**7.73**		1.56	
95% CI		16-40		8.15-17		2.98-5.09			5.63-13		5.35-11		1.3-1.87	
Seroprotection rate	**>70%**	70/75	**93%**	73/75	**97%**	52/75	69%	**>60%**	46/61	**75%**	60/61	**98%**	34/61	56%
95% CI		85-98		91-100		58-79			63-86		91-100		42-68	

Bold = CHMP criteria met; 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 (titer ≥ 40); [5] Seroconversion rate: proportion of subjects with antibody increase from < 10 prevaccination to ≥40 postvaccination.; [6] Significant increase: proportion of subjects with an antibody titer of ≥10 prevaccination and at least 4-fold antibody increase postvaccination; [7] GM increase = Geometric mean increase; [8] CHMP criteria

Table 6: Vaccine Immunogenicity Assessed by SRH Assay - Per Protocol Population

	18-60 YOA (N=75)							≥ 61 YOA (N=61)						
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**	**%**
GMA[2]		12		8.35		26			9.38		8.91		37	
95% CI[3]		9.23-16		6.84-10		21-31			7.06-12		7.06-11		29-46	
Seroprotection rate[4]		26/75	35%	11/75	15%	40/75	53%		17/61	28%	11/61	18%	41/61	67%
95% CI		24-47		8-25		41-65			17-41		9-30		54-79	
POSTVACCINATION														
	CHMP[7]	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**CHMP[7]**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Seroconversion rate[5]		30/33	91%	26/36	72%	2/3	67%		26/34	76%	17/30	57%	2/4	50%
Significant increase in antibody titers[6]		32/42	76%	31/39	79%	51/72	71%		19/27	70%	24/31	77%	21/57	37%
Seroconversion rate or significant increase	**> 40%**	62/75	**83%**	57/75	**76%**	53/75	**71%**	**> 30%**	45/61	**74%**	41/61	**67%**	23/61	**38%**
95% CI[3]		72-90		65-85		59-81			61-84		54-79		26-51	
GMA[2]		83		45		70			53		36		57	
95% CI[3]		71-97		37-55		62-78			40-69		30-43		49-68	
GM Increase[8]	**> 2.5**	**6.85**		**5.39**		**2.73**		**> 2.0**	**5.64**		**4.02**		1.55	
95% CI[3]		5.13-9.15		4.18-6.95		2.23-3.34			4.09-7.77		3.18-5.09		1.33-1.82	
Seroprotection rate[4]	**> 70%**	71/75	**95%**	63/75	**84%**	72/75	**96%**	**> 60%**	53/61	**87%**	46/61	**75%**	56/61	**92%**
95% CI[3]		87-99		74-91		89-99			76-94		63-86		82-97	

Bold = CHMP criteria met; YOA = years of age ; [1]n/N: responders (n) as part of number of subjects of the (sub-)population (N); [2]GMA: geometric mean area; [3]95% CI: 95% confidence interval; [4]Seroprotection rate: proportion of subjects with a pre- or post-vaccination area ≥ 25 mm^2; [5]Seroconversion rate: proportion of subjects with negative pre-vaccination serum and a postvaccination serum area ≥ 25 mm^2; [6]Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum; [7] CHMP Criteria;; [8] GM increase = Geometric mean increase

Table 7: Overview of Solicited Reactions

	Number (%) of Subjects With Solicited Reactions		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=68**	**N=144**
Any[1]	51(67)	22(32)	73(51)
Local	39(51)	11(16)	50(35)
Systemic	35(46)	16(24)	51(35)

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 8: Overview of Solicited Local Reactions (1-4 Days Post-Vaccination)

		Number (%) of Subjects With Injection Site Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=76	**N=68**	**N=144**
Ecchymosis (mm)	Any	1(1)	3(4)	4(3)
	>50 mm	0	0	0
Erythema (mm)	Any	2(3)	3(4)	5(3)
	>50 mm	0	1(1)	1(1)
Induration (mm)	Any	9(12)	1(1)	10(7)
	>50 mm	2(3)	0	2(1)
Swelling (mm)	Any	8(11)	2(3)	10(7)
	>50 mm	2(3)	1(1)	3(2)
Pain	Any	37(49)	9(13)	46(32)
	Severe	0	0	0

YOA = years of age; Note: The numbers (N) in the header is the total number of subjects with documented reactions. Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter <10mm), mild (diameter 10-25mm), moderate (diameter 26-50mm) and severe (diameter >50mm)

Table 9: Overview of Solicited Systemic Reactions (1-4 Days Post-Vaccination)

		Number (%) of Subjects With Systemic Reactions		
		18-60 YOA	**≥ 61 YOA**	**TOTAL**
		N=76	**N=68**	**N=144**
Chills/Shivering	Any	2(3)	0	2(1)
	Severe	0	0	0
Malaise	Any	4(5)	3(4)	7(5)
	Severe	0	0	0
Myalgia	Any	12(16)	6(9)	18(13)
	Severe	0	0	0
Arthralgia	Any	5(7)	1(1)	6(4)
	Severe	0	0	0
Headache	Any	18(24)	7(10)	25(17)
	Severe	0	1(1)	1(1)
Sweating	Any	4(5)	2(3)	6(4)
	Severe	0	0	0
Fatigue	Any	17(22)	9(13)	26(18)
	Severe	0	1(1)	1(1)
Fever (≥ 38°C)	Yes	0	0	0

Note: The numbers (N) in the header is the total number of subjects with documented reactions; YOA = years of age;

Table 10: Overview of Other AEs

	Number (%) of Subjects with Adverse Events		
	18-60 YOA	**≥ 61 YOA**	**TOTAL**
	N=76	**N=68**	**N=144**
Any AEs	7 (9)	6 (9)	13 (9)
At least possibly related AEs	6 (8)	6 (9)	12 (8)
Serious AEs	0	0	0
At least possibly related SAEs	0	0	0
AEs leading to discontinuation	0	0	0
Death	0	0	0

YOA = years of age;

Table 11: Serious Adverse events by Preferred Term sorted by System Organ Class

None Reported

Table 12: Unsolicited AEs Reported by ≥ 5% of Subjects by Preferred Term sorted by System Organ Class

None Reported