Safety and Immunogenicity of One Dose of Seasonal Trivalent Influenza Virus Vaccine (TIVf, Purified Surface Antigen, Inactivated, Egg Derived) in Adults Aged 18 Years and Above

This study has been completed.

Sponsor:	Novartis Vaccines
Collaborators:	Novartis Vaccines
Information provided by (Responsible Party):	Novartis (Novartis Vaccines)
ClinicalTrials.gov Identifier:	NCT01640327

Purpose

This protocol was designed to evaluate the safety, clinical tolerability and immunogenicity of the Trivalent Influenza Virus Vaccine (TIVf, purified surface antigen, inactivated, egg derived), Northern Hemisphere formulation 2012/2013. The principal aim was to provide safety and immunogenicity data, in compliance to current EU Guidelines, with the intent of obtaining marketing approval of the vaccine formulation intended for use prior to the next influenza season in the Northern Hemisphere.

The antibody response to each influenza vaccine antigen, was measured by hemagglutination inhibition (HI) and single radial hemolysis (SRH) at approximately 21 days postimmunization in adult and elderly subjects. The safety and immunogenicity of a single intramuscular (IM) injection of the vaccine was evaluated in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96).

Condition	Intervention	Phase
Human Influenza	Biological/Vaccine: Trivalent influenza virus vaccine (TIVf)	Phase 3

Study Type: Interventional
Study Design: Prevention, Single Group Assignment, Open Label, N/A, Safety Study
Official Title: A Phase 3, Open Label, Uncontrolled, Multicenter Study to Evaluate Safety and Immunogenicity of a Surface Antigen, Inactivated, Influenza Vaccine (Fluvirin®), Formulation 2012/2013, When Administered to Adult and Elderly Subjects

Further study details as provided by Novartis (Novartis Vaccines):

Primary Outcome Measure:

- Percentage of Subjects With Seroconversion or Significant Increase in HI Titer Against Each of Three Vaccine Strains After One Vaccination of TIVf [Time Frame: Day 22] [Designated as safety issue: No]

  Immunogenicity was measured as the percentage of subjects who achieved seroconversion or significant increase in hemagglutination inhibition (HI) titer, against each of three vaccine strains, three weeks after vaccination (Day 22), evaluated using HI antigen assay. As per the European (CHMP) criteria seroconversion or significant increase in titer was defined as the percentage of subjects with a prevaccination HI titer <10 to a postvaccination HI titer ≥40; or in subjects with a prevaccination HI titer ≥10, a ≥4-fold increase in postvaccination HI antibody titer. This criterion was met according to CHMP guideline if percentage of subjects achieving seroconversion or significant increase in HI titer is >40% (≥18 years to ≤60 years) or >30% (≥61 years).
- Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of TIVf [Time Frame: Day 22] [Designated as safety issue: No]

  Geometric mean ratio (GMR) of subjects was calculated as the ratio of postvaccination to prevaccination HI geometric mean titers (GMTs), directed against each of three vaccine strains, three weeks after vaccination (Day 22). The CHMP criterion was met if the geometric mean increase (GMR, Day 22/Day 1) in HI antibody titer was >2.5 (≥18 years to ≤60 years) or >2.0 (≥61 years).
- Percentage of Subjects Who Achieved HI Titer ≥40 Against Each of Three Vaccine Strains After One Vaccination of TIVf [Time Frame: Day 1 and Day 22] [Designated as safety issue: No]

  Immunogenicity was measured as the percentage of subjects achieving HI titer ≥40 against each of three vaccine strains at baseline (Day 1) and three weeks after TIVf vaccination (Day 22). This criterion was met according to CHMP guideline if percentage of subjects achieving HI titer ≥40 is >70% (≥18 years to ≤60) or >60% (≥61 years).

Secondary Outcome Measures:

- Numbers of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination) [Time Frame: From Day 1 through Day 4 postvaccination] [Designated as safety issue: Yes]

  Safety was assessed as the number of subjects who reported solicited local and systemic reactions from Day 1 up to and including Day 4 after the TIVf vaccination.

Enrollment: 126
Study Start Date: July 2012
Primary Completion Date: August 2012
Study Completion Date: August 2012

Arms	Assigned Interventions
Experimental: TIVf	Biological/Vaccine: Trivalent influenza virus vaccine (TIVf) A single dose (0.5 mL) of vaccine supplied in prefilled syringes was administered intramuscularly in the deltoid muscle, preferably of the non dominant arm

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: Yes

Criteria

Inclusion Criteria:

1. Male and female volunteers of 18 years of age or older, mentally competent, were willing and gave written informed consent prior to study entry;
2. Individuals who complied with all the study requirements;
3. Individuals in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator.

Exclusion Criteria:

1. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, could have interfered with the subject's ability to participate in the study.
2. Individuals with any serious chronic or acute disease (in the judgment of the investigator), including but not limited to:
    - Medically significant cancer (except for benign or localized skin cancer, cancer in remission for ≥10 years or localized prostate cancer that has been clinically stable for more than 2 years without treatment);
    - Medically significant advanced congestive heart failure (i.e., NYHA class III and IV);
    - Chronic obstructive pulmonary disease (COPD; i.e., GOLD Stage III and IV);
    - Autoimmune disease (including rheumatoid arthritis, except for Hashimoto's thyroiditis that has been clinically stable for ≥5 years);
    - Diabetes mellitus type I;
    - Poorly controlled diabetes mellitus type II;
    - Advanced arteriosclerotic disease;
    - History of underlying medical condition such as major congenital abnormalities requiring surgery, chronic treatment, or associated with developmental delay (e.g., Down's syndrome);
    - Acute or progressive hepatic disease;
    - Acute or progressive renal disease;
    - Severe neurological (es. Guillain-Barré syndrome) or psychiatric disorder;
    - Severe asthma.
3. 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 eggs or eggs product as well as ovalbumin, chicken protein, chicken feathers, influenza viral protein, kanamycin and neomycin sulphate).
4. Individuals with known or suspected (or had 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 (any parenteral or oral corticosteroid or cancer chemotherapy/radiotherapy) within the past 60 days and for the full length of the study;
    - receipt of immunostimulants;
    - receipt of parenteral immunoglobulin preparation, blood products and/or plasma derivates within the past 3 months and for the full length of the study;
    - suspected or known HIV infection or HIV-related disease.
5. Individuals with known or suspected history of drug or alcohol abuse.
6. Individuals with a bleeding diathesis or conditions associated with prolonged bleeding time that in the investigator's opinion could have interfered with the safety of the subject.
7. Individuals who were not able to comprehend and to follow all required study procedures for the whole period of the study.
8. Individuals with history or any illness that, in the opinion of the investigator, posed additional risk to the subjects due to participation in the study.
9. Individuals who within the past 6 months (prior to study enrollement) have:
    - had any laboratory confirmed seasonal or pandemic influenza disease;

- received any seasonal or pandemic influenza vaccine.

10. Individuals who received any other vaccine within 4 weeks prior to enrollment in this study or who were planning to receive any vaccine during the study.
11. Individuals with any acute or chronic infections required systemic antibiotic treatment or antiviral therapy within the last 7 days.
12. Individuals who had experienced fever (i.e., axillary temperature ≥38°C) within the last 3 days of intended study vaccination.
13. Individuals who participated 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.
14. Individuals who were part of study personnel or close family members conducting this study.
15. BMI >35 kg/m2.
16. Females who were pregnant (confirmed by positive urine pregnancy test) or nursing (breastfeeding). Females of childbearing potential who refused to use an acceptable method of birth control for the whole duration of the study.

Contacts and Locations

Locations

Germany

University of Rostock, Department Tropical Medicine and Infectious Diseases

Rostock, Mecklenburg-Western Pomerania, Germany, 18057

Investigators

Study Chair:	Novartis Vaccines and Diagnostics	Novartis Vaccines and Diagnostics

More Information

Responsible Party:	Novartis Vaccines
Study ID Numbers:	V78_10S 2011-006271-18 [EudraCT Number]
Health Authority:	European Union: European Medicines Agency

Study Results

Participant Flow

Recruitment Details	Subjects were enrolled at one study centre in Germany.
Pre-Assignment Details	All enrolled subjects were included in the trial.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination

	Description
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Overall Study

	18-60 Y	≥61 Y
Started	63	63
Completed	63	63
Not Completed	0	0

Baseline Characteristics

Analysis Population Description

Analysis was done on all enrolled subjects.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Baseline Measures

	18-60 Y	≥61 Y	Total
Number of Participants	63	63	126
Age, Continuous [units: Years] Mean (Standard Deviation)	33.5 (10.6)	68.3 (5.1)	50.9 (19.3)
Gender, Male/Female [units: Subjects]			
Female	38	36	74
Male	25	27	52

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Subjects With Seroconversion or Significant Increase in HI Titer Against Each of Three Vaccine Strains After One Vaccination of TIVf

Measure Description	Immunogenicity was measured as the percentage of subjects who achieved seroconversion or significant increase in hemagglutination inhibition (HI) titer, against each of three vaccine strains, three weeks after vaccination (Day 22), evaluated using HI antigen assay. As per the European (CHMP) criteria seroconversion or significant increase in titer was defined as the percentage of subjects with a prevaccination HI titer <10 to a postvaccination HI titer ≥40; or in subjects with a prevaccination HI titer ≥10, a ≥4-fold increase in postvaccination HI antibody titer. This criterion was met according to CHMP guideline if percentage of subjects achieving seroconversion or significant increase in HI titer is >40% (≥18 years to ≤60 years) or >30% (≥61 years).
Time Frame	Day 22
Safety Issue?	No

Analysis Population Description

Analysis was done on the per-protocol (PP) set, i.e. the subjects who received the vaccine correctly; provided evaluable serum samples at the relevant time points; and had no major protocol violations as defined prior to analysis.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	63	63
Percentage of Subjects With Seroconversion or Significant Increase in HI Titer Against Each of Three Vaccine Strains After One Vaccination of TIVf [units: Percentages of Subjects] Number (95% Confidence Interval)		
A/H1N1	83 (71 to 91)	60 (47 to 72)
A/H3N2	70 (57 to 81)	48 (35 to 61)
B	49 (36 to 62)	10 (4 to 20)

2. Primary Outcome Measure:

Measure Title	Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of TIVf

Measure Description	Geometric mean ratio (GMR) of subjects was calculated as the ratio of postvaccination to prevaccination HI geometric mean titers (GMTs), directed against each of three vaccine strains, three weeks after vaccination (Day 22). The CHMP criterion was met if the geometric mean increase (GMR, Day 22/Day 1) in HI antibody titer was >2.5 (≥18 years to ≤60 years) or >2.0 (≥61 years).
Time Frame	Day 22
Safety Issue?	No

Analysis Population Description

Analysis was done on the PP set.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	63	63
Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of TIVf [units: Ratio] Number (95% Confidence Interval)		
A/H1N1	23 (15 to 34)	6.15 (4.36 to 8.66)
A/H3N2	6.78 (5.02 to 9.16)	3.81 (2.9 to 4.99)
B	4.37 (3.38 to 5.64)	1.61 (1.38 to 1.89)

3. Primary Outcome Measure:

Measure Title	Percentage of Subjects Who Achieved HI Titer ≥40 Against Each of Three Vaccine Strains After One Vaccination of TIVf
Measure Description	Immunogenicity was measured as the percentage of subjects achieving HI titer ≥40 against each of three vaccine strains at baseline (Day 1) and three weeks after TIVf vaccination (Day 22). This criterion was met according to CHMP guideline if percentage of subjects achieving HI titer ≥40 is >70% (≥18 years to ≤60) or >60% (≥61 years).

Time Frame	Day 1 and Day 22
Safety Issue?	No

Analysis Population Description

Analysis was done on the PP set.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	63	63
Percentage of Subjects Who Achieved HI Titer ≥40 Against Each of Three Vaccine Strains After One Vaccination of TIVf [units: Percentages of Subjects] Number (95% Confidence Interval)		
A/H1N1 (Day 1)	60 (47 to 72)	49 (36 to 62)
A/H1N1 (Day 22)	98 (91 to 100)	92 (82 to 97)
A/H3N2 (Day 1)	79 (67 to 89)	86 (75 to 93)
A/H3N2 (Day 22)	98 (91 to 100)	100 (94 to 100)
B (Day 1)	8 (3 to 18)	5 (1 to 13)
B (Day 22)	65 (52 to 77)	19 (10 to 31)

4. Secondary Outcome Measure:

Measure Title	Numbers of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination)
Measure Description	Safety was assessed as the number of subjects who reported solicited local and systemic reactions from Day 1 up to and including Day 4 after the TIVf vaccination.
Time Frame	From Day 1 through Day 4 postvaccination
Safety Issue?	Yes

Analysis Population Description

Analysis was done on the safety dataset i.e. the subjects in the exposed population who provided postvaccination safety data.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	63	63
Numbers of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination) [units: Subjects]		
Injection site ecchymosis	1	1
Injection site erythema	5	7
Injection site induration	6	2
Injection site swelling	2	4
Injection site pain	35	12
Chills/shivering	2	1
Malaise	10	4
Myalgia	18	10
Arthralgia	0	0
Headache	14	6
Sweating	11	9
Fatigue	15	9
Fever (≥38°C)	0	0

Reported Adverse Events

Time Frame	From Day 1 through Day 22.
Additional Description	Serious adverse events (SAEs) were collected from Day 1 through Day 22.

Reporting Groups

	Description
18-60 Y	Subjects ≥18 years to ≤60 years of age who received one TIVf vaccination
≥61 Y	Subjects ≥61 years of age who received one TIVf vaccination

Serious Adverse Events

	18-60 Y	≥61 Y
	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/63 (0%)	0/63 (0%)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	18-60 Y	≥61 Y
	Affected/At Risk (%)	Affected/At Risk (%)
Total	44/63 (69.84%)	29/63 (46.03%)
General disorders		
Fatigue [A] †	15/63 (23.81%)	9/63 (14.29%)
Injection site erythema [A] †	5/63 (7.94%)	6/63 (9.52%)
Injection site induration [A] †	4/63 (6.35%)	2/63 (3.17%)
Injection site pain [A] †	35/63 (55.56%)	12/63 (19.05%)
Malaise [A] †	10/63 (15.87%)	4/63 (6.35%)
Musculoskeletal and connective tissue disorders		
Myalgia [A] †	18/63 (28.57%)	10/63 (15.87%)
Nervous system disorders		

	18-60 Y	≥61 Y
	Affected/At Risk (%)	Affected/At Risk (%)
Headache [A] †	14/63 (22.22%)	6/63 (9.52%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis [A] *	11/63 (17.46%)	9/63 (14.29%)

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

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