

## Safety and Immunogenicity of a Trivalent Influenza Vaccine When Administered to Elderly Subjects

This study has been completed.

<b>Sponsor:</b>	Novartis Vaccines
<b>Collaborators:</b>	Novartis Vaccines
<b>Information provided by (Responsible Party):</b>	Novartis (Novartis Vaccines)
<b>ClinicalTrials.gov Identifier:</b>	NCT01651104

### ► Purpose

To evaluate the safety of a single intramuscular (IM) injection of trivalent adjuvanted influenza study vaccine, formulation 2012/2013, in elderly subjects and the antibody response to each influenza vaccine antigen, as measured by single radial hemolysis (SRH) and hemagglutination inhibition (HI) at approximately 21 days postimmunization in elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines.

Condition	Intervention	Phase
Human Influenza	Biological/Vaccine: Adjuvanted Trivalent Influenza Virus Vaccine (aTIV)	Phase 2

Study Type: Interventional

Study Design: Prevention, Single Group Assignment, Open Label, N/A, Safety/Efficacy Study

Official Title: A Phase 2, Open Label, Uncontrolled, Multicenter Study to Evaluate Safety and Immunogenicity of a Surface Antigen, Inactivated, Adjuvanted With MF59C.1 Influenza Vaccine (Fluad®), Formulation 2012/2013, When Administered to Elderly Subjects

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

Primary Outcome Measure:

- Percentages of Subjects Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of aTIV [Time Frame: Day 22] [Designated as safety issue: No]

Immunogenicity was measured as the percentage of subjects who achieved seroconversion or significant increase in single radial hemolysis (SRH) area, against each of three vaccine strains, three weeks after vaccination (day 22), evaluated using SRH assay. Seroconversion or significant increase in SRH area was defined as the percentage of subjects with a negative prevaccination serum (SRH area  $\leq 4$  mm<sup>2</sup>) to a postvaccination SRH area  $\geq 25$  mm<sup>2</sup>; or a significant increase in antibody titer from a non-negative prevaccination serum, i.e., at least a 50% increase in area. The European (CHMP) criterion is met if percentage of subjects achieving seroconversion or significant increase in SRH area is 30% ( $\geq 65$  years).

- Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of aTIV [Time Frame: Day 22] [Designated as safety issue: No]  
Geometric mean ratio (GMR) of subjects was calculated as the ratio of postvaccination to prevaccination SRH geometric mean areas (GMAs), 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 SRH antibody area is  $>2.0$  ( $\geq 65$  years).
- Percentages of Subjects Who Achieved SRH Area  $\geq 25$  mm<sup>2</sup> Against Each of Three Vaccine Strains After One Vaccination of aTIV [Time Frame: Day 1 and 22] [Designated as safety issue: No]  
Immunogenicity was measured as the percentage of subjects achieving SRH area  $\geq 25$  mm<sup>2</sup> against each of three vaccine strains at baseline (day 1) and three weeks after aTIV vaccination (day 22). This criterion is met according to CHMP guideline if percentage of subjects achieving SRH area  $\geq 25$  mm<sup>2</sup> is 60% ( $\geq 65$  years).

#### Secondary Outcome Measures:

- Number 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 aTIV vaccination.

Enrollment: 63

Study Start Date: July 2012

Study Completion Date: August 2012

Primary Completion Date: August 2012

Arms	Assigned Interventions
Experimental: Adjuvanted Trivalent Influenza Virus Vaccine	Biological/Vaccine: Adjuvanted Trivalent Influenza Virus Vaccine (aTIV) A single 0.5 mL dose of study vaccine supplied in prefilled syringes was administered intramuscularly in the deltoid muscle, preferably of the non dominant arm.

#### ► Eligibility

Ages Eligible for Study: 65 Years and older

Genders Eligible for Study: Both

Accepts healthy volunteers.

#### Inclusion Criteria:

1. Male and female volunteers of 65 years of age or older, mentally competent, willing and able to give written informed consent prior to study entry;
2. Individuals able to comply 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 interfere 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  $\geq 10$  years or localized prostate cancer that has been clinically stable for more than 2 years without treatment);

- Medically significant advanced congestive heart failure (ie. 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  $\geq 5$  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 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 (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 derivatives 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 would interfere 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, pose additional risk to the subjects due to participation in the study.
  9. Individuals who within the past 6 months 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 are planning to receive any vaccine during the study.
  11. Individuals with any acute or chronic infections requiring systemic antibiotic treatment or antiviral therapy within the last 7 days.
  12. Individuals that have experienced fever (i.e., axillary temperature  $\geq 38^{\circ}\text{C}$ ) within the last 3 days of intended study vaccination.
  13. 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.
  14. Individuals who were part of study personnel or close family members conducting this study.
  15. BMI  $>35$  kg/m<sup>2</sup>.



## Contacts and Locations

### Locations

#### Belgium

University Hospital Ghent Center for Vaccinology

De Pintelaan, BE-9000 Ghent, Belgium, 185

**Investigators**

Study Chair: Novartis Vaccines and Diagnostics Novartis Vaccines and Diagnostics

 More Information

Responsible Party: Novartis Vaccines  
 Study ID Numbers: V70\_39S  
 2012-000085-38 [EudraCT Number]  
 Health Authority: European Union: European Medicines Agency

## Study Results

 Participant Flow

**Recruitment Details** -- Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations:

Subjects were enrolled at one study center in Belgium.

**Pre-Assignment Details** -- Significant events and approaches for the overall study following participant enrollment, but prior to group assignment:

All enrolled subjects were included in the trial.

**Reporting Groups**

	Description
≥65 Y	Subjects ≥65 years of age who received one aTIV vaccination

**Overall Study**

	≥65 Y
<b>STARTED</b>	63
<b>COMPLETED</b>	63
<b>Not Completed</b>	<b>0</b>

 Baseline Characteristics

**Analysis Population Description** -- Explanation of how the number of participants for analysis was determined.

Baseline analysis was performed on all enrolled subjects.

**Reporting Groups**

	Description
≥65 Y	Subjects ≥65 years of age who received one aTIV vaccination

**Baseline Measures**

	<b>≥65 Y</b>
<b>Number of Participants</b>	63
<b>Age Continuous</b> [units: Years] Mean ± Standard Deviation	70.5 ± 3.9
<b>Gender, Male/Female</b> [units: Subjects]	
<b>Female</b>	28
<b>Male</b>	35

 Outcome Measures
**1. Primary Outcome Measure:**

<b>Measure Title</b>	<b>Percentages of Subjects Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of aTIV</b>
<b>Measure Description</b>	<p>Immunogenicity was measured as the percentage of subjects who achieved seroconversion or significant increase in single radial hemolysis (SRH) area, against each of three vaccine strains, three weeks after vaccination (day 22), evaluated using SRH assay.</p> <p>Seroconversion or significant increase in SRH area was defined as the percentage of subjects with a negative prevaccination serum (SRH area ≤4 mm<sup>2</sup>) to a postvaccination SRH area ≥25 mm<sup>2</sup>; or a significant increase in antibody titer from a non-negative prevaccination serum, i.e., at least a 50% increase in area.</p> <p>The European (CHMP) criterion is met if percentage of subjects achieving seroconversion or significant increase in SRH area is 30% (≥65 years).</p>
<b>Time Frame</b>	Day 22
<b>Safety Issue?</b>	No

**Analysis Population Description** -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

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**

	<b>Description</b>
<b>≥65 Y</b>	<b>Subjects ≥65 years of age who received one aTIV vaccination</b>

**Measured Values**

	<b>≥65 Y</b>
<b>Number of Participants Analyzed</b>	63
<b>Percentages of Subjects Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of aTIV</b> [units: Percentages]	
Number (95% Confidence Interval)	
<b>A/H1N1</b>	59 (46 to 71)
<b>A/H3N2</b>	65 (52 to 77)
<b>B</b>	81 (69 to 90)

**2. Primary Outcome Measure:**

<b>Measure Title</b>	<b>Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of aTIV</b>
<b>Measure Description</b>	Geometric mean ratio (GMR) of subjects was calculated as the ratio of postvaccination to prevaccination SRH geometric mean areas (GMAs), 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 SRH antibody area is >2.0 (≥65 years).
<b>Time Frame</b>	Day 22
<b>Safety Issue?</b>	No

**Analysis Population Description** -- Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:

Analysis was done on the PP set.

**Reporting Groups**

	<b>Description</b>
<b>≥65 Y</b>	<b>Subjects ≥65 years of age who received one aTIV vaccination</b>

**Measured Values**

	<b>≥65 Y</b>
<b>Number of Participants Analyzed</b>	63
<b>Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of aTIV</b> [units: Ratio]	

Number (95% Confidence Interval)	
<b>A/H1N1</b>	2.46 (1.93 to 3.12)
<b>A/H3N2</b>	2.68 (2.15 to 3.35)
<b>B</b>	4.44 (3.53 to 5.58)

### 3. Primary Outcome Measure:

<b>Measure Title</b>	<b>Percentages of Subjects Who Achieved SRH Area <math>\geq 25</math> mm<sup>2</sup> Against Each of Three Vaccine Strains After One Vaccination of aTIV</b>
<b>Measure Description</b>	Immunogenicity was measured as the percentage of subjects achieving SRH area $\geq 25$ mm <sup>2</sup> against each of three vaccine strains at baseline (day 1) and three weeks after aTIV vaccination (day 22).  This criterion is met according to CHMP guideline if percentage of subjects achieving SRH area $\geq 25$ mm <sup>2</sup> is 60% ( $\geq 65$ years).
<b>Time Frame</b>	Day 1 and 22
<b>Safety Issue?</b>	No

**Analysis Population Description** -- Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:

Analysis was done on the PP set.

### Reporting Groups

	Description
<b><math>\geq 65</math> Y</b>	<b>Subjects <math>\geq 65</math> years of age who received one aTIV vaccination</b>

### Measured Values

	<b><math>\geq 65</math> Y</b>
<b>Number of Participants Analyzed</b>	63
<b>Percentages of Subjects Who Achieved SRH Area <math>\geq 25</math> mm<sup>2</sup> Against Each of Three Vaccine Strains After One Vaccination of aTIV</b>	
<i>[units: Percentages]</i>	
Number (95% Confidence Interval)	
<b>A/H1N1 (Day 1)</b>	56 (42 to 68)
<b>A/H1N1 (Day 22)</b>	97 (89 to 100)
<b>A/H3N2 (Day 1)</b>	49 (36 to 62)
<b>A/H3N2 (Day 22)</b>	94 (85 to 98)
	19 (10

<b>B (Day 1)</b>	to 31)
<b>B (Day 22)</b>	87 (77 to 94)

#### 4. Secondary Outcome Measure:

<b>Measure Title</b>	<b>Number of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination)</b>
<b>Measure Description</b>	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 aTIV vaccination.
<b>Time Frame</b>	From day 1 through day 4 postvaccination
<b>Safety Issue?</b>	Yes

**Analysis Population Description** -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

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

#### Reporting Groups

	Description
<b>≥65 Y</b>	<b>Subjects ≥65 years of age who received one aTIV vaccination</b>

#### Measured Values

	<b>≥65 Y</b>
<b>Number of Participants Analyzed</b>	63
<b>Number of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination)</b> <i>[units: Number]</i>	
<b>Injection site ecchymosis</b>	3
<b>Injection site erythema</b>	7
<b>Injection site induration</b>	6
<b>Injection site swelling</b>	4
<b>Injection site pain</b>	22
<b>Chills/shivering</b>	0
<b>Malaise</b>	3
<b>Myalgia</b>	2
<b>Arthralgia</b>	2
<b>Headache</b>	4
<b>Sweating (N=62)</b>	2
<b>Fatigue (N=62)</b>	6

▶ Reported Adverse Events

### Reporting Groups

	Description
<b><math>\geq 65</math> Y</b>	Subjects $\geq 65$ years of age who received one aTIV vaccination

<b>Time Frame</b>	From day 1 through day 22.
<b>Additional Description</b>	Serious adverse events (SAEs) were collected from day 1 through day 22.

### Serious Adverse Events

	<b><math>\geq 65</math> Y</b>
<b>Total # participants affected/at risk</b>	<b>0/63 (0%)</b>

### Other Adverse Events

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

	<b><math>\geq 65</math> Y</b>
<b>Total # participants affected/at risk</b>	<b>29/63 (46.03%)</b>
<b>General disorders</b>	
<b>Fatigue</b> † A	
# participants affected/at risk	6/63 (9.52%)
# events	6
<b>Injection site erythema</b> † A	
# participants affected/at risk	7/63 (11.11%)
# events	7
<b>Injection site induration</b> † A	
# participants affected/at risk	6/63 (9.52%)
# events	6
<b>Injection site pain</b> † A	
# participants affected/at risk	22/63 (34.92%)
# events	22
<b>Injection site swelling</b> † A	
# participants affected/at risk	4/63 (6.35%)
# events	4
<b>Nervous system disorders</b>	
<b>Headache</b> † A	

# participants affected/at risk	4/63 (6.35%)
# events	4

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

## ▶ 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.

**Limitations and Caveats** -- *Limitations of the study, such as early termination leading to small numbers of subjects analyzed and technical problems with measurement leading to unreliable or uninterpretable data:*

[Not specified.]

### **Results Point of Contact:**

Name/Official Title: Posting Director

Organization: Novartis Vaccines and Diagnostics

Phone:

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