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Safety and Immunogenicity of a Subunit Trivalent Nonadjuvated Influenza Study Vaccine 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:	NCT01636102

Purpose

To evaluate the safety of a single intramuscular (IM) injection of trivalent nonadjuvated influenza study vaccine, formulation 2012/2013, in adult and 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 adult and 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: Trivalent influenza virus vaccine (TIV)	Phase 2

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

Official Title: A Phase II Open Label, Uncontrolled, Multicenter Study to Evaluate Safety and Immunogenicity of a Surface, Antigen, Inactivated, Influenza Vaccine (Agrippal®), 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 Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of TIV [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 ≤4 mm2) to a postvaccination SRH area ≥25 mm2; 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 >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 TIV [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 >2.5 (≥18 years to ≤60 years) or >2.0 (≥61 years).

- Percentage of Subjects Who Achieved SRH Area ≥25 mm2 Against Each of Three Vaccine Strains After One Vaccination of TIV [Time Frame: Day 1 and 22] [Designated as safety issue: No]
  Immunogenicity was measured as the percentage of subjects achieving SRH area ≥25 mm2 against each of three vaccine strains at baseline (day 1) and three weeks after TIV vaccination (day 22). This criterion was met according to CHMP guideline if percentage of subjects achieving SRH area ≥25 mm2 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 TIV vaccination.

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

Arms	Assigned Interventions
Experimental: Arm 1	Biological/Vaccine: Trivalent influenza virus vaccine (TIV) A single 0.5 mL dose of the study vaccine supplied in prefilled syringes and administered intramuscularly in the deltoid muscle of (preferably) the non dominant arm

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts healthy volunteers.

Inclusion Criteria:

1. Male and female volunteers of 18 years of age or older;
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 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 (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 ≥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 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 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 requiring systemic antibiotic treatment or antiviral therapy within the last 7 days.
12. Individuals who experienced fever (i.e., axillary temperature ≥38°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/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

Belgium

University Hospital Ghent, Center for Vaccinology, Prof.Dr. G Leroux Roels
Ghent, Ghent, Belgium, BC001

Investigators

Study Chair: Novartis Vaccines and Diagnostics Novartis Vaccines and Diagnostics

More Information

Responsible Party: Novartis Vaccines
Study ID Numbers: V71_32S
2012-000063-24 [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 1 site in Belgium.

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

All subjects enrolled were included in the trial.

Reporting Groups

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

Overall Study

	18-60 Y	≥61 Y
STARTED	63	63
COMPLETED	63	63
Not Completed	**0**	**0**

Baseline Characteristics

Analysis Population Description -- *Explanation of how the number of participants for analysis was determined.*
[Not specified.]

Reporting Groups

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

Baseline Measures

	18-60 Y	≥61 Y	Total
Number of Participants	63	63	**126**

Age Continuous *[units: years]* *Mean ± Standard Deviation*	37.9 ± 12.8	69.2 ± 5.7	**53.6 ± 18.5**
Gender, Male/Female *[units: participants]*			
Female	39	26	**65**
Male	24	37	**61**

Outcome Measures

1. Primary Outcome Measure:

Measure Title	**Percentage of Subjects Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of TIV**
Measure Description	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 ≤4 mm2) to a postvaccination SRH area ≥25 mm2; 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 >40% (≥18 years to ≤60 years) or 30% (≥61 years).
Time Frame	Day 22
Safety Issue?	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

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

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	62	62
Percentage of Subjects Who Achieved Seroconversion or Significant Increase in SRH Area Against Each of Three Vaccine Strains After One Vaccination of TIV		

[units: Percentages]		
Number (95% Confidence Interval)		
A/H1N1	84 (72 to 92)	53 (40 to 66)
A/H3N2	81 (69 to 90)	65 (51 to 76)
B	69 (56 to 80)	73 (60 to 83)

2. Primary Outcome Measure:

Measure Title	**Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of TIV**
Measure Description	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 >2.5 (≥18 years to ≤60 years) or >2.0 (≥61 years).
Time Frame	Day 22
Safety Issue?	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
18-60 Y	**Subjects ≥18 years to ≤60 years of age who received one TIV vaccination**
≥61 Y	**Subjects ≥61 years of age who received one TIV vaccination**

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	62	62
Geometric Mean Ratio of Subjects Against Each of Three Vaccine Strains After One Vaccination of TIV		
[units: Ratio]		
Number (95% Confidence Interval)		
A/H1N1	5.7 (4.3 to 7.55)	2.88 (2.26 to 3.65)
A/H3N2	5.52 (4.16 to 7.31)	3.02 (2.35 to 3.86)
B	3.72 (2.69 to 5.15)	4.06 (3.12 to 5.28)

3. Primary Outcome Measure:

Measure Title	**Percentage of Subjects Who Achieved SRH Area ≥25 mm2 Against Each of Three Vaccine Strains After One Vaccination of TIV**
Measure Description	Immunogenicity was measured as the percentage of subjects achieving SRH area ≥25 mm2 against each of three vaccine strains at baseline (day 1) and three weeks after TIV vaccination (day 22). This criterion was met according to CHMP guideline if percentage of subjects achieving SRH area ≥25 mm2 is >70% (≥18 years to ≤60) or 60% (≥61 years).
Time Frame	Day 1 and 22
Safety Issue?	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
18 - 60 Y	**Subjects ≥18 years to ≤60 years of age who received one TIV vaccination**
≥61 Y	**Subjects ≥61 years of age who received one TIV vaccination**

Measured Values

	18 - 60 Y	≥61 Y
Number of Participants Analyzed	62	62
Percentage of Subjects Who Achieved SRH Area ≥25 mm2 Against Each of Three Vaccine Strains After One Vaccination of TIV *[units: Percentages]* Number (95% Confidence Interval)		
A/H1N1 (Day 1)	34 (22 to 47)	27 (17 to 40)
A/H1N1 (Day 22)	95 (87 to 99)	71 (58 to 82)
A/H3N2 (Day 1)	23 (13 to 35)	45 (32 to 58)
A/H3N2 (Day 22)	85 (74 to 93)	92 (82 to 97)
B (Day 1)	61 (48 to 73)	21 (12 to 33)
B (Day 22)	97 (89 to 100)	82 (70 to 91)

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 TIV vaccination.

Time Frame	From day 1 through day 4 postvaccination
Safety Issue?	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
18-60 Y	**Subjects ≥18 years to ≤60 years of age who received one TIV vaccination**
≥61 Y	**Subjects ≥61 years of age who received one TIV vaccination**

Measured Values

	18-60 Y	≥61 Y
Number of Participants Analyzed	62	63
Numbers of Subjects Who Reported Solicited Local and Systemic Reactions (Day 1 - Day 4 Postvaccination) *[units: Numbers]*		
Injection site pain	24	9
Injection site ecchymosis	0	1
Injection site erythema	3	4
Injection site induration	4	0
Injection site swelling	4	1
Chills/shivering	0	0
Malaise	2	1
Myalgia	5	3
Arthralgia	2	1
Headache	9	6
Sweating	3	2
Fatigue	8	3
Body temperature (≥38°C)	0	0

Reported Adverse Events

Reporting Groups

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

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

Serious Adverse Events

	18-60 Y	≥61 Y
Total # participants affected/at risk	**0/63 (0%)**	**0/63 (0%)**

Other Adverse Events

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

	18-60 Y	≥61 Y
Total # participants affected/at risk	**28/63 (44.44%)**	**18/63 (28.57%)**
General disorders		
Fatigue †		
# participants affected/at risk	8/63 (12.7%)	3/63 (4.76%)
# events	8	3
Injection Site Erythema †		
# participants affected/at risk	3/63 (4.76%)	5/63 (7.94%)
# events	3	5
Injection Site Induration †		
# participants affected/at risk	4/63 (6.35%)	0/63 (0%)
# events	4	0
Injection Site Pain †		
# participants affected/at risk	24/63 (38.1%)	10/63 (15.87%)
# events	24	10
Injection Site Swelling †		
# participants affected/at risk	4/63 (6.35%)	1/63 (1.59%)
# events	4	1
Musculoskeletal and connective tissue disorders		
Arthralgia †		
# participants affected/at risk	3/63 (4.76%)	1/63 (1.59%)
# events	3	1
Myalgia †		
# participants affected/at risk	5/63 (7.94%)	3/63 (4.76%)
# events	5	3
Nervous system disorders		
Headache †		
# participants affected/at risk	9/63 (14.29%)	6/63 (9.52%)
# events	9	6

Skin and subcutaneous tissue disorders		
Hyperhidrosis *		
# participants affected/at risk	3/63 (4.76%)	2/63 (3.17%)
# events	3	2

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.

More Information

Certain Agreements:

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

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is more than 60 days but less than or equal to 180 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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:
Email: RegistryContactVaccinesUS@novartis.com

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