

**Clinical trial results:****A Phase II, Open-Label, Single-Arm, Multicenter Study to Evaluate the Safety and Immunogenicity of a Trivalent, Surface Antigen Inactivated Subunit Influenza Virus Vaccine (Arippal®) in Healthy Adults****Summary**

EudraCT number	2013-000545-39
Trial protocol	BE
Global end of trial date	20 August 2013

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	18 November 2014
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Required for the re-QC project because of the EudraCT system glitch and possible updates to results may be required. Moreover, a change in system user for this study is necessary.

Trial information**Trial identification**

Sponsor protocol code	V71_34S
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01879553
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l.
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Michelangelo Barone, Novartis Vaccines and Diagnostics S.r.l., +39 0577243516, michelangelo.barone@novartis.com
Scientific contact	Michelangelo Barone, Novartis Vaccines and Diagnostics S.r.l., +39 0577243516, michelangelo.barone@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 September 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity Objective

To evaluate the antibody response to each influenza vaccine antigen after vaccination with the TIV vaccine, as measured by single radial hemolysis (SRH) or hemagglutination inhibition (HI) assay in accordance with Guidance CPMP/BWP/214/96

Safety Objective

To evaluate the safety of TIV in adult subjects in compliance with the requirements of the current European Union recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96)

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and the Japanese Ministry of Health, Labor, and Welfare, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 126
Worldwide total number of subjects	126
EEA total number of subjects	126

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from one study center in Belgium.

Pre-assignment

Screening details:

All enrolled subjects were included in study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	TIV (18 to ≤ 60 Years)
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Arm description:

Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.

Arm type	Experimental
Investigational medicinal product name	trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

Arm title	TIV (≥ 61 Years)
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Arm description:

Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.

Arm type	Experimental
Investigational medicinal product name	trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

Number of subjects in period 1	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)
Started	63	63
Completed	62	63
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	TIV (18 to ≤ 60 Years)
Reporting group description: Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.	
Reporting group title	TIV (≥ 61 Years)
Reporting group description: Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.	

Reporting group values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)	Total
Number of subjects	63	63	126
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	63	12	75
From 65-84 years	0	50	50
85 years and over	0	1	1
Adults (18 to ≤ 60 Years)	0	0	0
Adults (≥ 61 Years)	0	0	0
Gender categorical			
Units: Subjects			
Female	40	29	69
Male	23	34	57

Subject analysis sets

Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All screened subjects who provided informed consent and provided demographic and/or baseline screening assessments and received a 'Subject ID'.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who have received study vaccination and provided immunogenicity data both at baseline and after vaccination, and were not excluded due to reasons defined prior to unblinding or analysis.	
Subject analysis set title	Safety Set (solicited AEs and other solicited events)
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the Exposed Set who provided postvaccination reactogenicity data.	

Subject analysis set title	Safety Set (unsolicited AEs)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed Set who had postvaccination unsolicited AE records.

Reporting group values	Enrolled Set	Per Protocol Set	Safety Set (solicited AEs and other solicited events)
Number of subjects	126	124	126
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18 to ≤ 60 Years)	63	61	63
Adults (≥ 61 Years)	63	63	63
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	Safety Set (unsolicited AEs)		
Number of subjects	126		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Adults (18 to ≤ 60 Years)	63		
Adults (≥ 61 Years)	63		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	TIV (18 to ≤ 60 Years)
Reporting group description: Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.	
Reporting group title	TIV (≥ 61 Years)
Reporting group description: Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.	
Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All screened subjects who provided informed consent and provided demographic and/or baseline screening assessments and received a 'Subject ID'.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: All subjects who have received study vaccination and provided immunogenicity data both at baseline and after vaccination, and were not excluded due to reasons defined prior to unblinding or analysis.	
Subject analysis set title	Safety Set (solicited AEs and other solicited events)
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the Exposed Set who provided postvaccination reactogenicity data.	
Subject analysis set title	Safety Set (unsolicited AEs)
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the Exposed Set who had postvaccination unsolicited AE records.	

Primary: Percentages of Subjects With Single Radial Hemolysis (SRH) Areas ≥25mm², Against Each of Three Vaccine Strains After Receiving One Dose of TIV

End point title	Percentages of Subjects With Single Radial Hemolysis (SRH) Areas ≥25mm ² , Against Each of Three Vaccine Strains After Receiving One Dose of TIV ^[1]
End point description: Immunogenicity was assessed in terms of percentages of subjects in both age groups with SRH areas ≥25mm ² against each of the three vaccine strains, three weeks after receiving one dose of TIV. The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving post vaccination SRH areas ≥ 25mm ² is >70% for adults aged 18 to ≤60 years and >60% for subjects aged ≥61 years.	
End point type	Primary
End point timeframe: Day 22 post vaccination	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: There were no statistical analysis done.	

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 1 (H1N1 strain)	52 (39 to 65)	41 (29 to 54)		
Day 22 (H1N1 strain)	100 (94 to 100)	78 (66 to 87)		
Day 1 (H3N2 strain)	31 (20 to 44)	46 (33 to 59)		
Day 22 (H3N2 strain)	92 (82 to 97)	78 (66 to 87)		
Day 1 (B strain)	38 (26 to 51)	67 (54 to 78)		
Day 22 (B strain)	92 (82 to 97)	89 (78 to 95)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of Subjects With Seroconversion or Significant Increase in SRH Area, against Each of Three Vaccine Strains After Receiving One Dose of TIV

End point title	Percentages of Subjects With Seroconversion or Significant Increase in SRH Area, against Each of Three Vaccine Strains After Receiving One Dose of TIV ^[2]
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End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups achieving seroconversion or significant increase by SRH area against each of the three vaccine strains, three weeks after receiving one dose of TIV.

Seroconversion is defined as percentage of subjects with a pre vaccination SRH area ≤4mm² achieving a post vaccination SRH area ≥25 mm². Significant increase is defined as percentage of subjects with a pre-vaccination SRH area >4mm² achieving at least 50% increase in post vaccination SRH area. The related European (CHMP) criterion for the assessment of immunogenicity is met if >40% for adults aged 18 to ≤60 years and >30% for subjects aged ≥61 years achieve seroconversion or significant increase in post-vaccination SRH areas.

End point type	Primary
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End point timeframe:

Day 22 post vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	69 (56 to 80)	49 (36 to 62)		
H3N2 strain	70 (57 to 81)	43 (30 to 56)		
B strain	70 (57 to 81)	30 (19 to 43)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination GMAs, After one Dose of TIV

End point title	Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination GMAs, After one Dose of TIV ^[3]
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End point description:

The antibody responses were evaluated in terms of GMRs of post vaccination GMAs to pre vaccination GMAs against each of the three vaccine strains, three weeks after receiving one dose of TIV. The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is >2.5 for adults aged 18 to ≤60 years and > 2.0 in for subjects aged ≥61 years.

End point type	Primary
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End point timeframe:

Day 22 post vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	3.41 (2.51 to 4.63)	1.85 (1.52 to 2.25)		
H3N2 strain	3.07 (2.45 to 3.85)	1.74 (1.46 to 2.08)		
B strain	2.06 (1.75 to 2.42)	1.49 (1.29 to 1.73)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, against Each of Three Vaccine Strains After Receiving One Dose of TIV

End point title	Percentages of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, against Each of Three Vaccine Strains After Receiving One Dose of TIV ^[4]
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End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups with HI titers ≥40, against each of the three vaccine strains, three weeks after receiving one dose of TIV.

The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving HI titers ≥ 40 is >70% for adults aged 18 to ≤60 years and >60% for subjects aged ≥61 years.

End point type	Primary
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End point timeframe:

Day 22 post vaccination

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 1 (H1N1 strain)	59 (46 to 71)	60 (47 to 72)		
Day 22 (H1N1 strain)	100 (94 to 100)	90 (80 to 96)		
Day 1 (H3N2 strain)	66 (52 to 77)	86 (75 to 93)		
Day 22 (H3N2 strain)	100 (94 to 100)	98 (91 to 100)		
Day 1 (B strain)	66 (52 to 77)	70 (57 to 81)		
Day 22 (B strain)	98 (91 to 100)	89 (78 to 95)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers After Receiving One Dose of TIV

End point title	Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers After Receiving One Dose of TIV ^[5]
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End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups achieving seroconversion or significant increase in HI antibody titers after receiving one dose of TIV.

Seroconversion is defined as percentage of subjects with a pre vaccination HI titer <10 to a post vaccination titer ≥40. Significant increase is defined as percentage of subjects with a pre vaccination HI titer ≥10 to at least a 4-fold increase in post vaccination HI antibody titers.

The related European (CHMP) criterion for the assessment of immunogenicity is met if >40% for adults aged 18 to ≤60 years and >30% for subjects aged ≥61 years achieve seroconversion or significant increase in post-vaccination HI titers.

End point type	Primary
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End point timeframe:

Day 22 post vaccination

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	64 (51 to 76)	32 (21 to 45)		

H3N2 strain	64 (51 to 76)	16 (8 to 27)		
B strain	52 (39 to 65)	13 (6 to 23)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, After Receiving One Dose of TIV

End point title	Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, After Receiving One Dose of TIV ^[6]
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End point description:

The antibody responses following one dose of TIV were evaluated in terms of GMRs of post vaccination against pre vaccination geometric mean HI titers against each of the three vaccine strains, three weeks after receiving one dose of TIV.

The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is >2.5 for adults aged 18 to ≤60 years and > 2.0 for subjects aged ≥61 years.

End point type	Primary
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End point timeframe:

Day 22 post vaccination

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	9.65 (5.96 to 16)	2.6 (1.97 to 3.45)		
H3N2 strain	8.47 (5.44 to 13)	1.85 (1.37 to 2.5)		
B strain	4.56 (3.26 to 6.37)	1.49 (1.22 to 1.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Unsolicited Adverse Events After Receiving One Dose of TIV

End point title	Number of Subjects Reporting Unsolicited Adverse Events After Receiving One Dose of TIV ^[7]
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End point description:

The number of subjects in both age groups reporting any unsolicited AEs (between Day 1 to 4), serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal (Day 1 to Day 22), after receiving one dose of TIV is reported.

End point type Primary

End point timeframe:

Day 1 to Day 22 post vaccination

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: Subjects				
Any AE (Day 1 to 4)	10	8		
At least Possibly related AE	9	6		
Any SAE	0	0		
At least Possibly related SAE	0	0		
Medically attended AE	0	0		
AE leading to discontinuation	0	0		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Solicited Adverse Events After

End point title Number of Subjects Reporting Solicited Adverse Events After^[8]

End point description:

End point type Primary

End point timeframe:

Day 1 to Day 4 post vaccination

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no statistical analysis done.

End point values	TIV (18 to ≤ 60 Years)	TIV (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: Subjects				
Any Local	38	18		
Injection site induration	13	9		
Injection site erythema	10	8		
Injection site ecchymosis	4	1		
Injection site pain	34	12		

Any Systemic	17	10		
Shivering/Chills	0	0		
Myalgia	1	1		
Arthralgia	0	1		
Fatigue	15	8		
Headache	5	3		
Malaise	2	4		
Fever ($\geq 38^{\circ}\text{C}$)	0	0		
Prophylactic use of analgesics/antipyretics	0	0		
Therapeutic use of analgesics/antipyretics	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited AEs and unsolicited AEs were collected from Day 1 to Day 4; all unsolicited SAEs, medically attended AEs, AEs leading to withdrawal from the study were collected from Day 1 to Day 22.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	TIV (≥ 61 Years)
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Reporting group description:

Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.

Reporting group title	TIV (18 to ≤ 60 Years)
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Reporting group description:

Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated subunit influenza virus vaccine (TIV) formulation 2013/2014 Northern Hemisphere.

Serious adverse events	TIV (≥ 61 Years)	TIV (18 to ≤ 60 Years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TIV (≥ 61 Years)	TIV (18 to ≤ 60 Years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 63 (42.86%)	41 / 63 (65.08%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 63 (4.76%)	5 / 63 (7.94%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 63 (12.70%)	15 / 63 (23.81%)	
occurrences (all)	8	17	

Injection site erythema subjects affected / exposed occurrences (all)	9 / 63 (14.29%) 17	9 / 63 (14.29%) 16	
Injection site haemorrhage subjects affected / exposed occurrences (all)	1 / 63 (1.59%) 2	4 / 63 (6.35%) 8	
Injection site induration subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 12	11 / 63 (17.46%) 19	
Injection site pain subjects affected / exposed occurrences (all)	16 / 63 (25.40%) 16	35 / 63 (55.56%) 36	
Malaise subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 5	2 / 63 (3.17%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported