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

Summary

EudraCT number	2013-000601-23
Trial protocol	DE
Global end of trial date	02 September 2013
Results information	
Result version number	v2 (current)
This version publication date	23 December 2016
First version publication date	22 February 2015
Version creation reason	• Correction of full data set QC of the posted data and possible corrections prior to re-release

Trial information

Trial identification	
Sponsor protocol code	V78_11S
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01885117
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	Posting Director, Novartis Vaccines, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines, RegistryContactVaccinesUS@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	14 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 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 trivalent, surface antigen inactivated influenza vaccine (TIVf) 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 TIVf 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:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines.
Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	08 August 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	Germany: 125
Worldwide total number of subjects	125
EEA total number of subjects	125

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from one center in Germany.

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	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	TIVf (18 to ≤ 60 Years)

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived, Fluvirin platform)
Investigational medicinal product code	
Other name	Fluvirin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Single 0.5-mL dose of TIVf vaccine is administered IM.

Arm title	TIVf (≥ 61Years)

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived, Fluvirin platform)
Investigational medicinal product code	
Other name	Fluvirin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Single 0.5-mL dose of TIVf vaccine is administered IM.

Number of subjects in period 1	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)
Started	61	64
Completed	61	64

Baseline characteristics

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

Reporting group values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)	Total
Number of subjects	61	64	125
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
Age continuous			
Adult subjects aged 18 to ≤ 60 years and ≥ 61 years received one dose of trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVf), formulation 2013/2014 Northern Hemisphere			
Units: years			
arithmetic mean	39.2	68.2	
standard deviation	± 11.2	± 4.7	-
Gender categorical			
Adult subjects aged 18 to ≤ 60 years and ≥ 61 years received one dose of trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVf), formulation 2013/2014 Northern Hemisphere.			
Units: Subjects			
Female	29	34	63
Male	32	30	62

End points

End points reporting groups

Reporting group title	TIVf (18 to ≤ 60 Years)

Reporting group description:

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

Reporting group title	TIVf (≥ 61Years)

Reporting group description:

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

Subject analysis set title	Full Analysis Set (FAS) Immunogenicity
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the enrolled set who received a study vaccination and provided immunogenicity data both before (baseline) and after vaccination.

Subject analysis set title	All Enrolled Set
Subject analysis set type	Full analysis

Subject analysis set description:

All screened subjects who provide informed consent and provide 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 in the FAS immunogenicity who were not excluded due to reasons defined prior to unblinding or analysis Examples of subjects excluded due to reasons other than predefined major protocol deviations are:
- Subjects who withdrew informed consent
- Subjects with real-time RT-PCR confirmed influenza during study participation

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

End point title	Percentage of Subjects With Single Radial Hemolysis (SRH) Areas ≥25mm2, Against Each of Three Vaccine Strains After Receiving One Dose of TIVf.[1]

End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups with SRH areas ≥25mm2 against each of the three vaccine strains, three weeks after receiving one dose of TIVf.
The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving post vaccination SRH areas ≥ 25mm2 is >70% for adults aged 18 to ≤60 years and >60% for subjects aged ≥61 years.
Analysis was done on the per-protocol population.

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Day 1/baseline (H1N1 strain)	17 (8 to 29)	36 (24 to 49)		
Day 1/baseline (H3N2 strain)	20 (11 to 32)	20 (11 to 32)		
Day 1/baseline (B strain)	57 (43 to 69)	55 (42 to 67)		
Day 22 (H1N1 strain)	95 (86 to 99)	80 (68 to 89)		
Day 22 (H3N2 strain)	82 (70 to 90)	84 (73 to 92)		
Day 22 (B strain)	92 (82 to 97)	92 (83 to 97)		

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 TIVf

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 TIVf[2]

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 TIVf.
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 the percentage of subjects achieving post vaccination SRH areas ≥ 25mm2 is >40% for adults aged 18 to ≤60 years and >30% for subjects aged ≥61 years.
Analysis was done on the per-protocol population.

End point type	Primary

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1 strain	85 (73 to 93)	58 (45 to 70)		
H3N2 strain	88 (77 to 95)	73 (61 to 84)		
B strain	68 (55 to 80)	67 (54 to 78)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratio (GMR) of Post Vaccination Versus Pre Vaccination Geometric Mean Areas(GMAs), After One Dose of TIVf

End point title	Geometric Mean Ratio (GMR) of Post Vaccination Versus Pre Vaccination Geometric Mean Areas(GMAs), After One Dose of TIVf[3]

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 TIVf.
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.
Analysis was done on the per-protocol population.

End point type	Primary

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	7.62 (5.83 to 9.95)	3.42 (2.65 to 4.41)		
H3N2 strain	3.66 (2.98 to 4.5)	3.05 (2.49 to 3.74)		
B strain	2.62 (2.09 to 3.27)	2.33 (1.92 to 2.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, Against Each of Three Vaccine Strains After Receiving One Dose of TIVf.

End point title	Percentage of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, Against Each of Three Vaccine Strains After Receiving One Dose of TIVf.[4]

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 TIVf.
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.
Analysis was done on the per-protocol population.

End point type	Primary

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Day 1/baseline (H1N1 strain)	50 (37 to 63)	56 (43 to 69)		
Day 1/baseline (H3N2 strain)	62 (48 to 74)	73 (61 to 84)		
Day 1/baseline (B strain)	45 (32 to 58)	45 (33 to 58)		
Day 22 (H1N1 strain)	100 (94 to 100)	100 (94 to 100)		
Day 22 (H3N2 strain)	98 (91 to 100)	100 (94 to 100)		
Day 22 (B strain)	93 (84 to 98)	80 (68 to 89)		

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 TIVf.

End point title	Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers After Receiving One Dose of TIVf.[5]

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 TIVf.
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.
Analysis was done on the per-protocol population.

End point type	Primary

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1 strain	78 (66 to 88)	70 (58 to 81)		

H3N2 strain	82 (70 to 90)	56 (43 to 69)		
B strain	53 (40 to 66)	27 (16 to 39)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, Against Each of Three Vaccine Strains After Receiving One Dose of TIVf

End point title	Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, Against Each of Three Vaccine Strains After Receiving One Dose of TIVf[6]

End point description:

The antibody responses following one dose of TIVf 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 TIVf.
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.
Analysis was done on the per-protocol population.

End point type	Primary

End point timeframe:

Day 22/Day 1

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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	64		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	27 (16 to 46)	11 (7.36 to 18)		
H3N2 strain	10 (7.31 to 14)	7.34 (4.73 to 11)		
B strain	5.34 (3.67 to 7.77)	2.54 (1.94 to 3.33)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Solicited Adverse Events (AEs) After Receiving One Dose of TIVf.

End point title	Number of Subjects Reporting Solicited Adverse Events (AEs) After Receiving One Dose of TIVf.[7]

End point description:

The number of adult and elderly subjects reporting solicited local and systemic AEs and other solicited AEs after receiving one dose of TIVf are reported.
Analysis was done on the safety set population.

End point type	Primary

End point timeframe:

Day 1 through Day 4 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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Number of Subjects				
Any Local	34	24		
Injection site pain	31	18		
Injection site ecchymosis	4	1		
Injection site erythema	2	10		
Injection site induration	7	8		
Any Systemic	21	10		
Chills/shivering	3	0		
Malaise	8	1		
Myalgia	2	2		
Arthralgia	5	1		
Headache	14	5		
Fatigue	14	6		
Fever (≥38°C)	0	0		
Prophylactic use of analgesic/antipyretics N=61,62	0	0		
Therapeutic use of analgesics/antipyretics N=61,62	3	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects Reporting Unsolicited Adverse Events After Receiving One Dose of TIVf.[8]

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 (throughout the study period), after receiving one dose of TIVf is reported.
Analysis was done on the safety analysis set.

End point type	Primary

End point timeframe:

Day 1 through Day 22 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: No statistical analysis was performed.

End point values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Number of Subjects				
Any AE	3	3		
Possibly/Probably related AE	1	3		
Any SAE	0	0		
Possibly/Probably related SAE	0	0		
Medically attended AE	1	0		
AE leading to premature withdrawal	0	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 Day1 to Day 4; all unsolicited SAEs, medically attended AEs, AEs leading to withdrawal from the study were collected from Day1 to Day 22.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	TIVf (18 to ≤ 60 Years)

Reporting group description:

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

Reporting group title	TIVf (≥ 61Years)

Reporting group description:

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

Serious adverse events	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61Years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 61 (67.21%)	24 / 64 (37.50%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 61 (8.20%)	14 / 64 (21.88%)	
occurrences (all)	7	18	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 61 (9.84%)	14 / 64 (21.88%)	
occurrences (all)	6	18	

Injection site pain			
subjects affected / exposed	33 / 61 (54.10%)	19 / 64 (29.69%)	
occurrences (all)	33	20	
Malaise			
subjects affected / exposed	1 / 61 (1.64%)	9 / 64 (14.06%)	
occurrences (all)	1	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 61 (1.64%)	5 / 64 (7.81%)	
occurrences (all)	1	5	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not specified

Notes: