Clinical trial results:
A Phase II, Open-Label, Uncontrolled, Single Center Study to Evaluate Safety and Immunogenicity of FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur], Formulation 2008-2009, when Administered to Non-Elderly Adult and Elderly Subjects

Summary

EudraCT number	2008-000939-17
Trial protocol	GB
Global end of trial date	07 August 2008

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	06 March 2015
Version creation reason	• Correction of full data set Required for the re-QC because of EudraCT system glitch as possible updates to results are required. Moreover, the study is now transferred to another primary user.

Trial information

Trial identification

Sponsor protocol code	V78P6S

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00748150
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l.
Sponsor organisation address	Frimley, Camberley, Surrey, United Kingdom,
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	15 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antibody response to each influenza vaccine antigen, as measured by haemagglutination inhibition (HI) test at 21 days post-immunization in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96).

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practices (GCPs) and the applicable regulatory requirement(s) for the country in which the trial was conducted, GCP according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2008
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	United Kingdom: 143
Worldwide total number of subjects	143
EEA total number of subjects	143

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)	77
From 65 to 84 years	64

85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at one study center in United Kingdom.

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

Arms

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

Arm description:

Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 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:

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

Arm title	TIVf (≥ 61 Years)

Arm description:

Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 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:

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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)
Started	66	77
Completed	63	73
Not completed	3	4
Lost to follow-up	3	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	TIVf (18 to ≤ 60 Years)
Reporting group description:	
Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.	
Reporting group title	TIVf (≥ 61 Years)
Reporting group description:	
Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.	

Reporting group values	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)	Total
Number of subjects	66	77	143
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			
Units: years			
arithmetic mean	45.9	72.3	
standard deviation	± 13	± 6.8	-
Gender categorical			
Units: Subjects			
Female	39	36	75
Male	27	41	68

End points

End points reporting groups

Reporting group title	TIVf (18 to ≤ 60 Years)

Reporting group description:

Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.

Reporting group title	TIVf (≥ 61 Years)

Reporting group description:

Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.

Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who have been enrolled.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the full analysis set who received the relevant dose of vaccine correctly on Day 0, who provided evaluable serum samples with the relevant time windows and had no major protocol violations.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed Set (all enrolled subjects who actually received a study vaccine) who provided post-baseline safety data.

Primary: 1) Percentages of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, against Each of Three Vaccine Strains After Receiving One Dose of TIVf

End point title	1) Percentages of Subjects With Haemagglutination Inhibition (HI) Titers ≥40, 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 HI titers ≥40, against each of the three vaccine strains, three weeks after receiving one dose of TIVf.
The related European [committee for medicinal products for human use (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.
The analysis was performed on the per protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 0 (H1N1 strain)	48 (35 to 62)	40 (28 to 52)		
Day 21 (H1N1 strain)	93 (84 to 98)	80 (69 to 89)		

Day 0 (H3N2 strain)	45 (32 to 58)	47 (35 to 59)		
Day 21 (H3N2 strain)	95 (86 to 99)	91 (82 to 97)		
Day 0 (B strain)	10 (4 to 21)	16 (8 to 26)		
Day 21 (B strain)	58 (45 to 71)	31 (21 to 44)		

Statistical analyses

No statistical analyses for this end point

Primary: 2) Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers After Receiving One Dose of TIVf

End point title	2) Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers 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 in HI antibody titers after receiving one dose of TIVf. Seroconversion is defined as percentage of subjects with negative prevaccination serum/postvaccination serum titer ≥40. Significant increase is defined as percentage of subjects with at least a 4-fold increase in postvaccination 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 postvaccination HI titers.
The analysis was performed on the per protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Percentages of subjects				
number (confidence interval 95%)				
H1N1 strain	45 (32 to 58)	24 (15 to 36)		
H3N2 strain	72 (59 to 83)	71 (59 to 82)		
B strain	37 (25 to 50)	14 (7 to 25)		

Statistical analyses

No statistical analyses for this end point

Primary: 3) Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, After Receiving One Dose of TIVf

End point title	3) Geometric Mean Ratio of Post Vaccination Versus Pre Vaccination HI Antibody Titers, After Receiving One Dose of TIVf[3]

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 TIVf.
The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 21/day 0 is >2.5 for adults aged 18 to ≤60 years and > 2.0 for subjects aged ≥61 years.
The analysis was performed on the per-protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	4.92 (3.32 to 7.31)	2.23 (1.89 to 2.64)		
H3N2 strain	6.35 (4.62 to 8.73)	4.59 (3.77 to 5.61)		
B strain	3.07 (2.36 to 3.98)	1.92 (1.61 to 2.29)		

Statistical analyses

No statistical analyses for this end point

Primary: 4) Percentages of Subjects With Single Radial Hemolysis (SRH) Areas ≥25mm2, for B strain After Receiving One Dose of TIVf

End point title	4) Percentages of Subjects With Single Radial Hemolysis (SRH) Areas ≥25mm2, for B strain After Receiving One Dose of TIVf[4]

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.
The analysis was performed on the per-protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 0 (B strain)	63 (50 to 75)	69 (56 to 79)		
Day 21 (B strain)	92 (82 to 97)	91 (82 to 97)		

Statistical analyses

No statistical analyses for this end point

Primary: 5) 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	5) Percentages of Subjects With Seroconversion or Significant Increase in SRH Area, against Each of Three Vaccine Strains After Receiving One Dose of TIV[5]

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 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.
The analysis was performed on the per-protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Percentage of subjects				
number (confidence interval 95%)				
B strain	47 (34 to 60)	34 (23 to 47)		

Statistical analyses

No statistical analyses for this end point

Primary: 6) Geometric Mean Ratio of Postvaccination Versus Prevaccination geometric mean SRH areas, After one Dose of TIVf

End point title	6) Geometric Mean Ratio of Postvaccination Versus Prevaccination geometric mean SRH areas, After one Dose of TIVf[6]

End point description:

The antibody responses were evaluated in terms of GMRs of post vaccination to pre vaccination geometric mean SRH areas 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 21/day 0 is >2.5 for adults aged 18 to ≤60 years and > 2.0 in for subjects aged ≥61 years.
The analysis was performed on the per-protocol dataset.

End point type	Primary

End point timeframe:

Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	70		
Units: Ratio				
geometric mean (confidence interval 95%)				
B strain	2.21 (1.69 to 2.9)	1.64 (1.37 to 1.97)		

Statistical analyses

No statistical analyses for this end point

Primary: 7) Number of Subjects Reporting Solicited Adverse Events After Receiving One Dose of TIVf

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

End point description:

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

End point type	Primary

End point timeframe:

Day 0 to Day 3 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	77		
Units: Number of subjects				
Any Local	33	12		
Injection site induration	14	4		
Injection site erythema	19	7		
Injection site ecchymosis	0	4		
Injection site swelling	14	5		
Injection site pain	17	7		
Any Systemic	26	10		
Chills Shivering	2	0		
Malaise	6	0		
Myalgia	14	5		
Arthralgia	6	3		
Fatigue	17	2		
Headache	7	3		
Sweating	3	2		
Fever (≥ 38°C)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: 8) Number of Subjects Reporting Unsolicited Adverse Events After Receiving One Dose of TIVf

End point title	8) 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 unsolicited AEs between Day 0 and the study termination i.e., Day 21, after receiving one dose of TIVf is reported.
Analysis was done on the safety set population.

End point type	Primary

End point timeframe:

Day 0 to Day 21 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	TIVf (18 to ≤ 60 Years)	TIVf (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	77		
Units: Number of subjects				
Any AE	10	4		
At least Possibly related AE	8	2		
Any SAE	0	0		
At least Possibly related SAE	0	0		
AE leading to discontinuation	0	0		

Death	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 Day 0 to Day 3; all unsolicited SAEs, medically attended AEs, AEs leading to withdrawal from the study were collected from Day 0 to Day 21.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	TIVf (≥ 61 Years)

Reporting group description:

Adult subjects ≥61 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.

Reporting group title	TIVf (18 to ≤ 60 Years)

Reporting group description:

Adult subjects 18 to ≤60 years received one dose of a trivalent, surface antigen inactivated, egg-derived influenza virus vaccine (TIVf) formulation 2008/2009 Northern Hemisphere.

Serious adverse events	TIVf (≥ 61 Years)	TIVf (18 to ≤ 60 Years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 77 (0.00%)	0 / 66 (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 (≥ 61 Years)	TIVf (18 to ≤ 60 Years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 77 (32.47%)	45 / 66 (68.18%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 77 (3.90%)	7 / 66 (10.61%)	
occurrences (all)	3	8	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	2 / 77 (2.60%)	17 / 66 (25.76%)	
occurrences (all)	2	17	
Injection site erythema			
subjects affected / exposed	16 / 77 (20.78%)	26 / 66 (39.39%)	
occurrences (all)	16	27	
Injection site haemorrhage			
subjects affected / exposed	7 / 77 (9.09%)	4 / 66 (6.06%)	
occurrences (all)	7	4	
Injection site induration			
subjects affected / exposed	10 / 77 (12.99%)	25 / 66 (37.88%)	
occurrences (all)	10	28	
Injection site pain			
subjects affected / exposed	7 / 77 (9.09%)	17 / 66 (25.76%)	
occurrences (all)	7	18	
Injection site swelling			
subjects affected / exposed	8 / 77 (10.39%)	23 / 66 (34.85%)	
occurrences (all)	8	25	
Malaise			
subjects affected / exposed	0 / 77 (0.00%)	6 / 66 (9.09%)	
occurrences (all)	0	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 77 (3.90%)	6 / 66 (9.09%)	
occurrences (all)	4	7	
Myalgia			
subjects affected / exposed	5 / 77 (6.49%)	14 / 66 (21.21%)	
occurrences (all)	8	15	

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