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 Including MF59C.1 Adjuvant (Fluad®)in Healthy Adults 65 Years of Age.

Summary

EudraCT number	2013-000607-16
Trial protocol	BE
Global end of trial date	20 August 2013

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	21 November 2014
Version creation reason	• 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	V70_44S

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01879540
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines
Sponsor organisation address	Via Fiorentina, Siena, Italy, 53100
Public contact	Michelangelo Barone, Novartis Vaccines and Diagnostics S.r.l., 0039 0577243516, michelangelo.barone@novartis.com
Scientific contact	Michelangelo Barone, Novartis Vaccines and Diagnostics S.r.l., 0039 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 trivalent, surface antigen inactivated subunit influenza virus vaccine including MF59C.1 (aTIV) 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 aTIV in adult subjects ≥65 years of age.

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: -	
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: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	0
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from one study center in Belgium.

Pre-assignment

Screening details:

All the subject from Belgium were included in the trial.

Period 1

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

Blinding implementation details:

No blinding was performed.

Arms

Arm title	aTIV

Arm description:

Adult subjects ≥65 years of age received one dose of a trivalent, surface antigen, inactivated influenza vaccine including MF59C.1 adjuvant (aTIV), formulation 2013/2014 Northern Hemisphere.

Arm type	Experimental
Investigational medicinal product name	Trivalent, Surface Antigen Inactivated Subunit Influenza Virus Vaccine Including MF59C.1 Adjuvant
Investigational medicinal product code	NA
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Number of subjects in period 1	aTIV
Started	63
Completed	63

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	63	63	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	71.9		
standard deviation	± 5	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	34	34	

End points

End points reporting groups

Reporting group title	aTIV

Reporting group description:

Adult subjects ≥65 years of age received one dose of a trivalent, surface antigen, inactivated influenza vaccine including MF59C.1 adjuvant (aTIV), formulation 2013/2014 Northern Hemisphere.

Subject analysis set title	aTIV-PPS
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; did not withdraw informed consent and did not have RT-PCR confirmed influenza during the study.

Subject analysis set title	aTIV- Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who have post-vaccination AE or reactogenicity records.

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

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

End point description:

Immunogenicity was assessed in terms of percentages of adult subjects ≥65 years of age with SRH areas ≥25mm2 against each of the three vaccine strains, three weeks after receiving one dose of aTIV. The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving post vaccination SRH areas ≥ 25mm2 is >60%.

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 was no statistical null hypothesis associated with the immunogenicity objective.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: percentage				
number (confidence interval 95%)				
Day 1/baseline (H1N1 strain)	46 (33 to 59)			
Day 22 (H1N1 strain)	89 (78 to 95)			
Day 1/baseline (H3N2 strain)	43 (30 to 56)			
Day 22 (H3N2 strain)	90 (80 to 96)			
Day 1/baseline (B strain)	28 (17 to 41)			
Day 22 (B strain)	79 (66 to 88)			

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 aTIV

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 aTIV[2]

End point description:

Immunogenicity was assessed in terms of percentages of adult subjects ≥65 years of age achieving seroconversion or significant increase in SRH area against each of the three vaccine strains, three weeks after receiving one dose of aTIV.
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>30% of subjects achieve seroconversion or significant increase in post-vaccination SRH area.

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: Percentages of Subjects With Seroconversion or Significant Increase in SRH Area, Against Each of Three Vaccine

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	57 (44 to 70)			
H3N2 strain	61 (47 to 73)			
B strain	70 (57 to 81)			

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratio (GMR) of Post Vaccination Versus Pre Vaccination Geometric Mean Area, Against Each of Three Vaccine Strains After Receiving One Dose of aTIV

End point title	Geometric Mean Ratio (GMR) of Post Vaccination Versus Pre Vaccination Geometric Mean Area, Against Each of Three Vaccine Strains After Receiving One Dose of aTIV[3]

End point description:

The antibody responses following one dose of aTIV were evaluated in terms of geometric mean ratio of post vaccination to pre vaccination GMAs against each of the three vaccine strains, three weeks after receiving one dose of aTIV.
The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is > 2.0.

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: Safety objectives were analysed descriptively.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: Ratio				
number (confidence interval 95%)				
H1N1 strain	2.63 (2.04 to 3.39)			
H3N2 strain	2.34 (1.91 to 2.87)			
B strain	2.89 (2.35 to 3.57)			

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 aTIV.

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

End point description:

Immunogenicity was assessed in terms of percentages of adult subjects ≥65 years of age with HI titers ≥40, against each of the three vaccine strains, three weeks after receiving one dose of aTIV.
The related European (CHMP) criterion for the assessment of immunogenicity is met if the of subjects achieving HI titers ≥ 40 is >60%.

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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: Percentage of Subjects				
number (confidence interval 95%)				
Day 1/baseline (H1N1 strain)	75 (63 to 86)			
Day 22 (H1N1 strain)	97 (89 to 100)			
Day 1/baseline (H3N2 strain)	89 (78 to 95)			
Day 22 (H3N2 strain)	100 (94 to 100)			

Day 1/baseline (B strain)	61 (47 to 73)			
Day 22 (B strain)	98 (91 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers, Against Each of Three Vaccine Strains After Receiving One Dose of aTIV

End point title	Percentages of Subjects With Seroconversion or Significant Increase in HI Antibody Titers, Against Each of Three Vaccine Strains After Receiving One Dose of aTIV[5]

End point description:

Immunogenicity was assessed in terms of percentages of adult subjects ≥65 years of age achieving seroconversion or significant increase in HI antibody titers after receiving one dose of aTIV. 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 >30% of subjects achieve seroconversion or significant increase in post-vaccination HI titers.

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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	39 (27 to 53)			
H3N2 strain	43 (30 to 56)			
B strain	38 (26 to 51)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The antibody responses following one dose of aTIV were evaluated in terms of GMRs of post vaccination to pre vaccination geometric mean HI titers against each of the three vaccine strains, three weeks after receiving one dose of aTIV.
The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is > 2.0.

End point type	Primary

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: Safety objectives were analysed descriptively.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: Ratio				
number (confidence interval 95%)				
H1N1 strain	3.57 (2.59 to 4.91)			
H3N2 strain	3.32 (2.45 to 4.49)			
B strain	2.69 (2.22 to 3.26)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Solicited Adverse Events After Receiving One Dose of aTIV.

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

End point description:

The number of adult subjects ≥65 years of age reporting solicited local and systemic adverse events and other solicited adverse events after receiving one dose of aTIV are reported.

End point type	Primary

End point timeframe:

Day 1 to 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: participants				
Any Local	26			
Injection site induration	2			
Injection site erythema	3			
Injection site ecchymosis	2			
Injection site pain	21			
Any systemic	15			
Chills/shivering	1			
Malaise	2			
Myalgia	2			
Arthralgia	1			
Fatigue	11			
Headache	5			
Fever (≥ 38°C)	0			
Temperature ≥40°C	0			
Prophylactic use of analgesics/antipyretics (N=61)	0			
Therapeutic use of analgesics/antipyretics (N=61)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Unsolicited Adverse Events After Receiving One dose of aTIV.

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

End point description:

The number of adult subjects ≥65 years of age subjects reporting any unsolicited adverse event (AEs) between Day 1 to 4 and serious adverse events (SAEs), medically attended AEs, AEs leading to withdrawal from the study between Day 1 to Day 22 after receiving one dose of aTIV are reported.

End point type	Primary

End point timeframe:

Day 1 to 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: Safety objectives were analysed descriptively.

End point values	aTIV			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: Participants				
Any AE	12			
At least possibly related AEs	10			
Serious AEs	0			
At least possibly related SAEs	0			

Medically attended AEs	5			
AEs leading to withdrawal	0			
Death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study. (solicitated and unsolicited from Day 1 to Day 4)

Adverse event reporting additional description:

Any solicited and unsolicited adverse events were reported from day 1 to day 4. Unsolicited SAE, medically attended AEs, AEs leading to withdrawal from the study, and concomitant medications/vaccinations associated with these events were collected from day 1 through day 22.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	aTIV

Reporting group description:

Adult subjects ≥65 years of age received one dose of a trivalent, surface antigen, inactivated influenza vaccine including MF59C.1 adjuvant (aTIV), formulation 2013/2014 Northern Hemisphere.

Serious adverse events	aTIV		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	aTIV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 63 (50.79%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	12		
Injection site erythema			

subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Injection site pain			
subjects affected / exposed	21 / 63 (33.33%)		
occurrences (all)	21		

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