



## Clinical trial results:

### Immunogenicity, Reactogenicity and Safety of the Trivalent Influenza Subunit Vaccine Influvac® for the Northern Hemisphere Season 2013/2014. An Open-Label, Baseline-Controlled Study in Two Age Groups: Adult Subjects 18 and 60 Years and Elderly Subjects 61 Years of Age.

#### Summary

EudraCT number	2013-000881-12
Trial protocol	DE BE
Global end of trial date	03 August 2013

#### Results information

Result version number	v1 (current)
This version publication date	15 August 2019
First version publication date	15 August 2019

#### Trial information

##### Trial identification

Sponsor protocol code	M13-998
-----------------------	---------

##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Abbott Biologicals B.V
Sponsor organisation address	C.J. van Houtenlaan 36, CP Weesp, Netherlands, NL-1381
Public contact	Public Affairs Manager, Abbott Products Operations AG, hind.ounis@abbott.com
Scientific contact	Global Clinical Director, Abbott Healthcare Products B.V., serge.vandewitte@abbott.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	03 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 August 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the immunogenicity of the trivalent influenza subunit vaccine Influvac® for the northern hemisphere season 2013/2014, three weeks after vaccination according to the Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on Harmonization of Requirements for Influenza Vaccines (CPMP/BWP/214/96) in two groups: adults aged  $\geq 18$  and  $\leq 60$  years and elderly  $\geq 61$  years of age.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations so as to assure that the rights, safety, and well being of the participating study subjects were protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	63
From 65 to 84 years	56

85 years and over	1
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

This open-label, baseline-controlled study in two groups of subjects: adults aged  $\geq 18$  and  $\leq 60$  years and elderly  $\geq 61$  years was performed in one study center in Belgium between 12 July 2013 and 03 August 2013.

### Pre-assignment

Screening details:

Subjects underwent screening evaluations to determine eligibility during a period of 14 days preceding Visit 1 at an additional visit (Screening Visit) or on Day 1 (Visit 1). A total of 120 healthy adult and elderly subjects were screened and signed informed consent, and there were no screening failures.

### 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
<b>Arm title</b>	Adults Aged $\geq 18$ and $\leq 60$ Years

Arm description:

On Day 1 (Visit 1) subjects aged  $\geq 18$  and  $\leq 60$  years received a single dose of Influvac® 0.5 milliliter (mL) by intramuscular (IM) injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Arm type	Experimental
Investigational medicinal product name	Influvac®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of 0.5 mL Influvac® (influenza virus surface antigens (haemagglutinin and neuramidase) of the following strains: A (H1N1), A (H3N2) and B) by IM injection on Day 1 (Visit 1).

<b>Arm title</b>	Elderly Aged $\geq 61$ Years
------------------	------------------------------

Arm description:

On Day 1 (Visit 1) subjects aged  $\geq 61$  years received a single dose of Influvac® 0.5 mL by IM injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Arm type	Experimental
Investigational medicinal product name	Influvac®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of 0.5 mL Influvac® (influenza virus surface antigens (haemagglutinin and neuramidase) of the following strains: A (H1N1), A (H3N2) and B) by IM injection on Day 1 (Visit 1).

<b>Number of subjects in period 1</b>	Adults Aged $\geq 18$ and $\leq 60$ Years	Elderly Aged $\geq 61$ Years
Started	60	60
Completed	60	59
Not completed	0	1
Adverse event, serious	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Adults Aged $\geq 18$ and $\leq 60$ Years
-----------------------	---

Reporting group description:

On Day 1 (Visit 1) subjects aged  $\geq 18$  and  $\leq 60$  years received a single dose of Influvac® 0.5 milliliter (mL) by intramuscular (IM) injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Reporting group title	Elderly Aged $\geq 61$ Years
-----------------------	------------------------------

Reporting group description:

On Day 1 (Visit 1) subjects aged  $\geq 61$  years received a single dose of Influvac® 0.5 mL by IM injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Reporting group values	Adults Aged $\geq 18$ and $\leq 60$ Years	Elderly Aged $\geq 61$ Years	Total
Number of subjects	60	60	120
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	40.1	71.8	
standard deviation	$\pm 12.1$	$\pm 5.1$	-
Gender categorical Units: Subjects			
Female	34	29	63
Male	26	31	57

## End points

### End points reporting groups

Reporting group title	Adults Aged $\geq 18$ and $\leq 60$ Years
Reporting group description:	
On Day 1 (Visit 1) subjects aged $\geq 18$ and $\leq 60$ years received a single dose of Influvac® 0.5 milliliter (mL) by intramuscular (IM) injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.	
Reporting group title	Elderly Aged $\geq 61$ Years
Reporting group description:	
On Day 1 (Visit 1) subjects aged $\geq 61$ years received a single dose of Influvac® 0.5 mL by IM injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.	

### Primary: Percentage of Subjects With Seroprotection for Hemagglutination Inhibition (HI) and Single Radial Hemolysis (SRH) Antibody Titers

End point title	Percentage of Subjects With Seroprotection for Hemagglutination Inhibition (HI) and Single Radial Hemolysis (SRH) Antibody Titers <sup>[1]</sup>
End point description:	
The pre-vaccination (blood sample taken at Day 1) and the post-vaccination (blood sample taken at Day 22) seroprotection rates for each strain are presented. Seroprotection was defined as an HI antibody titer $\geq 40$ and a SRH antibody titer $\geq 25$ millimeter square (mm <sup>2</sup> ). The HI assay was performed for all three strains (A (H3N2), A (H1N1), and B strains) and the SRH assay was performed for the B strain only. The CHMP Note for Guidance defined a (the CHMP criteria for immunogenicity) seroprotection rate of $> 70\%$ for adults and $> 60\%$ for elderly as meeting the requirements for sufficient immunogenicity. The confidence intervals (CI) were calculated based on the Clopper-Pearson method. The efficacy sample set included all vaccinated subjects for whom both the pre- and the post-vaccination HI/SRH antibody titers were available, who did not present an intercurrent respiratory infection (IRI) diagnosed as influenza and who did not present any major protocol deviation.	
End point type	Primary
End point timeframe:	
Pre-vaccination at Day 1 (Visit 1) and Post-vaccination at Day 22 (Visit 3)	

#### 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: Descriptive statistical analysis was performed for the outcome measure.

End point values	Adults Aged $\geq 18$ and $\leq 60$ Years	Elderly Aged $\geq 61$ Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: percentage of subjects				
number (confidence interval 95%)				
HI antibody titer: A (H3N2) strain; Day 1	61.7 (48.21 to 73.93)	84.5 (72.58 to 92.65)		
HI antibody titer: A (H3N2) strain; Day 22	98.3 (91.06 to 99.96)	100 (93.84 to 100)		
HI antibody titer: A (H1N1) strain; Day 1	51.7 (38.39 to 64.77)	81.0 (68.59 to 90.13)		
HI antibody titer: A (H1N1) strain; Day 22	96.7 (88.47 to 99.59)	100 (93.84 to 100)		
HI antibody titer: B strain; Day 1	50.0 (36.81 to 63.19)	29.3 (18.09 to 42.73)		

HI antibody titer: B strain; Day 22	83.3 (71.48 to 91.71)	67.2 (53.66 to 78.99)		
SRH antibody titer: B strain; Day 1	68.3 (55.04 to 79.74)	65.5 (51.88 to 77.51)		
SRH antibody titer: B strain; Day 22	96.7 (88.47 to 99.59)	93.1 (83.27 to 98.09)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Seroconversion or Significant Increase in HI and SRH Antibody Titers

End point title	Percentage of Subjects With Seroconversion or Significant Increase in HI and SRH Antibody Titers <sup>[2]</sup>
-----------------	---

End point description:

The post-vaccination seroconversion or significant increase rates for each strain are presented. For the HI assay, seroconversion was defined as a pre-vaccination HI antibody titer < 10 and a post-vaccination HI antibody titer ≥ 40, and a significant increase was defined as a pre-vaccination HI antibody titer ≥ 10 and a post-vaccination relative increase of ≥ 4-fold. For the SRH assay, seroconversion or a significant increase was defined as a post-vaccination SRH antibody titer ≥ 25 mm<sup>2</sup> and a post-vaccination relative increase of 1.5-fold if the pre-vaccination SRH antibody titer was > 4 mm<sup>2</sup>. The HI assay was performed for all three strains (A (H3N2), A (H1N1), and B strains) and the SRH assay was performed for the B strain only. The CHMP Note for Guidance defined a (CHMP criteria for immunogenicity) seroconversion or significant increase in titer of > 40% for adults and > 30% for elderly as meeting the requirements for sufficient immunogenicity. Efficacy sample set were analysed.

End point type	Primary
----------------	---------

End point timeframe:

Post-vaccination at Day 22 (Visit 3)

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: Descriptive statistical analysis was performed for the outcome measure.

End point values	Adults Aged ≥ 18 and ≤ 60 Years	Elderly Aged ≥ 61 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: percentage of subjects				
number (confidence interval 95%)				
HI antibody titer: A (H3N2) strain	66.7 (53.31 to 78.31)	41.4 (28.60 to 55.07)		
HI antibody titer: A (H1N1) strain	60.0 (46.54 to 72.44)	37.9 (25.51 to 51.63)		
HI antibody titer: B strain	53.3 (40.00 to 66.33)	32.8 (21.01 to 46.34)		
SRH antibody titer: B strain	53.3 (40.00 to 66.33)	44.8 (31.74 to 58.46)		

## Statistical analyses



No statistical analyses for this end point

### Primary: Geometric Mean Fold Increase (MFI) in HI and SRH Antibody Titers

End point title	Geometric Mean Fold Increase (MFI) in HI and SRH Antibody Titers <sup>[3]</sup>
-----------------	---

End point description:

The post-vaccination (blood sample taken at Day 22) geometric MFI for each strain are presented. Geometric MFI was defined as the geometric mean of the intra-individual increases, that is post-vaccination HI or SRH antibody titer/pre-vaccination HI or SRH antibody titer. The HI assay was performed for all three strains (A (H3N2), A (H1N1), and B strains) and the SRH assay was performed for the B strain only. The CHMP Note for Guidance defined a (the CHMP criteria for immunogenicity) MFI of > 2.5 for adults and > 2.0 for elderly as meeting the requirements for sufficient immunogenicity. The efficacy sample set included all vaccinated subjects for whom both the pre- and the post-vaccination HI/SRH antibody titers were available, who did not present an IRI diagnosed as influenza and who did not present any major protocol deviation.

End point type	Primary
----------------	---------

End point timeframe:

Post-vaccination at Day 22 (Visit 3)

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: Descriptive statistical analysis was performed for the outcome measure.

End point values	Adults Aged ≥ 18 and ≤ 60 Years	Elderly Aged ≥ 61 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: antibody titer				
geometric mean (confidence interval 95%)				
HI antibody titer: A (H3N2) strain	8.43 (5.65 to 12.56)	3.06 (2.28 to 4.09)		
HI antibody titer: A (H1N1) strain	9.59 (6.06 to 15.18)	3.07 (2.30 to 4.09)		
HI antibody titer: B strain	4.40 (3.13 to 6.18)	2.88 (2.01 to 4.12)		
SRH antibody titer: B strain	1.95 (1.60 to 2.38)	1.77 (1.46 to 2.15)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Solicited Systemic Reactions

End point title	Percentage of Subjects With Solicited Systemic Reactions
-----------------	--

End point description:

A subject diary was used to record pre-specified systemic reactions which occurred during the 72 hours after vaccination (solicited reactogenicity). Systemic reactions were assessed for the following categories: fever (≥ 38.0°C), increased sweating, headache, malaise, fatigue, and shivering. These reactions were rated on a four-point scale (none, mild, moderate, severe): none: lack of reactogenicity/inconvenience, mild: presence of mild reactogenicity/inconvenience that did not interfere with normal daily activities, moderate: reactogenicity/inconvenience that had an impact on normal daily activities, and severe: reactogenicity/inconvenience which prevented normal daily activities. Data is presented for the Safety sample set which included all vaccinated subjects for whom both the pre- and the post-vaccination HI/SRH titers were available.

End point type	Secondary
End point timeframe:	
Up to 72 hours post-vaccination on Day 1 (Visit 1)	

End point values	Adults Aged ≥ 18 and ≤ 60 Years	Elderly Aged ≥ 61 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: percentage of subjects				
number (not applicable)				
Fever ≥ 38°C	0	0		
Increased sweating	1.7	1.7		
Headache	10.0	0		
Malaise	1.7	1.7		
Fatigue	16.7	5.0		
Shivering	1.7	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Solicited Local Reactions

End point title	Percentage of Subjects With Solicited Local Reactions
End point description:	
<p>A subject diary was used to record pre-specified local (vaccination site) reactions occurred which during the 72 hours after vaccination (solicited reactogenicity). Local reactions were assessed for the following categories: redness, swelling, itching, warmth, tenderness (pain or discomfort upon touch), pain, impairment of movement of the arm, induration, and ecchymosis (blue spots). These reactions were rated on a four-point scale (none, mild, moderate, severe): none: lack of reactogenicity/inconvenience, mild: presence of mild reactogenicity/inconvenience that did not interfere with normal daily activities, moderate: reactogenicity/inconvenience that had an impact on normal daily activities, and severe: reactogenicity/inconvenience which prevented normal daily activities. Data is presented for the Safety sample set which included all vaccinated subjects for whom both the pre- and the post-vaccination HI/SRH titers were available.</p>	
End point type	Secondary
End point timeframe:	
Up to 72 hours post-vaccination on Day 1 (Visit 1)	

End point values	Adults Aged ≥ 18 and ≤ 60 Years	Elderly Aged ≥ 61 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: percentage of subjects				
number (not applicable)				
Redness	3.3	1.7		

Swelling	10.0	0		
Itching	1.7	0		
Warmth	6.7	1.7		
Tenderness (pain or discomfort upon touch)	31.7	3.3		
Pain	28.3	0		
Impairment of movement of the arm	16.7	3.3		
Induration (hardening)	10.0	0		
Ecchymosis (blue spots)	1.7	1.7		

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From administration of study vaccination (Day 1) up to Day 22.

Adverse event reporting additional description:

Safety sample set included the sample of all vaccinated subjects for whom both the pre- and the post-vaccination HI/SRH titers were available.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.0
--------------------	------

### Reporting groups

Reporting group title	Adults Aged $\geq 18$ and $\leq 60$ Years
-----------------------	---

Reporting group description:

On Day 1 (Visit 1) subjects aged  $\geq 18$  and  $\leq 60$  years received a single dose of Influvac® 0.5 mL by IM injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Reporting group title	Elderly Aged $\geq 61$ Years
-----------------------	------------------------------

Reporting group description:

On Day 1 (Visit 1) subjects aged  $\geq 61$  years received a single dose of Influvac® 0.5 mL by IM injection into the upper arm, after taking a blood sample for baseline antibody titers against each of the vaccine antigens.

Serious adverse events	Adults Aged $\geq 18$ and $\leq 60$ Years	Elderly Aged $\geq 61$ Years	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

<b>Non-serious adverse events</b>	<b>Adults Aged ≥ 18 and ≤ 60 Years</b>	<b>Elderly Aged ≥ 61 Years</b>	
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 60 (11.67%)	4 / 60 (6.67%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Malaise subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)  Vaccination site erythema subjects affected / exposed occurrences (all)  Vaccination site pain subjects affected / exposed occurrences (all)  Vaccination site warmth subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3  1 / 60 (1.67%) 1  0 / 60 (0.00%) 0  1 / 60 (1.67%) 1  1 / 60 (1.67%) 1  1 / 60 (1.67%) 1  1 / 60 (1.67%) 1	1 / 60 (1.67%) 1  0 / 60 (0.00%) 0  1 / 60 (1.67%) 1  0 / 60 (0.00%) 0  0 / 60 (0.00%) 0  0 / 60 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0  0 / 60 (0.00%) 0	1 / 60 (1.67%) 1  1 / 60 (1.67%) 1	
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Rash generalised			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences (all)	1	0	

## 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