Clinical trial results:
Immunogenicity and Safety of the Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation (Intramuscular Route)

Summary

EudraCT number	2008-000943-33
Trial protocol	GB
Global end of trial date	23 July 2008

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	03 December 2014

Trial information

Trial identification

Sponsor protocol code	GRT83

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00718146
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 65 66 04, derek.wallace@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 65 66 04, derek.wallace@sanofipasteur.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	07 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the compliance, in terms of immunogenicity, of the inactivated, split-virion influenza vaccine Northern Hemisphere 2008-2009 formulation with the requirements of the Committee for Human Medicinal Products (CHMP) Note for Guidance (NfG) CPMP/BWP/214/96.

Protection of trial subjects:

Only subjects who met all the study inclusion and none of the exclusion criteria were vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 June 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: 130
Worldwide total number of subjects	130
EEA total number of subjects	130

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)	90

From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 26 June 2008 to 23 July 2008 in 2 clinical centers in the United Kingdom.

Pre-assignment

Screening details:

A total of 130 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	18 to 60 years

Arm description:

Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Influenza vaccine (split virion, inactivated)
Investigational medicinal product code	314
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, one dose on Day 0.

Arm title	61 years or older

Arm description:

Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Influenza vaccine (split virion, inactivated)
Investigational medicinal product code	314
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, one dose on Day 0.

Number of subjects in period 1	18 to 60 years	61 years or older
Started	65	65
Completed	65	65

Baseline characteristics

Reporting groups	
Reporting group title	18 to 60 years
Reporting group description:	
Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.	
Reporting group title	61 years or older
Reporting group description:	
Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.	

Reporting group values	18 to 60 years	61 years or older	Total
Number of subjects	65	65	130
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)	65	25	90
From 65-84 years	0	40	40
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.2	67.5	
standard deviation	± 14.28	± 4.24	-
Gender categorical Units: Subjects			
Female	31	32	63
Male	34	33	67
Previous influenza vaccination Units: Subjects			
Yes	23	47	70
No	42	18	60
Previous influenza infection last winter Units: Subjects			
Yes	3	1	4
No	62	64	126

End points

End points reporting groups

Reporting group title	18 to 60 years
Reporting group description:	
Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.	
Reporting group title	61 years or older
Reporting group description:	
Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.	

Primary: Summary of Geometric Mean Titers (GMTs) of influenza Vaccine Antibodies Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route

End point title	Summary of Geometric Mean Titers (GMTs) of influenza Vaccine Antibodies Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route[1]
End point description:	
Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique.	
End point type	Primary
End point timeframe:	
Day 0 (pre-vaccination) and 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Titers				
geometric mean (confidence interval 95%)				
A/Brisbane/59/2007 like strain (H1N1; Day 0)	18.1 (13.1 to 25.1)	26.4 (19.4 to 35.8)		
A/Brisbane/10/2007 like strain (H3N2; Day 0)	10.8 (8.31 to 14)	14.2 (10.3 to 19.7)		
B/Florida/4/2006 like strain (B; Day 0)	13.5 (10.6 to 17.1)	23.2 (18.2 to 29.7)		
A/Brisbane/59/2007 like strain (H1N1; Day 21)	311 (235 to 413)	127 (96.6 to 166)		
A/Brisbane/10/2007 like strain (H3N2; Day 21)	144 (97.7 to 211)	104 (73.2 to 149)		
B/Florida/4/2006 like strain (B; Day 21)	107 (82.4 to 139)	71.1 (56.5 to 89.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Geometric Mean Titers Ratios (GMTR) of influenza Vaccine Antibodies After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route

End point title	Summary of Geometric Mean Titers Ratios (GMTR) of influenza Vaccine Antibodies After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route[2]

End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Geometric mean titer ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer of antibodies to the influenza virus antigens.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Titer ratios				
geometric mean (confidence interval 95%)				
A/Brisbane/59/2007 like strain (H1N1)	17.2 (11.9 to 24.9)	4.8 (3.4 to 6.77)		
A/Brisbane/10/2007 like strain (H3N2)	13.3 (9.11 to 19.5)	7.35 (5.23 to 10.3)		
B/Florida/4/2006 like strain (B)	7.96 (5.65 to 11.2)	3.06 (2.36 to 3.98)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Seroprotection Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route

End point title	Percentage of Subjects with Seroprotection Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route[3]

End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Seroprotection was defined as titers ≥40 (1/dil) on Day 0 and Day 21.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Percentage of subjects				
number (not applicable)				
A/Brisbane/59/2007 like strain (H1N1; Day 0)	28.1	40		
A/Brisbane/10/2007 like strain (H3N2; Day 0)	17.2	26.2		
B/Florida/4/2006 like strain (B; Day 0)	20.3	33.8		
A/Brisbane/59/2007 like strain (H1N1; Day 21)	96.9	87.7		
A/Brisbane/10/2007 like strain (H3N2; Day 21)	81.3	81.5		
B/Florida/4/2006 like strain (B; Day 21)	89.1	80		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by Intramuscular Route

End point title	Percentage of Subjects Achieving Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by Intramuscular Route[4]

End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition technique. Seroconversion was defined as subjects with a titer <10 (1/dil) on Day 0 and a post-injection titer ≥40 (1/dil) on Day 21 or significant increase was defined as subjects with a titer ≥10 (1/dil) on Day 0 and a ≥4-fold increase of post-injection titer on Day 21.

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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Percentage of Subjects				
number (not applicable)				
A/Brisbane/59/2007 like strain (H1N1)	79.7	47.7		
A/Brisbane/10/2007 like strain (H3N2)	71.9	60		
B/Florida/4/2006 like strain (B)	64.1	27.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with at Least One Reaction Corresponding to those Listed in the EMEA Note for Guidance Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation (Intramuscular Route)

End point title	Percentage of Subjects with at Least One Reaction Corresponding to those Listed in the EMEA Note for Guidance Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation (Intramuscular Route)[5]

End point description:

Solicited injection site reactions: Induration and Ecchymosis. Solicited systemic reactions: Pyrexia, Malaise, and Shivering.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site induration ≥5 cm for 4 days	0	0		
Injection site ecchymosis	7.7	6.2		
Pyrexia (>38°C for at least 1 day)	1.5	0		
Malaise	12.3	9.2		
Shivering	3.1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route[6]

End point description:

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 injection site: Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis – ≥10 cm. Grade 3 systemic reactions: Fever – >39.0°C; Headache, Malaise, Myalgia, and Shivering – Prevents daily activity.

End point type	Primary

End point timeframe:

Day 0 up to Day 3 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	49.2	24.6		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	32.3	27.7		
Grade 3 Injection site Erythema	3.1	9.2		
Injection site Swelling	18.5	12.3		
Grade 3 Injection site Swelling	0	0		
Injection site Induration	27.7	12.3		
Grade 3 Injection site Induration	1.5	0		
Injection site Ecchymosis	7.7	6.2		
Grade 3 Injection site Ecchymosis	0	0		
Fever	10.8	4.6		
Grade 3 Fever	0	0		
Headache	20	13.8		
Grade 3 Headache	1.5	0		
Malaise	12.3	9.2		
Grade 3 Malaise	0	0		
Myalgia	15.4	15.4		
Grade 3 Myalgia	0	0		
Shivering	3.1	0		
Grade 3 Shivering	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions More than 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions More than 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2008-2009 Formulation by the Intramuscular Route[7]

End point description:

Solicited injection site: Pain, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering. Grade 3 injection site: Pain – Incapacitating, unable to perform usual activities; Erythema, Swelling, Induration, and Ecchymosis – ≥10 cm. Grade 3 systemic reactions: Fever – >39.0°C; Headache, Malaise, Myalgia, and Shivering – Prevents daily activity.

End point type	Primary

End point timeframe:

>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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	18 to 60 years	61 years or older		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	65		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	49.2	24.6		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	32.3	27.7		
Grade 3 Injection site Erythema	3.1	9.2		
Injection site Swelling	18.5	12.3		
Grade 3 Injection site Swelling	0	0		
Injection site Induration	27.7	12.3		
Grade 3 Injection site Induration	1.5	0		
Injection site Ecchymosis	7.7	6.2		
Grade 3 Injection site Ecchymosis	0	0		
Fever	0	0		
Grade 3 Fever	0	0		
Headache	1.5	4.6		
Grade 3 Headache	0	0		
Malaise	1.5	3.1		
Grade 3 Malaise	0	0		
Myalgia	3.1	3.1		
Grade 3 Myalgia	1.5	0		
Shivering	0	0		
Grade 3 Shivering	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to Day 21 post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	18 to 60 years

Reporting group description:

Subjects aged 18 to 60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.

Reporting group title	61 years or older

Reporting group description:

Subjects aged 61 years or older who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2008-2009 formulation on day 0.

Serious adverse events	18 to 60 years	61 years or older	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (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	18 to 60 years	61 years or older	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 65 (49.23%)	18 / 65 (27.69%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 65 (20.00%)	9 / 65 (13.85%)	
occurrences (all)	13	9	
General disorders and administration site conditions			
Injection site ecchymosis			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 65 (7.69%)	4 / 65 (6.15%)	
occurrences (all)	5	4	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 65 (12.31%)	6 / 65 (9.23%)	
occurrences (all)	8	6	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 65 (49.23%)	16 / 65 (24.62%)	
occurrences (all)	32	16	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 65 (32.31%)	18 / 65 (27.69%)	
occurrences (all)	21	18	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 65 (18.46%)	8 / 65 (12.31%)	
occurrences (all)	12	8	
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	18 / 65 (27.69%)	8 / 65 (12.31%)	
occurrences (all)	18	8	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 65 (10.77%)	3 / 65 (4.62%)	
occurrences (all)	7	3	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 65 (15.38%)	10 / 65 (15.38%)	
occurrences (all)	10	10	

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