Clinical trial results:
Immunogenicity and Safety of the Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2006-2007 Formulation (Intramuscular Route)

Summary

EudraCT number	2006-000671-15
Trial protocol	GB
Global end of trial date	09 August 2006

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	GRT63

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00343681
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 37 59 22, melanie.saville@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 (0)4 37 37 59 22, melanie.saville@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	24 August 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To check the compliance, in terms of immunogenicity, of the inactivated, split-virion influenza vaccine Northern Hemisphere 2006-2007 formulation with the requirements of the European Medicines Agency (EMEA) 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 were 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	17 July 2006
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: 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)	86

From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 17 July 2006 to 18 July 2006 in 1 clinical center in Switzerland and 1 clinical center in the United Kingdom.

Pre-assignment

Screening details:

A total of 120 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 2006-2007 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Inactivated, split virion Influenza Vaccine
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 into the deltoid muscle, one dose at day 0

Arm title	Over 60 years

Arm description:

Subjects aged >60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2006-2007 formulation on day 0.

Arm type	Experimental
Investigational medicinal product name	Inactivated, split virion Influenza Vaccine
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 into the deltoid muscle, one dose at day 0

Number of subjects in period 1	18 to 60 years	Over 60 years
Started	62	58
Completed	62	58

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 2006-2007 formulation on day 0.	
Reporting group title	Over 60 years
Reporting group description:	
Subjects aged >60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2006-2007 formulation on day 0.	

Reporting group values	18 to 60 years	Over 60 years	Total
Number of subjects	62	58	120
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)	62	24	86
From 65-84 years	0	34	34
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.3	67.4	
standard deviation	± 12.6	± 5.57	-
Gender categorical Units: Subjects			
Female	33	33	66
Male	29	25	54
Previous influenza vaccination Units: Subjects			
Yes	24	35	59
No	38	23	61
Previous influenza infection last winter Units: Subjects			
Yes	3	2	5
No	59	56	115

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 2006-2007 formulation on day 0.	
Reporting group title	Over 60 years
Reporting group description:	
Subjects aged >60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2006-2007 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 2006-2007 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 2006-2007 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Titers				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1; pre-vaccination)	14.6 (10.1 to 21.1)	18.5 (13.1 to 26.2)		
A/Wisconsin/67/2005 (H3N2; pre-vaccination)	17.2 (11.7 to 25.4)	30.4 (20.3 to 45.4)		
B/Malaysia/2506/2004 (B; pre-vaccination)	6.99 (5.98 to 8.18)	10.74 (8.51 to 13.56)		
A/New Caledonia/20/99 (H1N1; post-vaccination)	173 (119 to 251)	72.7 (55.7 to 94.9)		
A/Wisconsin/67/2005 (H3N2; post-vaccination)	260 (183 to 371)	236 (156 to 356)		
B/Malaysia/2506/2004 (B; post-vaccination)	48.4 (37 to 63.2)	50.5 (38.3 to 66.6)		

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 2006-2007 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 2006-2007 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Titer ratio				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1)	11.83 (7.72 to 18.13)	3.93 (2.77 to 5.58)		
A/Wisconsin/67/2005 (H3N2)	15.13 (9.55 to 23.98)	7.76 (4.63 to 13.03)		
B/Malaysia/2506/2004 (B)	6.92 (5.4 to 8.87)	4.7 (3.42 to 6.45)		

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 2006-2007 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 2006-2007 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1; pre-vaccination)	29	24.1		
A/Wisconsin/67/2005 (H3N2; pre-vaccination)	33.9	50		
B/Malaysia/2506/2004 (B; pre-vaccination)	4.8	12.1		
A/New Caledonia/20/99 (H1N1; post-vaccination)	88.7	75.9		
A/Wisconsin/67/2005 (H3N2; post-vaccination)	93.5	86.2		
B/Malaysia/2506/2004 (B; post-vaccination)	64.5	67.2		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2006-2007 Formulation by the Intramuscular Route

End point title	Percentage of Subjects With Seroconversion or Significant Increase Against the Influenza Vaccine Antigens Before and After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2006-2007 Formulation by the 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1)	67.7	36.2		
A/Wisconsin/67/2005 (H3N2)	74.2	48.3		
B/Malaysia/2506/2004 (B)	59.7	48.3		

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 Recommendation Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2006-2007 Formulation by Intramuscular Route

End point title	Percentage of Subjects with at Least One Reaction Corresponding to those Listed in the EMEA Recommendation Within 3 Days After Vaccination with Inactivated, Split-Virion Influenza Vaccine, Northern Hemisphere 2006-2007 Formulation by Intramuscular Route[5]

End point description:

Solicited injection site: Induration and Ecchymosis. Solicited systemic reactions: Fever, 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage of subjects				
number (not applicable)				
Injection site induration >5 cm for >3 days	0	0		
Injection site ecchymosis	3.2	1.7		
Fever (Oral temperature >37.5°C) for ≥24 hours)	1.6	3.4		
Malaise	8.1	1.7		
Shivering	0	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 2006-2007 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 2006-2007 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, may have/or require medical care or absenteeism; Erythema, Swelling, Induration, and Ecchymosis – ≥5 cm. Grade 3 systemic reactions: Fever – ≥39.1°C oral; Headache, Malaise, Myalgia, and Shivering – Prevents daily activities.

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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	33.9	13.8		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	22.6	8.6		
Grade 3 Injection site Erythema	1.6	1.7		
Injection site Swelling	12.9	12.1		
Grade 3 Injection site Swelling	1.6	1.7		
Injection site Induration	14.5	10.3		
Grade 3 Injection site Induration	1.6	1.7		
Injection site Ecchymosis	3.2	1.7		
Grade 3 Ecchymosis	0	0		
Fever	6.5	3.4		
Grade 3 Fever	0	0		
Headache	12.9	3.4		
Grade 3 Headache	0	0		
Malaise	8.1	1.7		
Grade 3 Malaise	0	0		
Myalgia	19.4	8.6		
Grade 3 Myalgia	0	0		
Shivering	0	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 2006-2007 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 2006-2007 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, may have/or require medical care or absenteeism; Erythema, Swelling, Induration, and Ecchymosis – ≥5 cm. Grade 3 systemic reactions: Fever – ≥39.1°C oral; Headache, Malaise, Myalgia, and Shivering – Prevents daily activities.

End point type	Primary

End point timeframe:

>3 days 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	Over 60 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	0	0		
Grade 3 Injection site Pain	0	0		
Injection site Erythema	1.6	0		
Grade 3 Injection site Erythema	0	0		
Injection site Swelling	0	0		
Grade 3 Injection site Swelling	0	0		
Injection site Induration	0	0		
Grade 3 Injection site Induration	0	0		
Injection site Ecchymosis	0	0		
Grade 3 Injection site Ecchymosis	0	0		
Fever	3.2	0		
Grade 3 Fever	0	0		
Headache	3.2	0		
Grade 3 Headache	0	0		
Malaise	4.8	3.4		
Grade 3 Malaise	0	0		
Myalgia	1.6	0		
Grade 3 Myalgia	0	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	6.0

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 2006-2007 formulation on day 0.	
Reporting group title	Over 60 years
Reporting group description:	
Subjects aged >60 years who received one dose of inactivated, split-virion influenza vaccine, Northern Hemisphere 2006-2007 formulation on day 0.	

Serious adverse events	18 to 60 years	Over 60 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 58 (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	Over 60 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 62 (33.87%)	8 / 58 (13.79%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 62 (12.90%)	2 / 58 (3.45%)	
occurrences (all)	8	2	
General disorders and administration site conditions			
Malaise			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 62 (8.06%)	1 / 58 (1.72%)	
occurrences (all)	5	1	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 62 (33.87%)	8 / 58 (13.79%)	
occurrences (all)	21	8	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 62 (22.58%)	5 / 58 (8.62%)	
occurrences (all)	14	5	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 62 (12.90%)	7 / 58 (12.07%)	
occurrences (all)	8	7	
Injection site induration			
subjects affected / exposed	9 / 62 (14.52%)	6 / 58 (10.34%)	
occurrences (all)	9	6	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 62 (6.45%)	2 / 58 (3.45%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 62 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	12 / 62 (19.35%)	5 / 58 (8.62%)	
occurrences (all)	12	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

None reported