



## Clinical trial results:

### Immunogenicity of the Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route in Comparison with the Intramuscular Reference Vaccine Vaxigrip in the Elderly

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

EudraCT number	2006-002366-18
Trial protocol	BE LT IT
Global end of trial date	16 June 2009

## Results information

Result version number	v2 (current)
This version publication date	18 February 2016
First version publication date	27 March 2015
Version creation reason	<ul style="list-style-type: none"><li>Correction of full data set</li></ul> CI of secondary outcome on GMTR for !D 15 ug group were shifted

## Trial information

### Trial identification

Sponsor protocol code	GID17
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00383526
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon cedex 07, France, F-69367
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 33 4 37 37 58 55, stephanie.pepin@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 33 4 37 37 58 55, stephanie.pepin@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	18 September 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 June 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that the intradermal (ID) investigational vaccine induces a better immunogenicity than the intramuscular (IM) reference vaccine in terms of seroprotection rate after the first vaccination.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and 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	11 September 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	Belgium: 775
Country: Number of subjects enrolled	France: 2397
Country: Number of subjects enrolled	Italy: 235
Country: Number of subjects enrolled	Lithuania: 300
Worldwide total number of subjects	3707
EEA total number of subjects	3707

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)	913
From 65 to 84 years	2740
85 years and over	54

## Subject disposition

### Recruitment

Recruitment details:

Study subjects were enrolled from 11 September 2006 to 31 October 2006 at 37 clinical centers (24 in France, 2 in Italy, 8 in Belgium, and 3 in Lithuania) at Year 0 and 1 and 35 centers (24 in France, 2 in Italy, 6 in Belgium and 3 in Lithuania) at Year 2.

### Pre-assignment

Screening details:

A total of 3707 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized, 3659 subjects were vaccinated.

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	ID 15µg
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Arm description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) investigational influenza vaccine via the intradermal (ID) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Arm type	Experimental
Investigational medicinal product name	Intradermal Influenza Vaccine
Investigational medicinal product code	333
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

0.1 mL dose, ID into the upper arm (deltoid area) with the Becton Dickinson (BD) ID micro-injection system, 3 vaccinations of inactivated, split-virion (with octoxynol-9) investigational influenza vaccine with the 2006-2007 Northern Hemisphere [NH] formulation administered on Day 0 (Year 0), the 2007-2008 NH formulation on Day 365 (Year 1), and the 2008-2009 NH formulation on Day 730 (Year 2).

<b>Arm title</b>	IM 15µg
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Arm description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) influenza vaccine via the intramuscular (IM) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Arm type	Active comparator
Investigational medicinal product name	VAXIGRIP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe, Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use, Intramuscular use

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**Dosage and administration details:**

0.5 mL dose, IM into the upper arm (deltoid area), 3 vaccinations of inactivated, split-virion (with octoxynol-9) influenza vaccine with the 2006-2007 Northern Hemisphere [NH] formulation administered on Day 0 (Year 0), the 2007-2008 NH formulation administered on Day 365 (Year 1), and the 2008-2009 NH formulation on Day 730 (Year 2).

<b>Number of subjects in period 1</b>	ID 15µg	IM 15µg
Started	2618	1089
Completed	2457	1023
Not completed	161	66
Consent withdrawn by subject	107	49
Adverse event, non-fatal	3	3
Serious adverse event	21	6
Lost to follow-up	-	1
Protocol deviation	30	7

## Baseline characteristics

### Reporting groups

Reporting group title	ID 15µg
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Reporting group description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) investigational influenza vaccine via the intradermal (ID) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Reporting group title	IM 15µg
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Reporting group description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) influenza vaccine via the intramuscular (IM) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Reporting group values	ID 15µg	IM 15µg	Total
Number of subjects	2618	1089	3707
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)	658	255	913
From 65-84 years	1918	822	2740
85 years and over	42	12	54
Age continuous			
Units: years			
arithmetic mean	70.7	70.9	
standard deviation	± 6.8	± 6.7	-
Gender categorical			
Units: Subjects			
Female	1428	590	2018
Male	1190	499	1689

## End points

### End points reporting groups

Reporting group title	ID 15µg
Reporting group description: Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) investigational influenza vaccine via the intradermal (ID) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).	
Reporting group title	IM 15µg
Reporting group description: Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) influenza vaccine via the intramuscular (IM) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).	

### Primary: Geometric Mean Titers of Influenza Antibodies Before and After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titers of Influenza Antibodies Before and After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly
End point description: Immunogenicity was assessed using the hemagglutination inhibition (HI) technique.	
End point type	Primary
End point timeframe: Day 0 (pre-vaccination) and Day 21 post-vaccination	

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2600	1077		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1; Day 0)	20.6 (19.6 to 21.5)	21.7 (20.2 to 23.3)		
A/Wisconsin/67/2005 (H3N2; Day 0)	36.3 (34.2 to 38.6)	33.8 (30.8 to 37.2)		
B/Malaysia/2506/2004 (Day 0)	11 (10.7 to 11.4)	11.5 (10.9 to 12.1)		
A/New Caledonia/20/99 (H1N1; Day 21)	81.9 (78.2 to 85.8)	69.1 (64.1 to 74.4)		
A/Wisconsin/67/2005 (H3N2; Day 21)	298 (282 to 315)	181 (167 to 197)		
B/Malaysia/2506/2004 (Day 21)	39.9 (38.2 to 41.6)	34.9 (32.7 to 37.3)		

## Statistical analyses

<b>Statistical analysis title</b>	Non-inferiority of ID Group for A/H3N2 Strain
Statistical analysis description: The non-inferiority of the ID investigational vaccine was assessed based on analysis performed on the Per Protocol Immunogenicity (PPI) population on each strain (A/H3N2, A/H1N1, and B).	
Comparison groups	IM 15µg v ID 15µg
Number of subjects included in analysis	3677
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.114

Notes:

[1] - Non-inferiority if for each strain, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above -0.176.

<b>Statistical analysis title</b>	Non-inferiority of ID Group for A/H1N1
Statistical analysis description: The non-inferiority of the ID investigational vaccine was assessed based on analysis performed on the Per Protocol Immunogenicity (PPI) population on each strain (A/H3N2, A/H1N1, and B).	
Comparison groups	ID 15µg v IM 15µg
Number of subjects included in analysis	3677
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	0.215
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.171
upper limit	0.259

Notes:

[2] - Non-inferiority if for each strain, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above -0.176.

<b>Statistical analysis title</b>	Non-inferiority of ID Group for B
Statistical analysis description: The non-inferiority of the ID investigational vaccine was assessed based on analysis performed on the Per Protocol Immunogenicity (PPI) population on each strain (A/H3N2, A/H1N1, and B).	
Comparison groups	ID 15µg v IM 15µg



Number of subjects included in analysis	3677
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.094

Notes:

[3] - Non-inferiority if for each strain, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above -0.176.

**Primary: Percentage of Elderly Subjects With Seroprotection After Vaccination Against Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®**

End point title	Percentage of Elderly Subjects With Seroprotection After Vaccination Against Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. Seroprotection was defined as HI antibody individual titer  $\geq 40$  (1/dil) 21 days (Day 21) after the first vaccination.

End point type	Primary
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End point timeframe:

Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2595	1078		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1)	77	71.2		
A/Wisconsin/67/2005 (H3N2)	93.3	87.8		
B/Malaysia/2506/2004	55.7	49.1		

**Statistical analyses**

Statistical analysis title	Superiority of ID investigational vaccine A/H1N1
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Statistical analysis description:

Superiority of the ID investigational vaccine was assessed, using the Full Analysis Set for Immunogenicity (FA SI) population. Superiority if for at least two strains, the two-sided 95% CI of the difference of the seroprotection rate ID-IM lies above 0.

Comparison groups	ID 15µg v IM 15µg
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Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	5.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.67
upper limit	8.97

<b>Statistical analysis title</b>	Superiority of ID investigational vaccine A/H3N2
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Statistical analysis description:

Superiority of the ID investigational vaccine was assessed, using the Full Analysis Set for Immunogenicity (FASI) population. Superiority if for at least two strains, the two-sided 95% CI of the difference of the seroprotection rate ID-IM lies above 0.

Comparison groups	ID 15µg v IM 15µg
Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	7.76

<b>Statistical analysis title</b>	Superiority of ID investigational vaccine B
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Statistical analysis description:

Superiority of the ID investigational vaccine was assessed, using the Full Analysis Set for Immunogenicity (FASI) population. Superiority if for at least two strains, the two-sided 95% CI of the difference of the seroprotection rate ID-IM lies above 0.

Comparison groups	ID 15µg v IM 15µg
Number of subjects included in analysis	3673
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.05
upper limit	10.1

**Secondary: Geometric Mean Titers of Influenza Antibodies Before and After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly**

End point title	Geometric Mean Titers of Influenza Antibodies Before and After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly
End point description:	Immunogenicity was assessed using the hemagglutination inhibition (HI) technique.
End point type	Secondary
End point timeframe:	Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2586	1077		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1; Day 0)	20.6 (19.7 to 21.5)	21.6 (20.1 to 23.2)		
A/Wisconsin/67/2005 (H3N2; Day 0)	36.3 (34.2 to 38.6)	33.9 (30.8 to 37.2)		
B/Malaysia/2506/2004 (Day 0)	11 (10.7 to 11.4)	11.5 (10.9 to 12.1)		
A/New Caledonia/20/99 (H1N1; Day 21)	81.7 (78 to 85.6)	68.8 (63.8 to 74.2)		
A/Wisconsin/67/2005 (H3N2; Day 21)	298 (282 to 315)	181 (167 to 197)		
B/Malaysia/2506/2004 (Day 21)	39.9 (38.3 to 41.6)	34.8 (32.6 to 37.2)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Elderly Subjects With Seroprotection Against Influenza Antigens Before and After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®**

End point title	Percentage of Elderly Subjects With Seroprotection Against Influenza Antigens Before and After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®
End point description:	Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. Seroprotection was defined as HI antibody individual titer $\geq 40$ (1/dil) 21 days (Day 21) after the first vaccination.
End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2586	1077		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1; Day 0)	32.5	33.8		
A/Wisconsin/67/2005 (H3N2; Day 0)	48.9	47		
B/Malaysia/2506/2004 (Day 0)	12	12.4		
A/New Caledonia/20/99 (H1N1; Day 21)	77	71.1		
A/Wisconsin/67/2005 (H3N2; Day 21)	93.3	87.9		
B/Malaysia/2506/2004 (Day 21)	55.7	48.9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies After Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2586	1077		
Units: Titers Ratios				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1)	3.97 (3.77 to 4.18)	3.19 (2.94 to 3.45)		
A/Wisconsin/67/2005 (H3N2)	8.19 (7.68 to 8.74)	5.35 (4.87 to 5.88)		
B/Malaysia/2506/2004	3.61 (3.47 to 3.76)	3.04 (2.85 to 3.24)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Influenza Antibodies After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Influenza Antibodies After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. Seroconversion was defined as subjects with a pre-vaccination HI antibody individual titer <10 (1/dil) and post-vaccination HI antibody individual titer ≥40 (1/dil) and significant increase defined as subjects with a pre-vaccination HI antibody individual titer ≥10 (1/dil): ≥ four-fold increase from pre- to post-vaccination HI antibody individual titer on Day 21.

End point type	Secondary
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End point timeframe:

Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2586	1077		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1)	38.7	30		
A/Wisconsin/67/2005 (H3N2)	61.3	46.9		
B/Malaysia/2506/2004	36.4	30.7		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titers of Influenza Antibodies Before and Up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titers of Influenza Antibodies Before and Up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®
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## End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set.

## End point type

Secondary

## End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	141		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1; Day 0)	23.5 (19.2 to 28.9)	24.5 (19.8 to 30.4)		
A/Wisconsin/67/2005 (H3N2; Day 0)	35.9 (26.8 to 48)	33.2 (25.6 to 43)		
B/Malaysia/2506/2004 (Day 0)	11.4 (9.78 to 13.2)	11.4 (9.8 to 13.2)		
A/New Caledonia/20/99 (H1N1; Day 21)	93.9 (77.6 to 114)	72.3 (59.4 to 88.1)		
A/Wisconsin/67/2005 (H3N2; Day 21)	301 (239 to 378)	197 (160 to 243)		
B/Malaysia/2506/2004 (Day 21)	42.3 (35.8 to 50.1)	39 (31.8 to 47.9)		
A/New Caledonia/20/99 (H1N1; Day 90)	71 (59.5 to 84.7)	61.2 (50.8 to 73.7)		
A/Wisconsin/67/2005 (H3N2; Day 90)	291 (233 to 363)	208 (167 to 258)		
B/Malaysia/2506/2004 (Day 90)	27.3 (22.8 to 32.6)	28.3 (23.5 to 34)		
A/New Caledonia/20/99 (H1N1; Day 180)	50.2 (42 to 60.1)	49.3 (40.5 to 60)		
A/Wisconsin/67/2005 (H3N2; Day 180)	226 (179 to 286)	169 (134 to 212)		
B/Malaysia/2506/2004 (Day 180)	21.6 (18.1 to 25.7)	24.6 (20.7 to 29.2)		
A/New Caledonia/20/99 (H1N1; Day 365)	30.9 (26.3 to 36.4)	31 (25.7 to 37.3)		
A/Wisconsin/67/2005 (H3N2; Day 365)	119 (92.8 to 151)	98.4 (79 to 122)		
B/Malaysia/2506/2004 (Day 365)	22.1 (18.7 to 26.1)	26.1 (22.1 to 30.7)		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Elderly Subjects With Seroprotection Before and up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference**

**Vaccine Vaxigrip®**

End point title	Percentage of Elderly Subjects With Seroprotection Before and up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®
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## End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. Seroprotection was defined as HI antibody individual titer  $\geq 40$  (1/dil) on 21, 90, 180, and 365 days after the first vaccination. This outcome was based on the Other Immunogenicity (OI) Analysis Set.

End point type	Secondary
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## End point timeframe:

Day 0 (pre-vaccination) and Day 21, 90, 180, and 365 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	141		
Units: Percentage of subjects				
number (not applicable)				
A/New Caledonia/20/99 (H1N1; Day 0)	36.7	35.5		
A/Wisconsin/67/2005 (H3N2; Day 0)	44.9	48.9		
B/Malaysia/2506/2004 (Day 0)	12.5	14.2		
A/New Caledonia/20/99 (H1N1; Day 21)	83.6	73.8		
A/Wisconsin/67/2005 (H3N2; Day 21)	96.1	92.1		
B/Malaysia/2506/2004 (Day 21)	61.7	53.9		
A/New Caledonia/20/99 (H1N1; Day 90)	74.2	66.7		
A/Wisconsin/67/2005 (H3N2; Day 90)	96.1	92.1		
B/Malaysia/2506/2004 (Day 90)	41.4	39		
A/New Caledonia/20/99 (H1N1; Day 180)	62.5	59.6		
A/Wisconsin/67/2005 (H3N2; Day 180)	95.3	85.6		
B/Malaysia/2506/2004 (Day 180)	30.5	34		
A/New Caledonia/20/99 (H1N1; Day 365)	44.5	42.6		
A/Wisconsin/67/2005 (H3N2; Day 365)	81.1	79.1		
B/Malaysia/2506/2004 (Day 365)	30.5	38.3		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip in the Elderly**

End point title	Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies up to 12 Months After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip in the Elderly
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21, 90, 180, and 365 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	141		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/New Caledonia/20/99 (H1N1; Day 90/Day 21)	0.757 (0.692 to 0.827)	0.846 (0.779 to 0.919)		
A/Wisconsin/67/2005 (H3N2; Day 90/Day 21)	0.968 (0.869 to 1.08)	1.06 (0.969 to 1.15)		
B/Malaysia/2506/2004 (Day 90/Day 21)	0.645 (0.579 to 0.718)	0.725 (0.658 to 0.798)		
A/New Caledonia/20/99 (H1N1; Day 180/Day 21)	0.535 (0.476 to 0.602)	0.682 (0.617 to 0.753)		
A/Wisconsin/67/2005 (H3N2; Day 180/Day 21)	0.753 (0.638 to 0.889)	0.859 (0.74 to 0.997)		
B/Malaysia/2506/2004 (Day 180/Day 21)	0.51 (0.45 to 0.578)	0.63 (0.563 to 0.705)		
A/New Caledonia/20/99 (H1N1; Day 365/Day 21)	0.33 (0.284 to 0.382)	0.428 (0.376 to 0.488)		
A/Wisconsin/67/2005 (H3N2; Day 365/Day 21)	0.394 (0.327 to 0.476)	0.5 (0.426 to 0.586)		
B/Malaysia/2506/2004 (Day 365/Day 21)	0.522 (0.458 to 0.595)	0.668 (0.586 to 0.763)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Titers of Influenza Antibodies According to EMEA Parameters Before and After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titers of Influenza Antibodies According to EMEA Parameters Before and After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip® in the Elderly
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination



<b>End point values</b>	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	143		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/Solomon Islands/3/2006 (H1N1; Day 0)	20.8 (18.2 to 23.7)	19 (15.6 to 23)		
A/Wisconsin/67/2005 (H3N2; Day 0)	112 (94.4 to 132)	102 (81.8 to 127)		
B/Malaysia/2506/2004 (Day 0)	24.3 (21.6 to 27.3)	22.4 (19.3 to 25.9)		
A/Solomon Islands/3/2006 (H1N1; Day 21)	204 (175 to 239)	137 (108 to 175)		
A/Wisconsin/67/2005 (H3N2; Day 21)	382 (334 to 438)	293 (240 to 357)		
B/Malaysia/2506/2004 (Day 21)	46.2 (41.4 to 51.6)	37.4 (32 to 43.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Elderly Subjects With Seroprotection According to EMEA Parameters After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects With Seroprotection According to EMEA Parameters After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Reference Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Seroprotection was defined as HI antibody individual titer  $\geq 40$  (1/dil) with EMEA immunogenicity criteria  $>60\%$  21 days (Day 21) after the first vaccination.

End point type	Secondary
End point timeframe:	
Day 0 (pre-vaccination) and Day 21 post-vaccination	

<b>End point values</b>	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	143		
Units: Percentage of subjects				
number (not applicable)				
A/Solomon Islands/3/2006 (H1N1; Day 0)	29.1	25.9		

A/Wisconsin/67/2005 (H3N2; Day 0)	80.3	80.3		
B/Malaysia/2506/2004 (Day 0)	34.4	35		
A/Solomon Islands/3/2006 (H1N1; Day 21)	93.1	81.8		
A/Wisconsin/67/2005 (H3N2; Day 21)	98.1	95.8		
B/Malaysia/2506/2004 (Day 21)	59.9	53.1		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Influenza Antibodies According to EMEA After Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Influenza Antibodies According to EMEA After Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Seroconversion was defined as subjects with a pre-vaccination HI antibody individual titer <10 (1/dil) and post-vaccination HI antibody individual titer ≥40 (1/dil) and significant increase defined as subjects with a pre-vaccination HI antibody individual titer ≥10 (1/dil): ≥ four-fold increase from pre- to post-vaccination HI antibody individual titer on Day 21 with EMEA immunogenicity criteria >30%.

End point type	Secondary
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End point timeframe:

Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	143		
Units: Percentage of subjects				
number (not applicable)				
A/Solomon Islands/3/2006 (H1N1)	76.2	63.6		
A/Wisconsin/67/2005 (H3N2)	45.9	40.1		
B/Malaysia/2506/2004	17.2	9.8		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titer Ratios of Influenza Antibodies According to EMEA Parameters After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine

## Vaxigrip® in the Elderly

End point title	Geometric Mean Titer Ratios of Influenza Antibodies According to EMEA Parameters After Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine Vaxigrip® in the Elderly
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### End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Based on EMEA immunogenicity criteria, the mean geometric increase between Day 0 and Day 21 was 2.0.

End point type	Secondary
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### End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	143		
Units: Titer Ratios				
geometric mean (confidence interval 95%)				
A/Solomon Islands/3/2006 (H1N1)	9.84 (8.43 to 11.5)	7.24 (5.82 to 9.02)		
A/Wisconsin/67/2005 (H3N2)	3.42 (2.99 to 3.91)	2.88 (2.43 to 3.41)		
B/Malaysia/2506/2004	1.9 (1.75 to 2.07)	1.67 (1.5 to 1.86)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Titers of Antibodies According to EMEA Before and After Third Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titers of Antibodies According to EMEA Before and After Third Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with Intramuscular Vaccine Vaxigrip® in the Elderly
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### End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set.

End point type	Secondary
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### End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	67		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/Brisbane/59/2007 (H1N1; Day 0)	25.8 (22.7 to 29.2)	20.7 (16.5 to 26.1)		
A/Uruguay/716/2007 (H3N2; Day 0)	18.6 (16.4 to 21.1)	15.5 (11.7 to 20.7)		
B/Florida/4/2006 (Day 0)	14.7 (13.2 to 16.3)	16.9 (13.2 to 21.6)		
A/Brisbane/59/2007 (H1N1; Day 21)	73.5 (65.3 to 82.7)	59.3 (44.4 to 79.2)		
A/Uruguay/716/2007 (H3N2; Day 21)	144 (124 to 166)	108 (75.6 to 154)		
B/Florida/4/2006 (Day 21)	46.5 (41.4 to 52.2)	40.4 (32.3 to 50.5)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Elderly Subjects With Seroprotection According to EMEA After Third Vaccination Against Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects With Seroprotection According to EMEA After Third Vaccination Against Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Seroprotection was defined as HI antibody individual titer  $\geq 40$  (1/dil) with EMEA immunogenicity criteria  $>60\%$  21 days (Day 21) after the first vaccination.

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	67		
Units: Percentage of subjects				
number (not applicable)				
A/Brisbane/59/2007 (H1N1; Day 0)	38.9	30.3		
A/Uruguay/716/2007 (H3N2; Day 0)	29.5	24.2		
B/Florida/4/2006 (Day 0)	21.1	25.4		
A/Brisbane/59/2007 (H1N1; Day 21)	80.5	74.2		
A/Uruguay/716/2007 (H3N2; Day 21)	89.6	77.3		

B/Florida/4/2006 (Day 21)	66.1	55.2		
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## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Antibodies According to EMEA After Third Vaccination of Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Achieving Seroconversion or Significant increase in Antibodies According to EMEA After Third Vaccination of Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®
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End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Seroconversion was defined as subjects with a pre-vaccination HI antibody individual titer <10 (1/dil) and post-vaccination HI antibody individual titer ≥40 (1/dil) and significant increase defined as subjects with a pre-vaccination HI antibody individual titer ≥10 (1/dil): ≥ four-fold increase from pre- to post-vaccination HI antibody individual titer on Day 21 with EMEA immunogenicity criteria >30%.

End point type	Secondary
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End point timeframe:

Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	67		
Units: Percentage of subjects				
number (not applicable)				
A/Brisbane/59/2007 (H1N1)	35.2	31.8		
A/Uruguay/716/2007 (H3N2)	71.8	60.6		
B/Florida/4/2006	37.2	26.9		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titer Ratios of Antibodies According to EMEA After Third Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine Vaxigrip® in the Elderly

End point title	Geometric Mean Titer Ratios of Antibodies According to EMEA After Third Vaccination with Investigational Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route Compared with the Intramuscular Vaccine Vaxigrip® in the
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## End point description:

Immunogenicity was assessed using the hemagglutination inhibition (HI) technique. This outcome was based on the Other Immunogenicity (OI) Analysis Set. Based on EMEA immunogenicity criteria, the mean geometric increase between Day 0 and Day 21 was 2.0.

## End point type

Secondary

## End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	67		
Units: Titer Ratios				
geometric mean (confidence interval 95%)				
A/Brisbane/59/2007 (H1N1)	2.85 (2.56 to 3.17)	2.86 (2.31 to 3.54)		
A/Uruguay/716/2007 (H3N2)	7.74 (6.77 to 8.85)	6.94 (5.15 to 9.36)		
B/Florida/4/2006	3.16 (2.84 to 3.52)	2.4 (1.93 to 2.98)		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the First Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®**

## End point title

Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the First Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®

## End point description:

Solicited injection site reactions: Injection site induration >5 cm for 3 days and Injection site ecchymosis. Solicited systemic reactions: Pyrexia (rectal temperature > 38°C) for ≥24 hours, Malaise, and Shivering.

## End point type

Secondary

## End point timeframe:

Day 0 up to Day 3 post-first vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2606	1089		
Units: Percentage of subjects				
number (not applicable)				
At least 1 reaction listed in EMEA recommendations	12.6	12.8		
Injection site induration >5 cm for 3 days	0.1	0		
Injection site ecchymosis	2.8	3		
Pyrexia (rectal temperature > 38°C) for ≥24 hours	1.1	1.4		
Malaise	7.6	6.8		
Shivering	3.9	4.6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the Second Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the Second Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®
End point description:	Solicited injection site reactions: Injection site induration >5 cm for 3 days and Injection site ecchymosis. Solicited systemic reactions: Pyrexia (rectal temperature > 38°C) for ≥24 hours, Malaise, and Shivering.
End point type	Secondary
End point timeframe:	Day 0 up to Day 3 post-second vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2618 <sup>[4]</sup>	511		
Units: Percentage of subjects				
number (not applicable)				
At least 1 reaction listed in EMEA recommendations	12.2	12		
Injection site induration >5 cm for 3 days	0.1	0		
Injection site ecchymosis	2.7	3		
Pyrexia (rectal temperature > 38°C) for ≥24 hours	2	2.2		
Malaise	5.9	5.5		
Shivering	4.6	4.7		

Notes:

[4] - The total number of subjects analyzed was 2965 and was based on the Safety Analysis Set population.

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the Third Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Reporting Solicited Reactions Listed in the EMEA Note for Guidance Within 3 Days after the Third Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Vaccine Vaxigrip®
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End point description:

Solicited injection site reactions: Injection site induration >5 cm for 3 days and Injection site ecchymosis. Solicited systemic reactions: Pyrexia (rectal temperature > 38°C) for ≥24 hours, Malaise, and Shivering.

End point type	Secondary
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End point timeframe:

Day 0 up to Day 3 post-third vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2618 <sup>[5]</sup>	229		
Units: Percentage of subjects				
number (not applicable)				
At least 1 reaction listed in EMEA recommendations	11.8	12.3		
Injection site induration >5 cm for 3 days	0	0		
Injection site ecchymosis	2.9	1.8		
Pyrexia (rectal temperature > 38°C) for ≥24 hours	2.8	1.8		
Malaise	4.6	5.7		
Shivering	4.4	4.8		

Notes:

[5] - The total number of subjects analyzed was 2920 and was based on the Safety Analysis Set population.

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After First Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular



**Reference Vaccine Vaxigrip®**

End point title	Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After First Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Reference Vaccine Vaxigrip®
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End point description:

Solicited injection site: Pain, Pruritus, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering.

End point type	Secondary
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End point timeframe:

Day 0 up to Day 7 post-first vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2606	1089		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	22.7	17.2		
Injection site Pruritus	29.5	6.1		
Injection site Erythema	70.9	15.1		
Injection site Swelling	35.8	8.4		
Injection site Induration	37.6	11.3		
Injection site Ecchymosis	3.4	3.7		
Fever	2.5	3.4		
Headache	13	12.7		
Malaise	8.5	7.8		
Myalgia	10.6	10.9		
Shivering	4.6	6.1		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After Second Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Reference Vaccine Vaxigrip®**

End point title	Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After Second Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Reference Vaccine Vaxigrip®
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End point description:

Solicited injection site: Pain, Pruritus, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering.

End point type	Secondary
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End point timeframe:

Day 0 up to Day 7 post-second vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2618 <sup>[6]</sup>	511		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	23.1	18.9		
Injection site Pruritus	27.5	8.9		
Injection site Erythema	62.8	19.9		
Injection site Swelling	32.5	10		
Injection site Induration	32.7	11.2		
Injection site Ecchymosis	3.3	3.1		
Fever	3.7	4.6		
Headache	12.3	10.6		
Malaise	6.8	7.3		
Myalgia	11.5	10.6		
Shivering	5.4	5.5		

Notes:

[6] - The total number of subjects analyzed was 2965 and was based on the Safety Analysis Set population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After Third Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Reference Vaccine Vaxigrip®

End point title	Percentage of Elderly Subjects Reporting Solicited Injection-site or Systemic Reaction Within 7 Days After Third Vaccination with Intradermal Inactivated, Split-Virion Influenza Vaccine Compared with the Intramuscular Reference Vaccine Vaxigrip®
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End point description:

Solicited injection site: Pain, Pruritus, Erythema, Swelling, Induration and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering.

End point type	Secondary
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End point timeframe:

Day 0 up to Day 7 post-third vaccination

End point values	ID 15µg	IM 15µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2618 <sup>[7]</sup>	229		
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	20.5	15.8		
Injection site Pruritus	28.3	7.5		
Injection site Erythema	62.8	18		

Injection site Swelling	34.1	12.3		
Injection site Induration	31.5	12.3		
Injection site Ecchymosis	3.8	2.2		
Fever	5.2	3.5		
Headache	11.6	9.2		
Malaise	5.6	7		
Myalgia	10.3	7.9		
Shivering	5.2	6.1		

Notes:

[7] - The total number of subjects analyzed was 2920 and was based on the Safety Analysis Set population.

### Statistical analyses

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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-any vaccination.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	7.1
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### Reporting groups

Reporting group title	IM 15µg
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Reporting group description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) influenza vaccine via the intramuscular (IM) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Reporting group title	ID 15µg
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Reporting group description:

Subjects who received 3 vaccinations of inactivated, split-virion (with octoxynol-9) investigational influenza vaccine via the intradermal (ID) route. For the first vaccination, subjects received the 2006-2007 Northern Hemisphere [NH] formulation on Day 0 (Year 0). For the second vaccination, subjects received the 2007-2008 NH formulation on Day 365 (Year 1). For the third vaccination, subjects received the 2008-2009 NH formulation on Day 730 (Year 2).

Serious adverse events	IM 15µg	ID 15µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 1089 (1.19%)	32 / 2965 (1.08%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed <sup>[1]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer female			
subjects affected / exposed <sup>[2]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed <sup>[3]</sup>	0 / 511 (0.00%)	2 / 2965 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed <sup>[4]</sup>	1 / 511 (0.20%)	0 / 2965 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord neoplasm			
subjects affected / exposed <sup>[5]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed <sup>[6]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed <sup>[7]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed <sup>[8]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed <sup>[9]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality disorder			

subjects affected / exposed <sup>[10]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Hand fracture			
subjects affected / exposed <sup>[11]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polytraumatism			
subjects affected / exposed <sup>[12]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed <sup>[13]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed <sup>[14]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
Angina pectoris			
subjects affected / exposed <sup>[15]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed <sup>[16]</sup>	0 / 511 (0.00%)	2 / 2965 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 1089 (0.18%)	0 / 2965 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed <sup>[17]</sup>	1 / 511 (0.20%)	3 / 2965 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical root pain			
subjects affected / exposed <sup>[18]</sup>	1 / 511 (0.20%)	0 / 2965 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed <sup>[19]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed <sup>[20]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed <sup>[21]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope vasovagal			
subjects affected / exposed <sup>[22]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed <sup>[23]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal tear			
subjects affected / exposed <sup>[24]</sup>	1 / 511 (0.20%)	0 / 2965 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed <sup>[25]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1089 (0.00%)	2 / 2965 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure chronic			
subjects affected / exposed <sup>[26]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis			
subjects affected / exposed <sup>[27]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed <sup>[28]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed <sup>[29]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed <sup>[30]</sup>	0 / 1089 (0.00%)	2 / 2606 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			



subjects affected / exposed <sup>[31]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed <sup>[32]</sup>	1 / 511 (0.20%)	0 / 2965 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium colitis			
subjects affected / exposed <sup>[33]</sup>	0 / 511 (0.00%)	1 / 2965 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed <sup>[34]</sup>	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed <sup>[35]</sup>	1 / 1089 (0.09%)	0 / 2606 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the

[illegible]

exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[26] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[27] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[28] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[29] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[30] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[31] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[32] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[33] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[34] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

[35] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The total number (N) represents vaccinated subjects with at least one safety record for the unsolicited adverse events is available.

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

<b>Non-serious adverse events</b>	IM 15µg	ID 15µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 1089 (17.08%)	1859 / 2965 (62.70%)	
Nervous system disorders			
Headache (Post-first vaccination)			
alternative assessment type: Systematic			

subjects affected / exposed <sup>[36]</sup>	138 / 1083 (12.74%)	339 / 2601 (13.03%)	
occurrences (all)	138	339	
General disorders and administration site conditions			
Injection site pain (Post-second vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[37]</sup>	96 / 508 (18.90%)	685 / 2960 (23.14%)	
occurrences (all)	96	685	
Injection site erythema (Post-first vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[38]</sup>	163 / 1082 (15.06%)	1845 / 2601 (70.93%)	
occurrences (all)	163	1845	
Injection site swelling (Post-first vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[39]</sup>	91 / 1082 (8.41%)	931 / 2601 (35.79%)	
occurrences (all)	91	931	
Injection site induration (Post-first vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[40]</sup>	122 / 1082 (11.28%)	979 / 2601 (37.64%)	
occurrences (all)	122	979	
Fever (Post-third vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[41]</sup>	8 / 228 (3.51%)	151 / 2916 (5.18%)	
occurrences (all)	8	151	
Malaise (Post-first vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[42]</sup>	85 / 1083 (7.85%)	220 / 2601 (8.46%)	
occurrences (all)	85	220	
Shivering (Post-second vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[43]</sup>	28 / 508 (5.51%)	159 / 2960 (5.37%)	
occurrences (all)	28	159	

Skin and subcutaneous tissue disorders Injection site pruritus (Post-first vaccination) alternative assessment type: Systematic subjects affected / exposed <sup>[44]</sup> occurrences (all)	66 / 1083 (6.09%) 66	766 / 2601 (29.45%) 766	
Musculoskeletal and connective tissue disorders Myalgia (Post-second vaccination) alternative assessment type: Systematic subjects affected / exposed <sup>[45]</sup> occurrences (all)	54 / 508 (10.63%) 54	339 / 2960 (11.45%) 339	

Notes:

[36] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[37] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[38] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[39] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[40] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[41] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[42] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[43] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[44] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for

which data were available for the event during the period.

[45] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This was a solicited adverse event that were recorded in a Diary Card within 7 days of vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2006	Change of the Principal Investigator for the center of Antwerp in Belgium (Dr. Buggenhout replacing Dr. Vets), addition of batches numbers of investigational and control product, and change of the Clinical Trial Manager (Hélène Berninger replacing Séverine Alric).
09 November 2006	An information note to the Belgian subjects regarding the new Principal Investigator Dr. de Decker was created.
22 May 2007	Specified the formulation of the 2007-2008 NH influenza vaccine recommended by the World Health Organization (WHO) and the Committee for Human Medicinal Products (CHMP), documented a change of Principal Investigator in Genoa, Italy (Professor Icardi replaced Professor Crovari), notified few minor updates on processes regarding the sample preparation, Vaccination Comfort Questionnaire (VCQ) form, SAE reporting and the data management system with the implementation of electronic Case Report Form (Case Book).
22 May 2008	Specified the formulation of the investigational and comparator vaccines to be administered for the third vaccination (2008-2009 NH strains recommended by the WHO and the CHMP BWP ad hoc Influenza working group), documented that two centers from Belgium stopped the study, added the reporting of adverse events of special interest (convulsions, encephalomyelitis, Guillain Barré syndrome, neuritis, severe allergic reactions, syncope, thrombocytopenia, and vasculitis) in addition to SAEs from visit 08 up to 6-month after the third vaccination, added the evaluation of the safety profile of suspected atopic subjects following the three vaccinations as an observational objective, documented changes in the second analysis, which was performed in two steps instead of one (1st step analysis covered all data from Visit 03 to Visit 06, including SAEs recorded until the 12th of March 2008, and excluding the serological results of Visit 05 and Visit 06 and 2nd step analysis updated the 1st step analysis when the serological results of Visit 05 and Visit 06 were available), updated the reference of the current Investigator Brochure, the last question of the VCQ form, the description of the randomization process at Visit 05 and at Visit 07 and updated the batch number of vaccines used for Year 1 vaccination, and specified that Electronic Data Capture solutions were provided by the Sponsor to the investigators.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported