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	L
Result version number	v2 (current)
This version publication date	18 February 2016
First version publication date	27 March 2015
Version creation reason	 Correction of full data set CI of secondary outcome on GMTR for !D 15 ug group were shifted

Trial information

Trial identification		
Sponsor protocol code	GID17	
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 No 1901/2006 apply to this trial? No Does article 46 of REGULATION (EC) No No 1901/2006 apply to this trial? No

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
Nataa	

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

<u> </u>	
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
Arm title	ID 15µg

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).

Arm title	IM 15µg

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

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).

Number of subjects in period 1	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

Reporting groups

Reporting group title	ID 15µg	
Reporting group description:		

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).

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 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 analysis title	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 ^[1]
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.

Statistical analysis title	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).

ID 15µg v IM 15µg
3677
Pre-specified
non-inferiority ^[2]
Logrank
Mean difference (final values)
0.215
95 %
2-sided
0.171
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.

Statistical analysis title	Non-inferiority of ID Group for B
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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). ID 15µg v IM 15µg

Number of subjects included in analysis	3677
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
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®

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
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 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	5.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.67
upper limit	8.97

Statistical analysis titleSuperiority 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.

ID 15µg v IM 15µg
3673
Pre-specified
Mean difference (final values)
5.49
95 %
2-sided
3.4
7.76

Statistical analysis title	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.

ID 15µg v IM 15µg
3673
Pre-specified
Mean difference (final values)
6.6
95 %
2-sided
3.05
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®

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

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	

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

	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

 End point timeframe:

 Description:

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)	

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®

	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 \geq 40 (1/dil) and significant increase defined as subjects with a pre-vaccination HI antibody individual titer \geq 10 (1/dil): \geq four-fold increase from pre- to post-vaccination HI antibody individual titer on Day 21.

End point type	Secondary
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®

in the El	derly
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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®

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

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

	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			
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%) 0.846 (0.779 A/New Caledonia/20/99 (H1N1; Day 0.757 (0.692 90/Day 21) to 0.827) to 0.919) 0.968 (0.869 1.06 (0.969 to A/Wisconsin/67/2005 (H3N2; Day 90/Day 21) to 1.08) 1.15)0.725 (0.658 0.645 (0.579 B/Malaysia/2506/2004 (Day 90/Day 21) to 0.718) to 0.798) A/New Caledonia/20/99 (H1N1; Day 0.535 (0.476 0.682 (0.617 180/Day 21) to 0.753) to 0.602) A/Wisconsin/67/2005 (H3N2; Day 0.753 (0.638 0.859 (0.74 to 180/Day 21) to 0.889) 0.997) B/Malaysia/2506/2004 (Day 180/Day 0.51 (0.45 to 0.63 (0.563 to 0.578) 0.705) 21) A/New Caledonia/20/99 (H1N1; Day 0.33 (0.284 to 0.428 (0.376 365/Day 21) 0.382) to 0.488) 0.394 (0.327 A/Wisconsin/67/2005 (H3N2; Day 0.5 (0.426 to 365/Day 21) to 0.476) 0.586)B/Malaysia/2506/2004 (Day 365/Day 0.522 (0.458 0.668 (0.586 to 0.595) to 0.763) 21)

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

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 typeSecondaryEnd 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: 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)	

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®

•	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 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

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; 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	

Vaxigrip® in the Elderly

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 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	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

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		
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)	

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®

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 $\ensuremath{\mathbb{R}}$

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		

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	

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®

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 \geq 40 (1/dil) and significant increase defined as subjects with a pre-vaccination HI antibody individual titer \geq 10 (1/dil): \geq four-fold increase from pre- to post-vaccination HI antibody individual titer on Day 21 with EMEA immunogenicity criteria >30%.

End point type	Secondary
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

End	point	description:
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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.

Elderly

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®

·	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	

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 Listed in the EMEA Note for Gu Second Vaccination with Intrad Influenza Vaccine Compared w Vaxigrip®	uidance Within 3 Days after the dermal Inactivated, Split-Virion
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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	
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 ^[4]	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 Analyis 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®

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 \geq 24 hours, Malaise, and Shivering.

Secondary

End point type

a	point type	e	

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 ^[5]	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 Analyis 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®

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
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 15.1Injection 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®

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

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 ^[6]	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 Analyis 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®

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 description:

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

End point type	Secondary
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 ^[7]	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:

 $\left[7\right]$ - The total number of subjects analyzed was 2920 and was based on the Safety Analyis Set population.

Statistical analyses

No statistical analyses for this end point

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
Dictionary used	
Dictionary name	MedDRA
Dictionary version	7.1
Reporting groups	

Reporting group title	IM 15µg
Poporting group description:	

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

Reporting group title 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 ^[1]	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 ^[2]	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 ^[3]	0 / 511 (0.00%)	2 / 2965 (0.07%)	
occurrences causally related to	0 / 0	0 / 2	
treatment / all	070	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed ^[4]	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 ^[5]	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 ^[6]	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 ^[7]	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 ^[8]	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 ^[9]	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 ^[10]	0 / 1089 (0.00%)	1 / 2606 (0.04%)	
occurrences causally related to	0 / 0	0/1	
treatment / all	0,0	0,1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed ^[11]	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 ^[12]	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 ^[13]	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 ^[14]	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	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed ^[15]	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 ^[16]	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	

1 / 511 (0.20%)	3 / 2965 (0.10%)	
0/1	0 / 3	
0 / 0	0 / 0	
1 / 511 (0.20%)	0 / 2965 (0.00%)	
0/1	0 / 0	
0 / 0	0 / 0	
0 / 511 (0.00%)	1 / 2965 (0.03%)	
0 / 0	0/1	
0 / 0	0 / 0	
0 / 1089 (0.00%)	1 / 2606 (0.04%)	
0 / 0	0 / 1	
0 / 0	0 / 0	
0 / 1089 (0.00%)	1 / 2606 (0.04%)	
0 / 0	0/1	
0 / 0	0 / 0	
0 / 1089 (0.00%)	1 / 2606 (0.04%)	
0 / 0	0/1	
0 / 0	0/1	
0 / 1089 (0.00%)	1 / 2606 (0.04%)	
0 / 0	0/1	
0 / 0	0 / 0	
1 / 511 (0.20%)	0 / 2965 (0.00%)	
0 / 1	0 / 0	
0 / 0	0 / 0	
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treatment / all 0 / 0 0 / 0 deaths causally related to treatment / all 0 / 0 0 / 0		0 / 1089 (0.00%)	2 / 2606 (0.08%)	
treatment / all 0 / 0 0 / 0		0 / 0	0 / 2	
Rheumatoid arthritis		0 / 0	0 / 0	
	Rheumatoid arthritis			

subjects affected / exposed ^[31]	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 ^[32]	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 ^[33]	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 ^[34]	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 ^[35]	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.

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unsolicited adverse events is available.

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[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.

Non-serious adverse events	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			

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

subjects affected / exposed ^[36]	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 ^[37]	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 ^[38]	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 ^[39]	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 ^[40]	122 / 1082 (11.28%)	979 / 2601 (37.64%)	
occurrences (all)	122	979	
Fever (Post-third vaccination) alternative assessment type: Systematic			
subjects affected / exposed ^[41]	8 / 228 (3.51%)	151 / 2916 (5.18%)	
occurrences (all)	8	151	
Malaise (Post-first vaccination)			
alternative assessment type: Systematic			
subjects affected / exposed ^[42] occurrences (all)	85 / 1083 (7.85%) 85	220 / 2601 (8.46%) 220	
		220	
Shivering (Post-second vaccination) alternative assessment type: Systematic			
subjects affected / exposed ^[43]	28 / 508 (5.51%)	159 / 2960 (5.37%)	
occurrences (all)	28	159	
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66 / 1083 (6.09%)	766 / 2601 (29.45%)	
66	766	
54 / 508 (10.63%)	339 / 2960 (11.45%)	
54	339	
	66 54 / 508 (10.63%)	66 / 1083 (6.09%) (29.45%) 66 766 54 / 508 (10.63%) 339 / 2960 (11.45%)

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.

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which data were available for the event during the period.

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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.

Substantial protocol amendments (globally)

Date Amendment Change of the Principal Investigator for the center of Antwerp in Belgium (Dr. 14 September 2006 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). An information note to the Belgian subjects regarding the new Principal 09 November 2006 Investigator Dr. de Decker was created. Specified the formulation of the 2007-2008 NH influenza vaccine recommended by 22 May 2007 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). Specified the formulation of the investigational and comparator vaccines to be 22 May 2008 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 guestion 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.

Were there any global substantial amendments to the protocol? Yes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported