



## Clinical trial results:

### Safety and immunogenicity of an intramuscular, inactivated, split-virion, pandemic influenza A/H5N1 vaccine in adults and the elderly

#### Summary

EudraCT number	2006-000477-29
Trial protocol	BE GB
Global end of trial date	23 December 2008

#### Results information

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

#### Trial information

##### Trial identification

Sponsor protocol code	GPA02
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00415129
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Director, Clinical Development, Sanofi Pasteur SA, 1 57 09 57 61 25, sanjay.gurunathan@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur SA, 1 57 09 57 61 25, sanjay.gurunathan@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	03 September 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 December 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To describe the injection site reactions and systemic safety profile during the 21 days after each of two primary series and one booster (as applicable) intramuscular (IM) injections in two age groups: subjects aged 18 to 60 years (adults) or >60 years (elderly).
- To describe the immune response 21 days after each of two primary series IM injections in two age groups: subjects aged 18 to 60 years and >60 years.
- To describe the antibody persistence at month 6 (all subjects) and months 15 and 22 (subsets of subjects) after the first vaccination in two age groups: subjects aged 18 to 60 years or >60 years.
- To describe the immune response 21 days after a booster vaccination administered at either 6 months (A/Vietnam booster) or 7 and 21 days after a booster vaccination administered at 22 months (A/Indonesia booster) after the first vaccination in two age groups: subjects aged 18 to 60 years or >60 years.
- To describe any serious adverse event during the trial.

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 were also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	16 May 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 150
Country: Number of subjects enrolled	Belgium: 450
Worldwide total number of subjects	600
EEA total number of subjects	600

Notes:

### Subjects enrolled per age group

In utero	0
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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)	390
From 65 to 84 years	210
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study subjects were enrolled from 16 May 2006 to 12 June 2006 in 3 clinical centers in Belgium and 1 in the United Kingdom.

### Pre-assignment

Screening details:

A total of 600 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	18-60 years 30µg+Adjuvant
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Arm description:

Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.

Arm type	Experimental
Investigational medicinal product name	A/H5N1 inactivated, adjuvanted, split virion influenza vaccine made in embryonated eggs
Investigational medicinal product code	402
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, two doses 21 days apart as primary series and booster at either 6 or 22 months after first vaccination or no booster vaccination.

<b>Arm title</b>	18-60 years 7.5µg
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Arm description:

Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA] ) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.

Arm type	Experimental
Investigational medicinal product name	A/H5N1 inactivated, adjuvanted, split virion influenza vaccine made in embryonated eggs
Investigational medicinal product code	402
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, two doses 21 days apart as primary series and booster at either 6 or 22 months after first vaccination or no booster vaccination.

<b>Arm title</b>	>60 years 30µg+Adjuvant
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**Arm description:**

Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.

Arm type	Experimental
Investigational medicinal product name	A/H5N1 inactivated, adjuvanted, split virion influenza vaccine made in embryonated eggs
Investigational medicinal product code	402
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

0.5 mL, intramuscular, two doses 21 days apart as primary series and booster at either 6 or 22 months after first vaccination or no booster vaccination.

<b>Arm title</b>	>60 years 7.5µg
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**Arm description:**

Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA]) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.

Arm type	Experimental
Investigational medicinal product name	A/H5N1 inactivated, adjuvanted, split virion influenza vaccine made in embryonated eggs
Investigational medicinal product code	402
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

0.5 mL, intramuscular, two doses 21 days apart as primary series and booster at either 6 or 22 months after first vaccination or no booster vaccination.

<b>Number of subjects in period 1</b>	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant
Started	151	149	150
Completed	148	148	150
Not completed	3	1	0
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	1	-	-
Protocol deviation	1	1	-

<b>Number of subjects in period 1</b>	>60 years 7.5µg
Started	150
Completed	149
Not completed	1
Adverse event, serious fatal	-
Adverse event, non-fatal	-
Protocol deviation	1



## Baseline characteristics

### Reporting groups

Reporting group title	18-60 years 30µg+Adjuvant
Reporting group description: Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.	
Reporting group title	18-60 years 7.5µg
Reporting group description: Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA] ) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.	
Reporting group title	>60 years 30µg+Adjuvant
Reporting group description: Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.	
Reporting group title	>60 years 7.5µg
Reporting group description: Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA]) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.	

Reporting group values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant
Number of subjects	151	149	150
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)	151	149	44
From 65-84 years	0	0	106
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.3	37.6	68.3
standard deviation	± 13.7	± 13.7	± 5.1
Gender categorical Units: Subjects			
Female	82	95	71
Male	69	54	79

Reporting group values	>60 years 7.5µg	Total	
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Number of subjects	150	600	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	46	390	
From 65-84 years	104	210	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	68.3		
standard deviation	± 5.3	-	
Gender categorical			
Units: Subjects			
Female	75	323	
Male	75	277	



## End points

### End points reporting groups

Reporting group title	18-60 years 30µg+Adjuvant
Reporting group description: Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.	
Reporting group title	18-60 years 7.5µg
Reporting group description: Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA] ) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.	
Reporting group title	>60 years 30µg+Adjuvant
Reporting group description: Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.	
Reporting group title	>60 years 7.5µg
Reporting group description: Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA]) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.	

### **Primary: Summary of Geometric Mean Titers (GMTs) of Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Summary of Geometric Mean Titers (GMTs) of Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[1]</sup>
End point description: Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.	
End point type	Primary
End point timeframe: Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	146	149
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	4.14 (3.98 to 4.31)	4.15 (3.97 to 4.34)	5.51 (4.84 to 6.29)	6.17 (5.2 to 7.32)
Day 21	8.61 (6.92 to 10.72)	8.76 (7 to 10.97)	18.7 (14 to 25)	16.6 (12.6 to 21.7)
Day 42	19.4 (15.1 to 24.9)	13 (10.3 to 16.4)	28.9 (22.1 to 37.9)	21.4 (16.5 to 27.8)

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[2]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	146	149
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Day 21/Day 0	2.08 (1.69 to 2.56)	2.11 (1.7 to 2.62)	3.36 (2.64 to 4.29)	2.71 (2.2 to 3.35)
Day 42/Day 21	2.26 (1.86 to 2.75)	1.48 (1.29 to 1.69)	1.54 (1.32 to 1.79)	1.33 (1.18 to 1.48)
Day 42/Day 0	4.68 (3.66 to 5.97)	3.13 (2.49 to 3.93)	5.21 (4.12 to 6.59)	3.6 (2.91 to 4.46)

## Statistical analyses

No statistical analyses for this end point

### **Primary: Percentage of Subjects with Antibody Titers <8 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects with Antibody Titers <8 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[3]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	146	149
Units: Percentage of subjects				
number (not applicable)				
Day 0	98	98	84.7	83.9
Day 21	72.2	72.5	50.7	50
Day 42	43.2	54.1	34	38.9

## Statistical analyses

No statistical analyses for this end point

### **Primary: Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic
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## End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method. Seroconversion (for subjects with a titer <10 [turkey] or <8 [horse] [1/dil] on Day 0: post-injection titer ≥40 [turkey] or ≥32 [horse] [1/dil]), or significant increase (for subjects with a titer ≥10 [turkey] or ≥8 [horse] [1/dil]: ≥four-fold increase of the titer) at Day 21 and Day 42.

## End point type

Primary

## End point timeframe:

Day 21 and Day 42 post-vaccination

## Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	146	149
Units: Percentage of subjects				
number (not applicable)				
Day 21	20.5	21.5	34.9	26.2
Day 42	45.9	33.1	51.7	36.5

## Statistical analyses

No statistical analyses for this end point

**Primary: Summary of Geometric Mean Titers (GMTs) of Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Summary of Geometric Mean Titers (GMTs) of Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[5]</sup>
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## End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using turkey erythrocytes method.

## End point type

Primary

## End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

## Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	42	38	36
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	5.04 (4.96 to 5.12)	5 (5 to 5)	6.41 (5.02 to 8.18)	8.94 (5.87 to 13.61)
Day 21	6.48 (4.88 to 8.61)	8.11 (5.84 to 11.28)	11.72 (7.33 to 18.76)	12.94 (7.88 to 21.23)
Day 42	9.37 (6.73 to 13.05)	9.82 (7.09 to 13.62)	13.79 (8.55 to 22.25)	12.15 (7.45 to 19.83)

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[6]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	42	38	36
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Day 21/Day 0	1.286 (0.981 to 1.684)	1.62 (1.17 to 2.26)	1.83 (1.29 to 2.6)	1.45 (1.14 to 1.84)
Day 42/Day 21	1.44 (1.15 to 1.79)	1.211 (0.987 to 1.486)	1.177 (0.981 to 1.411)	1.05 (0.938 to 1.175)
Day 42/Day 0	1.86 (1.35 to 2.56)	1.96 (1.42 to 2.72)	2.15 (1.53 to 3.02)	1.49 (1.1 to 2.03)

## Statistical analyses

No statistical analyses for this end point

### **Primary: Percentage of Subjects with Antibody titers <10 (1/dil) Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects with Antibody titers <10 (1/dil) Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[7]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using turkey erythrocytes method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	42	38	36
Units: Percentage of subjects				
number (not applicable)				
Day 0	100	100	84.2	77.8
Day 21	88.4	81	68.4	61.1
Day 42	61.9	66.7	55.3	62.9

## Statistical analyses

No statistical analyses for this end point

### **Primary: Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Assayed by HI Turkey Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion,
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## End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using turkey erythrocytes method. Seroconversion (for subjects with a titer <10 [turkey] or <8 [horse] [1/dil] on Day 0: post-injection titer ≥40 [turkey] or ≥32 [horse] [1/dil]), or significant increase (for subjects with a titer ≥10 [turkey] or ≥8 [horse] [1/dil]: ≥four-fold increase of the titer) at Day 21 and Day 42.

## End point type

Primary

## End point timeframe:

Day 21 and Day 42 post-vaccination

## Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	42	38	36
Units: Percentage of subjects number (not applicable)				
Day 21	4.7	14.3	15.8	11.1
Day 42	7.1	19	15.8	11.4

## Statistical analyses

No statistical analyses for this end point

**Primary: Summary of Geometric Mean Titers (GMTs) of Antibody Assayed Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Summary of Geometric Mean Titers (GMTs) of Antibody Assayed Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[9]</sup>
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## End point description:

Influenza vaccine antibodies were assessed using the seroneutralization method.

## End point type

Primary

## End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

## Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Titers				
geometric mean (confidence interval 95%)				

Day 0	10.09 (9.99 to 10.2)	10.22 (9.89 to 10.55)	10.9 (10.3 to 11.6)	11.8 (10.8 to 13)
Day 21	12.8 (11.5 to 14.2)	12.5 (11.3 to 13.9)	20 (16.7 to 24)	16.6 (14.2 to 19.5)
Day 42	20.7 (17.9 to 23.9)	15.6 (13.8 to 17.7)	23.4 (19.6 to 27.8)	17.6 (15 to 20.6)

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers Ratios (GMTR) Antibody Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[10]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Day 21/Day 0	1.27 (1.14 to 1.4)	1.23 (1.11 to 1.35)	1.83 (1.54 to 2.17)	1.41 (1.24 to 1.59)
Day 42/Day 21	1.61 (1.42 to 1.83)	1.25 (1.15 to 1.35)	1.17 (1.08 to 1.27)	1.08 (1.03 to 1.13)
Day 42/Day 0	2.05 (1.78 to 2.37)	1.53 (1.35 to 1.73)	2.13 (1.81 to 2.52)	1.51 (1.33 to 1.72)

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects with Antibody titers <20 (1/dil) Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine



End point title	Percentage of Subjects with Antibody titers <20 (1/dil) Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[11]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the seroneutralization method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Percentage of subjects				
number (not applicable)				
Day 0	100	98.7	96.7	92.7
Day 21	86.8	89.9	69.3	78.7
Day 42	61.2	77	57.3	73.8

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects with 2- and 4-fold Increase in Antibody titers Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Percentage of Subjects with 2- and 4-fold Increase in Antibody titers Assayed by Seroneutralization Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[12]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the seroneutralization method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Percentage of subjects				
number (not applicable)				
2-fold increase from Day 0 (Day 21/Day 0)	13.2	9.4	28.7	15.3
2-fold increase from Day 0 (Day 42/Day 0)	38.8	22.3	40	20.8
4-fold increase from Day 0 (Day 21/Day 0)	8.6	5.4	19.3	10
4-fold increase from Day 0 (Day 42/Day 0)	27.2	14.2	21.3	11.4

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers of Antibody (Ab) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain In Subjects with Undetectable Ab After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers of Antibody (Ab) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain In Subjects with Undetectable Ab After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[13]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	146	123	125
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	4 (4 to 4)	4 (4 to 4)	4.03 (4 to 4.07)	4 (4 to 4)
Day 21	8.06 (6.54 to 9.92)	8.27 (6.64 to 10.3)	12.14 (9.27 to 15.89)	10.64 (8.37 to 13.53)
Day 42	18.3 (14.3 to 23.5)	12.48 (9.9 to 15.73)	20 (15.4 to 26)	14.7 (11.6 to 18.7)

## Statistical analyses

No statistical analyses for this end point

### **Primary: Summary of Geometric Mean Titers Ratios Antibody (Ab) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain In Subjects with Undetectable Ab After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Summary of Geometric Mean Titers Ratios Antibody (Ab) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain In Subjects with Undetectable Ab After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[14]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	146	123	125
Units: Titer ratios				
geometric mean (confidence interval 95%)				
Day 21/Day 0	2.01 (1.64 to 2.48)	2.07 (1.66 to 2.57)	3.01 (2.3 to 3.93)	2.66 (2.09 to 3.38)
Day 42/Day 21	2.29 (1.88 to 2.79)	1.5 (1.31 to 1.72)	1.64 (1.37 to 1.95)	1.38 (1.21 to 1.58)
Day 42/Day 0	4.58 (3.58 to 5.87)	3.12 (2.47 to 3.93)	4.96 (3.82 to 6.45)	3.68 (2.89 to 4.68)

## Statistical analyses

No statistical analyses for this end point

### **Primary: Percentage of Subjects with Undetectable Antibody Achieving Antibody titers <8 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects with Undetectable Antibody Achieving Antibody titers <8 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[15]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 and Day 42 post-vaccination

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	146	123	125
Units: Percentage of subjects				
number (not applicable)				
Day 0	100	100	100	100
Day 21	73.6	74	60.2	59.2
Day 42	44.1	55.2	40.3	45.6

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects with Undetectable Antibody (Ab) Achieving Seroconversion/Significant Increase in Ab Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Inactivated Split-Virion, Influenza Vaccine

End point title	Percentage of Subjects with Undetectable Antibody (Ab) Achieving Seroconversion/Significant Increase in Ab Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Inactivated Split-Virion, Influenza Vaccine <sup>[16]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method. Seroconversion (for subjects with a titer <10 [turkey] or <8 [horse] [1/dil] on Day 0: post-injection titer ≥40 [turkey] or ≥32 [horse] [1/dil]), or significant increase (for subjects with a titer ≥10 [turkey] or ≥8 [horse] [1/dil]: ≥four-fold increase of the titer) at Day 21 and Day 42.

End point type	Primary
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End point timeframe:

Day 21 and Day 42 post-vaccination

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	146	123	125
Units: Percentage of subjects				
number (not applicable)				
Day 21	18.9	20.5	31.7	24.8
Day 42	44.8	32.4	49.2	36

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers (GMTs) of Neuraminidase Assay - Anti-neuraminidase Antibody Against A/Vietnam/1194/2004 (H5N1)\_RG14 Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers (GMTs) of Neuraminidase Assay - Anti-neuraminidase Antibody Against A/Vietnam/1194/2004 (H5N1)_RG14 Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[17]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the neuraminidase assay.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 42 post-vaccination

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	21	16	15
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	6.51 (4.45 to 9.52)	6.3 (4.64 to 8.54)	7.97 (5.15 to 12.33)	11.05 (5.49 to 22.26)
Day 42	7.33 (4.58 to 11.73)	7.66 (5.24 to 11.19)	11.77 (6.49 to 21.32)	13.77 (6.3 to 30.12)

## Statistical analyses

No statistical analyses for this end point

### Primary: Summary of Geometric Mean Titers Assayed by HI Horse Erythrocyte Method of Neuraminidase Assay - Anti-neuraminidase Antibody Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Vaccination with Inactivated

## Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers Assayed by HI Horse Erythrocyte Method of Neuraminidase Assay - Anti-neuraminidase Antibody Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain After Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[18]</sup>
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### End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.

End point type	Primary
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### End point timeframe:

Day 0 (pre-vaccination) and Day 21, Day 42, and Day 180 post-vaccination

### Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	149
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	4.14 (3.98 to 4.31)	4.15 (3.97 to 4.34)	5.51 (4.84 to 6.29)	6.17 (5.2 to 7.32)
Day 21	8.61 (6.92 to 10.72)	8.76 (7 to 10.97)	18.7 (14 to 25)	16.6 (12.6 to 21.7)
Day 42	19.4 (15.1 to 24.9)	13 (10.3 to 16.4)	28.9 (22.1 to 37.9)	21.4 (16.5 to 27.8)
Day 180	5.99 (5.33 to 6.73)	5.43 (4.85 to 6.08)	9.42 (7.78 to 11.42)	7.63 (6.41 to 9.08)

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects with Antibody titers <32 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Percentage of Subjects with Antibody titers <32 (1/dil) Assayed by HI Horse Erythrocytes Method Against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[19]</sup>
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### End point description:

Influenza vaccine antibodies were assessed using the hemagglutination inhibition using horse erythrocytes method.

End point type	Primary
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### End point timeframe:

Day 0 (pre-vaccination) and Day 21, Day 42, and Day 180 post-vaccination

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	149
Units: Percentage of subjects				
number (not applicable)				
Day 0	1.3	1.3	6	12.8
Day 21	20.5	22.1	42.5	36.7
Day 42	45.9	33.8	57.1	45.6
Day 180	6.2	6.2	18.9	14.4

## Statistical analyses

No statistical analyses for this end point

## Primary: Summary of Geometric Mean Titers (GMTs) Assayed by Seroneutralization Method – Neutralizing Antibody Against A/Vietnam (H5N1) Strains Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Summary of Geometric Mean Titers (GMTs) Assayed by Seroneutralization Method – Neutralizing Antibody Against A/Vietnam (H5N1) Strains Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[20]</sup>
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End point description:

Influenza vaccine antibodies were assessed using the seroneutralization method. [Day 0 to Day 42]: Neutralizing Antibody (1/dil) against A/Vietnam/1194/2004/NIBRG-14 (H5N1) Strain and [Day 180 to Day 201]: Neutralizing Antibody (1/dil) against rg A/Vietnam/1203/2004 (H5N1) Strain.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21, Day 42, and Day 180 post-vaccination

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0	10.09 (9.99 to 10.2)	10.22 (9.89 to 10.55)	10.9 (10.3 to 11.6)	11.8 (10.8 to 13)
Day 21	12.8 (11.5 to 14.2)	12.5 (11.3 to 13.9)	20 (16.7 to 24)	16.6 (14.2 to 19.5)
Day 42	20.7 (17.9 to 23.9)	15.6 (13.8 to 17.7)	23.4 (19.6 to 27.8)	17.6 (15 to 20.6)

Day 180	12.4 (11.3 to 13.5)	12.2 (11 to 13.5)	17.9 (15 to 21.4)	14.7 (12.5 to 17.3)
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## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions within 7 Days After Each Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions within 7 Days After Each Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[21]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 up to Day 7 post- each vaccination

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain (Post-injection 1)	49	26.8	17.3	4.7
Injection site Erythema (Post-injection 1)	13.9	10.7	4.7	5.3
Injection site Swelling (Post-injection 1)	11.3	4	0.7	1.3
Injection site Induration (Post-injection 1)	14.6	8.1	3.3	4.7
Injection site Ecchymosis (Post-injection 1)	4.6	6.7	1.3	4.7
Fever (Post-injection 1)	2	0.7	1.3	2
Headache (Post-injection 1)	29.1	29.5	12.7	15.3
Malaise (Post-injection 1)	11.9	16.1	8.7	10.7
Myalgia (Post-injection 1)	17.2	16.1	10	11.3
Shivering (Post-injection 1)	7.3	6	4.7	4
Injection site Pain (Post-injection 2)	31.1	18.8	19.3	9.4
Injection site Erythema (Post-injection 2)	12.8	10.1	4	4.7
Injection site Swelling (Post-injection 2)	8.8	1.3	1.3	1.3
Injection site Induration (Post-injection 2)	5.4	7.4	2	1.3
Injection site Ecchymosis (Post-injection 2)	6.1	2	3.3	1.3
Fever (Post-injection 2)	2	1.3	5.3	2.7



Headache (Post-injection 2)	18.9	22.1	11.3	12.8
Malaise (Post-injection 2)	10.8	6.7	6.7	8.1
Myalgia (Post-injection 2)	12.2	9.4	9.3	10.1
Shivering (Post-injection 2)	0.7	2.7	2.7	2.7

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects with at Least One Reaction Within 3 Days after Any Vaccine Injection Listed in the EMEA Note for Guidance Strains Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Percentage of Subjects with at Least One Reaction Within 3 Days after Any Vaccine Injection Listed in the EMEA Note for Guidance Strains Following Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[22]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 up to Day 3 post-each vaccination

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	151	149	150	150
Units: Percentage of subjects				
number (not applicable)				
Inj. site Induration >5cm for >3 days	0	0	0	0
Inj. site Induration >5cm for >3 days; Post-inj. 1	0	0	0	0
Inj. site Induration >5cm for >3 days; Post-inj. 2	0	0	0	0
Inj. site Ecchymosis (Hemorrhage)	9.9	8.1	4.7	5.3
Inj. site Ecchymosis (Hemorrhage); Post-inj. 1	4.6	6.7	1.3	4
Inj. site Ecchymosis (Hemorrhage); Post-inj. 2	6	1.3	3.3	1.3
Fever (rectal temp. >38°C) for ≥24 hr	2.6	0.7	3.3	0.7
Fever (rectal temp. >38°C) for ≥24 hr; Post-inj. 1	2	0.7	1.3	0.7
Fever (rectal temp. >38°C) for ≥24 hr; Post-inj. 2	1.3	0	2.7	0
Malaise	13.2	16.1	10	14.7
Malaise; Post-inj. 1	8.6	13.4	6.7	9.3
Malaise; Post-inj. 2	5.3	4	4.7	6.7
Shivering	5.3	7.4	5.3	4
Shivering; Post-inj. 1	5.3	6	4	2.7

Shivering; Post-inj. 2	0.7	2	2	2
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## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions Within 7 Days after Clade 1 A/Vietnam Booster Vaccine Injection Following Primary Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reactions Within 7 Days after Clade 1 A/Vietnam Booster Vaccine Injection Following Primary Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[23]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 up to Day 7 post-vaccination

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	39	41	36
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	28.9	20.5	7.3	8.3
Injection site Erythema	13.2	12.8	0	2.8
Injection site Swelling	2.6	0	0	5.6
Injection site Induration	2.6	7.7	0	0
Injection site Ecchymosis	0	0	2.4	0
Fever	2.6	0	2.4	2.8
Headache	18.4	17.9	9.8	13.9
Malaise	7.9	5.1	2.4	2.8
Myalgia	7.9	5.1	4.9	5.6
Shivering	5.3	0	0	0

## Statistical analyses

No statistical analyses for this end point

**Primary: Percentage of Subjects with at least one Reaction within 3 Days after the Clade 1 A/Vietnam Booster Vaccine Injection Listed in the EMEA Note for Guidance Following Primary Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine**

End point title	Percentage of Subjects with at least one Reaction within 3 Days after the Clade 1 A/Vietnam Booster Vaccine Injection Listed in the EMEA Note for Guidance Following Primary Vaccination with Inactivated Split-Virion, Pandemic Influenza Vaccine <sup>[24]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Day 0 up to Day 3 post-vaccination

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

<b>End point values</b>	18-60 years 30µg+Adjuvant	18-60 years 7.5µg	>60 years 30µg+Adjuvant	>60 years 7.5µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	39	41	36
Units: Percentage of subjects				
number (not applicable)				
Injection site Induration >5cm for >3 days	0	0	0	0
Injection site Ecchymosis (Hemorrhage)	0	0	2.4	0
Fever (rectal temperature >38°C) ≥24 hr	2.6	0	2.4	2.8
Malaise	5.3	2.6	2.4	2.8
Shivering (Chills)	0	0	0	0

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post vaccination) up to Day 7 post 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	18-60 years 30µg+Ad
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Reporting group description:

Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.

Reporting group title	18-60 years 7.5µg
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Reporting group description:

Subjects aged 18-60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA] ) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.

Reporting group title	>60 years 30µg+Ad
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Reporting group description:

Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 30µg anti-hemagglutination [HA]) with aluminum hydroxide adjuvant 21 days apart as primary series and a booster vaccination at either 6 months (A/Vietnam 7.5µg HA) or 22 months (A/Indonesia 30µg HA plus adjuvant) after the first vaccination or no booster vaccination.

Reporting group title	>60 years 7.5µg
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Reporting group description:

Subjects aged >60 years of age who received two doses of A/H5N1 inactivated, split-virion influenza virus (A/Vietnam 7.5µg anti-hemagglutination [HA] ) without adjuvant 21 days apart as primary series and a booster vaccination at 6 months (A/Vietnam 7.5µg HA) after the first vaccination or no booster at 22 months.

Serious adverse events	18-60 years 30µg+Ad	18-60 years 7.5µg	>60 years 30µg+Ad
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)	0 / 149 (0.00%)	0 / 150 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	>60 years 7.5µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 150 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

<b>Non-serious adverse events</b>	18-60 years 30µg+Ad	18-60 years 7.5µg	>60 years 30µg+Ad
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 151 (49.01%)	44 / 149 (29.53%)	29 / 150 (19.33%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	44 / 151 (29.14%)	44 / 149 (29.53%)	19 / 150 (12.67%)
occurrences (all)	44	44	19
General disorders and administration site conditions			
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed <sup>[1]</sup>	74 / 151 (49.01%)	40 / 149 (26.85%)	29 / 150 (19.33%)
occurrences (all)	74	40	29
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 151 (13.91%)	16 / 149 (10.74%)	7 / 150 (4.67%)
occurrences (all)	21	16	7
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 151 (11.26%)	6 / 149 (4.03%)	2 / 150 (1.33%)
occurrences (all)	17	6	2
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 151 (14.57%)	12 / 149 (8.05%)	5 / 150 (3.33%)
occurrences (all)	22	12	5
Injection site ecchymosis			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 151 (9.93%)	12 / 149 (8.05%)	7 / 150 (4.67%)
occurrences (all)	15	12	7

Fever alternative assessment type: Systematic subjects affected / exposed <sup>[2]</sup> occurrences (all)	3 / 148 (2.03%) 3	2 / 149 (1.34%) 2	8 / 150 (5.33%) 8
Malaise alternative assessment type: Systematic subjects affected / exposed occurrences (all)	20 / 151 (13.25%) 20	24 / 149 (16.11%) 24	15 / 150 (10.00%) 15
Shivering alternative assessment type: Systematic subjects affected / exposed occurrences (all)	11 / 151 (7.28%) 11	11 / 149 (7.38%) 11	8 / 150 (5.33%) 8
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	26 / 151 (17.22%) 26	24 / 149 (16.11%) 24	15 / 150 (10.00%) 15

<b>Non-serious adverse events</b>	>60 years 7.5µg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 150 (15.33%)		
Nervous system disorders			
Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)	23 / 150 (15.33%) 23		
General disorders and administration site conditions			
Injection site pain alternative assessment type: Systematic subjects affected / exposed <sup>[1]</sup> occurrences (all)	14 / 149 (9.40%) 14		
Injection site erythema alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 150 (5.33%) 8		

Injection site swelling alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 150 (1.33%) 2		
Injection site induration alternative assessment type: Systematic subjects affected / exposed occurrences (all)	7 / 150 (4.67%) 7		
Injection site ecchymosis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 150 (5.33%) 8		
Fever alternative assessment type: Systematic subjects affected / exposed <sup>[2]</sup> occurrences (all)	4 / 149 (2.68%) 4		
Malaise alternative assessment type: Systematic subjects affected / exposed occurrences (all)	22 / 150 (14.67%) 22		
Shivering alternative assessment type: Systematic subjects affected / exposed occurrences (all)	6 / 150 (4.00%) 6		
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	17 / 150 (11.33%) 17		

Notes:

[1] - 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 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.

[2] - 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 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
16 February 2006	Clarification of the timing and type of booster; inclusion of additional subjects aged 18 to 60 years to receive two administrations of the new vaccine strain (Clade 2 A/Indonesia) in order to assess the priming immunogenicity response to this strain and the concomitant production other randomization lists for the Clade 2 A/Indonesia vaccinations and an increase of planned sample size for the analysis; Ethnicity and seasonal influenza vaccination history added to the CRF; Deletion of the Single Radial Hemolysis (SRH) analysis method.
06 September 2006	Modification of the timing of the 12-month (Clade 2 A/Indonesia) booster vaccination and the timing of the assessment for 12-month Antibody persistence.
20 April 2007	Determination of the timing of the Clade 2 A/Indonesia booster in a subset of subjects primed with the 30µgHA+aluminum hydroxide vaccine; Modification of the design of the study regarding the administration of the booster, and the additional subjects included at the time of the Clade 2 A/Indonesia booster; addition of an additional visit 7 days after the Clade 2 A/Indonesia booster for immunogenicity assessment and elimination of the CMI evaluation after booster with the A/Indonesia strain.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported