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Study No.: 108251; 108252; 111275
Title: A phase II, randomised, open study to evaluate the immunogenicity and safety of a single or double-dose of the pandemic influenza candidate vaccine given in a two-administration schedule (21 days apart) in adults over 60 years of age.
Rationale: The present study was designed to evaluate the immunogenicity and safety of a single or double dose of pandemic influenza (H5N1) vaccine, for healthy adults over 60 years of age. Subjects who had not been vaccinated with an influenza vaccine for the 2006-2007 season received <i>Fluarix</i> TM at least 3 weeks before administration of the first dose(s) of the H5N1 vaccine. The persistence of H5N1 influenza antibodies was also evaluated up to two years after vaccination. H5N1 vaccine: GlaxoSmithKline (GSK) Biologicals' pandemic monovalent influenza vaccine. <i>Fluarix</i> TM (Flu): GSK Biologicals' seasonal influenza split vaccine Results up to Month 12 are presented in this document. This summary will be updated when additional data (Month 24) become available.
Phase: II
Study Period: 108251: 17 November 2006 to 27 October 2007. 108252: 14 June 2007 to 05 March 2008. 111275: 06 March 2008 to 12 September 2008
Study Design: Multi-centre, randomised (3:1:3:1), open study with 4 groups. Data from the group receiving the currently registered vaccine are presented. Data from the investigational vaccination regimens, which are not approved or marketed, are not reported.
Centres: 108251: 12 study centres: 7 in Belgium and 5 in Italy. 108252: 12 study centres: 7 in Belgium and 5 in Italy. 111275: 7 study centres in Belgium
Indication: Immunisation against influenza disease during a pandemic in subjects over 60 years of age.
Treatment: All subjects received 2 administrations of the vaccine. The study groups were as follows: <ul style="list-style-type: none"> • 2 groups received investigational H5N1 formulations. • H5N1 Group: received a single dose of H5N1 vaccine intramuscularly in the deltoid region of the non-dominant arm at Days 0 and 21. • Double H5N1 Group: received a double dose of the H5N1 vaccine intramuscularly in the deltoid region of each arm at Days 0 and 21 Subjects not previously vaccinated with an influenza vaccine for the 2006-2007 season were administered Flu vaccine intramuscularly at least 3 weeks before administration of the first dose(s) of the H5N1 vaccine.
Objectives: <i>Only objectives related to the licensed vaccine are presented.</i> <ul style="list-style-type: none"> • To evaluate the immunogenicity of the H5N1 vaccine administered as a single or double dose in terms of humoral immune response 21 days after the first and second vaccination (for anti-haemagglutinin [anti-HA] antibody response) and 21 days after the second vaccination (for neutralising antibody response). • To assess the persistence of antibodies 180 days, one year and two years after the first vaccination with the H5N1 vaccine.
Primary Outcome/Efficacy Variable: <i>Only outcome variables related to the licensed vaccine are presented.</i> <i>Immunogenicity</i> For the humoral immune response in terms of H5N1 haemagglutination-inhibition (HI) antibodies, the following parameters (with 95% confidence intervals [CIs]) were calculated: <ul style="list-style-type: none"> • Geometric mean titres (GMTs) of H5N1 antibody titres at Days 0, 21, 42 and 180 for all subjects and in addition, Month 12 and Month 24[#] for subjects in Belgium. • Seroconversion rates*[§] (SCR) at Days 21, 42 and 180 for all subjects and in addition, Month 12 and Month 24[#] for subjects in Belgium. • Seroconversion factors** (SCF) at Days 21, 42 and 180 for all subjects and in addition, Month 12 and Month 24[#] for subjects in Belgium.

- Seroprotection rates*** (SPR) at Days 0, 21, 42 and 180 for all subjects and in addition, Month 12 and Month 24# for subjects in Belgium.

In addition, humoral immune response in terms of neutralising antibodies was evaluated in a subset of subjects using the following parameters (with 95% CIs):

- GMTs of H5N1 antibody titres at Days 0, 42 and 180 and in addition, Month 12 and Month 24# for subjects in Belgium.
- SCR*§ at Days 42 and 180 and in addition, Month 12 and Month 24# for subjects in Belgium.

* SCR for H5N1 HI antibodies response was defined as the percentage of vaccinees who had either a pre-vaccination titre < 1:10 and a post-vaccination titre \geq 1:40 or a pre-vaccination titre \geq 1:10 and at least a 4-fold increase in post-vaccination titre.

**SCF was defined as the fold increase in serum H5N1 HI antibodies GMTs post-vaccination compared to Day 0.

***SPR was defined as the percentage of vaccinees with a serum H5N1 HI antibodies titre \geq 1:40 that usually was accepted as indicating protection.

§ SCR for neutralising antibody response was defined as the percentage of vaccinees with a minimum 4-fold increase in neutralising antibody titre at post-vaccination.

#Data for Month 24 were not available when this summary was posted. This summary will be updated when the data become available.

Secondary Outcome/Efficacy Variables:

Only outcome variables related to the licensed vaccine are presented.

Safety

- Percentage, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 7-day follow-up period (Day 0-6) after each dose of the H5N1 vaccine and overall.
- Percentage, intensity and relationship to vaccination of unsolicited local and general signs and symptoms during the 21 days following the first vaccination with the H5N1 vaccine (Day 0-20) and during the 30 days following the second vaccination (Day 0-29).
- Occurrence of serious adverse events (SAEs) during the entire study period.
- Occurrence of adverse events of specific interest (AESIs) during the entire study (for subjects in Belgium) #.
- Number and percentage of subjects with normal or abnormal values at each scheduled time point (Day 0, Day 2, Day 21, Day 23), for biochemical assessments and for haematological analysis.

Immunogenicity

For the cell-mediated immunity (CMI) response evaluation:

The following parameters (with 95% CIs) were calculated at Days 0, 21, 42 and 180 for all subjects and in addition, Month 12 and Month 24# for subjects in Belgium:

- Frequency of influenza-specific Cluster of Differentiation (CD) 4/CD8 T-cells per 10^6 in tests producing at least two different cytokines (CD40 ligand [CD40L], interleukin-2 [IL-2], tumour necrosis factor-alpha [TNF- α], interferon-gamma [IFN- γ]).
- Frequency of influenza-specific CD4/CD8 T-cells per 10^6 in tests producing at least CD40L and another signal molecule (IL-2, IFN- γ , TNF- α).
- Frequency of influenza-specific CD4/CD8 T-cells per 10^6 in tests producing at least IL-2 and another signal molecule (CD40L, IFN- γ , TNF- α).
- Frequency of influenza-specific CD4/CD8 T-cells per 10^6 in tests producing at least TNF- α and another signal molecule (IL-2, IFN- γ , CD40L).
- Frequency of influenza-specific CD4/CD8 T-cells per 10^6 in tests producing at least IFN- γ and another signal molecule (CD40L, IL-2, TNF- α).

#Data for Month 24 or covering the entire study period were not available when this CTRS was posted. This summary will be updated when the data become available.

Statistical Methods:

The analyses were performed on the Total Vaccinated Cohort, the According-To-Protocol (ATP) cohort for immunogenicity and the ATP cohort for persistence.

- The Total Vaccinated Cohort included all vaccinated subjects for whom data were available.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom immunogenicity data were available. This included all subjects for whom assay results for antibodies against at least one study vaccine antigen component after vaccination were available.
- The ATP cohort for analysis of persistence included all evaluable subjects who met all eligibility criteria, who complied

with the protocol procedures during the entire study period and with the intervals defined in the protocol for visit at each time point, who did not meet the elimination criteria during the study, for whom data concerning persistence were available. This included all subjects for whom assay results for antibodies against at least one study vaccine antigen component at each time point were available.

Analysis of immunogenicity:

The analysis was performed on the ATP cohort for immunogenicity and the ATP cohort for persistence.

Descriptive analysis:

For the humoral immune response in terms of H5N1 HI antibodies, the GMTs of H5N1 HI antibodies and SPR at Days 0, 21, 42, 180 and Month 12, the SCR and SCF at Days 21, 42, 180 and Month 12 with their 95% CIs were calculated for each group. For the humoral immune response in terms of neutralising antibodies, the GMTs of H5N1 HI antibodies at Days 0, 42, 180 and Month 12 and SCR at Days 42, 180 and Month 12 were evaluated in a subset of subjects in each vaccine group with 95% CI. Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation. The frequency of influenza-specific CD4/CD8 T lymphocytes cells was summarised (descriptive statistics) for each vaccine group at Days 0, 21, 42, 180 and Month 12.

Analysis of safety

The analysis was based on the Total Vaccinated Cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the 7-day (Day 0-6) solicited follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The number and proportion of subjects with normal or abnormal values for each haematology and biochemistry parameter was tabulated for each study group at each scheduled time point. The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported up to 21 days after the first vaccination with H5N1 vaccine and 30 days after the second vaccination was tabulated. The same tabulation was performed for grade 3 AEs and for AEs with a relationship to vaccination. The Occurrence of SAEs during the study period (up to Month 12) was tabulated according to MedDRA preferred terms.

Study Population: Healthy male or female subjects aged 61 years and above at the time of first vaccination were enrolled in the study. Written informed consent was obtained from the subjects prior to study entry.

Number of Subjects:	H5N1 Group	Double H5N1 Group
Planned, N	180	180
Randomised, N (Total Vaccinated Cohort)	165	159
Completed, n (%)	158 (96.0)	153 (96.2)
Total Number Subjects Withdrawn, n (%)	7 (4.2)	6 (3.8)
Withdrawn due to Adverse Events n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable	Not Applicable
Withdrawn for other reasons n (%)	7 (4.2)	6 (3.8)
Demographics	H5N1 Group	Double H5N1 Group
N,(Total Vaccinated Cohort)	165	159
Females: Males	72:93	77:82
Mean Age, years (SD)	69.7 (6.33)	69.7 (6.51)
White-Caucasian/European heritage, n (%)	163 (98.8)	151 (95.0)
Number of subjects at Day 180	H5N1 Group	Double H5N1 Group
Planned, N	164	158
Entered, N (Total Vaccinated Cohort)	164	158
Completed, n (%)	162 (98.8)	153 (96.8)
Total Number Subjects Withdrawn, n (%)	2 (1.2)	5 (3.2)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	2 (1.3)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	2 (1.2)	3 (1.9)
Demographics	H5N1 Group	Double H5N1 Group
N (Total Vaccinated Cohort)	164	158
Females: Males	72:92	74:84
Mean Age, years (SD)	69.7 (6.37)	69.6 (6.54)
Missing race, n (%)	164 (100)	158 (100)

Number of subjects at Month 12		H5N1 Group		Double H5N1 Group						
Planned, N		130		125						
Entered, N (Total Vaccinated Cohort)		130		125						
Completed, n (%)		130 (100)		125 (100)						
Total Number Subjects Withdrawn, n (%)		0 (0.0)		0 (0.0)						
Withdrawn due to Adverse Events, n (%)		0 (0.0)		0 (0.0)						
Withdrawn due to Lack of Efficacy, n (%)		Not applicable		Not applicable						
Withdrawn for other reasons, n (%)		0 (0.0)		0 (0.0)						
Demographics		H5N1 Group		Double H5N1 Group						
N (Total Vaccinated Cohort)		130		125						
Females: Males		58:72		63:62						
Mean Age, years (SD)		69.4 (6.67)		69.5 (6.43)						
White - Caucasian / European heritage, n (%)		128 (98.5)		118 (94.4)						
Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of H5N1 HI antibodies against the vaccine strain A/Vietnam/1194/2004 (ATP cohort for immunogenicity)										
Group	Timing	N	≥ 1: 10				GMT			
			n	%	95% CI		value	95% CI		
					LL	UL		LL	UL	
H5N1	PRE	152	62	40.8	32.9	49.0	11.3	9.2	13.9	
	PI(D21)	152	122	80.3	73.0	86.3	50.0	38.1	65.6	
	PII(D42)	152	142	93.4	88.2	96.8	126.8	99.4	161.7	
Double H5N1	PRE	145	52	35.9	28.1	44.2	10.2	8.4	12.5	
	PI(D21)	145	130	89.7	83.5	94.1	69.4	52.1	92.3	
	PII(D42)	145	142	97.9	94.1	99.6	237.3	191.9	293.6	
N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range 95% CI = 95% confidence interval, LL = Lower Limit; UL = Upper Limit PRE = Pre-vaccination at Day 0 PI (D21) = Post-vaccination at Day 21 PII (D42) = Post-vaccination at Day 42										
Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of H5N1 HI antibodies against the A/Indonesia/5/2005 strain (ATP cohort for immunogenicity)										
Group	Timing	N	≥ 1: 10				GMT			
			n	%	95% CI		value	95% CI		
					LL	UL		LL	UL	
H5N1	PRE	152	2	1.3	0.2	4.7	5.1	5.0	5.1	
	PI(D21)	152	36	23.7	17.2	31.3	6.9	6.2	7.7	
	PII(D42)	152	83	54.6	46.3	62.7	13.7	11.3	16.4	
Double H5N1	PRE	145	4	2.8	0.8	6.9	5.1	5.0	5.2	
	PI(D21)	145	48	33.1	25.5	41.4	8.6	7.3	10.1	
	PII(D42)	145	108	74.5	66.6	81.4	24.4	19.9	30.0	
N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range 95% CI = 95% confidence interval, LL = Lower Limit; UL = Upper Limit PRE = Pre-vaccination at Day 0 PI (D21) = Post-vaccination at Day 21 PII (D42) = Post-vaccination at Day 42										
Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 0 and Day 180 (ATP cohort for persistence)										
Antibodies against	Group	Timing	N	≥ 1: 10				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1	PRE	142	58	40.8	32.7	49.4	11.6	9.4	14.3
		PII(D180)	140	107	76.4	68.5	83.2	38.5	30.0	49.5
	Double	PRE	135	48	35.6	27.5	44.2	10.0	8.2	12.3

	H5N1	PII(D180)	131	113	86.3	79.2	91.6	53.5	41.9	68.4
A/Indonesia/5/2005	H5N1	PRE	142	3	2.1	0.4	6.0	5.1	5.0	5.2
		PII(D180)	140	30	21.4	14.9	29.2	6.6	6.0	7.3
	Double H5N1	PRE	135	3	2.2	0.5	6.4	5.1	5.0	5.2
		PII(D180)	131	54	41.2	32.7	50.2	8.6	7.5	9.9
<p>N = Number of subjects with available results n/% = number/percentage of seropositive subjects (HI titre \geq 1:10) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Post vaccination at Day 0 PII(D180) = Post-vaccination at Day 180</p>										
Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 0 and Month 12 (ATP cohort for persistence)										
Antibodies against	Group	Timing	N	\geq 1: 10				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1	PRE	112	43	38.4	29.4	48.1	11.6	9.0	15.0
		PII(M12)	112	67	59.8	50.1	69.0	21.4	16.4	28.0
	Double H5N1	PRE	105	39	37.1	27.9	47.1	10.9	8.5	14.0
		PII(M12)	106	81	76.4	67.2	84.1	26.5	20.3	34.6
A/Indonesia/5/2005	H5N1	PRE	112	3	2.7	0.6	7.6	5.1	5.0	5.3
		PII(M12)	112	43	38.4	29.4	48.1	9.8	8.2	11.7
	Double H5N1	PRE	105	3	2.9	0.6	8.1	5.1	5.0	5.3
		PII(M12)	106	61	57.5	47.6	67.1	13.1	10.9	15.8
<p>N = Number of subjects with available results n/% = number/percentage of seropositive subjects (HI titre \geq 1:10) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Post vaccination at Day 0 PII(M12) = Post-vaccination at Month 12</p>										
Primary Outcome/Efficacy Variable: SCR for H5N1 HI antibodies against A/Vietnam /1194/2004 and A/Indonesia/5/2005 strains at each post-vaccination at Day 21 and Day 42 (ATP cohort for immunogenicity)										
Antibodies against	Group	Timing	N	SCR						
				n	%	95% CI				
						LL	UL			
A/Vietnam/1194/2004	H5N1	PI(D21)	152	69	45.4	37.3	53.7			
		PII(D42)	152	110	72.4	64.5	79.3			
	Double H5N1	PI(D21)	145	76	52.4	44.0	60.8			
		PII(D42)	145	128	88.3	81.9	93.0			
A/Indonesia/5/2005	H5N1	PI(D21)	152	5	3.3	1.1	7.5			
		PII(D42)	152	35	23.0	16.6	30.5			
	Double H5N1	PI(D21)	145	13	9.0	4.9	14.8			
		PII(D42)	145	58	40.0	32.0	48.5			
<p>N = number of subjects with available results PI(D21) = Post vaccination at Day 21 PII(D42) = Post vaccination at Day 42 n (%) =number (percentage) of subjects with either a pre-vaccination titre <1:10 and post-vaccination titre \geq1:40 or a pre-vaccination titre \geq1:10 and a minimum 4-fold increase in post-vaccination titre 95% confidence interval, LL= Lower Limit, UL= Upper Limit</p>										
Primary Outcome/Efficacy Variable: SCR for H5N1 HI antibodies against A/Vietnam /1194/2004 and A/Indonesia/5/2005 strains at post-vaccination Day 180 (ATP cohort for persistence)										
Antibodies against	Group	Timing	N	SCR						
				n	%	95% CI				
						LL	UL			
A/Vietnam/1194/2004	H5N1	PII(D180)	140	52	37.1	29.1	45.7			
	Double H5N1	PII(D180)	130	70	53.8	44.9	62.6			
A/Indonesia/5/2005	H5N1	PII(D180)	140	5	3.6	1.2	8.1			

	Double H5N1	PII(D180)	130	8	6.2	2.7	11.8
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre $\geq 1:40$ after vaccination For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D180) = Post-vaccination at Day 180</p>							
<p>Primary Outcome/Efficacy Variable: SCR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at post-vaccination Month 12 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PII(M12)	112	24	21.4	14.2	30.2
	Double H5N1	PII(M12)	105	24	22.9	15.2	32.1
A/Indonesia/5/2005	H5N1	PII(M12)	112	17	15.2	9.1	23.2
	Double H5N1	PII(M12)	105	22	21.0	13.6	30.0
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre $\geq 1:40$ after vaccination For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M12) = Post-vaccination at Month 12</p>							
<p>Primary Outcome/Efficacy Variable: SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strain (ATP cohort for immunogenicity)</p>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1	PI(D21)	152	4.4	3.5	5.5	
		PII(D42)	152	11.2	8.9	14.1	
	Double H5N1	PI(D21)	145	6.8	5.3	8.6	
		PII(D42)	145	23.2	18.5	29.0	
A/Indonesia/5/2005	H5N1	PI(D21)	152	1.4	1.2	1.5	
		PII(D42)	152	2.7	2.2	3.2	
	Double H5N1	PI(D21)	145	1.7	1.4	2.0	
		PII(D42)	145	4.8	3.9	5.9	
<p>N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range PRE =Pre-vaccination PI(D21) = Post vaccination at Day 21 PII(D42) = Post vaccination at Day 42 95% confidence interval, LL= Lower Limit, UL= Upper Limit</p>							
<p>Primary Outcome/Efficacy Variable: SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at post-vaccination Day 180 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1	PII(D180)	140	3.3	2.7	4.0	
	Double H5N1	PII(D180)	130	5.4	4.4	6.7	
A/Indonesia/5/2005	H5N1	PII(D180)	140	1.3	1.2	1.4	
	Double H5N1	PII(D180)	130	1.7	1.5	1.9	
<p>N = Number of subjects with pre- and post-vaccination results available PII(D180) = Post-vaccination at Day 180 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit</p>							

Primary Outcome/Efficacy Variable: SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at post-vaccination Month 12 (ATP cohort for persistence)							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1	PII(M12)	112	1.8	1.5	2.2	
	Double H5N1	PII(M12)	105	2.5	2.0	3.0	
A/Indonesia/5/2005	H5N1	PII(M12)	112	1.9	1.6	2.3	
	Double H5N1	PII(M12)	105	2.6	2.2	3.1	
N = Number of subjects with pre- and post-vaccination results available PII(M12) = Post-vaccination at Month 12 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit							
Primary Outcome/Efficacy Variable: SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strain (ATP cohort for immunogenicity)							
Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PRE	152	28	18.4	12.6	25.5
		PI(D21)	152	93	61.2	53.0	69.0
		PII(D42)	152	127	83.6	76.7	89.1
	Double H5N1	PRE	145	23	15.9	10.3	22.8
		PI(D21)	145	90	62.1	53.6	70.0
		PII(D42)	145	139	95.9	91.2	98.5
A/Indonesia/5/2005	H5N1	PRE	152	0	0.0	0.0	2.4
		PI(D21)	152	5	3.3	1.1	7.5
		PII(D42)	152	35	23.0	16.6	30.5
	Double H5N1	PRE	145	0	0.0	0.0	2.5
		PI(D21)	145	13	9.0	4.9	14.8
		PII(D42)	145	59	40.7	32.6	49.2
N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range PRE =Pre-vaccination PI(D21) = Post vaccination at Day 21 PII(D42) = Post vaccination at Day 42 95% confidence interval, LL= Lower Limit, UL= Upper Limit							
Primary Outcome/Efficacy Variable: SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 0 and Day 180 (ATP cohort for persistence)							
Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PRE	142	29	20.4	14.1	28.0
		PII(D180)	140	74	52.9	44.2	61.3
	Double H5N1	PRE	135	21	15.6	9.9	22.8
		PII(D180)	131	91	69.5	60.8	77.2
A/Indonesia/5/2005	H5N1	PRE	142	0	0.0	0.0	2.6
		PII(D180)	140	5	3.6	1.2	8.1
	Double H5N1	PRE	135	0	0.0	0.0	2.7
		PII(D180)	131	8	6.1	2.7	11.7
N = Number of subjects with available results n/% = Number/percentage of seroprotected subjects (HI titre \geq 1:40) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PII(D180) = Post-vaccination at Day 180							
Primary Outcome/Efficacy Variable: SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 0 and Month 12 (ATP cohort for persistence)							

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PRE	112	22	19.6	12.7	28.2
		PII(M12)	112	49	43.8	34.4	53.4
	Double H5N1	PRE	105	19	18.1	11.3	26.8
		PII(M12)	106	45	42.5	32.9	52.4
A/Indonesia/5/2005	H5N1	PRE	112	0	0.0	0.0	3.2
		PII(M12)	112	17	15.2	9.1	23.2
	Double H5N1	PRE	105	0	0.0	0.0	3.5
		PII(M12)	106	22	20.8	13.5	29.7

N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titre \geq 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0
PII(M12) = Post-vaccination at Month 12

Primary Outcome/Efficacy Variable: Seropositivity rates and geometric means titres (GMTs) of neutralising antibody titres against A/Indonesia/5/2005 strain at Days 0 and 42 (ATP cohort for immunogenicity)

Group	Timing	N	\geq 1: 28				GMT			
			n	%	95% CI		value	95% CI		
					LL	UL		LL	UL	
H5N1	PRE	87	57	65.5	54.6	75.4	44.2	36.0	54.1	
	PII(D42)	87	82	94.3	87.1	98.1	107.5	88.9	130.0	
Double H5N1	PRE	82	48	58.5	47.1	69.3	39.7	32.0	49.3	
	PII(D42)	82	82	100	95.6	100	169.6	144.7	198.9	

N = Number of subjects with available results
n (%) = number (percentage) of seropositive subjects (neutra titre \geq 1:28)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0
PII(D42) = Post-vaccination at Day 42

Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of neutralising antibody titres against A/Indonesia/5/2005 strain at Day 180 –for subset of elderly subjects (ATP cohort for persistence)

Antibodies against	Group	Timing	N	\geq 1: 28				GMT			
				n	%	95% CI		value	95% CI		
						LL	UL		LL	UL	
A/Indonesia/5/2005	H5N1	PRE	77	49	63.6	51.9	74.3	43.2	34.6	53.9	
		PII(D180)	76	72	94.7	87.1	98.5	97.8	82.0	116.5	
	Double H5N1	PRE	76	42	55.3	43.4	66.7	37.6	30.0	47.2	
		PII(D180)	73	72	98.6	92.6	100	134.5	113.4	159.7	

N = Number of subjects with available results
n/% = number/percentage of seropositive subjects (neutra titre \geq 1:28)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0
PII(D180) = Post-vaccination at Day 180

Primary Outcome/Efficacy Variable: Seropositivity rates and GMTs of neutralising antibody titres against A/Indonesia/5/2005 and A/Vietnam/1194/2004 strains at Month 12 –for subset of elderly subjects (ATP cohort for persistence)

Antibodies against	Group	Timing	N	\geq 1: 28				GMT			
				n	%	95% CI		value	95% CI		
						LL	UL		LL	UL	
A/Vietnam/1194/2004	H5N1	PRE	69	65	94.2	85.8	98.4	134.0	101.1	177.7	
		PII(M12)	69	69	100	94.8	100	274.7	213.4	353.5	
	Double H5N1	PRE	71	67	94.4	86.2	98.4	108.5	86.6	135.9	
		PII(M12)	71	71	100	94.9	100	268.8	211.4	341.8	
A/Indonesia/5/2005	H5N1	PRE	69	45	65.2	52.8	76.3	46.9	37.0	59.5	

		PII(M12)	69	58	84.1	73.3	91.8	82.5	63.0	107.9
	Double H5N1	PRE	71	38	53.5	41.3	65.5	36.2	28.6	45.7
		PII(M12)	71	65	91.5	82.5	96.8	119.8	94.0	152.7
<p>N = Number of subjects with available results n/% = number/percentage of seropositive subjects (neutra titre \geq 1:28) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PII(M12) = Post-vaccination at Month 12</p>										
<p>Primary Outcome/Efficacy Variable: SCR for neutralising antibody response against A/Indonesia/5/2005 strain at Day 42 (ATP cohort for immunogenicity)</p>										
Group	Timing	N	SCR							
			n	%	95% CI					
					LL	UL				
H5N1	PII(D42)	87	25	28.7	19.5	39.4				
Double H5N1	PII(D42)	82	40	48.8	37.6	60.1				
<p>SCR defined as: For initially seronegative subjects, antibody titre \geq 1:56 after vaccination; For initially seropositive subjects, antibody titre after vaccination \geq 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n (%) = number (percentage) of seroconverted subjects; 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PII(D42) = Post-vaccination 2 at Day 42</p>										
<p>Primary Outcome/Efficacy Variable: Seroconversion rate (SCR) for neutralising antibody response against A/Indonesia/5/2005 strain at Day 180 - for <i>subset of elderly subjects</i> (ATP cohort for persistence)</p>										
Antibodies against	Group	Timing	N	SCR						
				n	%	95% CI				
						LL	UL			
A/Indonesia/5/2005	H5N1	PII(D180)	76	20	26.3	16.9	37.7			
	Double H5N1	PII(D180)	73	32	43.8	32.2	55.9			
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre \geq 1:56 after vaccination For initially seropositive subjects, antibody titre after vaccination \geq 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D180) = Post-vaccination at Day 180</p>										
<p>Primary Outcome/Efficacy Variable: Seroconversion rate (SCR) for neutralising antibody response against A/Indonesia/5/2005 and A/Vietnam/1194/2004 strains at Month 12 - for <i>subset of elderly subjects</i> (ATP cohort for persistence)</p>										
Antibodies against	Group	Timing	N	SCR						
				n	%	95% CI				
						LL	UL			
A/Vietnam/1194/2004	H5N1	PII(M12)	69	18	26.1	16.3	38.1			
	Double H5N1	PII(M12)	71	21	29.6	19.3	41.6			
A/Indonesia/5/2005	H5N1	PII(M12)	69	13	18.8	10.4	30.1			
	Double H5N1	PII(M12)	71	28	39.4	28.0	51.7			
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre \geq 1:56 after vaccination For initially seropositive subjects, antibody titre after vaccination \geq 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M12) = Post-vaccination at Month 12</p>										
<p>Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per 10⁶) for CD4.CD40L, CD4.all doubles (T-cells producing at least 2 cytokines), CD4.IL-2, CD4.TNFα, CD4.INFγ stimulated by H5N1 A/Vietnam/1194/2004 strain (ATP cohort for immunogenicity)</p>										
Test description	Group	Timing	N	GM	Mean	SD				

CD4. all doubles	H5N1	PRE	129	393.71	620.14	590.66
		PI(D21)	112	1407.29	1845.30	1354.44
		PII(D42)	120	2260.19	3034.88	2242.14
	Double H5N1	PRE	122	495.77	670.50	606.84
		PI(D21)	110	1793.92	2315.24	1867.92
		PII(D42)	118	3049.03	4171.24	4208.17
CD4.CD40L	H5N1	PRE	129	388.69	604.88	571.91
		PI(D21)	112	1374.26	1782.67	1304.02
		PII(D42)	120	2198.66	2943.00	2165.46
	Double H5N1	PRE	122	485.71	655.20	594.88
		PI(D21)	110	1731.58	2247.71	1828.74
		PII(D42)	118	2971.34	4056.64	4076.52
CD4.IL-2	H5N1	PRE	129	376.03	571.24	545.75
		PI(D21)	112	1318.03	1716.82	1250.79
		PII(D42)	120	2086.84	2813.43	2086.66
	Double H5N1	PRE	122	461.23	609.22	552.91
		PI(D21)	110	1651.88	2146.25	1776.72
		PII(D42)	118	2762.65	3778.94	3720.42
CD4.INFγ	H5N1	PRE	129	270.99	459.03	500.13
		PI(D21)	112	685.44	1026.93	884.75
		PII(D42)	120	1123.16	1626.48	1356.18
	Double H5N1	PRE	122	343.35	505.50	549.24
		PI(D21)	110	997.15	1291.85	1023.96
		PII(D42)	118	1535.37	2293.17	2864.48
CD4.TNFα	H5N1	PRE	129	310.91	464.85	486.27
		PI(D21)	112	932.64	1239.38	974.72
		PII(D42)	120	1595.64	2227.27	1798.95
	Double H5N1	PRE	122	358.27	518.70	538.07
		PI(D21)	110	1207.95	1641.36	1527.86
		PII(D42)	118	2170.46	3100.96	3380.48

PRE =Pre-vaccination

PI(D21) = Post vaccination at Day 21

PII(D42) = Post vaccination at Day 42

All doubles: T-cells producing at least 2 cytokines

N = number of subjects with available results

GM= Geometric Mean

SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD4.CD40L, CD4.all doubles, CD4.IL-2, CD4.TNF α , CD4.INF γ stimulated by H5N1 A/Vietnam/1194/2004 strain at Day 180 (ATP cohort for persistence)

Test description	Group	Timing	N	GM	Mean	SD
CD4. all doubles	H5N1	PRE	120	386.36	626.66	609.62
		PII(D180)	132	1247.34	1521.60	1000.47
	Double H5N1	PRE	114	478.17	642.69	580.86
		PII(D180)	122	1515.07	1985.20	1982.71
CD4.CD40L	H5N1	PRE	120	382.75	611.22	588.69
		PII(D180)	132	1188.86	1449.26	939.31
	Double H5N1	PRE	114	468.50	627.99	570.09
		PII(D180)	122	1455.68	1886.15	1789.27
CD4.IL-2	H5N1	PRE	120	369.09	577.90	563.25
		PII(D180)	132	1172.16	1434.47	957.55
	Double H5N1	PRE	114	441.56	582.12	538.27
		PII(D180)	122	1433.08	1887.17	1921.82
CD4.INFγ	H5N1	PRE	120	264.43	461.18	514.57

CD4.TNF- α	Double H5N1	PII(D180)	132	654.11	850.89	661.08
		PRE	114	325.98	476.00	531.62
		PII(D180)	122	763.06	1078.66	1243.60
	H5N1	PRE	120	310.14	472.11	498.36
		PII(D180)	132	937.82	1182.06	839.91
	Double H5N1	PRE	114	342.26	496.33	530.44
PII(D180)		122	1143.69	1525.03	1444.11	

PRE = Pre-vaccination at Day 0
PII(D180) = Post-vaccination at Day 180
All doubles: T-cells producing at least 2 cytokines
N = number of subjects with available results
GM = Geometric Mean
SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD4.CD40L, CD4.all doubles, CD4.IL-2, CD4.TNF α , CD4.INF γ stimulated by H5N1 A/Vietnam/1194/2004 strain at Month 12 (ATP cohort for persistence)

Test description	Group	Timing	N	GM	Mean	SD
CD4. all doubles	H5N1	PRE	96	367.90	610.44	640.49
		PII(M12)	90	898.52	1270.86	1050.39
	Double H5N1	PRE	89	476.14	619.53	414.17
		PII(M12)	91	1170.36	1480.40	1021.43
CD4.CD40L	H5N1	PRE	96	364.80	595.16	620.28
		PII(M12)	90	934.35	1252.94	1020.83
	Double H5N1	PRE	89	463.00	606.72	411.14
		PII(M12)	91	1146.47	1453.32	1002.22
CD4.IL-2	H5N1	PRE	96	355.29	566.08	595.83
		PII(M12)	90	902.69	1217.27	1006.77
	Double H5N1	PRE	89	453.83	562.74	380.64
		PII(M12)	91	1118.63	1405.66	973.32
CD4.INF- γ	H5N1	PRE	96	242.71	456.28	553.41
		PII(M12)	90	442.66	703.12	743.99
	Double H5N1	PRE	89	321.28	453.17	348.03
		PII(M12)	91	586.60	772.51	577.71
CD4.TNF- α	H5N1	PRE	96	307.62	473.28	536.35
		PII(M12)	90	678.60	993.50	870.28
	Double H5N1	PRE	89	345.91	478.76	355.38
		PII(M12)	91	884.64	1155.80	847.51

PRE = Pre-vaccination at Day 0
PII(M12) = Post-vaccination at Month 12
All doubles: T-cells producing at least 2 cytokines
N = number of subjects with available results
GM = Geometric Mean
SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per 10⁶) for CD8.all doubles, CD8.CD40L, CD8.IL-2, CD8.TNF α , CD8.INF γ stimulated by H5N1 A/Vietnam/1194/2004 strain (ATP cohort for immunogenicity)

Test description	Group	Timing	N	GM	Mean	SD
CD8.all doubles	H5N1	PRE	129	83.30	299.57	407.94
		PI(D21)	111	70.23	297.30	391.63
		PII(D42)	120	77.73	296.52	499.25
	Double H5N1	PRE	121	71.93	352.07	626.44
		PI(D21)	109	77.70	312.37	661.43
		PII(D42)	118	79.56	370.58	765.47
CD8.CD40L	H5N1	PRE	129	3.37	24.04	52.35
		PI(D21)	111	3.90	26.86	52.29

	Double H5N1	PII(D42)	120	5.32	34.11	100.78
		PRE	121	3.58	20.88	48.88
		PI(D21)	109	5.61	24.78	34.07
		PII(D42)	118	5.23	30.97	51.86
CD8.IL-2	H5N1	PRE	129	53.90	190.62	241.03
		PI(D21)	111	45.48	197.19	251.49
		PII(D42)	120	42.77	181.76	261.13
	Double H5N1	PRE	121	59.70	218.11	340.60
		PI(D21)	109	45.97	200.17	342.71
		PII(D42)	118	50.37	228.35	413.85
CD8.INF γ	H5N1	PRE	129	83.14	287.51	394.32
		PI(D21)	111	61.44	289.99	390.60
		PII(D42)	120	55.71	280.14	506.29
	Double H5N1	PRE	121	80.54	339.86	618.55
		PI(D21)	109	55.07	290.79	661.84
		PII(D42)	118	63.71	353.79	767.88
CD8.TNF α	H5N1	PRE	129	63.19	239.59	355.75
		PI(D21)	111	55.42	225.67	306.06
		PII(D42)	120	59.51	239.68	434.37
	Double H5N1	PRE	121	45.34	294.21	573.91
		PI(D21)	109	63.94	261.77	609.54
		PII(D42)	118	59.10	315.86	689.32

PRE =Pre-vaccination

PI(D21) = Post vaccination at Day 21

PII(D42) = Post vaccination at Day 42

All doubles: T-cells producing at least 2 cytokines

N = number of subjects with available results

GM= Geometric Mean

SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD8.all doubles, CD8.CD40L, CD8.IL-2, CD8.TNF- α , CD8.INF- γ stimulated by H5N1 A/Vietnam/1194/2004 strain at Day 180 (ATP cohort for persistence)

Test description	Group	Timing	N	GM	Mean	SD
CD8.all doubles	H5N1	PRE	120	77.34	275.28	332.50
		PII(D180)	132	32.11	185.05	293.81
	Double H5N1	PRE	113	69.86	360.58	644.26
		PII(D180)	121	41.28	282.34	753.94
CD8.CD40L	H5N1	PRE	120	3.21	20.57	44.56
		PII(D180)	132	2.04	11.54	26.32
	Double H5N1	PRE	113	3.60	22.23	51.42
		PII(D180)	121	2.47	57.69	499.31
CD8.IL-2	H5N1	PRE	120	51.91	177.63	201.96
		PII(D180)	132	18.78	113.14	178.46
	Double H5N1	PRE	113	58.85	222.50	349.86
		PII(D180)	121	23.70	200.64	704.78
CD8.INF γ	H5N1	PRE	120	80.00	264.55	321.00
		PII(D180)	132	26.37	171.13	288.43
	Double H5N1	PRE	113	82.46	352.20	635.24
		PII(D180)	121	41.21	257.12	663.40
CD8.TNF α	H5N1	PRE	120	61.36	222.37	286.67
		PII(D180)	132	22.30	157.54	270.88
	Double H5N1	PRE	113	46.58	303.72	590.59
		PII(D180)	121	36.68	212.20	390.84

PRE = Pre-vaccination at Day 0

PII(D180) = Post-vaccination at Day 180
 N = number of subjects with available results
 GM= Geometric Mean
 SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD8.all doubles, CD8.CD40L, CD8.IL-2, CD8.TNF- α , CD8.INF- γ stimulated by H5N1 A/Vietnam/1194/2004 strain at Month 12 (ATP cohort for persistence)

Test description	Group	Timing	N	GM	Mean	SD
CD8.all doubles	H5N1	PRE	96	76.10	259.68	284.24
		PII(M12)	90	34.28	175.46	275.22
	Double H5N1	PRE	88	64.77	350.23	653.58
		PII(M12)	91	27.88	167.02	261.68
CD8.CD40L	H5N1	PRE	96	2.78	15.96	30.19
		PII(M12)	90	2.08	11.93	28.46
	Double H5N1	PRE	88	3.21	18.03	33.42
		PII(M12)	91	2.99	15.43	28.90
CD8.IL-2	H5N1	PRE	96	48.96	175.27	194.43
		PII(M12)	90	18.84	112.71	167.58
	Double H5N1	PRE	88	60.23	207.74	307.82
		PII(M12)	91	19.95	108.04	164.36
CD8.INF γ	H5N1	PRE	96	76.43	250.39	281.06
		PII(M12)	90	29.13	155.96	271.12
	Double H5N1	PRE	88	76.94	343.09	649.61
		PII(M12)	91	20.75	151.33	260.19
CD8.TNF α	H5N1	PRE	96	55.98	206.97	232.89
		PII(M12)	90	35.67	159.66	251.66
	Double H5N1	PRE	88	41.97	293.76	597.80
		PII(M12)	91	28.15	154.10	246.49

PRE = Pre-vaccination at Day 0
 PII(M12) = Post-vaccination at Month 12
 N = number of subjects with available results
 GM= Geometric Mean
 SD = Standard Deviation

Secondary Outcome/Efficacy Variables: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)

Symptom	Intensity	H5N1 Group					Double H5N1 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Ecchymosis	Any	164	1	0.6	0.0	3.4	159	5	3.1	1.0	7.2
	> 100 mm	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Induration	Any	164	7	4.3	1.7	8.6	159	6	3.8	1.4	8.0
	> 100 mm	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Pain	Any	164	56	34.1	26.9	41.9	159	63	39.6	32.0	47.7
	Grade 3	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Redness	Any	164	9	5.5	2.5	10.2	159	19	11.9	7.4	18.0
	> 100 mm	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
Swelling	Any	164	9	5.5	2.5	10.2	159	8	5.0	2.2	9.7
	> 100 mm	164	0	0.0	0.0	2.2	154	0	0.0	0.0	2.3
Dose 2											
Ecchymosis	Any	161	0	0.0	0.0	2.3	154	0	0.0	0.0	2.4
	> 100 mm	161	0	0.0	0.0	2.3	154	0	0.0	0.0	2.4
Induration	Any	161	4	2.5	0.7	6.2	154	11	7.1	3.6	12.4
	> 100 mm	161	0	0.0	0.0	2.3	154	0	0.0	0.0	2.4

Pain	Any	161	50	31.1	24.0	38.8	154	57	37.0	29.4	45.2
	Grade 3	161	0	0.0	0.0	2.3	154	2	1.3	0.2	4.6
Redness	Any	161	12	7.5	3.9	12.7	154	20	13.0	8.1	19.3
	> 100 mm	161	0	0.0	0.0	2.3	154	0	0.0	0.0	2.4
Swelling	Any	161	14	8.7	4.8	14.2	154	10	6.5	3.2	11.6
	> 100 mm	161	0	0.0	0.0	2.3	313	0	0.0	0.0	2.4
Across doses											
Ecchymosis	Any	164	1	0.6	0.0	3.4	159	5	3.1	1.0	7.2
	> 100 mm	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Induration	Any	164	10	6.1	3.0	10.9	159	15	9.4	5.4	15.1
	> 100 mm	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Pain	Any	164	69	42.1	34.4	50.0	159	75	47.2	39.2	55.2
	Grade 3	164	0	0.0	0.0	2.2	159	2	1.3	0.2	4.5
Redness	Any	164	19	11.6	7.1	17.5	159	30	18.9	13.1	25.8
	> 100 mm	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
Swelling	Any	164	19	11.6	7.1	17.5	159	15	9.4	5.4	15.1
	> 100 mm	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Any = occurrence of any solicited local symptom regardless of their intensity grade											
Grade 3 pain = pain that prevented normal activity											
N= number of subjects with at least one documented dose											
n (%) = number (percentage) of subjects reporting at least once the symptom											
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit											
Secondary Outcome/Efficacy Variables: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)											
		H5N1 Group					Double H5N1				
Symptom	Intensity/ Relationship	N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Arthralgia	Any	164	5	3.0	1.0	7.0	159	7	4.4	1.8	8.9
	Grade 3	164	0	0.0	0.0	2.2	159	2	1.3	0.2	4.5
	Related	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
Fatigue	Any	164	16	9.8	5.7	15.4	159	26	16.4	11.0	23.0
	Grade 3	164	1	0.6	0.0	3.4	159	2	1.3	0.2	4.5
	Related	164	1	0.6	0.0	3.4	159	4	2.5	0.7	6.3
Fever/ (Axillary) (°C)	>37.5	164	0	0.0	0.0	2.2	159	2	1.3	0.2	4.5
	>39.0	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
	Related	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Headache	Any	164	15	9.1	5.2	14.6	159	18	11.3	6.8	17.3
	Grade 3	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
	Related	164	0	0.0	0.0	2.2	159	4	2.5	0.7	6.3
Myalgia	Any	164	13	7.9	4.3	13.2	159	23	14.5	9.4	20.9
	Grade 3	164	0	0.0	0.0	2.2	159	3	1.9	0.4	5.4
	Related	164	0	0.0	0.0	2.2	159	3	1.9	0.4	5.4
Shivering	Any	164	0	0.0	0.0	2.2	159	3	1.9	0.4	5.4
	Grade 3	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
	Related	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
Sweating	Any	164	8	4.9	2.1	9.4	159	11	6.9	3.5	12.0
	Grade 3	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5
	Related	164	0	0.0	0.0	2.2	159	0	0.0	0.0	2.3
Dose 2											
Arthralgia	Any	161	10	6.2	3.0	11.1	154	9	5.8	2.7	10.8
	Grade 3	161	1	0.6	0.0	3.4	154	0	0.0	0.0	2.4
	Related	161	0	0.0	0.0	2.3	154	2	1.3	0.2	4.6

Fatigue	Any	161	26	16.1	10.8	22.8	154	28	18.2	12.4	25.2				
	Grade 3	161	1	0.6	0.0	3.4	154	4	2.6	0.7	6.5				
	Related	161	0	0.0	0.0	2.3	154	5	3.2	1.1	7.4				
Fever/ (Axillary) (°C)	>37.5	161	2	1.2	0.2	4.4	154	3	1.9	0.4	5.6				
	>39.0	161	1	0.6	0.0	3.4	154	0	0.0	0.0	2.4				
	Related	161	0	0.0	0.0	2.3	154	1	0.6	0.0	3.6				
Headache	Any	161	20	12.4	7.8	18.5	154	27	17.5	11.9	24.5				
	Grade 3	161	0	0.0	0.0	2.3	154	1	0.6	0.0	3.6				
	Related	161	2	1.2	0.2	4.4	154	4	2.6	0.7	6.5				
Myalgia	Any	161	15	9.3	5.3	14.9	154	13	8.4	4.6	14.0				
	Grade 3	161	1	0.6	0.0	3.4	154	1	0.6	0.0	3.6				
	Related	161	2	1.2	0.2	4.4	154	2	1.3	0.2	4.6				
Shivering	Any	161	2	1.2	0.2	4.4	154	7	4.5	1.8	9.1				
	Grade 3	161	1	0.6	0.0	3.4	154	0	0.0	0.0	2.4				
	Related	161	0	0.0	0.0	2.3	154	2	1.3	0.2	4.6				
Sweating	Any	161	12	7.5	3.9	12.7	154	12	7.8	4.1	13.2				
	Grade 3	161	0	0.0	0.0	2.3	154	0	0.0	0.0	2.4				
	Related	161	0	0.0	0.0	2.3	154	1	0.6	0.0	3.6				
Across doses															
Arthralgia	Any	164	13	7.9	4.3	13.2	159	13	8.2	4.4	13.6				
	Grade 3	164	1	0.6	0.0	3.4	159	2	1.3	0.2	4.5				
	Related	164	0	0.0	0.0	2.2	159	2	1.3	0.2	4.5				
Fatigue	Any	164	32	19.5	13.7	26.4	159	39	24.5	18.1	32.0				
	Grade 3	164	2	1.2	0.1	4.3	159	6	3.8	1.4	8.0				
	Related	164	1	0.6	0.0	3.4	159	8	5.0	2.2	9.7				
Fever/ (Axillary) (°C)	>37.5	164	2	1.2	0.1	4.3	159	5	3.1	1.0	7.2				
	>39.0	164	1	0.6	0.0	3.4	159	1	0.6	0.0	3.5				
	Related	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5				
Headache	Any	164	27	16.5	11.1	23.0	159	34	21.4	15.3	28.6				
	Grade 3	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5				
	Related	164	2	1.2	0.1	4.3	159	6	3.8	1.4	8.0				
Myalgia	Any	164	24	14.6	9.6	21.0	159	28	17.6	12.0	24.4				
	Grade 3	164	1	0.6	0.0	3.4	159	4	2.5	0.7	6.3				
	Related	164	2	1.2	0.1	4.3	159	4	2.5	0.7	6.3				
Shivering	Any	164	2	1.2	0.1	4.3	159	9	5.7	2.6	10.5				
	Grade 3	164	1	0.6	0.0	3.4	159	1	0.6	0.0	3.5				
	Related	164	0	0.0	0.0	2.2	159	2	1.3	0.2	4.5				
Sweating	Any	164	16	9.8	5.7	15.4	159	19	11.9	7.4	18.0				
	Grade 3	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5				
	Related	164	0	0.0	0.0	2.2	159	1	0.6	0.0	3.5				
Any: occurrence of any solicited general symptom regardless of their intensity grade or relationship to vaccination Grade 3 arthralgia, fatigue, headache, myalgia, shivering, sweating: symptom that prevented normal activity Related = general symptom assessed by the investigator as causally related to the study vaccination N= number of subjects with at least one documented dose n (%)= number (percentage) of subjects reporting at least once the symptom 95%CI= Exact 95% confidence interval, LL = lower limit, UL = upper limit															
Secondary Outcome/Efficacy Variables: Haematological and biochemical levels with respect to normal ranges (Total Vaccinated cohort)															
Laboratory parameter	Timing	H5N1 Group						Double H5N1							
		Below		Within		Above		Below		Within		Above			
		N	n	%	n	%	n	%	N	n	%	n	%	n	%
Alanine Aminotransferase	PRE	165	0	0.00	152	92.12	13	7.88	159	1	0.63	152	95.60	6	3.77
	PI(Day 2)	165	0	0.00	152	92.12	13	7.88	158	1	0.63	151	95.57	6	3.80

	PI(Day 21)	163	0	0.00	153	93.87	10	6.13	156	1	0.64	144	92.31	11	7.05
	PII(Day 23)	163	0	0.00	152	93.25	11	6.75	155	1	0.65	146	94.19	8	5.16
Aspartate Aminotransferase	PRE	165	0	0.00	154	93.33	11	6.67	159	0	0.00	150	94.34	9	5.66
	PI(Day 2)	165	0	0.00	154	93.33	11	6.67	158	0	0.00	152	96.20	6	3.80
	PI(Day 21)	163	0	0.00	154	94.48	9	5.52	156	0	0.00	146	93.59	10	6.41
	PII(Day 23)	163	0	0.00	153	93.87	10	6.13	155	0	0.00	149	96.13	6	3.87
	PRE	163	0	0.00	163	100.0	0	0.00	159	0	0.00	159	100.0	0	0.00
Basophils	PI(Day 2)	165	0	0.00	164	99.39	1	0.61	158	0	0.00	158	100.0	0	0.00
	PI(Day 21)	163	0	0.00	163	100.0	0	0.00	155	0	0.00	155	100.0	0	0.00
	PII(Day 23)	163	0	0.00	163	100.0	0	0.00	155	0	0.00	155	100.0	0	0.00
	PRE	165	0	0.00	149	90.30	16	9.70	158	0	0.00	136	86.08	22	13.92
Creatinine Phosphokinase	PI(Day 2)	165	0	0.00	150	90.91	15	9.09	158	1	0.63	141	89.24	16	10.13
	PI(Day 21)	163	1	0.61	140	85.89	22	13.50	156	0	0.00	130	83.33	26	16.67
	PII(Day 23)	163	0	0.00	146	89.57	17	10.43	155	0	0.00	136	87.74	19	12.26
	PRE	165	0	0.00	144	87.27	21	12.73	159	0	0.00	148	93.08	11	6.92
Creatinine	PI(Day 2)	165	1	0.61	144	87.27	20	12.12	158	1	0.63	146	92.41	11	6.96
	PI(Day 21)	163	0	0.00	134	82.21	29	17.79	156	1	0.64	142	91.03	13	8.33
	PII(Day 23)	163	1	0.61	142	87.12	20	12.27	155	1	0.65	139	89.68	15	9.68
	PRE	163	4	2.45	159	97.55	0	0.00	159	5	3.14	153	96.23	1	0.63
Eosinophils	PI(Day 2)	165	4	2.42	161	97.58	0	0.00	158	5	3.16	152	96.20	1	0.63
	PI(Day 21)	163	4	2.45	158	96.93	1	0.61	155	4	2.58	150	96.77	1	0.65
	PII(Day 23)	163	4	2.45	159	97.55	0	0.00	155	4	2.58	149	96.13	2	1.29
	PRE	163	11	6.75	137	84.05	15	9.20	159	14	8.81	130	81.76	15	9.43
Haemoglobin	PI(Day 2)	165	21	12.73	139	84.24	5	3.03	158	16	10.13	135	85.44	7	4.43
	PI(Day 21)	163	13	7.98	144	88.34	6	3.68	155	15	9.68	130	83.87	10	6.45
	PII(Day 23)	163	20	12.27	139	85.28	4	2.45	155	17	10.97	133	85.81	5	3.23
	PRE	164	1	0.61	147	89.63	16	9.76	156	2	1.28	136	87.18	18	11.54
Lactate Dehydrogenase	PI(Day 2)	165	2	1.21	148	89.70	15	9.09	158	2	1.27	144	91.14	12	7.59
	PI(Day 21)	162	0	0.00	151	93.21	11	6.79	156	1	0.64	142	91.03	13	8.33
	PII(Day 23)	163	4	2.45	147	90.18	12	7.36	155	2	1.29	141	90.97	12	7.74
	PRE	163	145	88.96	18	11.04	0	0.00	159	137	86.16	22	13.84	0	0.00
Lymphocytes	PI(Day 2)	165	148	89.70	17	10.30	0	0.00	158	136	86.08	22	13.92	0	0.00
	PI(Day 21)	163	144	88.34	19	11.66	0	0.00	155	135	87.10	20	12.90	0	0.00
	PII(Day 23)	163	145	88.96	17	10.43	1	0.61	155	135	87.10	20	12.90	0	0.00
	PRE	163	143	87.73	20	12.27	0	0.00	159	136	85.53	23	14.47	0	0.00
Monocytes	PI(Day 2)	165	143	86.67	21	12.73	1	0.61	158	134	84.81	24	15.19	0	0.00
	PI(Day 21)	163	140	85.89	23	14.11	0	0.00	155	134	86.45	21	13.55	0	0.00
	PII(Day 23)	163	141	86.50	19	11.66	3	1.84	155	134	86.45	17	10.97	4	2.58
	PRE	163	148	90.80	13	7.98	2	1.23	158	141	89.24	17	10.76	0	0.00
Neutrophils	PI(Day 2)	165	149	90.30	13	7.88	3	1.82	158	141	89.24	17	10.76	0	0.00
	PI(Day 21)	163	147	90.18	14	8.59	2	1.23	155	138	89.03	15	9.68	2	1.29
	PII(Day 23)	163	148	90.80	14	8.59	1	0.61	155	138	89.03	17	10.97	0	0.00
	PRE	163	4	2.45	145	88.96	14	8.59	159	3	1.89	148	93.08	8	5.03
Platelets	PI(Day 2)	165	2	1.21	152	92.12	11	6.67	158	4	2.53	147	93.04	7	4.43
	PI(Day 21)	163	3	1.84	147	90.18	13	7.98	155	4	2.58	145	93.55	6	3.87
	PII(Day 23)	163	2	1.23	150	92.02	11	6.75	155	2	1.29	147	94.84	6	3.87
	PRE	163	21	12.88	132	80.98	10	6.13	159	21	13.21	125	78.62	13	8.18
Red Blood Cell count	PI(Day 2)	165	25	15.15	134	81.21	6	3.64	158	20	12.66	133	84.18	5	3.16
	PI(Day 21)	163	24	14.72	133	81.60	6	3.68	155	20	12.90	127	81.94	8	5.16
	PII(Day 23)	163	33	20.25	127	77.91	3	1.84	155	19	12.26	134	86.45	2	1.29
	PRE	165	0	0.00	90	54.55	75	45.45	159	4	2.52	101	63.52	54	33.96
Urea	PI(Day 2)	164	1	0.61	96	58.54	67	40.85	158	4	2.53	114	72.15	40	25.32
	PI(Day 21)	163	0	0.00	91	55.83	72	44.17	156	3	1.92	100	64.10	53	33.97
	PII(Day 23)	163	0	0.00	105	64.42	58	35.58	155	2	1.29	106	68.39	47	30.32

White Blood Cell count	PRE	163	5	3.07	152	93.25	6	3.68	159	3	1.89	155	97.48	1	0.63
	PI(Day 2)	165	4	2.42	152	92.12	9	5.45	158	4	2.53	152	96.20	2	1.27
	PI(Day 21)	163	4	2.45	150	92.02	9	5.52	155	3	1.94	149	96.13	3	1.94
	PII(Day 23)	163	6	3.68	145	88.96	12	7.36	155	7	4.52	148	95.48	0	0.00

N = number of subjects with available results
n/%= number/percentage of subjects in the specified category
PRE = Pre-vaccination at Day 0
PI (Day 2) = Post-vaccination at Day 2
PI (Day 21) = Post-vaccination at Day 21
PII (Day 23) = Post-vaccination at Day 23

Safety results: Number (%) of subjects with unsolicited adverse events (Total vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Day 0- 20 after first vaccination and within Day 0-29 after second vaccination)	H5N1 Group N=165	Double H5N1 Group N=159
Subjects with any AE(s), n (%)	36 (21.8)	28 (17.6)
Subjects with Grade 3 AE(s), n (%)	5 (3.0)	3 (1.9)
Subjects with related AE(s), n (%)	9 (5.5)	10 (6.3)
Diarrhea	3 (1.8)	1 (0.6)
Nausea	2 (1.2)	3 (1.9)
Vertigo	2 (1.2)	1 (0.6)
Tracheitis	4 (2.4)	-
Erythema	2 (1.2)	1 (0.6)
Gastroenteritis	-	1 (0.6)
Injection site pruritus	-	4 (2.5)
Nasopharyngitis	2 (1.2)	-
Rhinitis	2 (1.2)	1 (0.6)
Cough	2 (1.2)	1 (0.6)
Neck pain	-	2 (1.3)
Pain in extremity	3 (1.8)	-
Pharyngitis	-	2 (1.3)
Abdominal pain upper	2 (1.2)	-
Arthralgia	2 (1.2)	-
Lymphadenopathy	-	1 (0.6)
Congestive cardiomyopathy	-	1 (0.6)
Coronary artery disease	-	1 (0.6)
Tachycardia	-	1 (0.6)
Tinnitus	-	1 (0.6)
Cheilitis	-	1 (0.6)
Paraesthesia oral	-	1 (0.6)
Toothache	-	1 (0.6)
Fatigue	-	1 (0.6)
Influenza like illness	-	1 (0.6)
Injection site rash	-	1 (0.6)
Drug hypersensitivity	-	1 (0.6)
Influenza	-	1 (0.6)
Otitis media	-	1 (0.6)
Sinusitis	-	1 (0.6)
Tooth abscess	-	1 (0.6)
Back pain	-	1 (0.6)
Muscle spasms	-	1 (0.6)
Osteoarthritis	-	1 (0.6)
Scleroderma	-	1 (0.6)
Paraesthesia	-	1 (0.6)
Sensory disturbance	-	1 (0.6)

Dyspnoea	-	1 (0.6)
Rhinitis allergic	-	1 (0.6)
Rhinorrhoea	-	1 (0.6)
-: Adverse event absent or not meeting the counting rule:> 30 subjects/treatment group and > 3 groups, display the most frequent 5 events in each treatment group		
*Grade 3 AE: AE that prevented normal activity		
**Related AE: AE assessed by the investigator as causally related to the study vaccination		
Safety results: Number (%) of subjects with SAEs between Day 0 and Day 51 (Total vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N=165	Double H5N1 Group N=159
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	1 (0.6) [0]	1 (0.6) [0]
Coronary artery disease	0 (0.0) [0]	1 (0.6) [0]
Gastroenteritis	1 (0.6) [0]	0 (0.0) [0]
Fatal SAEs	H5N1 Group N=165	Double H5N1 Group N=159
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]
Safety results: Number (%) of subjects with SAEs between Day 52 and Day 180 (Total vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N = 164	Double H5N1 Group N = 158
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	5 (3.0) [0]	4 (2.5) [0]
Cardiac failure congestive	0 (0.0) [0]	1 (0.6) [0]
Adenocarcinoma pancreas	1 (0.6) [0]	0 (0.0) [0]
Atrial fibrillation	1 (0.6) [0]	0 (0.0) [0]
Cardiac failure acute	0 (0.0) [0]	1 (0.6) [0]
Cerebral ischaemia	1 (0.6) [0]	0 (0.0) [0]
Cerebrovascular accident	0 (0.0) [0]	1 (0.6) [0]
Femoral neck fracture	0 (0.0) [0]	1 (0.6) [0]
Renal cell carcinoma stage unspecified	1 (0.6) [0]	0 (0.0) [0]
Sciatica	1 (0.6) [0]	0 (0.0) [0]
Fatal SAEs	H5N1 Group N = 164	Double H5N1 Group N = 158
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	2 (1.3) [0]
Cardiac failure congestive	0 (0.0) [0]	1 (0.6) [0]
Cerebrovascular accident	0 (0.0) [0]	1 (0.6) [0]
Safety results: Number (%) of subjects with SAEs between Month 6 and Month 12 (ATP cohort for persistence)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N = 130	Double H5N1 Group N = 125
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	4 (3.1) [0]	3 (2.4) [0]
Cerebrovascular accident	2 (1.5) [0]	0 (0.0) [0]
Pneumonia	1 (0.8) [0]	1 (0.8) [0]
Lower limb fracture	1 (0.8) [0]	0 (0.0) [0]
Lung neoplasm malignant	1 (0.8) [0]	0 (0.0) [0]
Phlebitis	0 (0.0) [0]	1 (0.8) [0]

Prostate cancer metastatic	0 (0.0) [0]	1 (0.8) [0]
Schizophrenia	0 (0.0) [0]	1 (0.8) [0]
Fatal SAEs	H5N1 Group N = 130	Double H5N1 Group N = 125
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: In H5N1 group, at least 18.4% of subjects reported pre-vaccination SPRs for H5N1 HI antibody against the A/Vietnam/1194/2004 strain. At Day 21, 42, 180 and Month 12, 61.2%, 83.6%, 52.9% and 43.8% of the subjects had H5N1 HI antibody titres \geq 1:40 against the A/Vietnam/1194/2004 strain. At Day 21, 42, 180 and Month 12, 3.3%, 23.0%, 3.6% and 15.2% of the subjects had H5N1 HI antibody titres \geq 1:40 against A/Indonesia/5/2005 strain.

In Double H5N1 group, at least 15.9% of subjects reported pre-vaccination SPRs for H5N1 HI antibody against the A/Vietnam/1194/2004 strain. At Day 21, 42, 180 and Month 12, 62.1%, 95.9%, 69.5% and 42.5% of the subjects had H5N1 HI antibody titres \geq 1:40 against the A/Vietnam/1194/2004 strain. At Day 21, 42, 180 and Month 12, 9.0%, 40.7 %, 6.1% and 20.8% of the subjects had H5N1 HI antibody titres \geq 1:40 against A/Indonesia/5/2005 strain.

At least one unsolicited AE was reported during the follow-up period after vaccination by 36 (21.8%) subjects of H5N1 group and 28 (17.6%) subjects of Double H5N1 group. From Day 0 up to Day 51, two SAEs were reported (one in each group). None of these SAEs were assessed by the investigators as related to the study vaccination.

Between Day 51 and Day 180, SAEs were reported for 5 (3.0%) subjects of H5N1 group and 4 (2.5%) subjects of Double H5N1 group. Two fatal SAEs were reported in Double H5N1 group during the entire study period. None of the reported SAEs were assessed by the investigators as related to the study vaccination.

Between Month 6 and Month 12, SAEs were reported for 4 (3.1%) subjects of H5N1 group and 3 (2.4%) subjects of Double H5N1 group. None of the reported SAEs were assessed by the investigators as related to the study vaccination. No fatal SAEs were reported between Month 6 and Month 12.

Publications: None

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