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Study No.: 109630, 109873
Title: Assess the consistency of the immunogenicity of a GlaxoSmithKline Biologicals' pandemic influenza vaccine (GSK1562902A) in adults aged between 18 and 60 years. GSK1562902A (H5N1): GlaxoSmithKline (GSK) Biologicals' pandemic influenza vaccine
Rationale: The purpose of this study was to assess the consistency of the immune response elicited by 4 different lots of H5N1 vaccine (A/Vietnam/1194/2004 strain). The immunogenicity of a booster administration with a H5N1 vaccine derived from A/Indonesia/5/2005 (H5N1) strain, 6 months after priming, was also assessed in a subset of subjects.
Phase: III
Study Period: 109630: 24 March 2007 to 12 July 2007. 109873: 30 September 2007 to 10 June 2008 (up to Month 12).
Study Design: Multi-centric, randomized (2:2:2:2:1:1) controlled study. The primary study was observer blind while the booster study was open. Data from the groups receiving the currently registered vaccines are presented. Data from the investigational vaccine regimen, which is not approved or marketed, are not reported at this time.
Centers: 6 study centers (1 center in Thailand, 2 centers in Taiwan, 2 centers in Singapore and 1 center in Hong Kong).
Indication: Immunization against influenza disease in subjects aged 18 to 60 years.
Treatment: The 6 study groups <u>during the primary phase</u> (109630) were as follows: <ul style="list-style-type: none"> • H5N1/F1 Group: received 2 doses of H5N1 vaccine lot 1. • H5N1/F2 Group: received 2 doses of H5N1 vaccine lot 2. • H5N1/F3 Group: received 2 doses of H5N1 vaccine lot 3. • H5N1/F4 Group: received 2 doses of H5N1 vaccine lot 4. Safety data analyses were performed for the 4 groups above pooled into H5N1 Group. <ul style="list-style-type: none"> • 2 groups (H5N1/Dil-1 and H5N1/Dil-2) received 2 doses of an investigational formulation of H5N1 vaccine. The vaccines (A/Vietnam/1194/2004 strain) were administered intramuscularly into the deltoid region of the non-dominant arm at Day 0 and Day 21. The 2 study groups <u>during the booster phase</u> (109873) were as follows: <ul style="list-style-type: none"> • H5N1 Group: A subset of subjects from the H5N1/F1, H5N1/F2, H5N1/F3 and H5N1/F4 Groups received a single dose of H5N1 vaccine at Month 6. The remaining subjects from those 4 groups received a single dose of H5N1 vaccine at Month 12 or 36 after initial priming in study 111443. • H5N1/Dil Group: Subjects from H5N1/Dil-1 and H5N1/Dil-2 Groups received 2 doses of H5N1 vaccine (A/Indonesia/5/2005 strain) at Month 6 and Month 6+21 days. This group was used as a control in the booster phase. The vaccine (A/Indonesia/5/2005 strain) was administered intramuscularly into the deltoid region of the non-dominant arm.
Objectives: <i>Only objectives related to the licensed vaccine are presented.</i> To demonstrate the consistency of the immune response (in terms of geometric mean titer [GMT] ratio for anti-hemagglutinin (anti-HA) antibody response 21 days after the second vaccination) elicited by four compositions of H5N1 vaccine.
Primary Outcome/Efficacy Variable: <i>Only outcome variables related to the licensed vaccine are presented.</i> <i>Observed variables at Day 0 and Day 42:</i> <ul style="list-style-type: none"> • Serum H5N1 hemagglutinin inhibition (HI) antibody titers. <i>Derived variables (with 95% confidence intervals [CI]): GMT at Day 42.</i> <ul style="list-style-type: none"> • To demonstrate the lot-to-lot consistency of the H5N1 vaccine in terms of immunogenicity as measured by

serum H5N1 HI antibodies 21 days after the second vaccination.

Secondary Outcome/Efficacy Variables:

Only outcome variables related to the licensed vaccine are presented.

For the humoral immune response (in terms of both H5N1 HI antibodies and neutralizing antibodies), the following parameters (with 95% CI) were calculated:

- GMT at Day 0, Day 21^δ, Day 42, Month 6, Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12.
- Seroconversion rates*[§] (SCR) at Day 21^δ, Day 42, Month 6[#], Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12.

In addition, humoral immune response in terms of H5N1 HI antibodies were evaluated using the following parameters (with 95% CIs):

- Booster SCR^ε at Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group).
- Seroconversion factors** (SCF) at Day 21, Day 42, Month 6, Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12.
- Booster SCF^ε at Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group)
- Seroprotection rates*** (SPR) at Day 0, Day 21, Day 42, Month 6, Month 6 + 21 days (or Month 6 + 42 days, for subjects from the H5N1/Dil Group), Month 12 ((for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12.

*Seroconversion rate for H5N1 HI antibody response was defined as the percentage of vaccinees who had either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer.

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

***Seroprotection rate was defined as the percentage of vaccinees with a serum H5N1 HI antibody titer ≥ 1:40 that usually was accepted as indicating protection.

§ Seroconversion rate for neutralizing antibody response was defined as the percentage of vaccinees with a minimum 4-fold increase in neutralizing antibody titer at post-vaccination.

δ For humoral immune response in terms of neutralizing antibodies, the GMTs and SCR at Day 21 were not analyzed.

ε Only for boosted subjects.

For the cell mediated immune (CMI) response (*in a subset of subjects*): the following parameters (with 95% CIs) were calculated at Day 0[#], Day 21[#], Day 42[#], Month 6, Month 6 + 21 days, Month 6 + 42 days[#] (for subjects from the H5N1/Dil Group) and Month 12:

- Frequency of influenza-specific cluster of differentiation (CD) 4/CD8 T-cells per 10⁶ in tests producing at least 2 different cytokines (CD40 ligand [CD40L], interleukin - 2 [IL-2], tumor necrosis factor-α [TNF-α], Interferon-γ [IFN-γ]).
- Frequency of influenza-specific CD4/CD8 T-cells per 10⁶ 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 10⁶ 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 10⁶ in tests producing at least TNF-α and another signal molecule (IL-2, IFN-γ, CD40L).

Analyses were not performed for these time points.

Statistical Methods:

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

- The Total Cohort included all subjects enrolled in the study for whom data were available.
- 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 the subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.
- The ATP cohort of persistence included all evaluable subjects who met all eligibility criteria, who complied with the procedures defined in the protocol during the entire study period and with the intervals defined in the protocol for Visit at Month 6, who did not meet the elimination criteria during the entire study, for whom

data concerning immunogenicity measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at Visit 3.

Analysis of immunogenicity

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

Inferential analysis (lot-to-lot consistency):

The 95% CI for H5N1 HI GMT ratio between vaccine groups was computed using the analysis of covariance (ANCOVA) model. The ANCOVA model included the vaccine group effect and the pre-vaccination as regressor. The lot-to-lot consistency 21 days after Dose 2 was demonstrated if, for all pairs of lots, the two-sided 95% CIs for the ratio of H5N1 HI antibody GMT was within the [0.5 ; 2] clinical limit interval.

Descriptive analysis:

For the humoral immune response in terms of both H5N1 HI antibodies and neutralizing antibodies, GMTs and SCR of antibody titers at days 0, 21 (only for HI antibodies), 42, Month 6, Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12 and were calculated with 95% CI. The humoral immune response in terms of anti-HA antibodies was also evaluated using the following parameters (with 95% CI): SCF at days 21, 42, Month 6, Month 6 + 21 days (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12 and the SPR at Day 0, Day 21, Day 42, Month 6, Month 6 + 21 days (or Month 6 + 42 days, for subjects from the H5N1/Dil Group), Month 12 (for subjects from the H5N1 Group), Month 6 + 42 days (for subjects from the H5N1/Dil Group), Month 12. In terms of CMI response, the frequency of influenza-specific CD4/CD8 T lymphocytes cells was summarized (descriptive statistics) for each vaccine group at Month 6, Month 6 + 21 days, Month 6 + 42 days (for subjects from the H5N1/Dil Group) and Month 12.

Analysis of safety

The analysis was performed on the Total Vaccinated Cohort and Total Cohort.

For each solicited local and general symptom, the percentage of subjects reporting a symptom during the 7-day (Day 0-6) follow-up period together with their exact 95% confidence interval (CI) was tabulated. The same tabulations were performed for Grade 3 local and general solicited symptoms, and for general solicited symptoms assessed by the investigator as related to the vaccine. The percentage of subjects with at least one report of unsolicited adverse events classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported up to 21 days (Day 0-20) after the first vaccination and 30 days (Day 0-29) after the second vaccination was tabulated. The occurrence of serious adverse events (SAEs) during the entire study was tabulated according to MedDRA preferred terms

Study Population: Healthy male or female subjects aged between and including, 18 and 60 years at the time of first vaccination. Women were to be of non-childbearing potential or, if of childbearing potential, had to practice adequate contraception for 30 days prior to vaccination, were to have a negative pregnancy test and to continue such precautions for 2 months after completion of the vaccination series. Written informed consent was obtained from the subject.

Number of Subjects (H5N1-002):	H5N1/F1 Group	H5N1/F2 Group	H5N1/F3 Group	H5N1/F4 Group
Planned, N	218	218	218	218
Randomized, N (Total Vaccinated Cohort)	240	239	242	240
Completed up to Day 51, n (%)	237 (98.7)	236 (98.7)	237 (97.9)	237 (98.7)
Total Number Subjects Withdrawn, n (%)	3 (1.2)	3 (1.2)	5 (2.1)	3 (1.2)
Withdrawn due to Adverse Events n (%)	1 (0.4)	0 (0)	0 (0)	0 (0)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable			
Withdrawn for other reasons n (%)	2 (0.8)	3 (1.2)	5 (2.1)	3 (1.2)
Demographics	H5N1/F1 Group	H5N1/F2 Group	H5N1/F3 Group	H5N1/F4 Group
N (Total Vaccinated Cohort)	240	239	242	240
Females: Males	126:114	121:118	116:126	132:108
Mean Age, years (SD)	33.6 (9.86)	34.2 (10.0)	33.2 (9.11)	34.0(10.32)
Asian-East Asian Heritage, n (%)	151 (62.9)	144 (60.3)	147 (60.7)	147 (61.3)
Number of subjects (H5N1-030)	H5N1 Group		H5N1/Dil Group	

Planned, N	872*	218
Randomized, N (Total Vaccinated Cohort)	265	236
Number of subjects completed up to Month 12	265	233
Total Number Subjects Withdrawn, n (%)	0 (0.0)	2 (0.85)
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)	2 (0.85)
Demographics	H5N1 Group	H5N1/Dil Group
N (Total Vaccinated Cohort)	265	236
Females: Males	144:121	118:118
Mean Age, years (SD)	33.2 (10.17)	33.5 (9.19)
Asian - East Asian Heritage, n (%)	159 (60.0)	139 (58.9)
* Planned for studies 109873 & 111443'		

Primary Efficacy Results: GMT ratio (with 95% CI) of H5N1 HI antibodies against the A/Vietnam/1194/2004 strain between vaccine lots at Day 42 (ATP cohort for immunogenicity)

Antibodies against	Group	N	Adjusted GMT	Group	N	Adjusted GMT	Adjusted GMT ratio			
							Ratio order	Value	95% CI	
									LL	UL
A/Vietnam/1194/2004	H5N1/F1	229	192.0	H5N1/F2	233	236.0	H5N1/F1/H5N1/F2	0.81	0.66	1.01
	H5N1/F1	229	192.0	H5N1/F3	229	225.0	H5N1/F1/H5N1/F3	0.85	0.69	1.06
	H5N1/F1	229	192.0	H5N1/F4	233	227.0	H5N1/F1/H5N1/F4	0.85	0.68	1.05
	H5N1/F2	233	236.0	H5N1/F3	229	225.0	H5N1/F2/H5N1/F3	1.05	0.85	1.30
	H5N1/F2	233	236.0	H5N1/F4	233	227.0	H5N1/F2/H5N1/F4	1.04	0.84	1.29
	H5N1/F3	229	225.0	H5N1/F4	233	227.0	H5N1/F3/H5N1/F4	0.99	0.80	1.23

Adjusted GMT = geometric mean antibody titer adjusted for baseline titer

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titer - pooled variance with more than 2 groups); LL = lower limit, UL = upper limit

Primary Efficacy Results: GMT ratio (with 95% CI) of H5N1 HI antibodies against the A/Indonesia/5/2005 strain between vaccine lots at Day 42 (ATP cohort for immunogenicity)

Antibodies against	Group	N	Adjusted GMT	Group	N	Adjusted GMT	Adjusted GMT ratio			
							Ratio order	Value	95% CI	
									LL	UL
A/Indonesia/5/2005	H5N1/F1	229	23.9	H5N1/F2	233	28.1	H5N1/F1/H5N1/F2	0.85	0.66	1.10
	H5N1/F1	229	23.9	H5N1/F3	229	25.7	H5N1/F1/H5N1/F3	0.93	0.72	1.20
	H5N1/F1	229	23.9	H5N1/F4	233	22.4	H5N1/F1/H5N1/F4	1.07	0.83	1.37
	H5N1/F2	233	28.1	H5N1/F3	229	25.7	H5N1/F2/H5N1/F3	1.10	0.85	1.41
	H5N1/F2	233	28.1	H5N1/F4	233	22.4	H5N1/F2/H5N1/F4	1.25	0.97	1.62
	H5N1/F4	233	22.4	H5N1/F3	229	25.7	H5N1/F4/H5N1/F3	0.87	0.68	1.12

Adjusted GMT = geometric mean antibody titer adjusted for baseline titer

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titer - pooled variance with more than 2 groups)

LL = lower limit, UL = upper limit

Primary Efficacy Results: GMTs of H5N1 HI antibody titers at days 0, 21 and 42 for A/Vietnam/1194/2004 and A/Indonesia/5/2005 – all vaccine lots (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	≥ 1:10				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1/F1	PRE	233	17	7.3	4.3	11.4	5.6	5.3	5.9
		PI(D21)	231	134	58	51.4	64.5	21.8	18.1	26.2
		PII(D42)*	229	216	94.3	90.5	96.9	192.7	164.2	226.2
	H5N1/F2	PRE	235	14	6	3.3	9.8	5.5	5.2	5.8
		PI(D21)	233	144	61.8	55.2	68.1	25.1	20.7	30.5
		PII(D42)*	233	223	95.7	92.2	97.9	235.2	203.1	272.5
	H5N1/F3	PRE	231	15	6.5	3.7	10.5	5.6	5.2	5.9
		PI(D21)	228	135	59.2	52.5	65.7	24	19.6	29.3
		PII(D42)*	229	219	95.6	92.1	97.9	225.6	193.5	263
	H5N1/F4	PRE	234	13	5.6	3	9.3	5.4	5.2	5.7
		PI(D21)	233	131	56.2	49.6	62.7	20.5	17	24.6
		PII(D42)*	233	223	95.7	92.2	97.9	226.3	194	264
A/Indonesia/5/2005	H5N1/F1	PRE	233	4	1.7	0.5	4.3	5.1	5	5.2
		PI(D21)	231	30	13	8.9	18	6.3	5.7	6.8
		PII(D42)*	229	150	65.5	59	71.6	24.3	20.4	29
	H5N1/F2	PRE	235	1	0.4	0	2.3	5	5	5.1
		PI(D21)	233	30	12.9	8.9	17.9	5.9	5.6	6.3
		PII(D42)*	233	155	66.5	60.1	72.6	27.9	23.4	33.3
	H5N1/F3	PRE	231	1	0.4	0	2.4	5	5	5.1
		PI(D21)	228	23	10.1	6.5	14.8	5.9	5.5	6.4
		PII(D42)*	229	144	62.9	56.3	69.2	25.5	21.2	30.7
	H5N1/F4	PRE	234	2	0.9	0.1	3.1	5.1	5	5.1
		PI(D21)	233	28	12	8.1	16.9	5.9	5.6	6.4
		PII(D42)*	233	138	59.2	52.6	65.6	22.4	18.6	27

*Primary Efficacy Variable

N = number of subjects with available results

n (%) = number (percentage) of subjects with titer 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) = 21 days after second vaccination (Day 42)

Secondary Outcome Variable(s): Seropositivity rates and GMTs for H5N1 HI against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 +21 days, Month 6 +42 days* for adults who received the booster dose at Month 6 – pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	≥ 1:10				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	256	159	62.1	55.9	68.1	19.1	16.5	22.2
		PIII(M6+21D)	256	248	96.9	93.9	98.6	397.4	342.5	461.0
	H5N1/Dil	PII(M6)	229	21	9.2	5.8	13.7	5.8	5.4	6.2
		PIII(M6+21D)	228	158	69.3	62.9	75.2	30.1	24.9	36.3
		PIV(M6+42D)	228	201	88.2	83.2	92.0	76.3	64.1	90.8
A/Indonesia/5/2005	H5N1	PII(M6)	256	47	18.4	13.8	23.7	6.4	6.0	6.9
		PIII(M6+21D)	256	245	95.7	92.4	97.8	321.3	274.3	376.2
	H5N1/Dil	PII(M6)	229	3	1.3	0.3	3.8	5.1	5.0	5.1
		PIII(M6+21D)	228	142	62.3	55.6	68.6	24.8	20.5	30.0
		PIV(M6+42D)	228	205	89.9	85.2	93.5	96.3	80.6	115.1

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PII(M6) = Pre-booster blood sample at Month 6 PIII(M6+21D)= Post-booster dose 1 blood sample at Day 21 *PIV(M6+42D)= Post-booster dose 2 blood sample at Day 42 for H5N1/Dil Group										
Secondary Outcome Variable(s): Seropositivity rates and GMTs of H5N1 HI antibodies against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 + 21 days, Month 6 + 42 days* and Month 12 for adults who received the booster dose at Month 6-pooled vaccine group (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	PIII(M12)	228	191	83.8	78.3	88.3	76.1	62.5	92.7
	H5N1/Dil	PIV(M12)	209	108	51.7	44.7	58.6	14.3	12.2	16.8
A/Indonesia/5/2005	H5N1	PIII(M12)	228	171	75.0	68.9	80.5	46.9	38.3	57.4
	H5N1/Dil	PIV(M12)	209	107	51.2	44.2	58.2	14.6	12.5	17.1
N = number of subjects with available results n/% = number/percentage of subjects with titer within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PII(M6) = Post vaccination at Day 180 PIII(M6+21D) = Post-vaccination Dose 3 at Day 21 after Month 6 *PIV(M6+42D) = Post-vaccination Dose 4 at Day 42 after Month 6 for control group PIII(M12) = Post-vaccination dose 3 at Month 12 PIV(M12) = Post-vaccination dose 4 at Month 12 for H5N1/Dil Group										
Secondary Outcome Variable(s): Seropositivity rates and GMTs of neutralizing (SN) antibody titers at Day 0 and Day 42 for A/Vietnam/1194/2004 and A/Indonesia/5/2005 – for all vaccine lots (ATP cohort for immunogenicity)										
Antibodies against	Group	Timing	N	≥ 1:28				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1/F1	PRE	68	13	19.1	10.6	30.5	17.8	15.4	20.5
		PII(D42)	67	67	100	94.6	100	274.4	232.7	323.5
	H5N1/F2	PRE	74	14	18.9	10.7	29.7	17.8	15.7	20.2
		PII(D42)	73	73	100	95.1	100	330.6	281.4	388.4
	H5N1/F3	PRE	69	15	21.7	12.7	33.3	18	15.7	20.8
		PII(D42)	69	68	98.6	92.2	100	283.1	234.2	342.3
	H5N1/F4	PRE	68	14	20.6	11.7	32.1	16.6	15.3	18.1
		PII(D42)	68	68	100	94.7	100	350.4	293.9	417.8
A/Indonesia/5/2005	H5N1/F1	PRE	68	4	5.9	1.6	14.4	14.6	14	15.3
		PII(D42)	68	63	92.6	83.7	97.6	74.3	61.9	89.3
	H5N1/F2	PRE	73	4	5.5	1.5	13.4	14.8	14	15.7
		PII(D42)	73	73	100	95.1	100	100.1	86	116.5
	H5N1/F3	PRE	69	4	5.8	1.6	14.2	15.3	13.7	17.2
		PII(D42)	69	64	92.8	83.9	97.6	80.4	66.7	96.9
	H5N1/F4	PRE	69	3	4.3	0.9	12.2	14.7	13.9	15.5
		PII(D42)	69	66	95.7	87.8	99.1	82.1	69.8	96.5
N = Number of subjects with available results n (%) = number (percentage) of seropositive subjects (SN titer ≥ 1:28) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit GMT = Geometric mean antibody titer PRE = Pre-vaccination Dose 1 (Day 0) PII(D42) = 21 days after second vaccination (Day 42)										
Secondary Outcome Variable(s): Seropositivity rates and GMTs for neutralizing antibody titers against the A/Vietnam1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 + 21 days, Month 6 + 42 days* for adults who received the booster dose at Month 6-pooled vaccine group (ATP cohort for Immunogenicity)										
Antibodies against	Group	Timing	N	≥ 1:28				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	184	183	99.5	97.0	100	170.5	154.6	188.0

		PIII(M6+21D)	184	184	100	98.0	100	1660.1	1435.9	1919.4
	H5N1/Dil	PII(M6)	47	24	51.1	36.1	65.9	29.4	23.0	37.6
		PIII(M6+21D)	47	46	97.9	88.7	99.9	248.1	187.0	329.0
		PIV(M6+42D)	45	44	97.8	88.2	99.9	447.1	331.9	602.1
A/Indonesia/5/2005	H5N1	PII(M6)	184	182	98.9	96.1	99.9	183.6	167.0	201.8
		PIII(M6+21D)	183	183	100	98.0	100	2917.5	2490.8	3417.3
	H5N1/Dil	PII(M6)	47	23	48.9	34.1	63.9	30.3	22.8	40.1
		PIII(M6+21D)	47	46	97.9	88.7	99.9	451.9	357.5	571.3
		PIV(M6+42D)	47	47	100	92.5	100	1075.8	834.7	1386.6

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PII(M6) = Post vaccination at Day 180

PIII(M6+21D) = Post-vaccination dose 3 at Day 21 after Month 6

*PIV(M6+42D) = Post-vaccination dose 4 at Day 42 after Month 6 for H5N1/Dil Group

Secondary Outcome Variable(s): Seropositivity rate and GMTs for H5N1 HI antibodies against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 0, Day 21, Day 42 and Month 6 for adults who have not received booster vaccination – pooled vaccine groups (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	663	45	6.8	5.0	9.0	5.6	5.4	5.7
		PI(D21)	661	386	58.4	54.5	62.2	23.3	20.8	26.1
		PII(D42)	659	631	95.8	93.9	97.2	215.7	197.4	235.7
		PII(M6)	665	410	61.7	57.8	65.4	18.5	17.0	20.3
		PII(M12)	559	239	42.8	38.6	47.0	11.4	10.4	12.5
A/Indonesia/5/2005	H5N1	PRE	663	6	0.9	0.3	2.0	5.1	5.0	5.1
		PI(D21)	661	84	12.7	10.3	15.5	6.1	5.8	6.3
		PII(D42)	659	421	63.9	60.1	67.6	24.8	22.3	27.5
		PII(M6)	665	119	17.9	15.1	21.0	6.3	6.0	6.5
		PII(M12)	559	69	12.3	9.7	15.4	6.2	5.9	6.5

N = number of subjects with available results

n/% = number/percentage of subjects with titer 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 dose 1 at Day 21

PII(D42) = Post-vaccination dose 2 at Day 42

PII(M6) = Post vaccination at Day 180

PII(M12) = Post-vaccination dose 2 at Month 12

Secondary Outcome Variable(s): Seropositivity rates and GMTs for neutralizing antibody titers against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 for adults who had not received the booster dose at Month 6-pooled vaccine group (ATP cohort for persistence)

Antibodies against	Group	Timing	N	≥ 1:28				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1	PII(M12)	166	165	99.4	96.7	100	215.5	191.4	242.7
A/Indonesia/5/2005	H5N1	PII(M12)	166	137	82.5	75.9	88.0	57.9	50.5	66.4

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PII(M12) = Post-vaccination dose 2 at Month 12

Secondary Outcome Variable(s): SCR for H5N1 HI antibody titer at Day 21 and Day 42 for A/Vietnam/1194/2004 and A/Indonesia/5/2005 – all vaccine lots (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL

A/Vietnam/1194/2004	H5N1/F1	PI(D21)	231	97	42	35.5	48.6
		PII(D42)	229	213	93	88.9	96
	H5N1/F2	PI(D21)	233	103	44.2	37.7	50.8
		PII(D42)	233	220	94.4	90.6	97
	H5N1/F3	PI(D21)	228	97	42.5	36	49.2
		PII(D42)	229	214	93.4	89.4	96.3
	H5N1/F4	PI(D21)	233	96	41.2	34.8	47.8
		PII(D42)	233	219	94	90.1	96.7
A/Indonesia/5/2005	H5N1/F1	PI(D21)	231	9	3.9	1.8	7.3
		PII(D42)	229	108	47.2	40.6	53.8
	H5N1/F2	PI(D21)	233	4	1.7	0.5	4.3
		PII(D42)	233	128	54.9	48.3	61.4
	H5N1/F3	PI(D21)	228	5	2.2	0.7	5
		PII(D42)	229	118	51.5	44.9	58.2
	H5N1/F4	PI(D21)	233	6	2.6	1	5.5
		PII(D42)	233	110	47.2	40.7	53.8

Seroconversion defined as:

- For initially seronegative subjects, antibody titer \geq 1:40 after vaccination
- For initially seropositive subjects, antibody titer after vaccination \geq 4 fold the pre-vaccination antibody titer

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

PI(D21) = Post-vaccination at Day 21

PII(D42) = 21 days after second vaccination (Day 42)

Secondary Outcome Variable(s): SCR for H5N1 HI antibodies against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 +21 days, Month 6 +42 days* for adults who received the booster dose at Month 6 – pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	254	96	37.8	31.8	44.1
		PIII(M6+21D)	254	244	96.1	92.9	98.1
	H5N1/Dil	PII(M6)	228	2	0.9	0.1	3.1
		PIII(M6+21D)	227	110	48.5	41.8	55.2
		PIV(M6+42D)	227	174	76.7	70.6	82.0
A/Indonesia/5/2005	H5N1	PII(M6)	254	9	3.5	1.6	6.6
		PIII(M6+21D)	254	241	94.9	91.4	97.2
	H5N1/Dil	PII(M6)	228	0	0.0	0.0	1.6
		PIII(M6+21D)	227	105	46.3	39.6	53.0
		PIV(M6+42D)	227	188	82.8	77.3	87.5

Seroconversion defined as:

- For initially seronegative subjects, antibody titer \geq 1:40 after vaccination
- For initially seropositive subjects, antibody titer after vaccination \geq 4 fold the pre-booster antibody titer

N = Number of subjects with pre- and post-booster vaccination results available

n/% = Number/percentage of seroconverted subjects

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

PII(M6) = Pre-booster blood sample at Month 6

PIII(M6+21D) = Post-booster dose 1 blood sample at Day 21

*PIV(M6+42D) = Post-booster dose 2 blood sample at Day 42 for control group

Secondary Outcome Variable(s): Booster SCR for H5N1 HI antibodies against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6 +21 days, Month 6 +42 days* for adults who received the booster dose at Month 6 – pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL

A/Vietnam/1194/2004	H5N1	PIII(M6+21D)	256	233	91.0	86.8	94.2
	H5N1/Dil	PIII(M6+21D)	228	112	49.1	42.5	55.8
		PIV(M6+42D)	228	173	75.9	69.8	81.3
A/Indonesia/5/2005	H5N1	PIII(M6+21D)	256	241	94.1	90.5	96.7
	H5N1/Dil	PIII(M6+21D)	228	106	46.5	39.9	53.2
		PIV(M6+42D)	228	189	82.9	77.4	87.5
<p>Seroconversion defined as:</p> <ul style="list-style-type: none"> For initially seronegative subjects, antibody titer $\geq 1:40$ after vaccination For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-booster antibody titer <p>N = Number of subjects with pre- and post-booster vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M6) = Pre-booster blood sample at Month 6 PIII(M6+21D) = Post-booster dose 1 blood sample at Day 21 *PIV(M6+42D) = Post-booster dose 2 blood sample at Day 42 for H5N1/Dil Group</p>							
<p>Secondary Outcome Variable(s): Booster SCR for H5N1 HI antibodies against the A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 for adults who received the booster dose at Month 6 – pooled vaccine group (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PIII(M12)	228	93	40.8	34.3	47.5
	H5N1/Dil	PIV(M12)	209	57	27.3	21.4	33.8
A/Indonesia/5/2005	H5N1	PIII(M12)	228	140	61.4	54.8	67.8
	H5N1/Dil	PIV(M12)	209	67	32.1	25.8	38.8
<p>Seroconversion defined as:</p> <ul style="list-style-type: none"> For initially seronegative subjects, antibody titer $\geq 1:40$ after vaccination For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer <p>N = Number of subjects with pre- and post-booster vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PIII(M12) = Post-vaccination dose 3 at Month 12 PIV(M12) = Post-vaccination dose 4 at Month 12 for H5N1/Dil Group</p>							
<p>Secondary Outcome Variable(s): SCR for neutralizing antibody titer at Day 42 for A/Vietnam/1194/2004 and A/Indonesia/5/2005 – all vaccine lost (ATP cohort for immunogenicity)</p>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/F1	PII(D42)	67	64	95.5	87.5	99.1
	H5N1/F2	PII(D42)	73	70	95.9	88.5	99.1
	H5N1/F3	PII(D42)	69	64	92.8	83.9	97.6
	H5N1/F4	PII(D42)	68	68	100	94.7	100
A/Indonesia/5/2005	H5N1/F1	PII(D42)	68	61	89.7	79.9	95.8
	H5N1/F2	PII(D42)	73	70	95.9	88.5	99.1
	H5N1/F3	PII(D42)	69	61	88.4	78.4	94.9
	H5N1/F4	PII(D42)	69	63	91.3	82	96.7
<p>Seroconversion defined as: antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer 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) = 21 days after second vaccination (Day 42)</p>							
<p>Secondary Outcome Variable(s): Booster SCR for neutralizing antibody titers against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6 + 21 days and Month 6 + 42 days* for adults who received the booster dose at Month 6 – pooled vaccine group (ATP cohort for Immunogenicity)</p>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	

						LL	UL
A/Vietnam/1194/2004	H5N1	PIII(M6+21D)	184	140	76.1	69.3	82.1
	H5N1/Dil	PIII(M6+21D)	47	36	76.6	62.0	87.7
		PIV(M6+42D)	45	41	91.1	78.8	97.5
A/Indonesia/5/2005	H5N1	PIII(M6+21D)	183	165	90.2	84.9	94.1
	H5N1/Dil	PIII(M6+21D)	47	41	87.2	74.3	95.2
		PIV(M6+42D)	47	45	95.7	85.5	99.5
Seroconversion defined as: <ul style="list-style-type: none"> – For initially seronegative subjects, antibody titer $\geq 1:56$ after vaccination – For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer N = Number of subjects with pre- and post-booster vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PIII(M6+21D) = Post-vaccination dose 3 at Day 21 after Month 6 *PIV(M6+42D) = Post-vaccination dose 4 at Day 42 after Month 6 for H5N1/Dil Group							
Secondary Outcome Variable(s): SCR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 21, Day 42, Month 6 and Month 12 for adults who have not received booster at Month 6 – pooled vaccine groups (ATP cohort for persistence)							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PI(D21)	661	293	44.3	40.5	48.2
		PII(D42)	659	620	94.1	92.0	95.8
		PII(M6)	663	228	34.4	30.8	38.1
		PII(M12)	558	108	19.4	16.2	22.9
A/Indonesia/5/2005	H5N1	PI(D21)	661	18	2.7	1.6	4.3
		PII(D42)	659	328	49.8	45.9	53.7
		PII(M6)	663	11	1.7	0.8	2.9
		PII(M12)	558	25	4.5	2.9	6.5
Seroconversion defined as: <ul style="list-style-type: none"> – For initially seronegative subjects, antibody titer $\geq 1:40$ after vaccination – For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-booster antibody titer N = Number of subjects with pre- and post-booster vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PI (D21) = Post-dose 1 blood sample at day 21 PII(D42) = Post-dose 2 blood sample at day 42 PII(M6) = Pre-booster blood sample at month 6 PII(M12) = Post-vaccination dose 2 at Month 12							
Secondary Outcome Variable(s): SCR for neutralizing antibody titer against A/Vietnam/1194/2004 at Month 12 for subjects not boosted at Month 6 – pooled vaccine groups (pre-vaccination time point as Day 0) (ATP cohort for persistence)							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PII(M12)	23	20	87.0	66.4	97.2
A/Indonesia/5/2005	H5N1	PII(M12)	23	15	65.2	42.7	83.6
Seroconversion defined as: <ul style="list-style-type: none"> For initially seronegative subjects, antibody titer $\geq 1:56$ after vaccination For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer N = Number of subjects with pre- and post-booster vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M12) = Post-vaccination dose 2 at Month 12							
Secondary Outcome Variable(s): SCF at Day 21 and Day 42 for A/Vietnam/1194/2004 and A/Indonesia/5/2005 – all vaccine lots (ATP cohort for immunogenicity)							

Antibodies against	Group	Timing	N	SCF		
				Value	95% CI	
					LL	UL
A/Vietnam/1194/2004	H5N1/F1	PI(D21)	231	3.9	3.3	4.6
		PII(D42)	229	34.4	29.2	40.5
	H5N1/F2	PI(D21)	233	4.6	3.8	5.6
		PII(D42)	233	43.2	37	50.5
	H5N1/F3	PI(D21)	228	4.3	3.5	5.2
		PII(D42)	229	40.5	34.6	47.5
	H5N1/F4	PI(D21)	233	3.8	3.2	4.5
		PII(D42)	233	41.6	35.6	48.5
A/Indonesia/5/2005	H5N1/F1	PI(D21)	231	1.2	1.1	1.3
		PII(D42)	229	4.8	4	5.7
	H5N1/F2	PI(D21)	233	1.2	1.1	1.3
		PII(D42)	233	5.6	4.6	6.6
	H5N1/F3	PI(D21)	228	1.2	1.1	1.3
		PII(D42)	229	5.1	4.2	6.1
	H5N1/F4	PI(D21)	233	1.2	1.1	1.3
		PII(D42)	233	4.4	3.7	5.3

N = Number of subjects with pre- and post-vaccination results available

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

PI(D21) = Post-vaccination at Day 21

PII(D42) = 21 days after second vaccination (Day 42)

Secondary Outcome Variable(s): SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 + 21 days, Month 6 + 42* days for adults who received the booster dose at Month 6 – pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCF		
				Value	95% CI	
					LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	254	3.6	3.1	4.1
		PIII(M6+21D)	254	74.0	63.1	86.7
	H5N1/Dil	PII(M6)	228	1.0	1.0	1.1
		PIII(M6+21D)	227	5.3	4.4	6.4
		PIV(M6+42D)	227	13.4	11.2	16.0
A/Indonesia/5/2005	H5N1	PII(M6)	254	1.3	1.2	1.4
		PIII(M6+21D)	254	63.8	54.4	74.9
	H5N1/Dil	PII(M6)	228	1.0	1.0	1.0
		PIII(M6+21D)	227	4.9	4.0	5.9
		PIV(M6+42D)	227	18.9	15.8	22.6

N = Number of subjects with pre- and post-vaccination results available

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

PII(M6) = Pre-booster blood sample at Month 6

PIII(M6+21D) = Post-booster dose 1 blood sample at Day 21

*PIV(M6+42D) = Post-booster dose 2 blood sample at Day 42 for H5N1/Dil Group

Secondary Outcome Variable(s): Booster SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6 + 21 days, Month 6 + 42* days for adults who received the booster dose at Month 6 – pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCF		
				Value	95% CI	
					LL	UL
A/Vietnam/1194/2004	H5N1	PIII(M6+21D)	256	20.8	17.3	24.9
	H5N1/Dil	PIII(M6+21D)	228	5.2	4.3	6.2
		PIV(M6+42D)	228	13.2	11.1	15.8
A/Indonesia/5/2005	H5N1	PIII(M6+21D)	256	50.0	42.5	58.8
	H5N1/Dil	PIII(M6+21D)	228	4.9	4.1	5.9

		PIV(M6+42D)	228	19.0	15.9	22.7	
<p>N = Number of subjects with pre- and post-booster vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PIII(M6+21D)= Post-booster dose 1 blood sample at Day 21 *PIV(M6+42D)= Post-booster dose 2 blood sample at Day 42 for H5N1/Dil Group</p>							
<p>Secondary Outcome Variable(s): Booster SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 at Month 12 for Month 6-boosted subjects – pooled vaccine groups (ATP cohort for persistence – Pre booster time point Month 6)</p>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1	PIII(M12)	228	3.7	3.1	4.5	
	H5N1/Dil	PIV(M12)	209	2.5	2.1	2.9	
A/Indonesia/5/2005	H5N1	PIII(M12)	228	7.2	5.9	8.8	
	H5N1/Dil	PIV(M12)	209	2.9	2.5	3.4	
<p>N = Number of subjects with pre- and post-booster vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PIII(M12) = Post-vaccination dose 3 at Month 12 PIV(M12) = Post-vaccination dose 4 at Month 12</p>							
<p>Secondary Outcome Variable(s): SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 21, Day 42, Month 6 and Month 12 for adults who have not received booster at Month 6 – pooled vaccine groups (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1	PI(D21)	661	4.2	3.8	4.7	
		PII(D42)	659	38.8	35.4	42.5	
		PII(M6)	663	3.3	3.1	3.6	
		PII(M12)	558	2.0	1.9	2.2	
A/Indonesia/5/2005	H5N1	PI(D21)	661	1.2	1.2	1.3	
		PII(D42)	659	4.9	4.4	5.4	
		PII(M6)	663	1.2	1.2	1.3	
		PII(M12)	558	1.2	1.2	1.3	
<p>N = Number of subjects with pre- and post-booster vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PI(D21) = Post-dose 1 blood sample at Day 21 PII(D42) = Post-dose 2 blood sample at Day 42 PII(M6) =Pre-booster blood sample at month 6 PII(M12) = Post-vaccination dose 2 at Month 12</p>							
<p>Secondary Outcome Variable(s): SPR for anti-HA antibody titer at Days 0, 21 and 42 – all vaccine lots (ATP cohort for immunogenicity)</p>							
Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/F1	PRE	233	4	1.7	0.5	4.3
		PI(D21)	231	102	44.2	37.6	50.8
		PII(D42)	229	213	93	88.9	96
	H5N1/F2	PRE	235	3	1.3	0.3	3.7
		PI(D21)	233	108	46.4	39.8	53
		PII(D42)	233	223	95.7	92.2	97.9
	H5N1/F3	PRE	231	5	2.2	0.7	5
		PI(D21)	228	102	44.7	38.2	51.4
		PII(D42)	229	215	93.9	90	96.6
	H5N1/F4	PRE	234	3	1.3	0.3	3.7
		PI(D21)	233	100	42.9	36.5	49.5

		PII(D42)	233	220	94.4	90.6	97
A/Indonesia/5/2005	H5N1/F1	PRE	233	1	0.4	0	2.4
		PI(D21)	231	10	4.3	2.1	7.8
		PII(D42)	229	108	47.2	40.6	53.8
	H5N1/F2	PRE	235	0	0	0	1.6
		PI(D21)	233	4	1.7	0.5	4.3
		PII(D42)	233	128	54.9	48.3	61.4
	H5N1/F3	PRE	231	0	0	0	1.6
		PI(D21)	228	6	2.6	1	5.6
		PII(D42)	229	118	51.5	44.9	58.2
	H5N1/F4	PRE	234	0	0	0	1.6
		PI(D21)	233	7	3	1.2	6.1
		PII(D42)	233	110	47.2	40.7	53.8

N = Number of subjects with available results

n (%) = Number (percentage) of seroprotected subjects (anti-HA antibody titer \geq 1:40)

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) = 21 days after second vaccination (Day 42)

Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 + 21 days, Month 6 + 42* days for adults who received the booster dose at Month 6 –pooled vaccine groups (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	256	103	40.2	34.2	46.5
		PIII(M6+21D)	256	247	96.5	93.4	98.4
	H5N1/Dil	PII(M6)	229	4	1.7	0.5	4.4
		PIII(M6+21D)	228	121	53.1	46.4	59.7
		PIV(M6+42D)	228	180	78.9	73.1	84.1
A/Indonesia/5/2005	H5N1	PII(M6)	256	9	3.5	1.6	6.6
		PIII(M6+21D)	256	243	94.9	91.5	97.3
	H5N1/Dil	PII(M6)	229	0	0.0	0.0	1.6
		PIII(M6+21D)	228	106	46.5	39.9	53.2
		PIV(M6+42D)	228	189	82.9	77.4	87.5

N = Number of subjects with available results

n/% = Number/percentage of seroprotected subjects (HI titer \geq 1:40)

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

PII(M6) = Pre-booster blood sample at Month 6

PIII(M6+21D)= Post-booster dose 1 blood sample at Day 21

*PIV(M6+42D)= Post-booster dose 2 blood sample at Day 42 for H5N1/Dil Group

Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 6, Month 6 + 21 days, Month 6 + 42 days* and Month 12 for adults who have received booster at Month 6- pooled vaccine group (ATP cohort for persistence)

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PII(M6)	251	103	41.0	34.9	47.4
		PIII(M6+21D)	251	242	96.4	93.3	98.3
		PIII(M12)	228	178	78.1	72.1	83.3
	H5N1/Dil	PII(M6)	224	4	1.8	0.5	4.5
		PIII(M6+21D)	223	120	53.8	47.0	60.5
		PIV(M6+42D)	223	177	79.4	73.5	84.5
		PIV(M12)	209	65	31.1	24.9	37.9
A/Indonesia/5/2005	H5N1	PII(M6)	251	9	3.6	1.7	6.7
		PIII(M6+21D)	251	238	94.8	91.3	97.2

		PIII(M12)	228	151	66.2	59.7	72.3
	H5N1/Dil	PII(M6)	224	0	0.0	0.0	1.6
		PIII(M6+21D)	223	105	47.1	40.4	53.9
		PIV(M6+42D)	223	186	83.4	77.9	88.0
		PIV(M12)	209	67	32.1	25.8	38.8

N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer \geq 40 1/DIL)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PII(M6) = Post vaccination at Day 180
PIII(M6+21D) = Post-vaccination dose 3 at Day 21 after Month 6
*PIV(M6+42D) = Post-vaccination dose 4 at Day 42 after Month 6 for control group
PIII(M12) = Post-vaccination dose 3 at Month 12
PIV(M12) = Post-vaccination dose 4 at Month 12 for H5N1/Dil Group

Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Day 0, Day 21, Day 42, Month 6 and Month 12 for adults who have not received booster at Month 6 – pooled vaccine groups (ATP cohort for persistence)

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1	PRE	663	11	1.7	0.8	2.9
		PI(D21)	661	307	46.4	42.6	50.3
		PII(D42)	659	623	94.5	92.5	96.1
		PII(M6)	665	247	37.1	33.5	40.9
		PII(M12)	559	131	23.4	20.0	27.2
A/Indonesia/5/2005	H5N1	PRE	663	1	0.2	0.0	0.8
		PI(D21)	661	21	3.2	2.0	4.8
		PII(D42)	659	328	49.8	45.9	53.7
		PII(M6)	665	13	2.0	1.0	3.3
		PII(M12)	559	26	4.7	3.1	6.7

N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer \geq 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE= Pre-booster blood sample at day 0
PI (D21) = Post-dose 1 blood sample at Day 21
PII(D42) = Post-dose 2 blood sample at Day 42
PII(M6) =Pre-booster blood sample at Month 6
PII(M12) = Post-vaccination dose 2 at Month 12

Secondary Outcome Variable(s): Descriptive statistics on the frequency cytokine-positive T-cells (per million) for CD4-CD40L, CD4-All doubles, CD4-IL2, CD4-TNF- α , and CD4-IFN- γ at Month 6, Month 6 + Day 21 and Month 6 + Day 42 and Month 12 for subjects boosted at Month 6 (ATP cohort for Immunogenicity)

Test description	Stimulating antigen	Group	Timing	N	GM	Mean	SD
CD4-All doubles	H5N1 Vietnam	H5N1	PII(M6)	3	1642.79	1773.00	748.95
			PIII(M6+21D)	5	6078.81	7049.60	3832.18
			PIII(M12)	7	2886.09	3197.29	1428.81
		H5N1/Dil	PII(M6)	3	651.35	681.00	243.30
			PIII(M6+21D)	5	3775.68	3898.00	1133.03
			PIV(M6+42D)	8	3734.34	4472.75	2352.87
			PIV(M12)	7	2064.26	2141.57	617.49
CD4-CD40L	H5N1 Vietnam	H5N1	PII(M6)	3	1579.97	1720.00	765.05
			PIII(M6+21D)	5	5873.28	6849.60	3814.40
			PIII(M12)	7	2854.55	3164.43	1419.03
		H5N1/Dil	PII(M6)	3	647.47	666.00	187.51
			PIII(M6+21D)	5	3764.63	3885.60	1116.51
			PIV(M6+42D)	8	3632.63	4330.88	2255.37
			PIV(M12)	7	2070.28	2148.57	617.94

CD4-IFN-γ	H5N1 Vietnam	H5N1	PII(M6)	3	805.12	921.00	489.49
			PIII(M6+21D)	5	2903.51	3585.40	2106.34
			PIII(M12)	7	1393.06	1592.57	781.64
		H5N1/Dil	PII(M6)	3	369.42	409.00	227.75
			PIII(M6+21D)	5	1556.24	1665.60	659.04
			PIV(M6+42D)	8	1720.62	2332.25	1640.24
			PIV(M12)	7	918.79	1016.86	509.21
CD4-IL2	H5N1 Vietnam	H5N1	PII(M6)	3	1563.55	1653.33	608.11
			PIII(M6+21D)	5	5642.14	6526.40	3484.66
			PIII(M12)	7	2752.29	3043.86	1386.80
		H5N1/Dil	PII(M6)	3	667.57	688.33	212.18
			PIII(M6+21D)	5	3555.09	3674.00	1062.72
			PIV(M6+42D)	8	3596.13	4177.25	2092.28
			PIV(M12)	7	2031.78	2098.86	558.63
CD4-TNF-α	H5N1 Vietnam	H5N1	PII(M6)	3	1356.46	1443.00	554.28
			PIII(M6+21D)	5	4635.29	5544.20	3219.20
			PIII(M12)	7	2198.62	2501.43	1190.18
		H5N1/Dil	PII(M6)	3	503.30	538.33	224.38
			PIII(M6+21D)	5	2562.64	2671.00	863.72
			PIV(M6+42D)	8	2481.01	3296.25	2060.05
			PIV(M12)	7	1580.88	1649.14	504.41

All doubles: T-cells producing at least 2 cytokines

N = number of subjects with available results

GM= Geometric Mean

SD = Standard Deviation

Secondary Outcome Variable(s): Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD8-All doubles, CD8-CD40L, CD8-IL2, CD8-TNF- α and CD8-IFN- γ at Month 6, Month 6 + Day 21 and Month 6 + day 42 and Month 12 for subjects boosted at Month 6 (ATP cohort for immunogenicity)

Test description	Stimulating antigen	Group	Timing	N	GM	Mean	SD
CD8-All doubles	H5N1 Vietnam	H5N1	PII(M6)	3	18.60	55.00	49.76
			PIII(M6+21D)	5	23.62	50.00	47.94
			PIII(M12)	7	16.06	50.86	75.46
		H5N1/Dil	PII(M6)	3	175.51	306.00	363.19
			PIII(M6+21D)	5	30.03	62.60	47.45
			PIV(M6+42D)	8	32.00	257.63	484.86
			PIV(M12)	7	34.44	232.00	383.34
CD8-CD40L	H5N1 Vietnam	H5N1	PII(M6)	3	2.08	3.67	4.62
			PIII(M6+21D)	5	8.51	23.80	24.65
			PIII(M12)	7	5.46	12.29	12.11
		H5N1/Dil	PII(M6)	3	2.41	5.33	7.51
			PIII(M6+21D)	5	5.19	31.20	52.39
			PIV(M6+42D)	8	1.89	5.38	10.85
			PIV(M12)	7	1.60	4.71	9.83
CD8-IFN-γ	H5N1 Vietnam	H5N1	PII(M6)	3	16.25	44.00	37.24
			PIII(M6+21D)	5	19.05	36.00	30.74
			PIII(M12)	7	15.30	53.00	83.70
		H5N1/Dil	PII(M6)	3	180.37	331.33	407.67
			PIII(M6+21D)	5	24.91	50.60	40.50
			PIV(M6+42D)	8	26.20	257.00	485.24
			PIV(M12)	7	19.21	211.71	375.25
CD8-IL2	H5N1 Vietnam	H5N1	PII(M6)	3	7.15	22.67	33.29
			PIII(M6+21D)	5	29.47	39.40	38.00
			PIII(M12)	7	13.49	38.00	52.50
		H5N1/Dil	PII(M6)	3	67.78	162.00	229.00

			PIII(M6+21D)	5	19.03	36.60	33.08
			PIV(M6+42D)	8	21.83	147.88	246.47
			PIV(M12)	7	32.83	133.14	168.94
CD8-TNF-α	H5N1 Vietnam	H5N1	PII(M6)	3	18.88	58.67	58.52
			PIII(M6+21D)	5	13.28	24.60	23.56
			PIII(M12)	7	5.39	34.00	63.90
		H5N1/Dil	PII(M6)	3	171.53	290.00	335.72
			PIII(M6+21D)	5	26.17	50.60	34.95
			PIV(M6+42D)	8	42.67	219.88	443.70
			PIV(M12)	7	28.10	204.43	376.77
All doubles: T-cells producing at least 2 cytokines N = number of subjects with available results GM= Geometric Mean SD = Standard Deviation							
Secondary Outcome Variable(s): Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD4-CD40L, CD4-All doubles, CD4-IL2, CD4-TNF- α and CD4-IFN- γ at Month 6 and Month 12 for subjects not boosted at Month 6 (ATP cohort for immunogenicity)							
Test description	Stimulating antigen	Group	Timing	N	GM	Mean	SD
CD4-All doubles	H5N1 Vietnam	H5N1	PII(M6)	13	2308.82	2529.54	1063.65
			PII(M12)	30	1830.56	2098.17	1287.49
CD4 CD40L	H5N1 Vietnam	H5N1	PII(M6)	13	2198.02	2407.31	1009.26
			PII(M12)	30	1756.95	2004.27	1193.53
CD4 IFN-γ	H5N1 Vietnam	H5N1	PII(M6)	13	1145.98	1387.38	840.81
			PII(M12)	30	946.69	1184.07	992.44
CD4 IL2	H5N1 Vietnam	H5N1	PII(M6)	13	2156.20	2341.15	936.20
			PII(M12)	30	1675.60	1912.60	1130.58
CD4 TNF-α	H5N1 Vietnam	H 5N1	PII(M6)	13	1761.34	1960.62	891.12
			PII(M12)	30	1405.08	1599.20	945.88
All doubles: T-cells producing at least 2 cytokines N = number of subjects with available results. GM= Geometric Mean SD = Standard Deviation							
Secondary Outcome Variable(s): Descriptive Statistics on the frequency cytokine-positive T-cells (per million T-cells) for CD8-All doubles, CD8-CD40L, CD8-IL2, CD8-TNF α and CD8-IFN- γ at Month 6 and Month 12 for subjects not boosted at Month 6 (ATP cohort for immunogenicity)							
Test description	Stimulating antigen	Group	Timing	N	GM	Mean	SD
CD8-All doubles	H5N1 Vietnam	H5N1	PII(M6)	13	9.39	82.69	166.59
			PII(M12)	30	25.40	106.13	173.19
CD8 CD40L	H5N1 Vietnam	H5N1	PII(M6)	13	2.80	9.62	13.90
			PII(M12)	30	1.67	4.53	8.18
CD8 IFNγ	H5N1 Vietnam	H5N1	PII(M6)	13	8.51	67.23	145.99
			PII(M12)	30	20.70	102.93	161.31
CD8 IL2	H5N1 Vietnam	H5N1	PII(M6)	13	14.71	66.00	117.35
			PII(M12)	30	15.75	70.90	128.03
CD8 TNF-α	H5N1 Vietnam	H5N1	PII(M6)	13	12.93	59.08	111.73
			PII(M12)	30	24.68	89.30	140.96
All doubles: T-cells producing at least 2 cytokines N = number of subjects with available results; GM= Geometric Mean SD = Standard Deviation							
Secondary Outcome Variable(s): Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-primary vaccination period following each dose and overall (Total vaccinated cohort) - modified grading							
				H5N1 Group			
				95 % CI			

Symptom	Intensity	N	n	%	LL	UL
Dose 1						
Ecchymosis	Any	954	8	0.8	0.4	1.6
	> 100 mm	954	0	0.0	0.0	0.4
Induration	Any	954	54	5.7	4.3	7.3
	> 100 mm	954	0	0.0	0.0	0.4
Pain	Any	954	779	81.7	79.1	84.1
	Grade 3	954	31	3.2	2.2	4.6
Redness	Any	954	36	3.8	2.7	5.2
	> 100 mm	954	0	0.0	0.0	0.4
Swelling	Any	954	84	8.8	7.1	10.8
	> 100 mm	954	1	0.1	0.0	0.6
Dose 2						
Ecchymosis	Any	944	3	0.3	0.1	0.9
	> 100 mm	944	0	0.0	0.0	0.4
Induration	All	944	38	4.0	2.9	5.5
	> 100 mm	944	0	0.0	0.0	0.4
Pain	Any	944	674	71.4	68.4	74.3
	Grade 3	944	21	2.2	1.4	3.4
Redness	Any	944	33	3.5	2.4	4.9
	> 100 mm	944	1	0.1	0.0	0.6
Swelling	Any	944	70	7.4	5.8	9.3
	> 100 mm	944	0	0.0	0.0	0.4
Across Doses						
Ecchymosis	Any	954	10	1.0	0.5	1.9
	> 100 mm	954	0	0.0	0.0	0.4
Induration	Any	954	76	8.0	6.3	9.9
	> 100 mm	954	0	0.0	0.0	0.4
Pain	Any	954	830	87.0	84.7	89.1
	Grade 3	954	49	5.1	3.8	6.7
Redness	Any	954	64	6.7	5.2	8.5
	> 100 mm	954	1	0.1	0.0	0.6
Swelling	Any	954	114	11.9	10.0	14.2
	> 100 mm	954	1	0.1	0.0	0.6
<p>Any = occurrence of any solicited local symptom regardless of their intensity grade Grade 3 pain = significant pain at rest; prevented normal activities as assessed by inability to attend/do work or school 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</p>						
Secondary Outcome Variable(s): Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-primary vaccination period following each dose and overall (Total vaccinated cohort) - modified grading						
H5N1 Group						
95 % CI						
Symptom	Intensity/Relationship	N	n	%	LL	UL
Dose 1						
Arthralgia	Any	954	118	12.4	10.3	14.6
	Grade 3	954	5	0.5	0.2	1.2
	Related	954	109	11.4	9.5	13.6
Fatigue	Any	954	411	43.1	39.9	46.3
	Grade 3	954	18	1.9	1.1	3.0
	Related	954	395	41.4	38.3	44.6
Fever/(Axillary) (°C)	Any	954	21	2.2	1.4	3.3
	≥ 39.0	954	5	0.5	0.2	1.2
	Related	954	20	2.1	1.3	3.2
Headache	Any	954	238	24.9	22.2	27.8

	Grade 3	954	13	1.4	0.7	2.3
	Related	954	215	22.5	19.9	25.3
Myalgia	Any	954	478	50.1	46.9	53.3
	Grade 3	954	14	1.5	0.8	2.4
	Related	954	462	48.4	45.2	51.7
Shivering	Any	954	44	4.6	3.4	6.1
	Grade 3	954	2	0.2	0.0	0.8
	Related	954	42	4.4	3.2	5.9
Sweating	Any	954	86	9.0	7.3	11.0
	Grade 3	954	0	0.0	0.0	0.4
	Related	954	78	8.2	6.5	10.1
Dose 2						
Arthralgia	Any	944	147	15.6	13.3	18.0
	Grade 3	944	4	0.4	0.1	1.1
	Related	944	147	15.6	13.3	18.0
Fatigue	Any	944	435	46.1	42.9	49.3
	Grade 3	944	26	2.8	1.8	4.0
	Related	944	432	45.8	42.5	49.0
Fever/(Axillary) (°C)	Any	944	27	2.9	1.9	4.1
	≥ 39.0	944	3	0.3	0.1	0.9
	Related	944	27	2.9	1.9	4.1
Headache	Any	944	269	28.5	25.6	31.5
	Grade 3	944	16	1.7	1.0	2.7
	Related	944	265	28.1	25.2	31.1
Myalgia	Any	944	429	45.4	42.2	48.7
	Grade 3	944	17	1.8	1.1	2.9
	Related	944	427	45.2	42.0	48.5
Shivering	Any	944	75	7.9	6.3	9.9
	Grade 3	944	4	0.4	0.1	1.1
	Related	944	74	7.8	6.2	9.7
Sweating	Any	944	90	9.5	7.7	11.6
	Grade 3	944	4	0.4	0.1	1.1
	Related	944	87	9.2	7.4	11.2
Across Doses						
Arthralgia	Any	954	212	22.2	19.6	25.0
	Grade 3	954	8	0.8	0.4	1.6
	Related	954	206	21.6	19.0	24.3
Fatigue	Any	954	559	58.6	55.4	61.7
	Grade 3	954	38	4.0	2.8	5.4
	Related	954	550	57.7	54.4	60.8
Fever/(Axillary) (°C)	Any	954	45	4.7	3.5	6.3
	≥ 39.0	954	8	0.8	0.4	1.6
	Related	954	44	4.6	3.4	6.1
Headache	Any	954	380	39.8	36.7	43.0
	Grade 3	954	26	2.7	1.8	4.0
	Related	954	367	38.5	35.4	41.6
Myalgia	Any	954	610	63.9	60.8	67.0
	Grade 3	954	29	3.0	2.0	4.3
	Related	954	599	62.8	59.6	65.9
Shivering	Any	954	105	11.0	9.1	13.2
	Grade 3	954	6	0.6	0.2	1.4
	Related	954	103	10.8	8.9	12.9
Sweating	Any	954	143	15.0	12.8	17.4
	Grade 3	954	4	0.4	0.1	1.1
	Related	954	135	14.2	12.0	16.5
Any: occurrence of any solicited general symptom regardless of their intensity grade or relationship to vaccination						

Grade 3 symptom = prevented normal everyday activities as assessed by inability to attend/do work or school, or required intervention of a physician/healthcare provider						
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 Variable(s): Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-booster vaccination period – pooled vaccine groups (Total vaccinated cohort – <i>Booster at Month 6</i>) - modified grading						
		H5N1 Group				
		Booster Dose			95 % CI	
Symptom	Intensity	N	n	%	LL	UL
Ecchymosis	Any	265	2	0.8	0.1	2.7
	>100 mm	265	0	0.0	0.0	1.4
Induration	Any	265	21	7.9	5.0	11.9
	>100 mm	265	0	0.0	0.0	1.4
Pain	Any	265	214	80.8	75.5	85.3
	Grade 3	265	14	5.3	2.9	8.7
Redness	Any	265	16	6.0	3.5	9.6
	>100 mm	265	0	0.0	0.0	1.4
Swelling	Any	265	36	13.6	9.7	18.3
	>100 mm	265	0	0.0	0.0	1.4
		H5N1/Dil Group				
					95 % CI	
Symptom	Intensity	N	n	%	LL	UL
Booster Dose 1						
Ecchymosis	All	235	1	0.4	0.0	2.3
	>100 mm	235	0	0.0	0.0	1.6
Induration	All	235	14	6.0	3.3	9.8
	>100 mm	235	1	0.4	0.0	2.3
Pain	All	235	187	79.6	73.8	84.5
	Grade 3	235	11	4.7	2.4	8.2
Redness	All	235	7	3.0	1.2	6.0
	>100 mm	235	0	0.0	0.0	1.6
Swelling	All	235	24	10.2	6.7	14.8
	>100 mm	235	0	0.0	0.0	1.6
Booster Dose 2						
Ecchymosis	All	234	2	0.9	0.1	3.1
	>100 mm	234	0	0.0	0.0	1.6
Induration	All	234	14	6.0	3.3	9.8
	>100 mm	234	0	0.0	0.0	1.6
Pain	All	234	159	67.9	61.6	73.9
	Grade 3	234	8	3.4	1.5	6.6
Redness	All	234	15	6.4	3.6	10.4
	>100 mm	234	0	0.0	0.0	1.6
Swelling	All	234	22	9.4	6.0	13.9
	>100 mm	234	0	0.0	0.0	1.6
Across Booster Doses						
Ecchymosis	All	235	2	0.9	0.1	3.0
	>100 mm	235	0	0.0	0.0	1.6
Induration	All	235	21	8.9	5.6	13.3
	>100 mm	235	1	0.4	0.0	2.3
Pain	All	235	198	84.3	79.0	88.7
	Grade 3	235	17	7.2	4.3	11.3
Redness	All	235	16	6.8	3.9	10.8
	>100 mm	235	0	0.0	0.0	1.6

Swelling	All	235	33	14.0	9.9	19.2
	>100 mm	235	0	0.0	0.0	1.6

Any = occurrence of any solicited local symptom regardless of their intensity grade

Grade 3 pain = significant pain at rest; prevented normal activities as assessed by inability to attend/do work or school

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 Variable(s): Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period – pooled vaccine groups (Total vaccinated cohort – *Booster at Month 6*) - modified grading

		H5N1 Group				
		Booster Dose			95 % CI	
Symptom	Intensity/Relationship	N	n	%	LL	UL
Arthralgia	Any	265	57	21.5	16.7	27.0
	Grade 3	265	4	1.5	0.4	3.8
	Related	265	57	21.5	16.7	27.0
Fatigue	Any	265	165	62.3	56.1	68.1
	Grade 3	265	15	5.7	3.2	9.2
	Related	265	164	61.9	55.7	67.8
Fever/(Axillary) (°C)	Any	265	16	6.0	3.5	9.6
	≥ 39.0	265	3	1.1	0.2	3.3
	Related	265	16	6.0	3.5	9.6
Headache	Any	265	120	45.3	39.2	51.5
	Grade 3	265	8	3.0	1.3	5.9
	Related	265	117	44.2	38.1	50.4
Myalgia	Any	265	169	63.8	57.7	69.6
	Grade 3	265	15	5.7	3.2	9.2
	Related	265	168	63.4	57.3	69.2
Shivering	Any	265	47	17.7	13.3	22.9
	Grade 3	265	5	1.9	0.6	4.3
	Related	265	47	17.7	13.3	22.9
Sweating	Any	265	25	9.4	6.2	13.6
	Grade 3	265	0	0.0	0.0	1.4
	Related	265	23	8.7	5.6	12.7
		H5N1/Dil Group				
		Booster Dose 1			95 % CI	
Symptom	Intensity/Relationship	N	n	%	LL	UL
Arthralgia	Any	235	33	14.0	9.9	19.2
	Grade 3	235	1	0.4	0.0	2.3
	Related	235	32	13.6	9.5	18.7
Fatigue	Any	235	96	40.9	34.5	47.4
	Grade 3	235	3	1.3	0.3	3.7
	Related	235	95	40.4	34.1	47.0
Fever/(Axillary) (°C)	Any	235	7	3.0	1.2	6.0
	≥ 39.0	235	0	0.0	0.0	1.6
	Related	235	7	3.0	1.2	6.0
Headache	Any	235	66	28.1	22.4	34.3
	Grade 3	235	1	0.4	0.0	2.3
	Related	235	65	27.7	22.0	33.9
Myalgia	Any	235	126	53.6	47.0	60.1
	Grade 3	235	4	1.7	0.5	4.3
	Related	235	126	53.6	47.0	60.1
Shivering	Any	235	18	7.7	4.6	11.8

	Grade 3	235	0	0.0	0.0	1.6
	Related	235	18	7.7	4.6	11.8
Sweating	Any	235	15	6.4	3.6	10.3
	Grade 3	235	0	0.0	0.0	1.6
	Related	235	15	6.4	3.6	10.3
Booster Dose 2						
Arthralgia	Any	234	38	16.2	11.8	21.6
	Grade 3	234	3	1.3	0.3	3.7
	Related	234	37	15.8	11.4	21.1
Fatigue	Any	234	95	40.6	34.2	47.2
	Grade 3	234	4	1.7	0.5	4.3
	Related	234	94	40.2	33.8	46.8
Fever/(Axillary) (°C)	Any	234	9	3.8	1.8	7.2
	≥ 39.0	234	1	0.4	0.0	2.4
	Related	234	9	3.8	1.8	7.2
Headache	Any	234	69	29.5	23.7	35.8
	Grade 3	234	3	1.3	0.3	3.7
	Related	234	68	29.1	23.3	35.3
Myalgia	Any	234	101	43.2	36.7	49.8
	Grade 3	234	5	2.1	0.7	4.9
	Related	234	100	42.7	36.3	49.3
Shivering	Any	234	30	12.8	8.8	17.8
	Grade 3	234	2	0.9	0.1	3.1
	Related	234	29	12.4	8.5	17.3
Sweating	Any	234	21	9.0	5.6	13.4
	Grade 3	234	1	0.4	0.0	2.4
	Related	234	21	9.0	5.6	13.4
Across Doses						
Arthralgia	Any	235	54	23.0	17.8	28.9
	Grade 3	235	4	1.7	0.5	4.3
	Related	235	52	22.1	17.0	28.0
Fatigue	Any	235	121	51.5	44.9	58.0
	Grade 3	235	6	2.6	0.9	5.5
	Related	235	119	50.6	44.1	57.2
Fever/(Axillary) (°C)	Any	235	14	6.0	3.3	9.8
	≥ 39.0	235	1	0.4	0.0	2.3
	Related	235	14	6.0	3.3	9.8
Headache	Any	235	97	41.3	34.9	47.9
	Grade 3	235	3	1.3	0.3	3.7
	Related	235	96	40.9	34.5	47.4
Myalgia	Any	235	141	60.0	53.4	66.3
	Grade 3	235	9	3.8	1.8	7.1
	Related	235	141	60.0	53.4	66.3
Shivering	Any	235	38	16.2	11.7	21.5
	Grade 3	235	2	0.9	0.1	3.0
	Related	235	37	15.7	11.3	21.0
Sweating	Any	235	28	11.9	8.1	16.8
	Grade 3	235	1	0.4	0.0	2.3
	Related	235	28	11.9	8.1	16.8

Any: occurrence of any solicited general symptom regardless of their intensity grade or relationship to vaccination
Grade 3 symptom = prevented normal everyday activities as assessed by inability to attend/do work or school, or required intervention of a physician/healthcare provider
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

Safety Results: Number (%) of subjects with unsolicited adverse events during the primary phase (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 = 961
At least one unsolicited adverse event		308 (32.0)
Upper respiratory tract infection		34 (3.5)
Nasopharyngitis		28 (2.9)
Pharyngolaryngeal pain		26 (2.7)
Influenza like illness		24 (2.5)
Dizziness		23 (2.4)
Cough		19 (2.0)
Headache		17 (1.8)
Rhinorrhoea		15 (1.6)
Diarrhea		13 (1.4)
Abdominal pain upper		12 (1.2)
Injection site pruritus		12 (1.2)
- : Adverse event absent or not meeting the counting rule: > 30 subjects/treatment group and <= 3 groups: display the most frequent 10 events in each treatment group		
Safety Results: Number (%) of subjects with unsolicited AEs during the post-booster vaccination period – pooled vaccine groups (Total vaccinated cohort – Booster at Month 6)		
Most frequent adverse events - On-Therapy (occurring within Day 0-29 following vaccination)	H5N1 Group N = 265	H5N1/Dil Group N = 236
Subjects with any AE(s), n (%)	65 (24.5)	54 (22.9)
Nasopharyngitis	8 (3.0)	10 (4.2)
Upper respiratory tract infection	2 (0.8)	9 (3.8)
Influenza like illness	7 (2.6)	3 (1.3)
Lymphadenopathy	7 (2.6)	2 (0.8)
Pharyngolaryngeal pain	4 (1.5)	3 (1.3)
Headache	2 (0.8)	4 (1.7)
Dizziness	3 (1.1)	3 (1.3)
Axillary pain	4 (1.5)	-
Rhinitis allergic	4 (1.5)	-
Rhinorrhoea	-	3 (1.3)
Abdominal pain upper	2 (0.8)	-
Arthralgia	2 (0.8)	-
Asthenia	2 (0.8)	-
Conjunctival haemorrhage	2 (0.8)	-
Cough	-	2 (0.8)
Diarrhoea	2 (0.8)	-
Injection site pruritus	2 (0.8)	-
Injection site warmth	-	2 (0.8)
Muscle strain	-	2 (0.8)
Nausea	2 (0.8)	-
Pain	-	2 (0.8)
- : Adverse event absent or not meeting the selected rule: > 30 subjects per treatment group and ≤ 3 groups, display the most frequent 10 events in each group		
Safety Results: Number (%) of subjects with SAEs during the primary phase (Total Vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N = 961	
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	7 (0.7) [0]	
Appendicitis	2 (0.2) [0]	
Accident death	1 (0.1) [0]	
Cervical polyp	1 (0.1) [0]	
Head injury	1 (0.1) [0]	
Vaginal haemorrhage	1 (0.1) [0]	

Skin laceration	1 (0.1) [0]	
Radius fracture	1 (0.1) [0]	
Uterine leiomyoma	1 (0.1) [0]	
Fatal SAEs	H5N1 Group N = 961	
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	1 (0.1) [0]	
Accidental death	1 (0.1) [0]	
Safety Results: Number (%) of subjects with SAEs from Day 180 to Month 12 for Month 6-boosted subjects - pooled vaccine groups (Total Vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N = 265	H5N1/Dil Group N = 236
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	3 (1.1) [0]	5 (2.1) [0]
Colonic polyp	0 (0.0) [0]	1 (0.4) [0]
Ileus	1 (0.4) [0]	0 (0.0) [0]
Tooth disorder	1 (0.4) [0]	0 (0.0) [0]
Tooth impacted	1 (0.4) [0]	0 (0.0) [0]
Acute tonsillitis	1 (0.4) [0]	0 (0.0) [0]
Helicobacter gastritis	0 (0.0) [0]	1 (0.4) [0]
Pyelonephritis acute	1 (0.4) [0]	0 (0.0) [0]
Clavicle fracture	0 (0.0) [0]	1 (0.4) [0]
Ligament rupture	0 (0.0) [0]	1 (0.4) [0]
Benign ovarian tumour	0 (0.0) [0]	1 (0.4) [0]
Anxiety	0 (0.0) [0]	1 (0.4) [0]
Fatal SAEs	H5N1 Group N = 265	H5N1/Dil Group N = 236
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 from Day 180 to Month 12 for Month 6-non boosted subjects - pooled vaccine groups (Total cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
Preferred Term (CODE)	H5N1 Group N = 672	
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	15 (2.2) [0]	
Normochromic normocytic anaemia	1(0.1) [0]	
Atrioventricular block second degree	1(0.1) [0]	
Abdominal pain	1(0.1) [0]	
Anorectal disorder	1(0.1) [0]	
Gastritis	1(0.1) [0]	
Haemorrhoids	1(0.1) [0]	
Pyrexia	1(0.1) [0]	
Anal abscess	1(0.1) [0]	
Urinary tract infection	1(0.1) [0]	
Contusion	2(0.3) [0]	
Facial bones fracture	1(0.1) [0]	
Ligament rupture	3(0.4) [0]	
Meniscus lesion	1(0.1) [0]	
Skin laceration	1(0.1) [0]	
Hypoalbuminaemia	1(0.1) [0]	
Uterine leiomyoma	1(0.1) [0]	
Headache	1(0.1) [0]	
Adjustment disorder	1(0.1) [0]	
Endometriosis	1(0.1) [0]	
Fatal SAEs	H5N1 Group N = 672	

Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	
Safety Results: Number (%) of subjects with SAEs during the entire study period pooled vaccine groups (Total cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1 Group N = 961	H5N1/Dil Group N = 245
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	25 (2.6) [0]	5 (2.0) [0]
Normochromic normocytic anaemia	1 (0.1) [0]	0 (0.0) [0]
Abdominal pain	1 (0.1) [0]	0 (0.0) [0]
Anorectal disorder	1 (0.1) [0]	0 (0.0) [0]
Gastritis	1 (0.1) [0]	0 (0.0) [0]
Haemorrhoids	1 (0.1) [0]	0 (0.0) [0]
Accidental death	1 (0.1) [0]	0 (0.0) [0]
Pyrexia	1 (0.1) [0]	0 (0.0) [0]
Appendicitis	2 (0.2) [0]	0 (0.0) [0]
Pyelonephritis acute	1 (0.1) [0]	0 (0.0) [0]
Urinary tract infection	1 (0.1) [0]	0 (0.0) [0]
Head injury	1 (0.1) [0]	0 (0.0) [0]
Ligament rupture	3 (0.3) [0]	1 (0.4) [0]
Meniscus lesion	1 (0.1) [0]	0 (0.0) [0]
Radius fracture	1 (0.1) [0]	0 (0.0) [0]
Skin laceration	2 (0.2) [0]	0 (0.0) [0]
Hypoalbuminaemia	1 (0.1) [0]	0 (0.0) [0]
Benign ovarian tumour	0 (0.0) [0]	1 (0.4) [0]
Uterine leiomyoma	2 (0.2) [0]	0 (0.0) [0]
Headache	1 (0.1) [0]	0 (0.0) [0]
Adjustment disorder	1 (0.1) [0]	0 (0.0) [0]
Anxiety	0 (0.0) [0]	1 (0.4) [0]
Cervical polyp	1 (0.1) [0]	0 (0.0) [0]
Endometriosis	1 (0.1) [0]	0 (0.0) [0]
Vaginal haemorrhage	1 (0.1) [0]	0 (0.0) [0]
Colonic polyp	0 (0.0) [0]	1 (0.4) [0]
Helicobacter gastritis	0 (0.0) [0]	1 (0.4) [0]
Clavicle fracture	0 (0.0) [0]	1 (0.4) [0]
Tooth disorder	1 (0.1) [0]	0 (0.0) [0]
Tooth impacted	1 (0.1) [0]	0 (0.0) [0]
Acute tonsillitis	1 (0.1) [0]	0 (0.0) [0]
Ileus	1 (0.1) [0]	0 (0.0) [0]
Contusion	2 (0.2) [0]	0 (0.0) [0]
Atrioventricular block second degree	1 (0.1) [0]	0 (0.0) [0]
Facial bones fracture	1 (0.1) [0]	0 (0.0) [0]
Anal abscess	1 (0.1) [0]	0 (0.0) [0]
Fatal SAEs	H5N1 Group N = 961	H5N1/Dil Group N = 245
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	1 (0.1) [0]	0 (0.0) [0]
Accidental death	1 (0.1) [0]	0 (0.0) [0]

Conclusion:

For the primary study, please refer to the publication below.

During the extension study (up to month 12), at least one unsolicited adverse event was reported by 65 (24.5%) and 54 (22.9%) subjects in H5N1 Group and in H5N1/Dil Group, respectively.

During the extension study, SAEs were reported by 3 (1.1%) subjects in the H5N1 Group and by 5 (2.1%) subjects in the H5N1/Dil Group for subjects boosted at Month 6. Fifteen (2.2%) subjects reported SAEs in the H5N1 Group not boosted at Month 6. None of the reported SAEs were assessed by the investigators as related to vaccination. No fatal

SAEs were reported during the extension phase of the study.

Publications:

Chu DW et al. (2009) Immunogenicity and tolerability of an AS03(A)-adjuvanted prepandemic influenza vaccine: A phase III study in a large population of Asian adults. *Vaccine*. doi:10.1016/j.vaccine.2009.07.102

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