

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

<b>Study No.:</b> 106750
<b>Title:</b> A phase I observer-blind randomized monocentric study in adults aged between 18 and 60 years designed to evaluate the reactogenicity and immunogenicity of one and two administrations of different formulations of pandemic monovalent (H5N1) influenza vaccines (split virus formulation) administered at different antigen doses.
<b>Rationale:</b> This study was designed to test in healthy adults aged between 18-60 years, the immunogenicity of one and two administrations of different formulations of pandemic H5N1 vaccine against the H5N1 A/Vietnam/1194/04 influenza strain. In order to evaluate whether the candidate vaccine was able to afford some cross-protection against an avian influenza strain heterologous to the vaccine strain, the humoral response was also characterized against the A/Indonesia/5/05 (H5N1) strain.
<b>Phase:</b> I
<b>Study Period:</b> 27 April 2006 to 08 November 2006 (including the long-term follow-up).
<b>Study Design:</b> Monocentric, observer-blind, randomized study with 8 parallel 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.
<b>Centers:</b> Single study center at Belgium.
<b>Indication:</b> Immunization against influenza disease in subjects aged 18 to 60 years.
<b>Treatment:</b> The study groups were as follows: <ul style="list-style-type: none"> <li>• 7 groups received investigational H5N1 formulations.</li> <li>• H5N1 Group: received 2 doses of H5N1 vaccine. The vaccine was administered intramuscularly into the deltoid region of the non-dominant arm.</li> </ul>
<b>Objectives:</b> <i>Only objectives related to the licensed vaccine are presented.</i> <ul style="list-style-type: none"> <li>• To evaluate the humoral immune response induced by the study vaccine in terms of anti-haemagglutinin (HA) antibody titers.</li> <li>• To evaluate the safety of the study vaccine in terms of solicited local and general adverse events, unsolicited adverse events (AEs) and serious adverse events (SAEs).</li> </ul>
<b>Primary Outcome/Efficacy Variable:</b> <i>Only outcome variables related to the licensed vaccine are presented.</i> For humoral immune response evaluation: <i>Observed variables at days 0, 21, 42 and 180: serum antibody titers to H5N1 virus, tested by HA-inhibition.</i> <i>Derived variables (with 95% confidence intervals (95% CI)):</i> <ul style="list-style-type: none"> <li>• Geometric mean titers (GMTs) of serum antibodies at days 0, 21, 42 and 180.</li> <li>• Seroconversion rates* at days 21, 42 and 180.</li> <li>• Conversion factors** at days 21, 42 and 180.</li> <li>• Seroprotection rates*** at days 0, 21, 42 and 180.</li> </ul> <i>*Seroconversion rate for HA antibody response is defined as the percentage of vaccinees who have either an anti-HA pre-vaccination titer &lt; 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a fourfold increase in post-vaccination titer.</i> <i>**Conversion factor is defined as the fold increase in serum anti-HA GMTs post-vaccination compared to Day 0.</i> <i>***Seroprotection rate is defined as the percentage of vaccinees with a serum anti-HA titer ≥ 40 after vaccination that usually is accepted as indicating protection.</i> For safety evaluation:

- Percentage, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 7 day follow-up period (i.e. day of vaccination and 6 subsequent days) after each dose of vaccine and overall.
- Percentage, intensity and relationship to vaccination of unsolicited local and general signs and symptoms during a 21-day follow-up period after the first vaccination and 30-day follow-up period after the second vaccination.
- Occurrence of SAEs during the entire study.

**Secondary Outcome/Efficacy Variable(s):**

*Only outcome variables related to the licensed vaccine are presented.*

For analysis of the humoral immune response:

*Observed variables at days 0, 21, 42 and 180: serum neutralizing antibody titers to H5N1 virus.*

*Derived variables with 95% CI:*

- GMTs of serum antibodies at days 0, 21, 42 and 180.
  - Seroconversion rates\* at days 21, 42 and 180.  
\*Seroconversion rate for neutralizing antibody response is defined as the percentage of vaccinees with a minimum 4-fold increase in titer at post-vaccination.
- For analysis of the cell-mediated immune response at days 0, 21, 42 and 180
- Frequency of cytokine CD4/CDk8 cells per 10<sup>6</sup> in tests producing at least two different cytokines (CD40L, interleukin-2 [IL-2], tumor necrosis factor- $\alpha$  [TNF $\alpha$ ], interferon- $\gamma$  [IFN $\gamma$ ]).
  - Frequency of cytokine-positive CD4/CD8 cells per 10<sup>6</sup> in tests producing at least CD40L and another signal molecule (IL-2, IFN $\gamma$ , TNF $\alpha$ ).
  - Frequency of cytokine-positive CD4/CD8 cells per 10<sup>6</sup> in tests producing at least IL-2 and another signal molecule (CD40L, IFN $\gamma$ , TNF $\alpha$ ).
  - Frequency of cytokine-positive CD4/CD8 cells per 10<sup>6</sup> in tests producing at least TNF $\alpha$  and another signal molecule (IL-2, IFN $\gamma$ , CD40L).
  - Frequency of cytokine-positive CD4/CD8 cells per 10<sup>6</sup> in tests producing at least IFN $\gamma$  and another signal molecule (CD40L, IL-2, TNF $\alpha$ ).

**Statistical Methods:**

The analysis was done on the Total Vaccinated Cohort, on the According-To-Protocol (ATP) cohort for immunogenicity and on 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 subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.
- The ATP cohort for persistence included all subjects from the ATP cohort for immunogenicity with no elimination criteria during the long term follow-up and for whom immunogenicity results were available at Day 180.

*Analysis of immunogenicity*

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

For the humoral immune response in terms of both anti-HA antibodies and neutralizing antibodies, GMTs of antibody titers at days 0, 21, 42 and 180 and the seroconversion rates at days 21, 42 and 180 were calculated with 95% CI. The humoral immune response in terms of anti-HA antibodies was evaluated using the following parameters (with 95% CI): seroconversion factors at days 21, 42 and 180 and seroprotection rates at days 0, 21, 42 and 180.

For the cell-mediated immune response, the frequency of influenza-specific CD4/CD8 T lymphocytes was summarized (descriptive statistics) at days 0, 21, 42 and 180.

*Analysis of safety*

The analysis was done 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 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 and 30 days after the second vaccination was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The occurrence of serious adverse events (SAEs) was tabulated according to MedDRA preferred terms up to Day 51, and from Day 51 to Day 180.

**Study Population:** Healthy male or female subjects between, and including, 18 and 60 years of age at the time of the first vaccination. If the subject was female and of childbearing potential, she had to be abstinent or to have used contraceptive precautions for 30 days prior to vaccination; she was to have a negative pregnancy test at study entry and were to continue contraceptive precautions for 2 months after vaccination. Written informed consent was obtained from the subject prior to study entry.

Number of subjects	H5N1 Group
Planned, N	50
Randomized, N (Total Vaccinated Cohort)	51
Completed to Day 51, n (%)	51 (100)
Completed to Day 180, n (%)	51 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)
Demographics	H5N1 Group
N (Total Vaccinated Cohort)	51
Females: Males	36:15
Mean Age, years (SD)	35.3 (13.31)
White/Caucasian, n (%)	51 (100)

**Primary Efficacy Results:**

Seropositivity rates and GMTs for anti-HA antibody against the A/Vietnam/1194/2004 (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	N	≥ 10 1/DIL				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam	H5N1	PRE	50	2	4.0	0.5	13.7	5.4	4.8	6.0
		PI(D21)	50	20	40.0	26.4	54.8	12.9	8.9	18.7
		PII(D42)	50	42	84.0	70.9	92.8	149.3	93.2	239.1

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

PRE = pre-vaccination Dose 1 at Day 0

PI(D21) = post-vaccination at Day 21

PII(D42) = post-vaccination at Day 42

**Primary Efficacy Results:**

Seroconversion factor for anti-HA antibody titer against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Timing	Group	N	SCF		
				value	95% CI	
					LL	UL

<b>A/Vietnam</b>	PI(D21)	H5N1	50	2.4	1.7	3.5			
	PII(D42)	H5N1	50	27.9	17.2	45.2			
<p>N = number of subjects with available results  PRE = pre-vaccination Dose 1 at Day 0  PI(D21) = post vaccination at Day 21  PII(D42) = post vaccination at Day 42</p>									
<p><b>Primary Efficacy Results:</b>  Seroconversion rates for anti-HA antibody titers against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)</p>									
<b>Vaccine strain</b>	<b>Timing</b>	<b>Group</b>	<b>N</b>	<b>SCR</b>					
				<b>n</b>	<b>%</b>	<b>95% CI</b>			
						<b>LL</b>	<b>UL</b>		
<b>A/Vietnam</b>	PI(D21)	H5N1	50	12	24.0	13.1	38.2		
	PII(D42)	H5N1	50	41	82.0	68.6	91.4		
<p>N = number of subjects with available results  n (%) = number (percentage) of subjects with either a pre-vaccination titer &lt;1:10 and post-vaccination titer ≥1:40 or a pre-vaccination titer ≥ 1:10 and a minimum 4-fold increase in post-vaccination titer  95% CI = 95% confidence interval, LL= Lower Limit, UL = Upper Limit  PI(D21) = post vaccination at 21 days  PII(D42) = post vaccination at 42 days</p>									
<p><b>Primary Efficacy Results:</b>  Seroconversion rates for anti-HA antibody titer against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)</p>									
<b>Vaccine strain</b>	<b>Group</b>	<b>Timing</b>	<b>N</b>	<b>≥40 1/DIL</b>					
				<b>n</b>	<b>%</b>	<b>95% CI</b>			
						<b>LL</b>	<b>UL</b>		
<b>A/Vietnam</b>	H5N1	PRE	50	1	2.0	0.1	10.7		
		PI(D21)	50	13	26.0	14.6	40.3		
		PII(D42)	50	42	84.0	70.9	92.8		
<p>N = number of subjects with available results  n (%) = number (percentage) of subjects with titer within the specified range  PRE = pre-vaccination Dose 1 at Day 0  PI(D21) = post vaccination at Day 21  PII(D42) = post vaccination at Day 42</p>									
<p><b>Primary Efficacy Results:</b>  Seropositivity rates and GMTs for anti-HA antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 180 (ATP cohort for persistence)</p>									
<b>Vaccine strain</b>	<b>Group</b>	<b>N</b>	<b>≥ 10 1/DIL</b>				<b>GMT</b>		
			<b>n</b>	<b>%</b>	<b>95% CI</b>		<b>value</b>	<b>95% CI</b>	
					<b>LL</b>	<b>UL</b>		<b>LL</b>	<b>UL</b>
<b>A/Vietnam*</b>	H5N1	50	30	60.0	45.2	73.6	23.3	15.8	34.5
<b>A/Indonesia</b>	H5N1	50	3	6.0	1.3	16.5	5.4	4.9	6.0
<p>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  *Primary outcome variable</p>									
<p><b>Primary Efficacy Results:</b>  Seroconversion factor for anti-HA antibody titer against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 180 (ATP cohort for persistence)</p>									

Vaccine strain	Group	N	SCF			
			value	95% CI		
				LL	UL	
A/Vietnam*	H5N1	50	4.4	2.9	6.4	
A/Indonesia	H5N1	50	1.1	1.0	1.2	
N = number of subjects with available results SCF = seroconversion factor or GMR (mean[log10(POST/PRE)]) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit *Primary outcome variable						
<b>Primary Efficacy Results:</b>						
Seroconversion rates for anti-HA antibody titer against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 180 (ATP cohort for persistence)						
Vaccine strain	Group	N	SCR			
			n	%	95% CI	
					LL	UL
A/Vietnam*	H5N1	50	26	52.0	37.4	66.3
A/Indonesia	H5N1	50	0	0.0	0.0	7.1
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 *Primary outcome variable						
<b>Primary Efficacy Results:</b>						
Seroprotection rates for anti-HA antibody titer against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 180 (ATP cohort for persistence)						
Vaccine strain	Group	N	≥40 1/DIL			
			n	%	95% CI	
					LL	UL
A/Vietnam*	H5N1	50	27	54.0	39.3	68.2
A/Indonesia	H5N1	50	0	0.0	0.0	7.1
N = number of subjects with available results n (%) = number (percentage) of seroprotected subjects (HI titer ≥ 40 1/DIL) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit *Primary outcome variable						
<b>Primary Efficacy Results:</b>						
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	N	n	%	95% CI	
					LL	UL
<b>H5N1 Group</b>						
<b>Dose 1</b>						
Ecchymosis	>0mm	51	8	15.7	7.0	28.6
	>50 mm	51	0	0.0	0.0	7.0
Induration	>0mm	51	8	15.7	7.0	28.6
	>50 mm	51	1	2.0	0.0	10.4
Pain	Any	51	44	86.3	73.7	94.3
	Grade 3	51	0	0.0	0.0	7.0
Redness	>0mm	51	7	13.7	5.7	26.3
	>50 mm	51	2	3.9	0.5	13.5
Swelling	>0mm	51	6	11.8	4.4	23.9
	>50 mm	51	1	2.0	0.0	10.4
<b>Dose 2</b>						
Ecchymosis	>0mm	51	0	0.0	0.0	7.0
	>50 mm	51	0	0.0	0.0	7.0

<b>Induration</b>	>0mm	51	10	19.6	9.8	33.1
	>50 mm	51	0	0.0	0.0	7.0
<b>Pain</b>	Any	51	40	78.4	64.7	88.7
	Grade 3	51	0	0.0	0.0	7.0
<b>Redness</b>	>0mm	51	7	13.7	5.7	26.3
	>50 mm	51	0	0.0	0.0	7.0
<b>Swelling</b>	>0mm	51	6	11.8	4.4	23.9
	>50 mm	51	0	0.0	0.0	7.0

**Across Doses**

<b>Ecchymosis</b>	>0mm	51	8	15.7	7.0	28.6
	>50 mm	51	0	0.0	0.0	7.0
<b>Induration</b>	>0mm	51	14	27.5	15.9	41.7
	>50 mm	51	1	2.0	0.0	10.4
<b>Pain</b>	Any	51	46	90.2	78.6	96.7
	Grade 3	51	0	0.0	0.0	7.0
<b>Redness</b>	>0mm	51	9	17.6	8.4	30.9
	>50 mm	51	2	3.9	0.5	13.5
<b>Swelling</b>	>0mm	51	10	19.6	9.8	33.1
	>50 mm	51	1	2.0	0.0	10.4

N = number of subjects with at least one administered dose

n (%) = number (percentage) of subjects reporting at least once the symptom

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

Grade 3 Pain: pain that prevented normal activity

**Primary Efficacy Results:**

Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

<b>Symptom</b>	<b>Intensity/ relationship</b>	<b>N</b>	<b>n</b>	<b>%</b>	<b>95% CI</b>	
					<b>LL</b>	<b>UL</b>
<b>H5N1 Group</b>						
<b>Dose 1</b>						
<b>Arthralgia</b>	Any	51	9	17.6	8.4	30.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	7	13.7	5.7	26.3
<b>Fatigue</b>	Any	51	17	33.3	20.8	47.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	16	31.4	19.1	45.9
<b>Fever (Axillary)</b>	≥37.5°C	51	0	0.0	0.0	7.0
	>39.0°C	51	0	0.0	0.0	7.0
	Related	51	0	0.0	0.0	7.0
<b>Headache</b>	Any	51	15	29.4	17.5	43.8
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	12	23.5	12.8	37.5
<b>Myalgia</b>	Any	51	12	23.5	12.8	37.5
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	11	21.6	11.3	35.3
<b>Shivering</b>	Any	51	3	5.9	1.2	16.2
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	3	5.9	1.2	16.2
<b>Sweating</b>	Any	51	5	9.8	3.3	21.4
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	5	9.8	3.3	21.4
<b>Dose 2</b>						

<b>Arthralgia</b>	Any	51	8	15.7	7.0	28.6
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	8	15.7	7.0	28.6
<b>Fatigue</b>	Any	51	18	35.3	22.4	49.9
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	17	33.3	20.8	47.9
<b>Fever (Axillary)</b>	≥37.5°C	51	2	3.9	0.5	13.5
	>39.0°C	51	0	0.0	0.0	7.0
	Related	51	2	3.9	0.5	13.5
<b>Headache</b>	Any	51	21	41.2	27.6	55.8
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	19	37.3	24.1	51.9
<b>Myalgia</b>	Any	51	15	29.4	17.5	43.8
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	15	29.4	17.5	43.8
<b>Shivering</b>	Any	51	9	17.6	8.4	30.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	9	17.6	8.4	30.9
<b>Sweating</b>	Any	51	6	11.8	4.4	23.9
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	6	11.8	4.4	23.9
<b>Across Doses</b>						
<b>Arthralgia</b>	Any	51	14	27.5	15.9	41.7
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	12	23.5	12.8	37.5
<b>Fatigue</b>	Any	51	23	45.1	31.1	59.7
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	22	43.1	29.3	57.8
<b>Fever (Axillary)</b>	≥37.5°C	51	2	3.9	0.5	13.5
	>39.0°C	51	0	0.0	0.0	7.0
	Related	51	2	3.9	0.5	13.5
<b>Headache</b>	Any	51	27	52.9	38.5	67.1
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	23	45.1	31.1	59.7
<b>Myalgia</b>	Any	51	20	39.2	25.8	53.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	19	37.3	24.1	51.9
<b>Shivering</b>	Any	51	10	19.6	9.8	33.1
	Grade 3	51	2	3.9	0.5	13.5
	Related	51	10	19.6	9.8	33.1
<b>Sweating</b>	Any	51	9	17.6	8.4	30.9
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	9	17.6	8.4	30.9

N = number of subjects with at least one administered dose

n (%) = number (percentage) of subjects reporting at least once the symptom

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

Any = any occurrence of the specific symptom, irrespective of the intensity grade or relationship to vaccination

Grade 3: symptom that prevented normal activity

Related = occurrence of the specific was considered by the investigator to be causally related to the vaccination

**Primary Efficacy Results:**

Percentage, intensity and relationship to vaccination of unsolicited local and general signs and

symptoms during a 21-day follow-up period after the first vaccination and 30-day follow-up period after the second vaccination: please refer to the safety section at the end of this summary.

**Secondary Outcome Variable (s):**

Seropositivity rates and GMTs for anti-HA antibody against the A/Indonesia/5/20 05 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	N	≥ 10 1/DIL			GMT			
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Indonesia	H5N1	PRE	50	0	0.0	0.0	7.1	5.0	5.0	5.0
		PI(D21)	50	1	2.0	0.1	10.6	5.1	4.9	5.4
		PII(D42)	50	14	28.0	16.2	42.5	9.9	7.0	14.0

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 Dose 1 at Day 0

PI(D21) = post-vaccination at Day 21

PII(D42) = post-vaccination at Day 42

**Secondary Outcome Variable (s):**

Seroconversion factor for anti-HA antibody titers against the A/Indonesia/5/2005 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Timing	Group	N	SCF		
				value	95% CI	
					LL	UL
A/Indonesia	PI(D21)	H5N1	50	1.0	1.0	1.1
	PII(D42)	H5N1	50	2.0	1.4	2.8

N = number of subjects with available results

Value = seroconversion factor or geometric mean ratio (mean[log<sub>10</sub>(POST/PRE)])

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

PI(D21) = post vaccination at 21 days

PII(D42) = post vaccination at 42 days

**Secondary Outcome Variable (s):**

Seroconversion rates for anti-HA antibody titers against the A/Indonesia/5/2005 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Timing	Group	N	SCR			
				n	%	95% CI	
						LL	UL
A/Indonesia	PI(D21)	H5N1	50	0	0.0	0.0	7.1
	PII(D42)	H5N1	50	10	20.0	10.0	33.7

N = number of subjects with available results

n (%) = number (percentage) of subjects who seroconverted at the specified post vaccination time point

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

PI(D21) = post vaccination at 21 days

PII(D42) = post vaccination at 42 days

**Secondary Outcome Variable (s):**

Seroprotection rates for anti-HA antibody titer against the A/Indonesia/5/2005 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	N	≥40 1/DIL			
				n	%	95% CI	
						LL	UL

A/Indonesia	H5N1	PRE	50	0	0.0	0.00	7.11
		PI(D21)	50	0	0.0	0.00	7.11
		PII(D42)	50	10	20.0	10.03	33.72

N = number of subjects with available results  
n (%) = number (percentage) of subjects with titer within the specified range  
PRE = pre-vaccination Dose 1 at Day 0  
PI(D21) = post vaccination at Day 21  
PII(D42) = post vaccination at Day 42

**Secondary Outcome Variable (s):**

Seropositivity rates and GMTs for neutralizing antibody titers against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	N	≥ 28 1/DIL				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Vietnam	H5N1	PRE	50	16	32.0	19.5	46.7	21.7	17.8	26.4
		PI(D21)	50	48	96.0	86.3	99.5	117.9	93.7	148.3
		PII(D42)	49	48	98.0	89.1	99.9	314.7	243.1	407.3

N = number of subjects with available results  
n (%) = number (percentage) of seropositive subjects (titer ≥ 1:28)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
PRE = pre-vaccination Dose 1 at Day 0  
PI(D21) = 21 days after first vaccination (Day 21)  
PII(D42) = 21 days after second vaccination (Day 42)

**Secondary Outcome Variable (s):**

Seroconversion rates (SCR) for neutralizing antibody titers against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Timing	Group	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam	PI(D21)	H5N1	50	33	66.0	51.2	78.8
	PII(D42)	H5N1	49	42	85.7	72.8	94.1

N = number of subjects with available results  
n (%) = number (percentage) of subjects who seroconverted (at least a 4-fold increase at POST)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
PI(D21) = post vaccination at 21 days  
PII(D42) = post vaccination at 42 days

**Secondary Outcome Variable (s):**

Seropositivity rates and GMTs for neutralizing antibody titers against the A/Indonesia/5/2005 (H5N1) strain (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	N	≥ 28 1/DIL			GMT			
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL

A/Indonesia/5/2005	H5N1	PRE	48	4	8.3	2.3	20.0	15.8	13.9	17.9
		PI(D21)	48	32	66.7	51.6	79.6	36.6	28.8	46.5
		PII(D42)	48	42	87.5	74.8	95.3	80.3	62.0	103.9

N = number of subjects with available results  
n (%) = number (percentage) of seropositive subjects (titer  $\geq$  1:28)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
PRE = pre-vaccination Dose 1st Day 0  
PI(D21) = 21 days after first vaccination (Day 21)  
PII(D42) = 21 days after second vaccination (Day 42)

**Secondary Outcome Variable (s):**

Seroconversion rates for neutralizing antibody titers against the A/Indonesia/5/2005 strain (ATP cohort for immunogenicity)

Vaccine strain	Timing	Group	N	SCR			
				n	%	95% CI	
						LL	UL
A/Indonesia	PI(D21)	H5N1	48	15	31.3	18.7	46.3
	PII(D42)	H5N1	48	37	77.1	62.7	88.0

N = number of subjects with available results  
n (%) = number (percentage) of subjects who seroconverted (at least a 4-fold increase at POST)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit  
PI(D21) = post vaccination at 21 days  
PII(D42) = post vaccination at 42 days

**Secondary Outcome Variable (s):**

Seropositivity rates and GMTs (with 95% CI) for the neutralizing antibodies against the vaccine strain (A/Vietnam/1194/2004 strain) at Day 180 (ATP cohort for Persistence)

Vaccine strain	Group	N	$\geq$ 28 1/DIL				GMT		
			n	%	95% CI		value	95% CI	
					LL	UL		LL	UL
A/Vietnam	H5N1	50	49	98.0	89.4	99.9	101.8	84.8	122.3

N = number of subjects with available results  
n (%) = number (percentage) of seropositive subjects (titer  $\geq$  1:28)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

**Secondary Outcome Variable (s):**

Seroconversion rates (with 95% CI) for the neutralizing antibodies against the vaccine strain (A/Vietnam/1194/2004 strain) at Day 180 (ATP cohort for Persistence)

Vaccine strain	Vaccine Group	N	SCR			
			n	%	95% CI	
					LL	UL
A/Vietnam	H5N1	50	36	72.0	57.5	83.8

N = number of subjects with available results  
n (%) = number (percentage) of subjects who seroconverted (at least a 4-fold increase at POST)  
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

**Secondary Outcome Variable (s):**

Seropositivity rates and GMTs (with 95% CI) for the neutralizing antibodies against the A/Indonesia/5/2005 strain at Day 180 (ATP cohort for Persistence)

Vaccine strain	Group	N	≥ 28 1/DIL				GMT		
			n	95% CI		value	95% CI		
				LL	UL		LL	UL	
A/Indonesia	H5N1	50	41	82.0	68.6	91.4	46.1	36.9	57.6
N = number of subjects with available results n (%) = number (percentage) of seropositive subjects (titer ≥ 1:28) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit									
<b>Secondary Outcome Variable (s):</b> Seroconversion rates (with 95% CI) for the neutralizing antibodies against the A/Indonesia/5/2005 strain at Day 180 (ATP cohort for Persistence)									
Vaccine strain	Group	N	SCR						
			n	%	95% CI				
					LL	UL			
A/Indonesia	H5N1	48	19	39.6	25.8	54.7			
N = number of subjects with available results n (%) = number (percentage) of subjects who seroconverted (at least a 4-fold increase at POST) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit									
<b>Secondary Outcome Variable (s):</b> Descriptive Statistics on the frequency-positive CD4 T-cells (ATP cohort for immunogenicity)									
Vaccine strain	Test Description	Group	Timing	N	GM	Mean	SD		
A/Vietnam	CD4-All doubles	H5N1	Day 0	49	801.27	906.00	431.84		
			Day 21	49	2667.58	3448.02	2059.68		
			Day 42	49	3093.61	3424.80	1740.46		
	CD4-CD40L	H5N1	Day 0	49	771.85	868.67	412.88		
			Day 21	49	2576.31	3363.10	1995.37		
			Day 42	49	3005.85	3329.27	1688.91		
	CD4-IFN $\gamma$	H5N1	Day 0	49	476.45	597.67	365.64		
			Day 21	49	1003.77	1505.20	1185.63		
			Day 42	49	1321.30	1474.41	752.29		
	CD4-IL2	H5N1	Day 0	49	686.60	777.10	354.75		
			Day 21	49	2479.78	3176.00	1915.97		
			Day 42	49	2797.79	3126.00	1647.05		
CD4-TNF $\alpha$	H5N1	Day 0	49	595.65	699.94	328.14			
		Day 21	49	1703.32	2405.76	1570.60			
		Day 42	49	2286.39	2563.73	1380.23			
All doubles: T-cells producing at least 2 cytokines N = number of subjects with available results GM = geometric mean SD = standard deviation									
<b>Secondary Outcome Variable (s):</b> Descriptive Statistics on the frequency-positive CD8 T-cells (ATP cohort for immunogenicity)									
Vaccine strain	Test Description	Group	Timing	N	GM	Mean	SD		

<b>A/Vietnam</b>	CD8-All doubles	H5N1	Day 0	49	183.69	464.02	528.82
			Day 21	49	113.02	476.73	700.75
			Day 42	49	182.81	472.65	549.29
	CD8-CD40L	H5N1	Day 0	49	2.30	20.65	50.10
			Day 21	49	2.19	30.31	107.49
			Day 42	49	2.53	23.98	59.06
	CD8-IFN $\gamma$	H5N1	Day 0	49	169.93	439.04	518.53
			Day 21	49	133.90	449.37	640.19
			Day 42	49	146.27	436.02	503.96
	CD8-IL2	H5N1	Day 0	49	69.65	250.73	302.86
			Day 21	49	44.61	305.12	499.73
			Day 42	49	92.16	273.04	311.15
	CD8-TNF $\alpha$	H5N1	Day 0	49	146.94	405.04	480.68
			Day 21	49	78.30	405.78	653.10
			Day 42	49	140.58	400.08	489.30

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-positive CD4 T-cells (per million CD4 T-cells) at Day 180 for the vaccine strain (A/Vietnam/1194/2004) (ATP cohort for immunogenicity)

Vaccine strain	Group	Group	N	GM	Mean	SD
<b>A/Vietnam</b>	CD4-All doubles	H5N1	49	1201.54	1562.24	807.75
	CD4-CD40L	H5N1	49	1126.77	1478.02	789.22
	CD4-IFN $\gamma$	H5N1	49	592.95	741.06	417.27
	CD4-IL2	H5N1	49	1090.68	1439.76	775.97
	CD4-TNF $\alpha$	H5N1	49	778.68	1045.02	641.70

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-positive CD8 T-cells (per million CD4 T-cells) at Day 180 for the vaccine strain (A/Vietnam/1194/2004) (ATP cohort for immunogenicity)

Vaccine strain	Group	Group	N	GM	Mean	SD
<b>A/Vietnam</b>	CD8-All doubles	H5N1	49	74.11	302.10	412.55
	CD8-CD40L	H5N1	49	1.43	7.65	23.90
	CD8-IFN $\gamma$	H5N1	49	61.44	295.29	414.69
	CD8-IL2	H5N1	49	22.20	169.35	261.84
	CD8-TNF- $\alpha$	H5N1	49	51.03	249.04	349.53

All doubles: T-cells producing at least 2 cytokines

N = number of subjects with available result

GM = geometric mean

SD = standard deviation

**Safety Results:** Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort)

<b>Most Frequent Adverse Events On-Therapy (occurring within Day 0-20 post Dose 1 and Day 0-29 post Dose 2)</b>	<b>H5N1 Group N = 51</b>
Subjects with any AE(s), n (%)	28 (54.9)

Subjects with any Grade 3 AE(s), n (%)	5 (9.8)
Subjects with any related AE(s), n (%)	15 (29.4)
Rhinitis	5 (9.8)
Headache	4 (7.8)
Malaise	4 (7.8)
Upper respiratory tract infection	3 (5.9)
Diarrhea	3 (5.9)
Injection site reaction	3 (5.9)
Musculoskeletal stiffness	3 (5.9)
- : AE absent or not meeting the unsolicited AE counting rule: > 30 subjects/treatment group and > 3 groups, display the most frequent 5 events	
<b>Safety Results:</b> Number (%) of subjects with serious adverse events from Day 0 up to Day 51 (Total Vaccinated Cohort)	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>H5N1 Group N = 51</b>
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Fatal SAEs</b>	<b>H5N1 Group N = 51</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Safety Results:</b> Number (%) of subjects with Serious Adverse Events (SAEs) between Day 42 and Day 180 (Total Vaccinated Cohort)	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>H5N1 Group N = 51</b>
Subjects with any SAE(s), n (%) [n related]	2 (3.9) [0]
Ovarian cyst	1 (2.0) [0]
Peritonitis	1 (2.0) [0]
<b>Fatal SAEs</b>	<b>H5N1 Group N = 51</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]

**Conclusion:** In the H5N1 Group, the percentage of subjects with anti-HA antibody titer  $\geq$  1:40 against A/Vietnam/1194/2004 strain was 54% at Day 180; the percentage of seroconverted subjects was 52% at Day 180. GMT values 23.3 at Day 180. Please refer also to the publications below.

**Publications:**

Leroux-Roels I et al. (2007) Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine. Lancet. 370 (9587): 580-589.  
Leroux-Roels I et al. (2008) Broad clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. PlosOne. 3(2): e1665.

Date updated: 26 August 2009