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Study No.: 111443 (H5N1-038 Ext 002 Month 12)
Title: Immunogenicity of GSK Biologicals' pandemic influenza vaccine (GSK1562902A) at different boosting vaccination schedules.
Rationale: The aim of the study was to evaluate the immune response elicited by a booster dose of adjuvanted influenza candidate vaccine (derived from A/Indonesia/5/2005 strain) when administered at 12 or 36 months after a 2-dose primary vaccination with an influenza vaccine (derived from A/Vietnam/1194/2004 strain) in the study H5N1-002 (109630) and who were not boosted in the extension study at Month 6, H5N1-030 EXT:002 Day 180-360 (109873). In addition, subjects who received a booster vaccination at Month 6 in study H5N1-030 EXT: 002 were asked to participate for evaluation of long-term immunology and safety follow-up in this study H5N1-038 EXT 002. This CTRS presents results up to Month 18 and will be updated when additional data become available. Please refer to the CTRS on H5N1-002; H5N1-030 EXT: 002 Day 180-360 for the data on the primary vaccination course and extension study (Day 180-360, including booster at 6 months after primary vaccination).
Phase: III
Study Period: 23 March 2008 to 24 November 2008 (Month 18)
Study Design: Open, randomized, multi-center study with 3 parallel groups.
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 adults.
Treatment: The study groups were as follows: <ul style="list-style-type: none"> • H5N1/Adj/M6 Group: subjects boosted with a single dose of the adjuvanted candidate influenza vaccine (A/Indonesia/5/2005 strain) in study H5N1-030 EXT: 002, 6 months after the primary vaccination in study-H5N1-002. • H5N1/Adj/M12 Group: subjects boosted with a single dose of adjuvanted candidate influenza vaccine (A/Indonesia/5/2005 strain) in study H5N1-038 EXT 002, 12 months after the primary vaccination in study-H5N1-002. • H5N1/Adj/M36 Group: subjects boosted with a single dose of adjuvanted candidate influenza vaccine (A/Indonesia/5/2005 strain) in study H5N1-038 EXT 002, 36 months after the primary vaccination in study-H5N1-002. <p>The vaccine was administered intramuscularly into the deltoid region of the non-dominant arm. Please refer to the CTRS on H5N1-002; H5N1-030 EXT: 002 DAY 180-360 for the study design of the primary vaccination course and extension study (Day 180-360). Safety data for the 2 groups that did not receive a booster dose in study H5N1-038 Ext 002 Month 12 at Month 12 are presented for the 2 groups pooled.</p>
Objectives: To assess if the humoral immune response in terms of hemagglutination inhibition (HI) antibodies induced by a booster dose of the adjuvanted candidate influenza vaccine, formulated with a strain drifted from the A/Vietnam/1194/2004 strain and given either 12 months or 36 months after primary vaccination with two doses of a vaccine formulated from the A/Vietnam/1194/2004 strain fulfils the criteria established for influenza vaccines by the European Committee for Medicinal Products for Human Use (CHMP).
Primary Outcome/Efficacy Variable: <i>Immunogenicity</i> Humoral immune response: <i>Observed variables at Month 12 + 21 Days and Month 36 + 21 Days[#], for Month 12- and Month 36-boosted subjects, respectively:</i> <ul style="list-style-type: none"> • Serum H5N1 HI antibody titers (A/Indonesia/5/2005) for Month 12- and Month 36-boosted subjects. <i>Derived variables (with 95% confidence intervals [CI]) at Month 12 + 21 Days and Month 36 + 21 Days[#], for Month 12- and Month 36-boosted subjects:</i> <ul style="list-style-type: none"> • Geometric mean titers (GMTs) of H5N1 antibody titers. • Booster response defined as at least a 4-fold increase in serum H5N1 HI antibody titer between pre-booster vaccination and post-booster vaccination. • Booster factor defined as the fold increase in serum H5N1 HI antibody GMTs post-booster vaccination compared to pre-booster titer.

- Seroprotection rates (SPR), defined as the percentage of vaccinees with a serum H5N1 HI antibody titer $\geq 1:40$ that usually is accepted as indicating protection.

Data not available when this summary was posted. This summary will be updated when the data become available.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

For the humoral immune response in terms of H5N1 HI antibodies the following parameters (with 95% CIs) were calculated for all subjects:

Observed variables at Month 18, Month 24[#], Month 30[#], Month 36[#], Month 42[#], and Month 48[#]:

- Serum H5N1 HI antibody titers.
- Derived variables (with 95% CI) at Month 18, Month 24[#], Month 30[#], Month 36[#], Month 42[#] and Month 48[#]:*
- GMTs of H5N1 HI antibody titers.
 - Booster response defined as at least a 4-fold increase in serum H5N1 HI antibody titer between pre-booster vaccination and post-booster vaccination.
 - Booster factor defined as the fold increase in serum H5N1 HI antibody GMTs post-booster vaccination compared to pre-booster titer.
 - SPR defined as the percentage of vaccinees with a serum H5N1 HI antibody titer $\geq 1:40$ that usually is accepted as indicating protection.

For the humoral immune response in terms of neutralizing antibodies[‡], GMTs of H5N1 antibody titers and Booster response* (with 95% CI) were calculated:

- At Month 36[‡], for a subset of subjects boosted at Month 36.
- At Month 12 + 21 Days[‡] and Month 36 + 21 Days[‡] for a subset of subjects boosted at Month 12 and Month 36, respectively.
- At Month 48[‡] for all subjects in the subsets detailed above including a subset of subjects boosted at Month 6 in study H5N1-002/H5N1-030 EXT 002.

*Booster response for neutralizing antibody response is defined as the percentage of vaccinees with a minimum 4-fold increase in the neutralizing antibody titer between pre-booster and post-booster vaccination.

[‡]All micro neutralization testing will be performed at the end of the study and presented with the analyses of Month 48 data.

For the CMI response, the following parameters (with 95% CI) were calculated for a subgroup of subjects (chosen among all subject subsets) at Month 18[#], Month 24[#], Month 30[#], Month 36[#], Month 42[#] and Month 48[#]:

- Frequency of antigen-specific CD4/CD8 T-cells identified as producing at least two out of four different cytokines (CD40 ligand [CD40L], interleukin - 2 [IL-2], tumor necrosis factor- α [TNF- α], interferon- γ [IFN- γ]) upon in vitro stimulation.
- Furthermore, for the CMI response, the same parameters will be evaluated with 95% CIs at Month 12 + 21 Days and Month 36 + 21[#] Days for a subset of subjects from the Month 12- and Month 36-boosted subjects.

Safety

- 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 the booster vaccination.
- Percentage, intensity and relationship to vaccination of unsolicited local and general signs and symptoms during a 30-day follow-up period after the booster vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study.
- Recording of adverse events of specific interest (AESIs) during the entire study period, i.e. at visits Month 30[#] (in a retrospective manner), Month 36[#], Month 36+21 days[#], Month 36+30 days[#], Month 42[#] and Month 48[#].

Data not available when this summary was posted. This summary will be updated when the data become available.

Statistical Methods:

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

- The Total Vaccinated Cohort included all booster-vaccinated subjects for whom data were available.
- The Total Cohort only included all evaluable subjects not boosted at Month 12 for whom data were available.
- The ATP cohort for immunogenicity (at each protocol defined time points) 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 (at each protocol defined time points) included all evaluable subjects not boosted at Month 12, for whom data concerning immunogenicity data were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at Month 12 (or Month 18).

Analysis for immunogenicity:

The analysis was performed on the ATP cohort for immunogenicity and the ATP cohort for persistence. In terms of humoral immune response, serum H5N1 HI antibody titers, GMTs, booster response, booster factor and seroprotection rates at Month 12 + 21 days and Month 18 were calculated with their exact 95% CI for subjects who were boosted at Month 12 and those who were not boosted at Month 12.

Analysis for safety:

The analysis was performed on the Total Vaccinated Cohort.

The percentage of subjects with at least one report of solicited symptom within the 7-day follow-up period was tabulated with 95% CI. The same tabulation was performed for Grade 3 and for related solicited general symptoms. The percentage of subjects reporting at least one unsolicited adverse events (AEs) within 30 days after the booster vaccination was summarized according to Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The numbers of subjects with Grade 3 unsolicited AEs and with AEs assessed by the investigators as causally related to the study vaccination were also tabulated. SAEs reported during the study period were also tabulated according to MedDRA preferred term.

Study Population: Healthy male or female subjects who had completed participation in study H5N1-002/ H5N1-030 EXT: 002 Day 180-360. Women were to be of non-childbearing potential, or, if of childbearing potential, had to practice adequate contraception for 30 days prior to vaccination, had to have a negative pregnancy test and continued such precautions for two months after completion of the vaccination series. Written informed consent was obtained from the subjects.

Number of subjects		H5N1/Adj/M12 Group			
Planned, N		211			
Randomized, N (Total Vaccinated Cohort)		188			
Completed to month 12 + 30 D, n (%)		188 (100)			
Completed to month 18, n (%)		186 (98.9)			
Total Number Subjects Withdrawn, n (%)		2 (1.1)			
Withdrawn due to Adverse Events, n (%)		0 (0.0)			
Withdrawn due to Lack of Efficacy, n (%)		Not applicable			
Withdrawn for other reasons, n (%)		2 (1.1)			
Demographics		H5N1/Adj/M12 Group			
N (Total Vaccinated Cohort)		188			
Females: Males		97:91			
Mean Age, years (SD)		35.3 (9.23)			
Asian - East Asian heritage, n (%)		117 (62.2)			
Number of subjects		H5N1/Adj/M6 Group + H5N1/Adj/M36 Group			
Planned, N		750			
Randomized, N (Total Cohort)		656			
Completed to month 12, n (%)		655 (99.8)			
Completed to month 18, n (%)		648 (98.8)			
Total Number Subjects Withdrawn, n (%)		8 (1.2)			
Withdrawn due to Adverse Events, n (%)		1 (0.2)			
Withdrawn due to Lack of Efficacy, n (%)		Not applicable			
Withdrawn for other reasons, n (%)		7 (1.1)			
Demographics		H5N1/Adj/M6 Group + H5N1/Adj/ M36 Group			
N (Total Cohort)		656			
Females: Males		323:333			
Mean Age, years (SD)		34.9 (9.93)			
Asian - east Asian heritage, n (%)		418 (63.7)			
Primary Efficacy Results: Seropositivity rates and GMTs for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12, Month 12+21 Days and Month 18 for Month 12-boosted subjects (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/Adj/M12	P1I(M12)	180	78	43.3	36.0	50.9	11.8	9.9	13.9
		P1II(M12+21D)*	186	183	98.4	95.4	99.7	653.2	553.2	771.4
		P1III(M18)	182	170	93.4	88.8	96.5	145.2	118.1	178.6
A/Indonesia/05/2005	H5N1/Adj/M12	P1I(M12)	180	23	12.8	8.3	18.6	6.2	5.7	6.7
		P1II(M12+21D)*	186	178	95.7	91.7	98.1	340.3	282.8	409.6
		P1III(M18)	182	170	93.4	88.8	96.5	190.7	154.3	235.7

GMT = geometric mean antibody titer calculated on all subjects
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
P1I(M12) = Post-Vaccination Dose 2 at Month 12
P1II(M12+21D) = Post-vaccination Dose 3 on Day 21 after Month 12
P1III(M18) = Post-vaccination Dose 3 at Month 18
* Primary efficacy results

Primary Efficacy Results: Booster SCR for H5N1 HI antibodies titers against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12+21 Days and Month 18 for Month 12-boosted subjects – pre-vaccination time point as Month 12 (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M12	P1III(M12+21D)*	180	172	95.6	91.4	98.1
		P1III(M18)	176	135	76.7	69.8	82.7
A/Indonesia/05/2005	H5N1/Adj/M12	P1III(M12+21D)*	180	169	93.9	89.3	96.9
		P1III(M18)	176	159	90.3	85.0	94.3

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

P1III(M12+21D) = Post-vaccination Dose 3 on Day 21 after Month 12

P1III(M18) = Post-Vaccination Dose 3 at Month 18

* Primary efficacy results

Primary Efficacy Results: Booster SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12+21 Days and Month 18 for Month 12-boosted subjects (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SCF		
				Value	95% CI	
					LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M12	P1III(M12+21D)*	180	55.3	44.7	68.5
		P1III(M18)	176	12.3	9.8	15.3
A/Indonesia/05/2005	H5N1/Adj/M12	P1III(M12+21D)*	180	55.3	45.2	67.6
		P1III(M18)	176	30.8	24.8	38.2

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

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

P1III(M12+21D) = Post-vaccination dose 3 at Day 21 after Month 12

P1III(M18) = Post-vaccination Dose 3 at Month 18

* Primary efficacy results

Primary Efficacy Results: SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12, Month 12+21 Days and Month 18 for Month 12-boosted subjects (ATP cohort for immunogenicity)

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M12	P1I(M12)	180	39	21.7	15.9	28.4

		PIII(M12+21D)*	186	182	97.8	94.6	99.4
		PIII(M18)	182	163	89.6	84.2	93.6
A/Indonesia/05/2005	H5N1/Adj/M12	PII(M12)	180	8	4.4	1.9	8.6
		PIII(M12+21D)*	186	178	95.7	91.7	98.1
		PIII(M18)	182	167	91.8	86.8	95.3

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(M12) = Post-Vaccination Dose 2 at Month 12
PIII(M12+21D) = Post-vaccination Dose 3 on Day 21 after Month 12
PIII(M18) = Post-vaccination Dose 3 at Month 18
* Primary efficacy results

Secondary Outcome Variable(s): Seropositivity rates and GMTs for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 but boosted at Month 6 (ATP cohort for persistence)

Antibodies against	Group	Timing	N	\geq 1: 10				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M6	PIII(M12)	194	165	85.1	79.2	89.8	76.7	62.5	94.1
		PIII(M18)	216	176	81.5	75.6	86.4	43.7	36.7	52.0
A/Indonesia/05/2005	H5N1/Adj/M6	PIII(M12)	194	146	75.3	68.6	81.2	45.6	36.9	56.3
		PIII(M18)	216	178	82.4	76.7	87.2	54.9	45.6	66.1

GMT = geometric mean antibody titre calculated on all subjects
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
PIII(M12) = Post-vaccination Dose 3 at Month 12
PIII(M18) = Post-vaccination Dose 3 at Month 18

Secondary Outcome Variable(s): Seropositivity rates and GMTs for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 and not boosted at Month 6 (ATP cohort for persistence)

Antibodies against	Group	Timing	N	\geq 1: 10				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M36	PII(M12)	365	157	43.0	37.9	48.3	11.3	10.1	12.6
		PII(M18)	429	173	40.3	35.6	45.1	10.2	9.3	11.3
A/Indonesia/05/2005	H5N1/Adj/M36	PII(M12)	365	45	12.3	9.1	16.1	6.2	5.8	6.7
		PII(M18)	429	146	34.0	29.6	38.7	9.6	8.7	10.6

GMT = geometric mean antibody titre calculated on all subjects
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
PII(M18) = Post-vaccination Dose 2 at Month 18

Secondary Outcome Variable(s): Booster SCR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 but boosted at Month 6 (ATP cohort for persistence)

Antibodies against	Group	Timing	N	Booster SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M6	PIII(M12)	184	79	42.9	35.7	50.4
		PIII(M18)	216	68	31.5	25.3	38.1
A/Indonesia/05/2005	H5N1/Adj/M6	PIII(M12)	184	112	60.9	53.4	68.0
		PIII(M18)	216	149	69.0	62.4	75.1

Seroconversion defined as:

- For initially seronegative subjects, antibody titer \geq 1:40 after vaccination

<ul style="list-style-type: none"> For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer <p>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 PIII(M12) = Post-vaccination Dose 3 at Month 12 PIII(M18) = Post-vaccination Dose 3 at Month 18</p>							
<p>Secondary Outcome Variable(s): SCR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 and not boosted at Month 6 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M36	PII(M12)	365	71	19.5	15.5	23.9
		PII(M18)	428	61	14.3	11.1	17.9
A/Indonesia/05/2005	H5N1/Adj/M36	PII(M12)	365	18	4.9	2.9	7.7
		PII(M18)	428	75	17.5	14.0	21.5
<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-vaccination antibody titer <p>N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M12) = Post-vaccination Dose 2 at Month 12 PII(M18) = Post-vaccination Dose 2 at Month 18</p>							
<p>Secondary Outcome Variable(s): Booster SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 but boosted at Month 6 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	Booster SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1/Adj/M6	PIII(M12)	184	4.0	3.3	4.9	
		PIII(M18)	216	2.4	2.0	2.9	
A/Indonesia/05/2005	H5N1/Adj/M6	PIII(M12)	184	6.9	5.6	8.6	
		PIII(M18)	216	8.4	7.0	10.1	
<p>N = Number of subjects with pre- and post-vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PIII(M12) = Post-vaccination Dose 3 at Month 12 PIII(M18) = Post-vaccination Dose 3 at Month 18</p>							
<p>Secondary Outcome Variable(s): SCF for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 and not boosted at Month 6 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
A/Vietnam/1194/2004	H5N1/Adj/M36	PII(M12)	365	2.0	1.8	2.2	
		PII(M18)	428	1.8	1.7	2.0	
A/Indonesia/05/2005	H5N1/Adj/M36	PII(M12)	365	1.2	1.2	1.3	
		PII(M18)	428	1.9	1.7	2.1	
<p>N = Number of subjects with pre- and post-vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(M12) = Post-vaccination Dose 2 at Month 12 PII(M18) = Post-vaccination Dose 2 at Month 18</p>							
<p>Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 but boosted at Month 6 (ATP cohort for persistence)</p>							
Antibodies against	Group	Timing	N	SPR			

				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M6	PIII(M12)	194	153	78.9	72.4	84.4
		PIII(M18)	216	149	69.0	62.4	75.1
A/Indonesia/05/2005	H5N1/Adj/M6	PIII(M12)	194	128	66.0	58.8	72.6
		PIII(M18)	216	157	72.7	66.2	78.5

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
PIII(M12) = Post-vaccination Dose 3 at Month 12
PIII(M18) = Post-vaccination Dose 3 at Month 18

Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains at Month 12 and Month 18 for subjects not boosted at Month 12 and not boosted at Month 6 (ATP cohort for persistence)

Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Vietnam/1194/2004	H5N1/Adj/M36	PII(M12)	365	88	24.1	19.8	28.8
		PII(M18)	429	79	18.4	14.9	22.4
A/Indonesia/05/2005	H5N1/Adj/M36	PII(M12)	365	18	4.9	2.9	7.7
		PII(M18)	429	75	17.5	14.0	21.4

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(M12) = Post-vaccination Dose 2 at Month 12
PII(M18) = Post-vaccination Dose 2 at Month 18

Secondary Outcome Variable(s): Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

Symptom	Type	H5N1/Adj/M12 Group				
		N	n	%	95% CI	
					LL	UL
Ecchymosis (mm)	Any	188	2	1.1	0.1	3.8
	>100	188	0	0.0	0.0	1.9
Induration (mm)	Any	188	17	9.0	5.4	14.1
	>100	188	0	0.0	0.0	1.9
Pain	Any	188	158	84.0	78.0	89.0
	Grade 3	188	11	5.9	3.0	10.2
Redness (mm)	Any	188	13	6.9	3.7	11.5
	>100	188	0	0.0	0.0	1.9
Swelling (mm)	Any	188	23	12.2	7.9	17.8
	>100	188	0	0.0	0.0	1.9

N = number of subjects with the 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
Any = occurrence of any local symptom regardless of intensity grade
Grade 3 pain = pain that prevented normal activity

Secondary Outcome Variable(s): Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

Symptom	Type	H5N1/Adj/M12 Group				
		N	n	%	95% CI	
					LL	UL
Arthralgia	Any	188	48	25.5	19.5	32.4
	Grade 3	188	6	3.2	1.2	6.8
	Related	188	45	23.9	18.0	30.7
Fatigue	Any	188	112	59.6	52.2	66.7
	Grade 3	188	12	6.4	3.3	10.9

	Related	188	105	55.9	48.4	63.1
Headache	Any	188	76	40.4	33.3	47.8
	Grade 3	188	12	6.4	3.3	10.9
	Related	188	69	36.7	29.8	44.0
Myalgia	Any	188	123	65.4	58.2	72.2
	Grade 3	188	14	7.4	4.1	12.2
	Related	188	119	63.3	56.0	70.2
Shivering	Any	188	26	13.8	9.2	19.6
	Grade 3	188	3	1.6	0.3	4.6
	Related	188	26	13.8	9.2	19.6
Sweating	Any	188	22	11.7	7.5	17.2
	Grade 3	188	0	0.0	0.0	1.9
	Related	188	20	10.6	6.6	16.0
Temperature/(Axillary) (°C)	> 38.0	188	15	8.0	4.5	12.8
	≥ 39.0	188	1	0.5	0.0	2.9
	Related	188	14	7.4	4.1	12.2

N = number of subjects with the 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

Any = occurrence of any general symptom regardless of intensity grade or relationship to the study vaccination

Grade 3 = symptoms that prevented normal activity

Related = solicited symptom assessed by the investigator as casually related to the study vaccination

Safety Results: Number (%) of subjects with unsolicited adverse events – For subjects boosted at Month 12 (Total Vaccinated Cohort)

Most frequent [‡] adverse events–On-Therapy (occurring within Day 0-30 following vaccination)	H5N1/Adj/M12 Group N = 188
Subjects with any AE(s), n (%)	44 (23.4)
Subjects with adverse events classified as severe (Grade 3*), n (%)	6 (3.2)
Subjects with adverse events classified as related**, n (%)	22 (11.7)
Lymphadenopathy	7 (3.7)
Axillary pain	4 (2.1)
Nasopharyngitis	4 (2.1)
Diarrhoea	3 (1.6)
Dizziness	3 (1.6)
Influenza like illness	3 (1.6)
Injection site pruritus	3 (1.6)
Pyrexia	3 (1.6)
Rash	3 (1.6)
Back pain	2 (1.1)
Lymph node pain	2 (1.1)
Oropharyngeal pain	2 (1.1)
Upper respiratory tract infection	2 (1.1)

[‡]Detail of AE counting rule: > 30 subjects per treatment group and ≤ 3 groups, display the most frequent 10 events

*Grade 3 = event that prevented normal activities

**Related = event assessed by the investigator as causally related to the study vaccination

Safety Results: Number (%) of subjects with serious adverse events between Month 12 and Month 12 + 30 days (Total Vaccinated Cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1/Adj/M12 Group N = 188	H5N1/Adj/M6 Group + H5N1/Adj/M36 Group N = 656
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	1 (0.5) [0]	1 (0.2) [0]
Facial bones fracture	1 (0.5) [0]	0 (0.0) [0]
Appendicitis	0 (0.0) [0]	1 (0.2) [0]
Fatal SAEs	H5N1/Adj/M12 Group	H5N1/Adj/M6 Group +

	N = 188	H5N1/Adj/M36 Group N = 656
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 serious adverse events between Month 12+ 30 days and Month 18 (Total Vaccinated Cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	H5N1/Adj/M12 Group N = 188	H5N1/Adj/M6 Group + H5N1/Adj/M36 Group N = 656
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	12 (1.8) [0]
Joint injury	0 (0.0) [0]	1 (0.2) [0]
Back pain	0 (0.0) [0]	1 (0.2) [0]
Ligament rupture	0 (0.0) [0]	2 (0.3) [0]
Meniscus lesion	0 (0.0) [0]	2 (0.3) [0]
Appendicitis	0 (0.0) [0]	1 (0.2) [0]
Intestinal obstruction	0 (0.0) [0]	1 (0.2) [0]
Intervertebral disc displacement	0 (0.0) [0]	1 (0.2) [0]
Endometriosis	0 (0.0) [0]	1 (0.2) [0]
Pyelonephritis acute	0 (0.0) [0]	1 (0.2) [0]
Appendicitis perforated	0 (0.0) [0]	1 (0.2) [0]
Dengue fever	0 (0.0) [0]	1 (0.2) [0]
Acute myocardial infarction	0 (0.0) [0]	1 (0.2) [0]
Anoxic encephalopathy	0 (0.0) [0]	1 (0.2) [0]
Renal failure acute	0 (0.0) [0]	1 (0.2) [0]
Clavicle fracture	0 (0.0) [0]	1 (0.2) [0]
Rib fracture	0 (0.0) [0]	1 (0.2) [0]
Fatal SAEs	H5N1/Adj/M12 Group N = 188	H5N1/Adj/M6 Group + H5N1/Adj/M36 Group N = 656
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	1 (0.2) [0]
Anoxic encephalopathy	0 (0.0) [0]	1 (0.2) [0]
Renal failure acute	0 (0.0) [0]	1 (0.2) [0]

Conclusion:

For the A/Vietnam/1194/2004 strain, at Month 12 + 21 days, the percentage of subjects who had serum H5H1 HI antibodies titer $\geq 1:10$ was 98.4%, GMT value was 653.2, the percentage of subjects who were seroconverted was 95.6%, the booster SCF value was 55.3 and the percentage of the subjects who were seroprotected was 97.8%, in the H5N1/Adj/M12 Group.

For the A/Indonesia/05/2005 strain, at Month 12 + 21 days, the percentage of subjects who had serum H5H1 HI antibodies titer $\geq 1:10$ was 95.7%, GMT value was 340.3, the percentage of subjects who were seroconverted was 93.9%, the booster SCF value was 55.3 and the percentage of the subjects who were seroprotected was 95.7%, in the H5N1/Adj/M12 Group.

During the 30-day follow-up period after vaccination, at least one unsolicited adverse event was reported by 44 (23.4%) subjects in the H5N1/Adj/M12 Group. One subject from that group reported 1 SAE between Month 12 and Month 12 + 30 days, in the H5N1/Adj/M12 Group; it was assessed by the investigator as not causally related to study vaccination. No SAEs were reported between Month 12+ 30 days and Month 18 in the H5N1/Adj/M12 Group. No fatal SAEs were reported up to Month 18 study period in this group.

A total of 12 subjects not boosted at Month 12 reported at least one SAE between Month 12+ 30 days and Month 18. In one of those subjects, the SAEs were fatal. None of the SAEs reported in this group were assessed by the investigators as causally related to study vaccination.

For safety data analyzed during primary vaccination and extension (Month 6) study, please refer to the CTRS on H5N1-002; H5N1-030 EXT: 002 DAY 180-360.

Publications: None.

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