SYNOPSIS

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** Haemagglutinin from the A/Vietnam/1194/2004 (H5N1) Influenza strain	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: A phase III, observer-blind, randomised study to evaluate the safety and immunogenicity of one and two administrations of pandemic monovalent (H5N1) influenza vaccine (split virus formulation containing 15 µg HA and adjuvanted with AS03) in adults aged 18 years and older.

Principal Investigator: This study was conducted by 41 investigators in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Study Centres: Multicentric: 41 centers in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Publication (reference): Not published as of November 2006

Study period:	**Clinical phase: III**
Study Initiation Date: 02 May, 2006 Data lock point: 25 October 2006	

Objectives:

Primary: The primary objective was to evaluate the safety/reactogenicity of the pandemic influenza vaccine in terms of :

- Solicited local/general symptoms during 7 days post-vaccination,
- unsolicited symptoms during 21 days following the first vaccination and 30 days following the second one
- Serious adverse events during the entire study period (180 days).
- Occurrence of new onset chronic diseases during the entire study period in each group.
- Occurrence of medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases or routine visits, during the entire study period in each group

Secondary: The secondary objective was to evaluate the immunogenicity of the pandemic influenza vaccine in terms of

- The humoral immune response (anti-haemagglutinin antibody and neutralizing antibody) 21 days after each vaccination.
- The persistence of antibodies 180 days after the first vaccination

Study design: Multicentric, observer-blind, randomized study in subjects aged above 18 years. Two groups: H5N1 group (planned with 3788 subjects vaccinated twice with the pandemic influenza vaccine), Fluarix group (planned with 1264 subjects vaccinated once with Fluarix™ and once with a placebo). The two vaccinations were planned 21-days apart. The immunogenicity of the candidate vaccine was evaluated in a subset of subjects: 360 subjects planned from the H5N1 group and 120 planned from the Fluarix group. In subjects involved in the immunogenicity subset, blood sampling had to be performed at Day 0, Day 21, Day 42 and planned at Day 180.

Number of subjects:

Planned: 5052 subjects (3788 in H5N1 group, 1264 in Fluarix group)
Enrolled: 5075 subjects *Completed:* 4904 subjects (3667 in H5N1 group, 1237 in Fluarix group)*Safety*: Total vaccinated cohort: 5071 subjects (3802 in H5N1 group, 1269 in Fluarix group)
Immunogenicity: ATP Cohort: 609 subjects (455 in H5N1 group, 154 in Fluarix group)

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Diagnosis and criteria for inclusion: Healthy male or female aged above 18 years at the time of first vaccination.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule/site: two intramuscular administrations at day 0 and Day 21 in the non-dominant arm.
Vaccine composition/ dose/ lot number: **Adjuvanted pandemic influenza split vaccine H5N1/15/AS03:** 2 vaccine components consisting of the H5N1 antigens (15µg HA from the A/Vietnam/1194/2004 strain, lot number DFLUA032A) and the adjuvant (lot numbers DA3AA002A and DA3AA002B). The total injected volume was 1ml.

Reference vaccine, dose and mode of administration, lot no.:
Vaccination schedule/site: one intramuscular injection of influenza vaccine Fluarix™ at day 0, one injection of a placebo (saline solution) at Day 21, both in the non-dominant arm
Vaccine composition/ dose/ lot number:
The commercial Fluarix™ for the Southern Hemisphere 2006 containing HA from three influenza strains (total HA = 45µg): A/New Caledonia/20/99 [H1N1]; A/California/7/2004 [H3N2]; B/Malaysia/2506/2004 and Thiomersal (5µg/ml). Lot number: AFLUA184A.
The placebo is a saline solution. Lot number: AD02B094A.
The total injected volume for Fluarix and the placebo was 0.5ml.

Duration of treatment: Duration of study is approximately 6 months for each subject.

Criteria for evaluation:
Safety: *In order to evaluate the safety/reactogenicity, the following parameters were recorded:*

- Solicited local (pain, redness, swelling, ecchymosis, induration) and general (fatigue, fever, headache, myalgia, shivering, sweating increase, arthralgia) signs and symptoms during a 7 day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination.
- Unsolicited local and general signs and symptoms during 21 days following the first vaccination (i.e. day of first vaccination and 20 subsequent days) and during 30 days following the second vaccination (i.e. day of second vaccination and 29 subsequent days).
- Serious adverse events during the entire study period.
- New onset chronic diseases during the entire study period.
- Medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases or routine visits, during the entire study period

Immunogenicity: In order to evaluate the **humoral response**, the following parameters were calculated with 95 % confidence intervals:
From the anti-Haemagglutinin antibody titers: geometric mean titers pre and post vaccination (days 21 and 42), seroconversion rates and seroconversion factors at days 21 and 42, seroprotection rates at days 0, 21 and 42.
From the neutralisation antibody titer: geometric mean titers pre and post vaccinations (days 21, 42), seroconversion rates at days 21 and 42.

Statistical methods:
Analyses were performed as per protocol.
Analysis of demographics: Demographic characteristics (age, gender, race) of each study cohort were tabulated. The mean age (plus range and standard deviation) by gender of the enrolled subjects, as a whole, and per group, was calculated.

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Analysis of safety: The primary analysis was based on the Total Vaccinated cohort.
The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any adverse event during the solicited follow-up period was tabulated after each vaccination and overall. The percentage of doses followed by at least one local adverse event (solicited and unsolicited), by at least one general adverse event (solicited and unsolicited) and by any adverse event was tabulated, overall vaccination course.
The percentage of subjects reporting each individual solicited local and general adverse event during the solicited follow-up period was tabulated. The percentage of doses followed by each individual solicited local and general adverse event was tabulated, overall vaccination course.
The same tabulation was performed for grade 3 adverse events and for adverse events with relationship to vaccination.
The proportion of subjects with at least one report of unsolicited adverse event classified by the Medical Dictionary for Regulatory Activities (MedDRA) 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 adverse events and for unsolicited adverse events with a relationship to vaccination.
The proportion of subjects who started to receive at least one concomitant medication during the 21-days follow-up period after each vaccination was calculated.
Serious adverse events and withdrawal due to adverse event(s) were described in detail.
The proportion of subjects with at least one report of NOCD classified by the Medical Dictionary for Regulatory Activities (MedDRA), whenever available, and reported during the entire study period was tabulated. A separate table was produced for NOCD based on the GSK assessment and Investigator assessment respectively.
The proportion of subjects with at least one report of a medically significant AE classified by MedDRA, whenever available, and reported up to 30 days after vaccination was tabulated. Similar tables will be produced for medically significant AEs starting Day 30 after each dose till the end of the study.
All percentages were tabulated with their exact 95% confidence intervals.
Analysis of immunogenicity: The primary analysis was done on the ATP cohort.
For the humoral immune response in terms of both anti-HA antibodies and neutralising antibodies: For each treatment group, the following parameters (with 95% confidence intervals) were calculated:
- Geometric mean titers (GMTs) of antibody titers at days 0, 21, 42, calculated by taking the anti-log of the mean of the log titer transformations.
- Seroconversion rates at days 21, 42.

In addition, humoral immune response in terms of anti-HA antibodies was evaluated using the following parameters (with 95% confidence intervals):
- Seroconversion factors at days 21, 42.
- Seroprotection rates at days 0, 21, 42.

Summary:

Demography results: The overall mean age was 38.4 years with a standard deviation of 15.4 years. The overall female-to-male ratio was 1.39. The large majority of subjects were White Caucasian (95.1 % overall). In the same age-stratum (18-60 and >60 years), the demographic profile of the two treatment-groups was similar with respect to mean age, gender and racial distribution. Within the immunogenicity subset, the demographic profile of the two treatment-groups was also similar with respect to mean age, gender and racial distribution. The overall mean age was 47.8 years with a standard deviation of 17.79 years. The overall female to male ratio was 1.16.

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Safety results:
After vaccination with the candidate vaccine, a higher incidence of both local and general symptoms was observed in subjects aged between 18 and 60 years than in those aged above 60. The incidence of symptoms in subjects aged between 18 and 60 years significantly decreased after the second vaccination. In general, safety observations were in line with the safety profile of an adjuvanted vaccine.
In adults aged above 18 years, the incidence of symptoms reported after vaccination with the candidate vaccine was higher than after administration of Fluarix. Symptoms remained however mostly mild to moderate in intensity and resolved rapidly. Pain at the injection site, fatigue, headache and myalgia were the most frequent symptoms reported in adults aged above 18 years.
There was no unusual high frequency of unsolicited symptoms after administration of the candidate vaccine. Incidence of unsolicited symptoms was similar as compared to administration of Fluarix or a placebo.
A total of 11 subjects aged between 18 and 60 years (7 from the H5N1 group) and 6 subjects aged above 60 years (4 from the H5N1 group) reported SAEs during the study (up to Day 51). None of those SAEs were however considered as related to vaccination.
No relationship between the vaccination with the candidate vaccine and the onset of any new chronic disease or medically significant condition was observed during the study.

Incidence of symptoms reported during the 7-day post-vaccination period

			General symptoms			Local symptoms		
			95% CI			95% CI		
	Treatment	Age	%	LL	UL	%	LL	UL
Dose 1	H5N1/AS03	18-60	68.4	66.8	70.0	90.0	88.9	91.0
		>60	41.9	37.1	46.9	69.7	65.0	74.2
	Fluarix	18-60	54.5	52.7	56.1	79.8	78.3	74.6
		>60	29.3	21.8	37.8	42.9	34.3	51.7
Dose 2	H5N1/AS03	18-60	54.4	52.7	56.1	79.8	78.3	81.1
		>60	39.7	34.9	44.8	61.3	56.3	66.1
	Placebo	18-60	27.0	24.4	29.7	23.2	20.8	25.8
		>60	24.2	17.2	32.5	18.9	12.6	26.7

Immunogenicity results: The candidate vaccine elicited a significant humoral response in terms of anti-HA antibodies production against the vaccine strain. After two injections, this antibody production was significantly superior in adults aged between 18 and 60 years than in those aged above 60.
In pre-vaccination seronegative subjects, the candidate vaccine already fulfilled all three CHMP criteria after the first vaccination of adults aged above 60 years. In adults aged between 18 and 60 years, two of the three criteria were already met after the first vaccination and all three after the second one.

Pre-vacc. seronegative subjects		Seroconversion factor		Seroconversion rate (%)		Seroprotection rate (%)	
Treatment	Age (years)	Day 21	Day 42	Day 21	Day 42	Day 21	Day 42
H5N1/AS03	18-60	6.4	61.4	54.6	91.4	54.6	91.4
	>60	8.8	37.4	61.4	91.4	61.4	91.4

Conclusions:
Although the candidate vaccine elicited a higher incidence of both local and general symptoms as compared to Fluarix, it was safe and had a clinically acceptable reactogenicity profile in adults aged 18 years and above. As observed with Fluarix, the candidate vaccine was less reactogenic in elderly aged above 60 years than in adults aged between 18 and 60 years. No SAEs considered to be related to vaccination were reported during the study period up to Day 51.

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The candidate vaccines elicited a good humoral immune response in terms of anti-HA antibodies production against the vaccine strain. Already after the first injection in adults aged 60 years and above, the candidate vaccine fulfilled the three CHMP criteria currently in use for evaluation of the humoral immune response in terms of anti-HA antibody production. In adults aged between 18 and 60 years, two injections were needed to fulfil all those criteria as expected in naïve subjects..

Date of report: November 2006

SYNOPSIS

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** Haemagglutinin from the A/Vietnam/1194/2004 (H5N1) Influenza strain	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: A phase III, observer-blind, randomised study to evaluate the safety and immunogenicity of one and two administrations of pandemic monovalent (H5N1) influenza vaccine (split virus formulation containing 15 µg HA and adjuvanted with AS03) in adults aged 18 years and older.

Principal Investigator: This study was conducted by 41 investigators in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Study Centres: Multicentric: 41 centres in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Publication (reference): No publications as of October 2007.

Study period:	**Clinical phase: III**
Study Initiation Date: 02 May, 2006 Study completion date: 02 February 2007	

Objectives pertaining to this study report (refer to the protocol in Appendix 3B for the detailed study objectives)

Primary: The primary objective was to evaluate the safety/reactogenicity of the pandemic influenza vaccine in terms of :

- Serious adverse events during the entire study period (180 days).
- Occurrence of new onset chronic diseases during the entire study period in each group.
- Occurrence of medically significant conditions prompting emergency room visits or physician visits that are not related to common diseases or routine visits, during the entire study period in each group

Secondary: The secondary objective was to evaluate the immunogenicity (anti-haemagglutinin antibody and neutralizing antibody responses) of the pandemic influenza vaccine in terms of:

- The persistence of anti-haemagglutinin antibody and neutralizing antibody 180 days after the first vaccination

Study design: Multicentric, observer-blind, randomized study in subjects aged above 18 years. Two groups: H5N1 group (two vaccinations with the pandemic influenza vaccine 21 days apart), Fluarix group (two vaccinations once with Fluarix™ and once with a placebo, 21 days apart). The immunogenicity of the candidate vaccine was evaluated in a subset of subjects from the H5N1 group and the Fluarix group. Blood sampling for subjects in the immunogenicity subset was at Day 0, Day 21, Day 42 and Day 180.

Number of subjects:

Planned (according to the source population of study H5N1-008): 5052 subjects (3788 in the H5N1 group, 1264 in the Fluarix group)

Enrolled into study H5N1-011 (Extended follow-up): 4874 subjects (3643 in the H5N1 group, 1231 in the Fluarix group)*Completed:* 4874 subjects (3643 in the H5N1 group, 1231 in the Fluarix group)*Safety*: Total vaccinated cohort: 4874 subjects (3643 in the H5N1 group, 1231 in the Fluarix group)

Immunogenicity subset: 622 subjects; ATP cohort for persistence at Day 180: 600 subjects (450 in the H5N1 group, 150 in the Fluarix group).

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** **Name of active substance:** Haemagglutinin from the A/Vietnam/1194/2004 (H5N1) Influenza strain	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Diagnosis and criteria for inclusion: Healthy male or female aged above 18 years at the time of first vaccination.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule/site: two intramuscular administrations at Day 0 and 21 in the non-dominant arm.
Vaccine composition/ dose/ lot number:
Adjuvanted pandemic influenza split vaccine H5N1/15/AS03: 2 vaccine components consisting of the H5N1 antigens (15µg HA from the A/Vietnam/1194/2004 strain, lot number DFLUA032A) and the adjuvant (lot numbers DA3AA002A and DA3AA002B). The total injected volume was 1ml.

Reference vaccine, dose, mode of administration, lot no.:
Vaccination schedule/site: one intramuscular injection of influenza vaccine Fluarix™ at day 0, one injection of a placebo (saline solution) at Day 21, both in the non-dominant arm
Vaccine composition/ dose/ lot number:
The commercial Fluarix™ for the Southern Hemisphere 2006 containing HA from three influenza strains (total HA = 45µg): A/New Caledonia/20/99 [H1N1]; A/California/7/2004 [H3N2]; B/Malaysia/2506/2004 and Thiomersal (5µg/ml). Lot number: AFLUA184A. The placebo is a saline solution. Lot number: AD02B094A. The total injected volume for Fluarix and the placebo was 0.5ml.

Duration of treatment: Duration of study was approximately 6 months for each subject.

Criteria for evaluation:
***Safety*:** Recording of serious adverse events during the entire study period.
***Immunogenicity*:** In order to evaluate the **humoral response**, the following parameters were calculated with 95 % confidence intervals.
From the anti-haemagglutinin antibody titers: geometric mean titers (GMT) post vaccination (Day 180), seroconversion rates (SCR) and seroconversion factors (SCF) at Day 180, seroprotection rates (SPR) at Day 180.
From the neutralisation antibody titer: geometric mean titers (GMT) at Day 180, seroconversion rates (SCR) at Day 180.

Statistical methods: Analyses were performed as per protocol.
Analysis of demographics: Demographic characteristics (age, gender, race) of each study cohort were tabulated. The mean age (plus range and standard deviation) by gender of the enrolled subjects, as a whole, and per group, was calculated.
Analysis of safety: The primary analysis was based on the Vaccinated cohort (Extended follow-up). Serious adverse events during the entire study period.
Analysis of immunogenicity: The primary analysis was based on the ATP cohort for persistence in the subset of subjects with a blood sample available at Day 180 and retrospectively at previous timepoints (Day 0, Day 21, and Day 42).
For the humoral immune response in terms of both anti-HA antibodies and neutralising antibodies (the latter in a subset of subjects >60 years of age only); for each treatment group, the following parameters (with 95% confidence intervals) were calculated:
- Geometric mean titers of antibody titers at Day 0, Day 21, Day 42, and Day 180, calculated by taking the anti-log of the mean of the log titer transformations.
- Seroconversion rates at Day 21, Day 42, and Day 180.
In addition, humoral immune response in terms of anti-HA antibodies was evaluated using the following parameters (with 95% confidence intervals):
- Seroconversion factors at Day 21, Day 42, and Day 180.
- Seroprotection rates at Day 0, Day 21, Day 42 and Day 180.

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Summary: The objective of this report is to summarize the immunological data obtained from blood samples taken 180 days after the first vaccination in study H5N1-008 (clinical study report dated November 2006) and retrospectively at previous time-points (Day 0, 21 and 42), and the occurrence of SAEs, new onset chronic diseases and medically significant conditions during the entire study period.
Demography results: the Vaccinated cohort (Extended follow-up) for the safety analysis consisted of 4874 and the ATP cohort for persistence consisted of 600 subjects at the Day 180 timepoint.
Safety results:

- Serious adverse events were reported for a total of 57 subjects with very similar percentages in the subgroups of study vaccine recipients and controls (see table below). No distinct pattern of symptomatology could be noted. None of the severe adverse events reported was assessed by the investigator as causally related to the vaccination.
- Medically significant conditions were reported in 320 subjects. No distinct pattern of symptomatology could be noted.
- New onset chronic diseases were reported in 19 subjects. The observations were equally distributed between the group of study vaccine recipients and controls. No pattern of symptomatology could be noted.

Vaccine	Age (years)	n	SAE		Medically significant conditions		NOCD	
			n	%	n	%	n	%
H5N1	18-60	3253	27	0.8	219	6.7	9	0.3
	>60	390	15	3.8	30	7.7	7	1.8
Fluarix	18-60	1102	10	0.9	61	5.5	3	0.3
	>60	129	5	3.9	10	7.8	0	0.0

Immunogenicity results:
To evaluate the level of antibody persistence, results at Day 42 as the supposed antibody peak, were used as reference.
Humoral immune response in terms of anti-HA antibodies against the A/Vietnam/1194/2004 strain:

- The percentage of subjects with pre-existing antibodies increased with age. A clear age-effect on antibody presence at baseline was observed. The percentage was significantly higher in the study vaccine group than the control (Fisher's Exact Test, chi-squared, 1dgf, 3.930, p=0.0474). As allocation into study groups was done by random, this had to be attributed to chance.
- GMT and SPR, the two key parameters for antibody persistence, were very similar in the subgroups of 18-30 and 31-60 years. Therefore these two subgroups (derived from stratified enrolment), could be pooled into the group 18-60 years of age.
- The SPR difference between Day 42 and Day 180 was 33.3% in 18-60 year-olds and 14.5% in >60 year-olds.
- The seropositivity in the control group >60 years increased after the first vaccination and reached 29% at Day 180. The SCF in this group was 1.5.

H5N1/AS03 Age (years)		Seropositive (>=10 1/dil) %	GMT	SCF (ratio)	SCR (%)	SPR (%)
18-60	Day 42	91.4	302.5	57.8	91.0	91.0
	Day 180	61.3	27.2	5.2	56.6	57.7
>60	Day 42	93.4	213.1	30.1	89.2	93.4
	Day 180	84.8	58.6	8.3	73.5	78.9

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Humoral immune response in terms of neutralizing antibodies:

- Six months after the first vaccination, seroconversion rates and GMTs for neutralizing antibodies for elderly subjects in the H5N1/AS03 group were higher than in the Fluarix/placebo group.
- Remarkably the percentage of subjects with pre-existing antibodies was 83.6% in study vaccine group and 90.0% in the control group.

		Seropositive (>=10 1/dil) %	GMT	SCR (%)
H5N1/AS03	**Day 42**	100.0	362.0	63.9
	Day 180	99.3	219.8	43.4
Fluarix/placebo	**Day 42**	97.9	104.8	12.5
	Day 180	82.4	61.8	6.0

Conclusions:

In all age groups anti-HA antibody levels remained high at six months after primary vaccination with 2 doses of the candidate pre-pandemic vaccine. As expected the anti-HA antibody levels against the A/Vietnam/1194/2004 vaccine strain had declined after six months (Day 180) following the first vaccination.

Still the three CHMP criteria established for evaluating immunogenicity after primary vaccination based on the point estimate were reached for group >60 years old at Day 180. For group 18-60 years old, two (SCF, SCR) of these criteria were reached at Day 180. The same conclusion could be drawn by the use of the lower limit of the 95% confidence interval, as applied by the FDA for these criteria.

The influence of age on the immune response and antibody persistence was non-linear. Antibody persistence measured by different outcome parameters was considerably higher in the group aged > 60 years.

The data of study H5N1-011 presented here were consistent with the results of the 15µg/AS03 arm of study H5N1-007 (18-40 years olds). In this study, SPRs of 95.9%.and 61.0% were observed at Day 42 and Day 180, respectively.

In conclusion, the H5N1 candidate vaccine with an antigen dose of 15µg and adjuvanted with AS03 was safe and did not raise any safety concerns with respect to new onset chronic diseases and was associated with antibody persistence six months after the first vaccination.

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Title of the study : A phase III, observer-blind, randomised study to evaluate the safety and immunogenicity of one and two administrations of pandemic monovalent (H5N1) influenza vaccine (split virus formulation containing 15 µg HA and adjuvanted with AS03) in adults aged 18 years and older.

Principal investigator: This study was conducted by 41 investigators in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Study centres: Multicentric: 41 centres in 7 countries (Germany, France, Estonia, The Netherlands, Russia, Spain and Sweden).

Publication (reference): Rümke et al., Vaccine (2008) 26, 2378-2388

Study period:	**Clinical phase:** III
Study initiation date: 02 May 2006 Study completion datet: 02 February 2007	

Objectives pertaining to this study annex report (refer to the protocol for the detailed study objectives):
Secondary

- To evaluate the immunogenicity of the pandemic influenza vaccine in terms of the humoral immune response (neutralising antibodies) 21 days after each vaccination.
- To assess the persistence of neutralising antibodies 180 days after the first vaccination

Note: The results described in this Annex report are restricted to the subset of subjects aged 18 to 60 years, the other results have been previously reported in report H5N1-011 EXT 008 Day 180.

Study design:

- Multicentric, observer-blind, randomised study in subjects aged above 18 years in two parallel groups: H5N1 group (vaccinated twice with the pandemic influenza vaccine)
- Fluarix group (vaccinated once with Fluarix™ and once with a placebo).

Number of subjects:
Immunogenicity subset: 622 subjects; ATP cohort for persistence at Day 180: 374 subjects aged 18 to 60 years (279 in the H5N1 group, 95 in the Fluarix group).
Note: ATP cohort for persistence are those subjects qualifying for ATP cohort for immunogenicity and with available results for neutralising antibodies up to and including Day 180.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule/site: two intramuscular administrations at Day 0 and 21 in the non-dominant arm.
Vaccine composition/ dose/ lot number:
Adjuvanted pandemic influenza split vaccine H5N1/15/AS03: 2 vaccine components consisting of the H5N1 antigens (15µg HA from the A/Vietnam/1194/2004 strain, lot number DFLUA032A) and the adjuvant (lot numbers DA3AA002A and DA3AA002B). The total injected volume was 1ml.

Duration of treatment: Duration of study was approximately 6 months for each subject.

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Criteria for evaluation:

***Immunogenicity*:**

In order to evaluate the humoral response in terms of neutralising antibody titres against A/Vietnam/1194/2004 (homologous to the vaccine strain), the following parameters were calculated with 95 % confidence intervals:

- GMTs at Day 0, Day 21, Day 42 and Day 180
- Seroconversion rates at Day 21, Day 42 and Day 180
- Percentage of subjects who reached titres of 1:40 and 1:80 at Day 0, Day 21, Day 42 and Day 180

Statistical methods:

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for immunogenicity in the subset of subjects with a blood sample available at Day 180 and retrospectively at previous timepoints (Day 0, Day 21, and Day 42).

For the humoral immune response in terms of neutralising antibodies (in subjects aged 18 to 60 years), for each treatment group, the following parameters (with 95% confidence intervals) were calculated:

- Geometric mean titres of antibody titres at Day 0, Day 21, Day 42, and Day 180, calculated by taking the anti-log of the mean of the log titre transformations.
- Seroconversion rates at Day 21, Day 42, and Day 180.

Summary:

- It is noticeable that 21.4 to 41.5 % of the subjects investigated in this study already had neutralising antibodies against A/Vietnam at baseline. In the absence of circulating H5N1 strains in the human population it must be inferred that this represents cross-reactive antibodies.
- The neutralising antibody response developed after vaccination against the vaccine A/Vietnam strain is significantly higher in the H5N1/AS03 group. The GMT titres resulting from vaccination with the H5N1 pandemic vaccine are approximately 10-fold higher compared to the GMT titres of the putatively cross-reactive antibodies that appear of the Fluarix control vaccination.
- There is a high level of persistence of the neutralising antibody response against the vaccine A/Vietnam strain 6 months after the primary vaccination in the H5N1/AS03 group. At the 6 months persistence time point the GMTs in the H5N1 vaccine group are approximately 4-fold higher compared to the Fluarix control group.

Conclusions:

- The results in terms of neutralising antibody responses and persistence hereof in adults aged 18 to 60 years receiving 2 dose of the H5N1 vaccine (15µg HA with AS03) described in this annex clinical study report parallel, complement and entirely support the immune response results in terms of H5N1 HI antibodies described in the previous clinical reports.
- In sharp contrast to the near absence of any H5N1 HI antibody response in the Fluarix control group we observed an H5N1 neutralising antibody response against the A/Vietnam/1194/04 vaccine strain. It must be inferred that these represent cross-reactive antibodies these are of uncertain protective and clinical significance.

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