Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) a/vietnam/1194/2004 nibrg-14

Procedure No.: EMEA/H/C/001206/II/0004

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

17 March 2011
EMA/CHMP/191486/2011
Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/001206/II/0004

Name:	Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals
Common name:	Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) a/vietnam/1194/2004 nibrg-14
Indication summary (as last approved):	Prophylaxis of influenza in a pandemic situation
Marketing authorisation holder:	GlaxoSmithKline Biologicals S.A.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of SmPC, Annex II, Labelling and Package Leaflet To reflect new data obtained from study D-Pan H5N1-009 in section 4.2, 4.4, 4.8 and 5.1 of the SmPC, as well as in the Package Leaflet (sections 3 and 4). This clinical study is conducted in children aged 3 to 9 years, to evaluate the immunogenicity, reactogenicity and safety of three formulations of AS03 adjuvanted H5N1 vaccine, given following a two dose schedule on Days 0 and 21. The MAH is also taking the opportunity of this procedure to update Annex II in order to reflect the wording on the Pharmacovigilance System as requested by CHMP and to include the Marketing Authorisation numbers in the Labelling.
Rapporteur:	Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	SmPC, Annex II, Labelling and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	22 December 2010
Start of procedure:	16 January 2011
Rapporteur's assessment report circulated on:	17 January 2011
CHMP opinion:	17 March 2011

3. Scientific discussion

3.1. Introduction

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals was granted Marketing Authorisations in the EU in May 2008 as an informed consent duplicate to Pandemrix.

The legal basis for the initial application for Marketing Authorisation refers to Article 10(c) of Directive 2001/83/EC, as amended –relating to informed consent from the marketing authorisation holder, for the authorised medicinal product: Pandemrix (EU/1/08/452/001).

This vaccine is the same as the Pandemrix H5N1 mock-up vaccine, which was previously authorised in the European Union (EU) and was changed in October 2009 into a vaccine containing the H1N1v strain.

The currently approved vaccine contains split influenza virus with a haemagglutinin content equivalent to 3.75 micrograms derived from A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14).

The vaccine also contains the marketing authorisation holder's (MAH's) proprietary adjuvant AS03, which is composed of squalene, DL-α-tocopherol and polysorbate 80.

The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

The current variation aims to update the Product Information to reflect data from a from a previously submitted study in children aged from 3-9 years (FUM 019 – Study D-Pan - H5N1-009, -022 and -023) The data consists of study reports data up to Day 51 for H5N1-009, -022 and -023.

The data provided in this variation were all previously reviewed as part of:

- FUMs 020 and 019 for Pandemrix and Prepandrix/duplicate, respectively, regarding provision of data to D42 from study 009 in children aged from 3-9 years.

- Rolling Review (RR) #1 and RR#3 for Pandemrix H1N1v since at the time of initial approval the Pandemrix H1N1v-specific data in children were not available.

The classification of the variation is as follows:

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the SmPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

To reflect new data obtained from study D-Pan H5N1-009 in section 4.2, 4.4, 4.8 and 5.1 of the SmPC, as well as in the Package Leaflet (sections 3 and 4). This clinical study is conducted in children aged 3 to 9 years, to evaluate the immunogenicity, reactogenicity and safety of three formulations of AS03 adjuvanted H5N1 vaccine, given following a two dose schedule on Days 0 and 21. The MAH is also taking the opportunity of this procedure to update Annex II in order to reflect the wording on the Pharmacovigilance System as requested by CHMP and to include the Marketing Authorisation numbers in the Labelling.

3.2. Clinical aspects

Study H5N1-009, -022, -023 – use in children aged from 3-9 years

Study design

The entire study was divided into three phases as shown below:

Sequential staggered study design of study H5N1-009

	Phase A H5N1-009	Phase B H5N1-022	Phase C H5N1-023
Half Adult Dose HA antigen **Half** Adult Dose AS03	•6-9 yr olds •3-5 yr olds		
Full Adult Dose HA antigen **Half** Adult Dose AS03		•6-9 yr olds •3-5 yr olds	
Full Adult Dose HA antigen **Full** Adult Dose AS03			•6-9 yr olds •3-5 yr olds

1. Full adult dose HA = 3.8 µg, Half adult dose HA = 1.9 µg HA

Two intramuscular injections of the assigned formulation were given on Days 0 and 21 in the deltoid region of the non-dominant arm.

Each Phase enrolled healthy children in the specified age groups. Subjects from each group were enrolled sequentially into the two age strata (6-9 years and then 3-5 years) with the ratio 1:1.

Based on safety data collected on Days 0 to 6 after the first injection for the subjects aged 6-9 years included in Phase A the decision was taken to vaccinate subjects aged 3-5 years and to administer a second injection to subjects aged 6-9 years. In addition, within each age group, two interim safety analyses were performed on Days 7 and 28 to provide safety information that was analysed by the IDMC and/or the Sponsor Safety Review Team.

Similarly, there were two IDMC consultations in Phases B and C for progression to the younger age group. For each cohort in Phase B and Phase C and within each age group (6-9 years and 3-5 years) the Day 7 interim safety analysis was reviewed by the Sponsor Safety Review Team to provide the go-ahead for the second injection. A further interim safety analysis was produced in each age group of all solicited symptoms experienced between Day 21 and Day 28 plus SAEs and withdrawals reported since Day 0.

In each Phase a first core analysis was performed when all data on the humoral immune response and safety up to Day 51 became available. Subsequent analyses were to be performed when data were available for the Months 6, 12 and 24 time points.

The Co-primary objectives of study 009 were:

- To evaluate the humoral immune response induced by the H5N1 vaccine candidate in terms of anti-haemagglutinin antibody titre.
- To evaluate the safety and reactogenicity of the H5N1 vaccine candidate in terms of solicited local and general AEs, unsolicited AEs and serious adverse events (SAEs).
- To evaluate the biological safety in terms of selected biochemistry parameters (ALT, AST, CREA, BUN, LDH, CPK).

The Secondary objective was:

- To evaluate the humoral immune response induced by the H5N1 vaccine candidate in terms of neutralising antibody titre.

The Exploratory objectives were:

- To evaluate the cell-mediated immune response induced by the H5N1 vaccine candidate in terms of the expression of Th1 markers (CD40L, IFN-γ, IL-2, and TNF-α) after in vitro re-stimulation of influenza-specific CD4/CD8 T-lymphocytes in a subset of subjects.
- To evaluate the cell-mediated immune response induced by the H5N1 vaccine candidate, in terms of Th2-specific activation marker expression (for example, IL-5, IL-10 and/or IL-13 after in vitro re-stimulation of influenza-specific CD4 T-lymphocytes.

Total Vaccinated cohort

The total study cohort included all vaccinated subjects for whom safety data were available.

The total analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity included all evaluable subjects for whom data concerning immunogenicity endpoint measures were available.

ATP cohort for analysis of safety:

Typically, the ATP cohort for analysis of safety included subjects who had received at least one dose of study vaccine and had sufficient data to perform an analysis of safety.

In Phase A

Randomisation was to (allocation ratio 3:1):

- Half HA/Half AS03: Half the adult dose (1.9 µg of HA) + half the AS03
- Control: *Fluarix*

Children in the 6-9 years stratum, enrolled during Q3 of 2007 received *Fluarix* for the Northern Hemisphere 2006/2007 influenza season.

Children in the 3-5 years stratum enrolled during Q4 of 2007 received *Fluarix* for the Northern Hemisphere 2007/2008 influenza season.

In Phase B and Phase C

Randomisation was to (allocation ratio 3:1):

- Full HA/Half AS03 (Phase B): 3.8 µg HA) and half the dose of AS03
- Control: Fluarix

- Full HA/Full AS03 (Phase C)
- Control: Fluarix

This was *Fluarix formulated* for the Northern Hemisphere 2007/2008 influenza season.

Immunogenicity results to D42

Phase A from study H5N1-009

All of the 138 subjects enrolled were vaccinated.

In the Half HA/Half AS03 group: 102 subjects were enrolled with 51 subjects in each age stratum

In the control group: 36 subjects were enrolled with 18 subjects in each age stratum

Fifteen of the 138 (10 aged 6-9 years and 5 aged 3-5 years) were excluded from the ATP immunogenicity cohort. The predominant reasons for exclusion were:

- unknown initial antibody status (8)
- non-compliance with the vaccination schedule (4).

The immune response results (HI and NA) were consistent between the ATP and Total Vaccinated cohort and therefore only the former are reported below.

The overall mean ages per cohort at the time of the first vaccination were 3.8 years and 7.6 years. One subject above 9 years was aged 10 years and 3 months. The overall male-female ratios were 1.03 and 1.23 in respective age cohorts and the majority (94%) were of white-Caucasian/European heritage.

The pre-vaccination HI GMTs for A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 and so seropositivity rates were zero.

On Day 21, the GMTs against A/Vietnam/1194/2004 strain were slightly increased in the Half HA/Half AS03 group in both age strata and then increased markedly after the second dose (540.3 for 6-9 years; 392.7 for 3-5 years). A similar pattern but lower response was seen against A/Indonesia/05/2005 (60.8 for 6-9 years; 53.5 for 3-5 years).

Increments in HI seropositivity rates followed the GMTs for the AS03 vaccine group but in the control group the seropositivity rates against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains were zero at all time points.

Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
1.9 µg HA / Half AS03 - 3-5 years													
PRE	49	5.0	5.0	5.0	0.0	0.0	7.3						
PI(D21)	49	8.7	6.2	12.3	12.2	4.6	24.8	12.2	4.6	24.8	1.7	1.2	2.5
PII(D42)	49	392.7	280.4	550.2	95.9	86.0	99.5	95.9	86.0	99.5	78.5	56.1	110.0
1.9 µg HA / Half AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2						
PI(D21)	43	12.1	8.4	17.5	30.2	17.2	46.1	30.2	17.2	46.1	2.4	1.7	3.5
PII(D42)	43	540.3	424.5	687.7	100	91.8	100	100	91.8	100	108.1	84.9	137.5
H5N1 HI Antibodies against A/Indonesia/05/2005													
1.9 µg HA / Half AS03 - 3-5 years													
PRE	49	5.0	5.0	5.0	0.0	0.0	7.3						
PI(D21)	49	5.2	4.9	5.6	0.0	0.0	7.3	0.0	0.0	7.3	1.0	1.0	1.1
PII(D42)	49	53.5	35.0	81.7	71.4	56.7	83.4	71.4	56.7	83.4	10.7	7.0	16.3
1.9 µg HA / Half AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2						
PI(D21)	43	5.2	4.8	5.8	2.3	0.1	12.3	2.3	0.1	12.3	1.0	1.0	1.2
PII(D42)	43	60.8	38.7	95.5	74.4	58.8	86.5	74.4	58.8	86.5	12.2	7.7	19.1

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03-adjuvanted vaccine group

There were no or small increments between D0 and D21 followed by very marked increments in all parameters between D21 and D42.

- By Day 42 the SCRs and the SPRs against the vaccine strain were 95.9% to 100% while SCRs against A/Indonesia/05/2005 were 71.4% to 74.4 %. The ≥70% threshold for the lower bound of the 95% CI for seroprotection as defined in the CBER Guidance was only met for HI against A/Vietnam/1194/2004.

- On Day 42 the SCFs against A/Vietnam/1194/2004 were 78.5 and 108.1 while SCFs against A/Indonesia/05/2005 strain were 10.7 and 12.2.

In the Fluarix group

No subject seroconverted for HI antibody to A/Vietnam/1194/2004 or A/Indonesia/05/2005 and no subject was seroprotected.

On Day 21, the GMTs for NA against A/Vietnam/1194/2004 strain were nearly 2-fold higher in the Half HA/Half AS03 group in both age strata (177.5 for 6-9 years; 173.5 for 3-5 years) when compared with the control group (97.2 for 6-9 years; 98.2 for 3-5 years).

On Day 42 the NA GMTs against the A/Vietnam/1194/2004 in the Half HA/Half AS03 group had reached 1155.1 in the 6-9 years age stratum and 1044.4 in the 3-5 years age stratum, whereas the increase from baseline in the control group was very small (104.5 for 6-9 years; 158.4 for 3-5 years).

The NA seropositivity rates against A/Vietnam/1194/2004 in the Half HA/Half AS03 group increased to 90.7% in the 6-9 years age stratum and to 91.7% in the 3-5 years age stratum on Day 21, with non-overlapping CIs (when compared with Day 0). All subjects in the Half HA/Half AS03 group were seropositive for NA at d42.

In the control group, the seropositivity rates for NA against the vaccine strain on Days 21 and 42 were within the same range (78.6% - 80.0%).

Humoral immune response – neutralising antibodies against A/Vietnam/1194/2004

		≥ 28 1/DIL			GMT				SCR		
			95% CI			95% CI				95% CI	
Timing	N	%	LL	UL	value	LL	UL	N	%	LL	UL
1.9 µg HA / Half AS03 - 3-5 years											
PRE	47	34.0	20.9	49.3	31.0	21.8	44.0				
PI(D21)	48	91.7	80.0	97.7	173.5	123.3	244.0	46	67.4	52.0	80.5
PII(D42)	47	100	92.5	100	1044.4	845.4	1290.3	45	95.6	84.9	99.5
1.9 µg HA / Half AS03 - 6-9 years											
PRE	43	41.9	27.0	57.9	32.2	23.1	44.9				
PI(D21)	43	90.7	77.9	97.4	177.5	127.0	248.0	43	65.1	49.1	79.0
PII(D42)	42	100	91.6	100	1155.1	920.9	1448.7	42	100	91.6	100

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. Seroconversion defined as: For initially seronegative subjects, antibody titre ≥56 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre
3. N = number of subjects with pre- and post-vaccination results available; n/% = number/percentage of seroconverted subjects; 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

On Day 21 there were no significant differences between the Half HA/Half AS03 and control groups or between the age strata within each group for NA SCRs against the vaccine strain (range 65.1% - 67.4% for Half HA/Half AS03 group and 42.9% - 71.4% for control group).

On Day 42 the NA SCR against the vaccine strain in the Half HA/Half AS03 group had reached 100% in the 6-9 years age stratum and 95.6% in the 3-5 years age stratum.

In contrast there was no further increment in SCRs in the control group after a second dose of Fluarix.

The MAH concluded that:

The half-adult dose formulation (1.9 µg of HA antigen and ½ the adult dose of AS03) elicited strong vaccine-homologous HI and NA responses after two doses administered 21 days apart.

There was no significant difference between the two prospective age strata for any of the immunology parameters studied.

The vaccine also induced a heterologous humoral immune response in terms of HI with SCR/SPRs against A/Indonesia/05/2005 of 71.4 % to 74.4%.

The HI and NA titres were comparable with those observed in adults with 3.8 µg of HA antigen and a full dose of AS03.

Phase B from study H5N1-022

In the Full HA/Half AS03 group: 100 subjects were enrolled with 49 subjects aged 6-9 years and 51 aged 3-5 years.

In the control group: 34 subjects were enrolled with 17 subjects in each age stratum.

The overall mean ages at the time of the first vaccination were 4.2 years and 7.3 years per age stratum. The overall percentage of males was 48.5% and 66.7% per cohort. Almost all subjects were of white-Caucasian/European heritage.

The pre-vaccination HI GMTs for antibody against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 in all vaccine groups and age strata except for one subject in the 3-5 years cohort. Thus seropositivity rates were 0.0% to 2.4%.

- On Day 21, GMTs for HI against A/Vietnam/1194/2004 were slightly increased in both age strata in the AS03 vaccine group (23.7 for 6-9 years; 22.7 for 3-5 years) and were slightly increased against A/Indonesia but remained below the cut-off value in the control group.
- By Day 42 GMTs for HI against A/Vietnam/1194/2004 in the AS03 vaccine group were markedly higher (615.8 for 6-9 years; 678.1 for 3-5 years) and reached 64.9 to 73.7 against A/Indonesia but were still below the cut-off value in the control group.
- Seropositivity rates followed the same pattern as the GMTs.

Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
3.8 µg HA / Half AS03 - 3-5 years													
PRE	42	5.1	4.9	5.4	0.0	0.0	8.4	-	-	-	-	-	-
PI(D21)	41	22.7	14.6	35.3	48.8	32.9	64.9	48.8	32.9	64.9	4.4	2.9	6.8
PII(D42)	42	678.1	475.7	966.6	97.6	87.4	99.9	97.6	87.4	99.9	132.3	91.8	190.7
3.8 µg HA / Half AS03 - 6-9 years													
PRE	45	5.1	4.9	5.4	0.0	0.0	7.9	-	-	-	-	-	-
PI(D21)	45	22.7	14.6	35.3	42.2	27.7	57.8	42.2	27.7	57.8	4.7	2.9	7.8
PII(D42)	45	678.1	475.7	966.6	97.8	88.2	99.9	97.8	88.2	99.9	123.2	85.8	176.8
H5N1 HI Antibodies against A/Indonesia/05/2005													
3.8 µg HA / Half AS03 - 3-5 years													
PRE	42	5.0	5.0	5.0	0.0	0.0	8.4	-	-	-	-	-	-
PI(D21)	41	5.5	4.9	6.2	0.0	0.0	8.6	0.0	0.0	8.6	1.1	1.0	1.2
PII(D42)	42	73.7	45.2	120.3	76.2	60.5	87.9	76.2	60.5	87.9	14.7	9.0	24.1
3.8 µg HA / Half AS03 - 6-9 years													
PRE	45	5.0	5.0	5.0	0.0	0.0	7.9	-	-	-	-	-	-
PI(D21)	45	5.3	4.9	5.8	0.0	0.0	7.9	0.0	0.0	7.9	1.1	1.0	1.2
PII(D42)	45	64.9	38.7	108.9	68.9	53.4	81.8	68.9	53.4	81.8	13.0	7.7	21.8

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03-adjuvanted vaccine group

By Day 21 the SCRs and SPRs against A/Vietnam/1194/2004 ranged from 42.2% to 48.8% but there was no seroconversion and no subject was seroprotected with respect to A/Indonesia/05/2005.

On Day 42 the SCRs and SPRs against the vaccine strain had reached 97.8% for subjects aged 6-9 years and 97.6% for subjects aged 3-5 years. SCRs and SPRs against A/Indonesia/05/2005 had increased to 68.9% and 76.2% in respective age groups. The ≥70% threshold for the lower bound of the 95% CI for seroprotection as defined in the CBER Guidance was met for HI against A/Vietnam/1194/2004.

Day 21 SCFs against both strains were from 1.1 to 4.7 but at Day 42 the SCFs against A/Vietnam/1194/2004 were 123.2 for 6-9 years and 132.3 for 3-5 years. The increments in SCFs against A/Indonesia/05/2005 strain were relatively modest (13.0 and 14.7).

In the Fluarix group

No subject seroconverted for HI antibody to A/Vietnam/1194/2004 or A/Indonesia/05/2005 and no subject was seroprotected.

The pre-vaccination NA GMTs were ≥1:28 and comparable between the age strata range 25.6 to 65.5 while baseline seropositivity rates ranged from 47.1% to 78.6%.

By Day 21 the NA GMTs against A/Vietnam/1194/2004 were approximately 3-fold higher in the AS03 vaccine group in both age strata compared with the control group. On Day 42 GMTs exceeded 1500 in the AS03 group but there was a negligible increase in the control group.

The seropositivity rates and seroconversion rates followed the same pattern as the GMTs.

Humoral immune response – neutralising antibodies against A/Vietnam/1194/2004

		≥28 1/DIL			GMT				SCR		
			95% CI			95% CI				95% CI	
Timing	N	%	LL	UL	value	LL	UL	N	%	LL	UL
3.8 µg HA / Half AS03 - 3-5 years											
PRE	42	78.6	63.2	89.7	65.5	47.3	90.7	-	-	-	-
PI(D21)	39	97.4	86.5	99.9	344.7	260.9	455.3	39	64.1	47.2	78.8
PII(D42)	42	97.6	87.4	99.9	1553.2	1105.9	2181.5	42	95.2	83.8	99.4
3.8 µg HA / Half AS03 - 6-9 years											
PRE	45	64.4	48.8	78.1	46.2	33.2	64.2	-	-	-	
PI(D21)	45	100	92.1	100	461.7	376.2	566.5	45	77.8	62.9	88.8
PII(D42)	45	100	92.1	100	1519.4	1229.9	1877.0	45	93.3	81.7	98.6

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 56 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre
3. N = number of subjects with pre- and post-vaccination results available; n/% = number/percentage of seroconverted subjects; 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

Phase C from study H5N1-023

In the Full HA/Full AS03 group: 98 subjects were enrolled with 49 subjects in each age stratum

In the control group: 35 subjects were enrolled with 18 and 17 subjects in each age stratum

The overall mean ages at the time of the first vaccination were 4.2 years and 7.1 years per age cohort. Male subjects accounted for 50-59.7% per age cohort and almost all were of white-Caucasian/European heritage.

The pre-vaccination GMTs for HI antibody against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 regardless of age stratum or vaccine group and so seropositivity rates were zero.

Day 21 HI GMTs against A/Vietnam/1194/2004 were slightly increased in the AS03 vaccine group in both age strata and by Day 42 they had reached 883.5 for 6-9 years and 956.4 for 3-5 years.

HI GMTs against A/Indonesia/05/2005 in the AS03 group were also much higher at D42 (92.5 for 6-9 years; 167.9 for 3-5 years) compared with D21.

Corresponding seropositivity rates followed a similar pattern and by D42 all subjects in both age strata were seropositive against A/Vietnam while rates against A/Indonesia/05/2005 had reached 83.7% in the 6-9 years age stratum and 95.5% in the 3-5 years age stratum.

In the control group, the seropositivity rates against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were zero at all time points except for one subject who was seropositive after the first *Fluarix* dose. All corresponding GMTs were low or below the cut-off value.

Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
3.8 µg HA / Full AS03 - 3-5 years													
PRE	44	5.0	5.0	5.0	0.0	0.0	8.0	-	-	-	-	-	-
PI(D21)	43	25.0	16.0	39.3	46.5	31.2	62.3	46.5	31.2	62.3	5.0	3.2	7.9
PII(D42)	44	956.4	769.2	1189.3	100	92.0	100	100	92.0	100	191.3	153.8	237.9
3.8 µg HA / Full AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2	-	-	-	-	-	-
PI(D21)	30	27.3	16.2	46.0	56.7	37.4	74.5	56.7	37.4	74.5	5.5	3.2	9.2
PII(D42)	43	883.5	737.3	1058.6	100	91.8	100	100	91.8	100	176.7	147.5	211.7
H5N1 HI Antibodies against A/Indonesia/05/2005													
3.8 µg HA / Full AS03 - 3-5 years													
PRE	44	5.0	5.0	5.0	0.0	0.0	8.0	-	-	-	-	-	-
PI(D21)	43	7.7	6.0	9.8	7.0	1.5	19.1	7.0	1.5	19.1	1.5	1.2	2.0
PII(D42)	44	167.9	121.7	231.5	95.5	84.5	99.4	95.5	84.5	99.4	33.6	24.3	46.3
3.8 µg HA / Full AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2	-	-	-	-	-	-
PI(D21)	30	6.0	5.0	7.2	3.3	0.1	17.2	3.3	0.1	17.2	1.2	1.0	1.4
PII(D42)	43	92.5	59.3	144.2	79.1	64.0	90.0	79.1	64.0	90.0	18.5	11.9	28.8

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03 vaccine group

The Day 21 SCRs and SPRs against A/Vietnam/1194/2004 ranged from 46.5% to 56.7% but were only 3.3% to 7% against A/Indonesia/05/2005. By Day 42 rates were 100% for both age strata against

A/Vietnam and 79.1% to 95.5% against A/Indonesia. The ≥70% threshold for the lower bound of the 95% CI for seroprotection as defined in the CBER Guidance was met for HI antibody against A/Vietnam/1194/2004 in both age strata and was met against A/Indonesia/05/2005 in the 3-5 year age stratum.

The Day 21 SCFs against A/Vietnam/1194/2004 and A/Indonesia/05/2005 ranged from 1.2 to 5.5. However, on Day 42 the SCFs against A/Vietnam/1194/2004 were 176.7 and 191.3 compared to 18.5 and 33.6 against A/Indonesia/05/2005.

In the control group

No subject seroconverted for HI against either strain and none was seroprotected with the exception of one subject with a response to A/Vietnam/1194/2004 on Day 21 only.

Pre-vaccination NA GMTs were ≥1:28 and were generally comparable between the age strata (range 25.6 to 37.3). Despite the low GMTs, the baseline seropositivity rates ranged from 30.8% to 46.7%.

Humoral immune response – neutralising antibodies against A/Vietnam/1194/2004

		≥28 1/DIL			GMT				SCR		
			95% CI			95% CI				95% CI	
Timing	N	%	LL	UL	value	LL	UL	N	%	LL	UL
3.8 µg HA / Full AS03 - 3-5 years											
PRE	40	37.5	22.7	54.2	37.3	23.9	58.1	-	-	-	-
PI(D21)	40	100	91.2	100	473.8	351.2	639.3	36	80.6	64.0	91.8
PII(D42)	42	100	91.6	100	4578.3	3786.6	5535.6	38	97.4	86.2	99.9
3.8 µg HA / Full AS03 - 6-9 years											
PRE	43	32.6	19.1	48.5	25.6	18.6	35.3	-	-	-	-
PI(D21)	29	93.1	77.2	99.2	313.5	193.3	508.4	29	79.3	60.3	92.0
PII(D42)	42	100	91.6	100	3032.5	2431.8	3781.6	42	100	91.6	100

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. Seroconversion defined as: For initially seronegative subjects, antibody titre ≥56 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre
3. N = number of subjects with pre- and post-vaccination results available; n/% = number/percentage of seroconverted subjects; 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

On Day 21, NA GMTs against A/Vietnam/1194/2004 were 1.5-4-fold in the AS03 group compared with the control group.

By Day 42 NA GMTs against A/Vietnam/1194/2004 increased about 10-fold in the AS03 group in both age strata and all children were seropositive whereas there was no further increase in GMTs in the control group and the seropositivity rates ranged from 61.5% to 87.5%. The seroconversion rates also showed the marked differences between AS03 and control for both age strata.

Comparison between the three formulations up to D42

The MAH performed a comparison between the three AS03-adjuvanted vaccine formulations (i.e. ½ HA/½ AS03, Full HA/ ½ AS03, and Full HA/Full AS03 used in Phases A, B, and C, respectively. See Table 16 below.

Responses in terms of SCR, SPR and SCF were high in all three study phases and in both age strata.

There was a trend for higher HI GMTs and SCFs against both strains and a higher NA GMT against the vaccine strain with the formulations tested in Phases C and B compared to the half/half formulation used in Phase A. The immune also response tended to be higher in Phase C when compared with Phase B.

When comparing the formulation used in Phase C or in Phase B with that used in Phase A the difference between A and C was marked whereas the difference between A and B was much less apparent.

There were advantages for C over B for HI and NA GMTs and for responses to A/Indonesia.

The MAH concluded that:

At Day 42 the CBER criterion for seroconversion was reached against both strains and in both age strata in children who received Full HA/Half AS03 or Full HA/Full AS03 groups.

At Day 42 the CBER criterion for seroprotection was met against A/Vietnam/1194/2004 in both age strata that received Full HA/Half AS03 or Full HA/Full AS03 while the criterion was met against A/Indonesia/05/2005 by 3-5 year-olds who received Full HA/Full AS03.

There were marked increments in responses to both strains from first to second doses in groups that received Full HA/Half AS03 or Full HA/Full AS03.

Responses to A/Vietnam were higher than to A/Indonesia in all AS03 formulation groups.

No major differences between the age strata (6-9 years and 3-5 years) were detected for any of the immune response parameters considered.

Comparisons between the three formulations used in Phases A, B, and C generally favoured C over both A and B. However the HI SCR/SPRs did not show marked differences between the three formulations tested.

Immunogenicity data at Month 6

By Month 6 the HI GMTs had fallen but were still at least 6-fold higher than the pre-vaccination GMTs in the groups that had received AS03 vaccines.

Against A/Vietnam the seroprotection rates at Month 6 in children who received the adult dose vaccine in Part C of the study were 82.8% for 3-5 year-olds and 78% for 6-9 year-olds. These rates compare with 56% and 63.6% in respective age groups who received the half/half vaccine in Part A and with 70.2% and 68.9% who received full dose HA and half AS03 in Part B. The 95% CI overlap between Parts A, B and C within each age stratum. The results for the other parameters shown follow a similar pattern.

Vaccine strain homologous (against H5N1 A/Vietnam) immune response persistence in terms of HI antibodies at month 6

		≥ 10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H5N1 HI Antibodies against A/Vietnam/1194/2004																
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	50	0.0	0.0	7.1	5.0	5.0	5.0	0.0	0.0	7.1						
PII(M6)	50	64.0	49.2	77.1	29.3	19.2	44.6	56.0	41.3	70.0	56.0	41.3	70.0	5.9	3.8	8.9
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	42	0.0	0.0	8.4	5.0	5.0	5.0	0.0	0.0	8.4						
PII(M6)	44	65.9	50.1	79.5	33.4	21.2	52.7	63.6	47.8	77.6	61.0	44.5	75.8	6.1	3.8	9.7
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	47	2.1	0.1	11.3	5.1	4.9	5.3	0.0	0.0	7.5						
PII(M6)	47	72.3	57.4	84.4	46.3	29.8	72.0	70.2	55.1	82.7	68.1	52.9	80.9	9.1	5.8	14.1
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	45	73.3	58.1	85.4	43.2	27.9	66.8	68.9	53.4	81.8	68.9	53.4	81.8	8.6	5.6	13.4
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	32	0.0	0.0	10.9	5.0	5.0	5.0	0.0	0.0	10.9						
PII(M6)	29	82.8	64.2	94.2	80.0	47.0	136.4	82.8	64.2	94.2	82.8	64.2	94.2	16.0	9.4	27.3
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	43	0.0	0.0	8.2	5.0	5.0	5.0	0.0	0.0	8.2						
PII(M6)	41	78.0	62.4	89.4	61.5	38.9	97.3	78.0	62.4	89.4	78.0	62.4	89.4	12.3	7.8	19.5

SPR = percentage with antibody titre ≥ 40 1/DIL; SCR = percentage with antibody titre ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥ 4-fold the pre-vaccination antibody titre for initially seropositive subjects; SCF = fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PII(M6) = post-vaccination at Month 6

In the **Fluarix groups** in each Part of the study there was no difference between the D0 and the Month 6 HI seropositivity rates and GMTs against either A/Vietnam or A/Indonesia in 3-5 year-olds or 6-9 year-olds. Therefore there was no evidence of any augmentation of the HI immune response as a result of intervening natural exposure to cross-reacting antigens between D42 and Month 6.

Against the heterologous A/Indonesia strain 69% of children aged 3 to 5 years who had received the adult dose were seroprotected at Month 6 compared to 6.0% from Part A and 48.9% from Part B of the study. Corresponding rates in children aged 6 to 9 years were 61% versus 4.5% and 26.7%.

Vaccine strain heterologous (against H5N1 A/Indonesia) immune response persistence in terms of HI antibodies at month 6

		≥ 10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H5N1 HI Antibodies against A/Indonesia/05/2005																
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	50	0.0	0.0	7.1	5.0	5.0	5.0	0.0	0.0	7.1						
PII(M6)	50	20.0	10.0	33.7	6.9	5.6	8.4	6.0	1.3	16.5	6.0	1.3	16.5	1.4	1.1	1.7
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	42	0.0	0.0	8.4	5.0	5.0	5.0	0.0	0.0	8.4						
PII(M6)	44	18.2	8.2	32.7	6.6	5.2	8.4	4.5	0.6	15.5	2.4	0.1	12.9	1.2	1.0	1.5
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	47	55.3	40.1	69.8	21.7	14.3	33.0	48.9	34.1	63.9	48.9	34.1	63.9	4.3	2.9	6.6
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	45	40.0	25.7	55.7	11.9	8.4	16.9	26.7	14.6	41.9	26.7	14.6	41.9	2.4	1.7	3.4
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	32	0.0	0.0	10.9	5.0	5.0	5.0	0.0	0.0	10.9						
PII(M6)	29	69.0	49.2	84.7	42.5	23.7	76.3	69.0	49.2	84.7	69.0	49.2	84.7	8.5	4.7	15.3
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	43	0.0	0.0	8.2	5.0	5.0	5.0	0.0	0.0	8.2						
PII(M6)	41	65.9	49.4	79.9	36.8	22.3	60.6	61.0	44.5	75.8	61.0	44.5	75.8	7.4	4.5	12.1

SPR = percentage with antibody titre ≥ 40 1/DIL; SCR = percentage with antibody titre ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥ 4-fold the pre-vaccination antibody titre for initially seropositive subjects; SCF = fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PII(M6) = post-vaccination at Month 6

NA was assessed against **A/Vietnam** at **Month 6** for **Part A** subjects only (i.e. half adult dose versus Fluarix).

In the AS03 vaccine group the NA GMTs dropped to a similar degree in both age strata so that, as at D42 (GMTs 1026 and 1111), the actual GMTs at D180 were comparable for children aged 3-5 years and 6-9 years (776 and 759). At Month 6 all children who had received the AS03 vaccine had NA titres of at least 1:80.

However, in the **Fluarix** group the GMTs increased between D42 and D180. In the younger age group (3-5 years) the increment was small (from 166 to 200) but is none the less remarkable since a drop in GMT would usually have been expected. In the older age group (6-9 years) the increase was by 6-fold (from 75 at D42 to 482 at D180). These results suggest that natural exposure to cross-reacting antigens had occurred in the interim period.

As a result the seroconversion rates in the 6-9 year-olds at Month 6 were 95% for the AS03 group and 93% for the Fluarix group. Also, all children aged 6-9 years who received Fluarix had NA titres of at least 1:80 at Month 6, while the corresponding rate in the 3-5 year-olds was 80%.

Neutralising antibodies against A/Vietnam/1194/2004 up to Month 6 (ATP)

					≥ 28 1/DIL				GMT				
							95% CI			95% CI			
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
A/Vietnam	H5N1/2+AS03/2	3-5y	PRE	48	16	33.3	20.4	48.4	30.5	21.6	43.0	<28.0	905.0
			PI(D21)	49	45	91.8	80.4	97.7	173.6	124.3	242.4	<28.0	1420.0
			PII(D42)	48	48	100	92.6	100	1026.4	832.2	1266.0	226.0	5690.0
			PII(M6)	50	50	100	92.9	100	776.3	639.7	942.0	180.0	9050.0
		6-9y	PRE	43	18	41.9	27.0	57.9	32.2	23.1	44.9	<28.0	453.0
			PI(D21)	42	38	90.5	77.4	97.3	171.7	122.4	240.7	<28.0	905.0
			PII(D42)	41	41	100	91.4	100	1110.8	907.6	1359.4	284.0	4530.0
			PII(M6)	42	42	100	91.6	100	758.5	632.3	909.8	226.0	5690.0
	Fluarix™	3-5y	PRE	14	5	35.7	12.8	64.9	23.4	13.8	39.6	<28.0	226.0
			PI(D21)	15	12	80.0	51.9	95.7	107.8	55.4	209.6	<28.0	453.0
			PII(D42)	15	12	80.0	51.9	95.7	165.9	79.0	348.2	<28.0	453.0
			PII(M6)	15	15	100	78.2	100	200.2	108.8	368.1	28.0	905.0
		6-9y	PRE	14	2	14.3	1.8	42.8	18.6	12.0	28.7	<28.0	180.0
			PI(D21)	13	10	76.9	46.2	95.0	81.9	39.1	171.5	<28.0	453.0
			PII(D42)	14	10	71.4	41.9	91.6	74.6	35.3	157.8	<28.0	453.0
			PII(M6)	14	14	100	76.8	100	482.3	313.4	742.3	226.0	2840.0

Percentage with NA titres 1:40 and 1:80 against A/Vietnam/1194/2004 on Day 180 (ATP)

					≥1:40 1/DIL				≥1:80 1/DIL			
							95% CI				95% CI	
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Vietnam	H5N1/2+AS03/2	3-5y	PRE	48	16	33.3	20.4	48.4	13	27.1	15.3	41.8
			PI(D21)	49	43	87.8	75.2	95.4	37	75.5	61.1	86.7
			PII(D42)	48	48	100	92.6	100	48	100	92.6	100
			PII(M6)	50	50	100	92.9	100	50	100	92.9	100
		6-9y	PRE	43	17	39.5	25.0	55.6	11	25.6	13.5	41.2
			PI(D21)	42	38	90.5	77.4	97.3	33	78.6	63.2	89.7
			PII(D42)	41	41	100	91.4	100	41	100	91.4	100
			PII(M6)	42	42	100	91.6	100	42	100	91.6	100
	Fluarix™	3-5y	PRE	14	2	14.3	1.8	42.8	2	14.3	1.8	42.8
			PI(D21)	15	12	80.0	51.9	95.7	10	66.7	38.4	88.2
			PII(D42)	15	12	80.0	51.9	95.7	12	80.0	51.9	95.7
			PII(M6)	15	12	80.0	51.9	95.7	12	80.0	51.9	95.7
		6-9y	PRE	14	2	14.3	1.8	42.8	1	7.1	0.2	33.9
			PI(D21)	13	9	69.2	38.6	90.9	8	61.5	31.6	86.1
			PII(D42)	14	9	64.3	35.1	87.2	8	57.1	28.9	82.3
			PII(M6)	14	14	100	76.8	100	14	100	76.8	100

NA SCRs against A/Vietnam/1194/2004 on Day 180 (ATP)

					SCR			
							95% CI	
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL
A/Vietnam	H5N1/2+AS03/2	3-5y	PII(M6)	48	41	85.4	72.2	93.9
		6-9y	PII(M6)	42	40	95.2	83.8	99.4
	Fluarix™	3-5y	PII(M6)	14	10	71.4	41.9	91.6

					SCR			
							95% CI	
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL
		6-9y	PII(M6)	14	13	92.9	66.1	99.8

Due to the unexpected results in the Fluarix group the MAH subsequently performed further testing of selected sera against the A/Brisbane seasonal strain. The results showed:

1) Some level of concordance between anti A/Vietnam NA titres and anti-A/Brisbane/59 HI titres at baseline and after Fluarix vaccination;

2) An increase in anti-A/Brisbane/59 HI titres at Month 6 in some subjects suggesting H1N1 infection (>4 fold titer increase). In some but not all of these individuals the observed Month 6 increase in anti-A/Brisbane/59 HI titre paralleled the increase in anti A/Vietnam NA titre.

In conclusion, the MAH states that the results suggested that an increase in anti-Vietnam NA titres could be due to H1N1 infection in the study population between D42 and M6. The absence of a consistent parallelism between anti-Brisbane HI and anti-Vietnam NA titres may reflect the complexity of the relationship between the two assays. For example the MAH points to possible interference of post vaccine response and kinetics, post infectious response and kinetics, antibody activities captured by both assays and assay variability between D42 and M6 testing.

Immunogenicity data at Month 12

The heterologous immune response to vaccination was evaluated in terms of neutralising antibodies against the A/Indonesia/05/2005 strain at Day 42, at Month 6 and at Month 12 following vaccination with half dose HA + half ASO3 (Phase A subjects) or with Fluarix (control group). Note that the D0 samples were not tested but will be tested in parallel with the M24 samples and the results provided at a later date.

A significant heterologous immune response was observed at Day 42, Month 6 and Month 12 in subjects receiving half dose HA + half ASO3. The comparison between Phase A and Fluarix indicated that cross-reactive immunity was induced by the vaccine. In contrast to the A/Vietnam data the control group did not show an increment in NA titre against A/Indonesia over time. In the AS03 group there was a decrease in GMT at M6 and at M12 compared to D42 but the rate of subjects with a titre above 1/80 remained high in both age groups with 89.6% at M6 and 87.2% at M12 in the 3-6 years-old group and with 90% at M6 and 82.9% at M12 in the 6-9 years-old group.

Seropositivity rates and geometric means titres (GMTs) of neutralizing antibody titers against A/Indonesia/05/2005 at Day 42, Month 6 and Month 12 (ATP cohort for immunogenicity)

					≥ 28 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Indonesia	H5N1/2+AS03/2	3-5	PII(D42)	46	46	100	92.3	100	331.4	271.2	405.0	57.0	1138.0
			PII(M6)	48	47	97.9	88.9	99.9	242.1	189.2	309.8	<28.0	1138.0
			PII(M12)	47	47	100	92.5	100	177.7	141.3	223.6	28.0	905.0
		6-9	PII(D42)	42	42	100	91.6	100	412.1	337.0	504.0	71.0	1138.0
			PII(M6)	40	38	95.0	83.1	99.4	208.4	154.8	280.6	<28.0	1440.0
			PII(M12)	35	33	94.3	80.8	99.3	128.1	97.5	168.4	<28.0	569.0
	Fluarix	3-5	PII(D42)	15	7	46.7	21.3	73.4	30.8	16.3	58.1	<28.0	360.0
			PII(M6)	15	5	33.3	11.8	61.6	22.6	14.0	36.5	<28.0	226.0
			PII(M12)	15	2	13.3	1.7	40.5	17.9	11.6	27.7	<28.0	284.0
		6-9	PII(D42)	13	8	61.5	31.6	86.1	44.7	24.5	81.6	<28.0	180.0
			PII(M6)	13	4	30.8	9.1	61.4	23.1	12.6	42.5	<28.0	453.0
			PII(M12)	14	3	21.4	4.7	50.8	21.9	12.2	39.2	<28.0	284.0

3-5 = 3-5years; 6-9 = 6-9years
GMT = Geometric Mean antibody Titer; N = Number of subjects with available results
n/% = number/percentage of seropositive subjects (neutra titer >= 1:28)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit ; MIN/MAX = Minimum/Maximum
PII(D42) = Post-vaccination two at Day 42 ; PII(M6) = Post-vaccination two at month 6
PII(M12) = Post-vaccination two at month 12

Percentage of subjects that reached NT antibody titer of ≥1:40, ≥ 1:56 and ≥1:80 at Day 42, Month 6 and Month 12 (ATP cohort for immunogenicity)

					≥40 1/DIL				≥56 1/DIL				≥80 1/DIL			
							95% CI				95% CI				95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Indonesia	H5N1/2+AS03/2	3-5	PII(D42)	46	46	100	92.3	100	46	100	92.3	100	45	97.8	88.5	99.9
			PII(M6)	48	45	93.8	82.8	98.7	45	93.8	82.8	98.7	43	89.6	77.3	96.5
			PII(M12)	47	45	95.7	85.5	99.5	42	89.4	76.9	96.5	41	87.2	74.3	95.2
		6-9	PII(D42)	42	42	100	91.6	100	42	100	91.6	100	41	97.6	87.4	99.9
			PII(M6)	40	38	95.0	83.1	99.4	38	95.0	83.1	99.4	36	90.0	76.3	97.2
			PII(M12)	35	33	94.3	80.8	99.3	32	91.4	76.9	98.2	29	82.9	66.4	93.4
	Fluarix	3-5	PII(D42)	15	4	26.7	7.8	55.1	3	20.0	4.3	48.1	3	20.0	4.3	48.1
			PII(M6)	15	2	13.3	1.7	40.5	2	13.3	1.7	40.5	2	13.3	1.7	40.5
			PII(M12)	15	1	6.7	0.2	31.9	1	6.7	0.2	31.9	1	6.7	0.2	31.9
		6-9	PII(D42)	13	8	61.5	31.6	86.1	8	61.5	31.6	86.1	5	38.5	13.9	68.4
			PII(M6)	13	2	15.4	1.9	45.4	2	15.4	1.9	45.4	1	7.7	0.2	36.0
			PII(M12)	14	2	14.3	1.8	42.8	2	14.3	1.8	42.8	2	14.3	1.8	42.8

3-5 = 3-5years
6-9 = 6-9years
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(D42) = Post-vaccination two at Day 42
PII(M6) = Post-vaccination two at month 6
PII(M12) = Post-vaccination two at month 12

Safety

Phase A

In the 6-9 years age stratum, the overall incidence of AEs by subject was 96.1% in the AS03 group and 88.9% in the control group. The incidences of general symptoms were comparable between vaccine groups but local symptoms occurred more often in the AS03 group. There was no increased reactogenicity in either vaccine group after the second dose compared with the first dose.

In the **3-5 years** age stratum, AE rates were generally lower than in older children. Incidences of general symptoms per subject were comparable between vaccine groups but rates of local symptoms per subject were higher in the AS03 group. There was no increased reactogenicity in either vaccine group after the second dose compared with the first dose.

Incidence and nature of adverse events (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)

			Any symptom					General symptoms					Local symptoms				
	Group	Sub-group				95% CI					95% CI					95% CI	
			N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	18	11	61.1	35.7	82.7	18	7	38.9	17.3	64.3	18	8	44.4	21.5	69.2
		6-9y	18	13	72.2	46.5	90.3	18	6	33.3	13.3	59.0	18	12	66.7	41.0	86.7
	H5N1/2 +AS03/2	3-5y	51	29	56.9	42.2	70.7	51	19	37.3	24.1	51.9	51	27	52.9	38.5	67.1
		6-9y	51	47	92.2	81.1	97.8	51	29	56.9	42.2	70.7	51	41	80.4	66.9	90.2
Dose 2	*Fluarix*™	3-5y	17	8	47.1	23.0	72.2	17	3	17.6	3.8	43.4	17	6	35.3	14.2	61.7
		6-9y	18	14	77.8	52.4	93.6	18	10	55.6	30.8	78.5	18	10	55.6	30.8	78.5
	H5N1/2 +AS03/2	3-5y	50	33	66.0	51.2	78.8	50	18	36.0	22.9	50.8	50	27	54.0	39.3	68.2
		6-9y	49	35	71.4	56.7	83.4	49	20	40.8	27.0	55.8	49	30	61.2	46.2	74.8
Overall/dose	*Fluarix*™	3-5y	35	19	54.3	36.6	71.2	35	10	28.6	14.6	46.3	35	14	40.0	23.9	57.9
		6-9y	36	27	75.0	57.8	87.9	36	16	44.4	27.9	61.9	36	22	61.1	43.5	76.9
	H5N1/2 +AS03/2	3-5y	101	62	61.4	51.2	70.9	101	37	36.6	27.3	46.8	101	54	53.5	43.3	63.5
		6-9y	100	82	82.0	73.1	89.0	100	49	49.0	38.9	59.2	100	71	71.0	61.1	79.6
Overall/subject	*Fluarix*™	3-5y	18	13	72.2	46.5	90.3	18	9	50.0	26.0	74.0	18	10	55.6	30.8	78.5
		6-9y	18	16	88.9	65.3	98.6	18	11	61.1	35.7	82.7	18	13	72.2	46.5	90.3
	H5N1/2 +AS03/2	3-5y	51	38	74.5	60.4	85.7	51	24	47.1	32.9	61.5	51	34	66.7	52.1	79.2
		6-9y	51	49	96.1	86.5	99.5	51	33	64.7	50.1	77.6	51	46	90.2	78.6	96.7

H5N1/2 + AS03/2 = Half HA / Half AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

The incidence of grade 3 AEs was generally low with no difference between the vaccine groups in older children but with rates of 13.7% versus zero in children aged 3-5 years. The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 94.1% in the Half HA/Half AS03 group compared with 83.3% in the control subjects. However, rates were comparable among subjects aged 3-5 years (66.7% and 61.1%).

In the 6-9 year-olds the rates of pain were 61% for Fluarix and 76.5% for AS03 vaccine after the first dose (none and 5.9% with Grade 3) but were comparable after the second dose (none and 4% with Grade 3). In the 3-5 year-olds the rates of pain were higher with AS03 vaccine after both doses but very few had Grade 3 pain.

Rates of solicited general symptoms per subject as shown below were not markedly different between vaccine groups in the **6-9 years** age stratum. The rate of any fever (> 37.5°C) after dose 1 of AS03 vaccine was 5.9% but no subject had Grade 3 fever (> 39°C) and no subject in the Fluarix group had any fever. The rates for any fever after the second dose were 16.7% for Fluarix and 10.2% for AS03 vaccine while rates for Grade 3 fever were 5.6% and zero. The per-dose rates for any antipyretic use were 8% in both vaccine groups with per subject rates of 17% and 14% in respective groups.

In the **3-5 years** age stratum rates of solicited general symptoms per subject were higher than in the control group. The rate of any fever after dose 1 of AS03 vaccine was 9.8% but 3.9% had Grade 3 fever (> 39°C). The corresponding rates after the second dose were 6% and zero. No subjects in the Fluarix group had fever after either dose. The per-dose rates of taking any antipyretic were 9% for Fluarix and 19% for AS03 vaccine, with per subject rates of 17% and 35%.

Unsolicited AEs reported up to 51 days after the first vaccination showed no particular signal or clinical pattern in any vaccine group.

No deaths or other SAEs were reported and there were no AEs leading to withdrawal during this study phase.

Phase B

In both age strata the overall incidence incidences of AEs and rates of local and general AEs by subject were higher in the AS03 vaccine group than in the control group. There was no increased reactogenicity in either vaccine group after the second vaccination when compared with the first vaccination. There were more Grade 3 AEs in subjects aged 6-9 years in the AS03 group (8.2%) when compared with the control group (0.0%). Similarly, the incidence of Grade 3 AEs in subjects aged 3-5 years was higher in the AS03 group (11.8%) when compared with the control group (5.9%), mainly driven by a higher incidence of Grade 3 local symptoms.

The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 75.5% in the AS03 vaccine group compared with 58.8% in the control subjects. Also, among subjects aged 3-5 years the incidence of AEs assessed as causally related to the vaccination was 70.6% in the AS03 vaccine group and 35.3% in the control group.

Incidence and nature of AEs (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase B)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	17	6	35.3	14.2	61.7	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9
		6-9y	17	9	52.9	27.8	77.0	17	5	29.4	10.3	56.0	17	8	47.1	23.0	72.2
	H5N1 +AS03/2	3-5y	51	32	62.7	48.1	75.9	51	23	45.1	31.1	59.7	51	22	43.1	29.3	57.8
		6-9y	49	35	71.4	56.7	83.4	49	17	34.7	21.7	49.6	49	33	67.3	52.5	80.1
Dose 2	*Fluarix*™	3-5y	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	17	2	11.8	1.5	36.4
		6-9y	17	8	47.1	23.0	72.2	17	3	17.6	3.8	43.4	17	8	47.1	23.0	72.2
	H5N1 +AS03/2	3-5y	49	34	69.4	54.6	81.7	49	21	42.9	28.8	57.8	49	22	44.9	30.7	59.8
		6-9y	47	32	68.1	52.9	80.9	47	17	36.2	22.7	51.5	47	29	61.7	46.4	75.5
Overall/dose	*Fluarix*™	3-5y	34	9	26.5	12.9	44.4	34	5	14.7	5.0	31.1	34	6	17.6	6.8	34.5
		6-9y	34	17	50.0	32.4	67.6	34	8	23.5	10.7	41.2	34	16	47.1	29.8	64.9
	H5N1 +AS03/2	3-5y	100	66	66.0	55.8	75.2	100	44	44.0	34.1	54.3	100	44	44.0	34.1	54.3
		6-9y	96	67	69.8	59.6	78.7	96	34	35.4	25.9	45.8	96	62	64.6	54.2	74.1
Overall/subject	*Fluarix*™	3-5y	17	7	41.2	18.4	67.1	17	4	23.5	6.8	49.9	17	5	29.4	10.3	56.0
		6-9y	17	10	58.8	32.9	81.6	17	6	35.3	14.2	61.7	17	10	58.8	32.9	81.6
	H5N1 +AS03/2	3-5y	51	42	82.4	69.1	91.6	51	32	62.7	48.1	75.9	51	29	56.9	42.2	70.7
		6-9y	49	38	77.6	63.4	88.2	49	24	49.0	34.4	63.7	49	37	75.5	61.1	86.7

H5N1 + AS03/2 = Full HA / Half AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited local symptoms per subject (see graph below) did not show marked differences between AS03 and control except for pain at the injection site.

In the **6-9** years age stratum the incidences per subject of solicited general symptoms were generally higher in the AS03 vaccine group but rates for Grade 3 symptoms were low. The rates of any fever (> 37.5°C) after dose 1 were zero for Fluarix and 2% for AS03 vaccine and no subject had Grade 3 fever (> 39°C). The corresponding rates after the second dose were zero and 6.4% for any fever in respective vaccine groups and zero and 2.1% had Grade 3 fever. The per dose rates for any antipyretic use were 9% and 12% in respective vaccine groups with per subject rates of 18% and 22% in respective groups.

In the **3-5 years** age stratum, solicited general symptoms occurred more often in the AS03 vaccine group than in the control group. The rates of any fever (> 37.5°C) after dose 1 were 11.8% for Fluarix and 7.8% for AS03 vaccine and no subject had Grade 3 fever (> 39°C). The corresponding rates after the second dose were 5.9% and 14.3% for any fever and 5.9% and zero had Grade 3 fever. Within this period the per dose rates of taking any antipyretic (regardless of the reason for use) were 18% for Fluarix and 17% for AS03 vaccine, with per subject rates of 29% and 30%.

In both age strata the incidences of unsolicited AEs were comparable but higher in the younger subjects. Grade 3 AEs and AEs assessed as causally related to the vaccination were infrequent. One subject in the Full HA/ ½ AS03 group experienced an AE leading to premature discontinuation. Please see the separate AR on possible auto-immune diseases in vaccinees. There were no SAEs in Phase B during the study conduct up to Day 51.

Phase C

In the both age strata the incidences of local and general AEs were higher in the AS03 group. The incidence of Grade 3 AEs in subjects aged 6-9 years was higher in the AS03 group (18.4%) when compared with the control group (5.6%). The incidence of Grade 3 AEs in subjects aged 3-5 years was also higher in the AS03 group (22.4%) when compared with the control group (0.0%) but did not seem to be driven by the incidence of local Grade 3 symptoms.

The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 93.9% in the AS03 vaccine group and 94.4% in the control group compared to 79.6% and 41.2% in respective groups in the younger age cohort.

Incidence and nature of AEs (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase C)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	17	7	41.2	18.4	67.1	17	1	5.9	0.1	28.7	17	6	35.3	14.2	61.7
		6-9y	18	14	77.8	52.4	93.6	18	7	38.9	17.3	64.3	18	13	72.2	46.5	90.3
	H5N1 +AS03	3-5y	49	37	75.5	61.1	86.7	49	19	38.8	25.2	53.8	49	35	71.4	56.7	83.4
		6-9y	49	43	87.8	75.2	95.4	49	25	51.0	36.3	65.6	49	39	79.6	65.7	89.8
Dose 2	*Fluarix*™	3-5y	17	6	35.3	14.2	61.7	17	4	23.5	6.8	49.9	17	3	17.6	3.8	43.4
		6-9y	18	11	61.1	35.7	82.7	18	7	38.9	17.3	64.3	18	10	55.6	30.8	78.5
	H5N1 +AS03	3-5y	48	30	62.5	47.4	76.0	48	23	47.9	33.3	62.8	48	27	56.3	41.2	70.5
		6-9y	49	41	83.7	70.3	92.7	49	30	61.2	46.2	74.8	49	35	71.4	56.7	83.4
Overall/dose	*Fluarix*™	3-5y	34	13	38.2	22.2	56.4	34	5	14.7	5.0	31.1	34	9	26.5	12.9	44.4
		6-9y	36	25	69.4	51.9	83.7	36	14	38.9	23.1	56.5	36	23	63.9	46.2	79.2
	H5N1 +AS03	3-5y	97	67	69.1	58.9	78.1	97	42	43.3	33.3	53.7	97	62	63.9	53.5	73.4
		6-9y	98	84	85.7	77.2	92.0	98	55	56.1	45.7	66.1	98	74	75.5	65.8	83.6
Overall/subject	*Fluarix*™	3-5y	17	10	58.8	32.9	81.6	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1
		6-9y	18	17	94.4	72.7	99.9	18	10	55.6	30.8	78.5	18	15	83.3	58.6	96.4
	H5N1 +AS03	3-5y	49	41	83.7	70.3	92.7	49	29	59.2	44.2	73.0	49	37	75.5	61.1	86.7
		6-9y	49	46	93.9	83.1	98.7	49	35	71.4	56.7	83.4	49	45	91.8	80.4	97.7

H5N1 + AS03 = Full HA / Full AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Pain was the predominant solicited local symptom in both age strata and vaccine groups. Rates of pain were not higher after the second dose in either age stratum.

Redness and swelling were also reported with a higher incidence in the AS03 group irrespective of age stratum. In the 3-5 years age stratum there was a trend for a higher incidence of induration, redness and pain upon re-vaccination but this was not observed in the 6-9 years age stratum and was not observed in either stratum with the control vaccine. The majority of these events were Grade 1 in intensity, and there were few isolated Grade 3 cases in the AS03 group (none in the control group).

Among **6-9** year-olds rates of general solicited symptoms were higher with AS03 vaccine and the incidence of fever, headache, myalgia, shivering and sweating tended to be higher after Dose 2. Rates of fever after dose 1 were zero in the Fluarix group and 12.2% in the AS03 group (1/6 of these subjects [2% overall] had Grade 3 fever). After the second dose rates for any fever were zero and 32.7% in respective vaccine groups (6/16 of these subjects [12% overall] had Grade 3 fever). These numbers give rates for fever overall/dose of zero for Fluarix and 22.4% for AS03 vaccine (7/22 of these doses [7% overall] being associated with Grade 3 fever). The per dose rates for any antipyretic use were 14% and 43% in respective vaccine groups with per subject rates of 22% and 65% in respective groups.

In the **3-5** years age stratum solicited general symptoms predominated in the AS03 group (range 8.2% - 36.7%) when compared with the control group (range 0.0% - 5.9%). After dose 1 the rates for any fever were zero in the Fluarix group and 8.2% in the AS03 group (3/4 of these subjects [6% overall] had Grade 3 fever). After dose 2 the fever rates were zero and 31.3% (2/15 [4% overall] of these subjects had Grade 3 fever) in respective vaccine groups. These numbers give overall/dose rates for fever of zero for Fluarix and 19.6% for AS03 vaccine (5/19 of these doses [5% overall] being associated with Grade 3 fever). Within this period the per dose rates of taking any antipyretic (regardless of the reason for use) in the 3-5 year-olds were 15% for Fluarix and 31% for AS03 vaccine, with per subject rates of 24% and 51%.

The incidence of unsolicited AEs was 55.1% in the AS03 group and 33.3% in the control group in the 6-9 years age stratum. There were very few Grade 3 unsolicited AEs and unsolicited AEs assessed as causally related to the vaccination were infrequent. In the 3-5 years stratum the incidence of unsolicited AEs was 53.1% in the AS03 group and 47.1% in the control group. Few subjects reported Grade 3 unsolicited AEs in the AS03 group (6.1%) and there were none in the control group. The incidence of unsolicited AEs assessed as causally related to the vaccination was 18.4% in the AS03 group compared to zero in the control group.

One subject in the AS03 group developed an AE of uveitis for which subsequent details specified a unilateral anterior chamber uveitis at 8 days after the second dose of the H5N1 vaccine, which was considered to have a potential causal relationship to vaccination. One subject in the AS03 group was hospitalised for gastroenteritis but the event was considered not related to vaccination and resolved after two days. There were no AEs leading to premature discontinuation in Phase C and no deaths were reported.

Additional data at Month 6 and Month 12

No additional safety concerns were raised by the M6 safety data.

Discussion on immunogenicity

In Parts A, B and C of the study in children aged 3-9 years the D42 HI immune response parameters (SCR, SPR, SCF) did not clearly distinguish any one of the three formulations tested. However, the administration of a higher HA dose and, especially, the full adult dose, demonstrated advantages in terms of several HI and NA immune parameters. In particular, use of the adult dose gave improved HI responses to the heterologous strain and much higher NA GMTs.

At Month 6 the HI data showed a clear advantage for the full adult dose in terms of persistence of vaccine-homologous and especially vaccine-heterologous HI immune responses.

The NA data against the vaccine strain up to D42 showed that GMTs were highest in the full dose group but the values were all over 1000 and the seroconversion rates were all very high regardless of vaccine group and age.

The Month 6 NA data from the Fluarix group in Part A of the study demonstrated that there was considerable augmentation of the NA titres against A/Vietnam between D42 and Month 6. Even though the actual increase in GMT in the 3-5 year-olds was small there would usually have been a drop expected and the increase in the 6-9 year-olds was by 6-fold. It must be assumed then that a natural augmentation effect on NA titres of at least the same magnitude must have occurred in the AS03 vaccine group. Indeed, with a very reasonable assumption of better priming by the AS03 vaccine it is quite possible that the magnitude of the effect of natural exposure would be even greater in the group that had received AS03 vaccine.

In contrast, there was no augmentation of NA titres in the control group against A/Indonesia from D42 up to M12. It is notable then that in the AS03 group the GMTs fell to about half the D42 values by M12 but over 80% retained titres of at least 1:80. These data suggest that the vaccine per se elicits a sustained circulating NA response.

Discussion on Safety

The differences between H5N1/AS03 and control vaccines for general and local symptoms and unsolicited AEs were most marked in Phase C when the adult dose was administered. As expected, the data indicate higher rates in the H5N1/AS03 vaccine groups for local symptoms, which mainly concerned pain although rates of other symptoms were also usually higher. However, as in adults, the rates of grade 3 pain have been low and were 6-10% even with the full adult dose.

- In Phase A there was a higher rate of fever in the H5N1 group in the younger age cohort only.
- In Phase B general symptoms occurred more often in the H5N1 vaccine group in both age strata. The most common symptoms in the 6-9 years age stratum were headache and myalgia whereas in the 3-5 years age stratum the most common were irritability and fever (but rates of grade 3 symptoms were ≤ 2%).
- In Phase C solicited general symptoms (with the most common being headache and fever in the 6-9 year-olds, and fever and irritability in the 3-5 year-olds) were much more frequently observed in the Full HA/Full AS03 group when compared with the control group. The incidence of grade 3 solicited symptoms was low except for a higher incidence of grade 3 fever (10-14% in the two age strata) and grade 3 loss of appetite (only 3-5 year-olds) in the Full HA/Full AS03 group.

When comparing the age strata, a higher incidence of unsolicited AEs was observed in the subjects aged 3-5 years irrespective of vaccine group. In Phase C, the occurrence of unsolicited AEs in the 6-9 year-olds was higher in the Full HA/Full AS03 group than in the control group, while there was no difference in the incidence of unsolicited AEs between the vaccine groups in the 3-5 year-olds. The cases of auto-immune hepatitis and anterior uveitis have been reviewed separately along with the case of auto-immune hepatitis in an adult from another study (see past assessment reports for details).

3.3. Changes to the Product Information

The detailed changes can be found in the final approved highlighted SmPC/ PL attached to this report. Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH.

SmPC

Sections 4.2 and 4.4: The initially proposed paragraph in section 4.4 was revised to reflect that there are no data with Prepandrix in individuals aged < 18 years. This was also stated in 4.2 In addition, it was stated that there are very limited data from a study with an AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1) in children aged from 3 to 9 years.

Section 4.8 was further revised as in contrast to the later findings with the first and second doses of H1N1/AS03 the data from study 009 did not tend to show markedly increased local or systemic reactogenicity with the second dose. Since section 4.2 of the SmPC does not give a clear recommendation for one or two half or full adult doses in children aged 3-9 years the CHMP recommended clarifying that the difference shown between half and full doses, was evident after each dose and that a second dose was not associated with enhanced reactogenicity.

In Section 5.1 the text above the table on responses against A/Indonesia was amended to reiterate that the table shows the responses to this strain. In addition, the NA responses out to M12 in Group A (half dose) were included as a table rather than just described as a text

3.4. Conclusions and Benefit / Risk Assessment

Concerning immune response, the D42 HI immune response parameters (SCR, SPR, SCF) did not clearly distinguish any one of the three formulations (Half HA/Half AS03, Full HA/Half AS03, Full HA/Full AS03) tested. However, the administration of a higher HA dose and, especially, the full adult dose, demonstrated advantages in terms of several HI and NA immune parameters. In particular, use of the adult dose gave improved HI responses to the heterologous strain and higher NA GMTs.

Concerning safety, the greatest differences between the H5N1 vaccine and control groups in this study were seen when the adult dose was administered. Despite the greater local and general reactogenicity with the adult dose uptake of the second dose was very high and only four subjects did not complete both doses in the entire study. In addition the data do not indicate that higher reactogenicity was associated with SAEs.

Overall, a difference in the frequency of adverse reactions between half adult and adult doses was observed after each dose. However, the administration of a second half adult or an adult dose did not enhance the reactogenicity, except for rates of general symptoms which were higher after the second adult dose.

Due to the intervening pandemic the MAH has not previously submitted a variation to add these data to the SmPCs for the H5N1 vaccines. It was therefore considered appropriate that the most pertinent features of these have been added with this procedure.

Taken together the data on immunogenicity and safety and considering the update of the product information the benefit - risk profile for Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals remains positive.

4. Conclusion

On 17 March 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the SmPC, Annex II, Labelling and Package Leaflet.