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/0011

Note

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

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Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/1206/II/11

Invented name/name:	Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals
International non-proprietary name/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 section 5.1 'Pharmacodynamic Properties' of the SmPC to include persistence/booster data from – Study H5N1-009/022/023 (conducted in children 3-9 years of age): Persistence Month 24 – Study H5N1-002/030/038 (conducted in adults 18-60 years of age): Persistence Month 36 & Booster given at Month 36 – Study H5N1-010 (in adults over 60 years of age): Persistence Month 24
Rapporteur:	Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1,2 and 5

Product Information affected:	Summary of Product Characteristics (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	4 August 2011
Start of procedure:	21 August 2011
Rapporteur's preliminary assessment report circulated on:	23 August 2011
CHMP opinion:	20 October 2011

3. Scientific discussion

3.1. Introduction

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals has the same composition and presentation as the Pandemrix H5N1 mock-up vaccine, which was previously authorised in the European Union (EU) and subsequently changed in October 2009 into a vaccine containing the H1N1v strain.

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).

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 persistence and/or booster data up to 36 months from three studies:

- Study H5N1-009/022/023 (conducted in children 3-9 years of age): Persistence Month 24
- Study H5N1-002/030/038 (conducted in adults 18-60 years of age): Persistence Month 36 & Booster given at Month 36
- Study H5N1-010 (in adults over 60 years of age): Persistence Month 24

Previous datasets from these studies have already been assessed by the CHMP and results have been reflected in the Product Information as appropriate.

The variation submitted can be classified as follows:

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

Update of section 5.1 'Pharmacodynamic Properties' of the SmPC to include persistence/booster data from

- Study H5N1-009/022/023 (conducted in children 3-9 years of age): Persistence Month 24
- Study H5N1-002/030/038 (conducted in adults 18-60 years of age): Persistence Month 36 & Booster given at Month 36
- Study H5N1-010 (in adults over 60 years of age): Persistence Month 24

3.2. Clinical aspects

Immunogenicity

Study D-Pan H5N1-009/022/023 in children aged from 3-9 years

This is a phase II, randomised, multicentre, open, controlled study designed to evaluate the safety and immunogenicity of three formulations of AS03-adjuvanted H5N1 influenza vaccine, given following a two-dose schedule on Days 0 and 21 in children 3 to 9 years of age.

Previous datasets have been assessed in the context of the Pandemrix and Prepandrix Marketing Authorisations.

The study commenced in Spain in 2008 and the three initial clinical study reports provided safety data (D51) and haemagglutination inhibition (HI) responses against A/Indonesia/2005/05 and A/Vietnam/1194/2004 (D42) for all phases of the study. Neutralising antibody (NA) responses against A/Vietnam/1194/2004 (homologous strain to the vaccine) up to D42 were reported for phase A only.

The current submission contains the final study report dated 31 March 2011. This presents the humoral immune response and safety data collected between Months 6 and 24 and the CMI data up to month 24 (M24).

Study design

The experimental design included 3 sequential phases to test three formulations of the H5N1 vaccine is described in Fig. 1 below:

Figure 1 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.

Within each study phase, a control group included subjects receiving two doses of GSK Biologicals' seasonal influenza vaccine *Fluarix* (100 subjects in total in the 3 phases).

Subject disposition

The Subject disposition at M24 was as follows:

Figure 2:

Number of subjects:	Phase A (H5N1-009)				Phase B (H5N1-022)				Phase C (H5N1-023)			
	Half HA/ Half AS03		Control (*Fluarix*™)		Full HA/ Half AS03		Control (*Fluarix*™)		Full HA/ Full AS03		Control (*Fluarix*™)	
	3-5y	6-9y	3-5y	6-9y	3-5y	6-9y	3-5y	6-9y	3-5y	6-9y	3-5y	6-9y
Planned	50	50	17	17	50	50	17	17	50	50	16	16
Enrolled	51	51	18	18	51	49	17	17	49	49	17	18
Completed (Month 12)	50	46	17	17	48	45	17	17	46	48	17	18
Completed (Month 24)	48	41	16	14	47	44	17	17	43	47	17	18
Total Vaccinated cohort	51	51	18	18	51	49	17	17	49	49	17	18
According-to-protocol (ATP) cohort for safety	51	51	18	17	49	49	17	17	48	48	17	16
ATP cohort for persistence	49	43	14	14	41	45	16	16	30	36	10	13

HI against A/Vietnam/1194/2004

As shown below, at M12 seropositivity rates were 44.0%, 66.3% and 74.2% for the dose groups A, B and C, respectively. The corresponding rates at M24 were comparable, suggesting a plateau effect had occurred (48.8%, 71.6% and 83.3%, respectively). The geometric mean titres (GMTs) at M12 and 24 were within the same range as those observed on D21.

The SPRs at M12 (32.1%-56.5%) and M24 (32.1%-70.0%) tended to be higher in Group C as compared to Group A. A paradoxical increase in H5N1 HI antibodies from M12 to 24 was observed in

some subgroups but the overall GMTs were low, which suggests that the observation was due to assay variability.

Figure 3:

Synopsis Table 1: H5N1 HI antibodies against A/Vietnam/1194/2004 for the different H5N1 vaccine formulations used in Phases A, B and C *(by age strata)*

	≥ 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
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	49	0.0	0.0	7.3	5.0	5.0	5.0	0.0	0.0	7.3						
PII(M12)	47	46.8	32.1	61.9	13.9	9.7	20.0	38.3	24.5	53.6	38.3	24.5	53.6	2.8	1.9	4.0
PII(M24)	47	48.9	34.1	63.9	14.9	10.3	21.5	38.3	24.5	53.6	38.3	24.5	53.6	3.0	2.1	4.3
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	41	0.0	0.0	8.6	5.0	5.0	5.0	0.0	0.0	8.6						
PII(M12)	37	40.5	24.8	57.9	12.0	8.0	18.1	24.3	11.8	41.2	22.9	10.4	40.1	2.2	1.5	3.3
PII(M24)	37	48.6	31.9	65.6	13.2	9.1	19.2	24.3	11.8	41.2	22.9	10.4	40.1	2.5	1.7	3.6
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	41	2.4	0.1	12.9	5.1	4.9	5.4	0.0	0.0	8.6						
PII(M12)	40	65.0	48.3	79.4	19.8	13.6	28.8	42.5	27.0	59.1	42.5	27.0	59.1	4.0	2.7	5.8
PII(M24)	39	79.5	63.5	90.7	52.2	33.6	81.1	76.9	60.7	88.9	76.9	60.7	88.9	10.4	6.7	16.2
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	45	0.0	0.0	7.9	5.0	5.0	5.0	0.0	0.0	7.9						
PII(M12)	43	67.4	51.5	80.9	22.4	15.4	32.5	46.5	31.2	62.3	46.5	31.2	62.3	4.5	3.1	6.5
PII(M24)	42	64.3	48.0	78.4	20.1	13.9	29.3	42.9	27.7	59.0	42.9	27.7	59.0	4.0	2.8	5.9
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	30	0.0	0.0	11.6	5.0	5.0	5.0	0.0	0.0	11.6						
PII(M12)	27	70.4	49.8	86.2	23.9	15.1	37.8	48.1	28.7	68.1	48.1	28.7	68.1	4.8	3.0	7.6
PII(M24)	26	84.6	65.1	95.6	55.8	33.2	93.8	73.1	52.2	88.4	73.1	52.2	88.4	11.2	6.6	18.8
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	36	0.0	0.0	9.7	5.0	5.0	5.0	0.0	0.0	9.7						
PII(M12)	35	77.1	59.9	89.6	27.7	19.1	40.4	62.9	44.9	78.5	62.9	44.9	78.5	5.5	3.8	8.1
PII(M24)	34	82.4	65.5	93.2	36.5	24.8	53.8	67.6	49.5	82.6	67.6	49.5	82.6	7.3	5.0	10.8

HI against A/Indonesia/05/2005

As shown below the seropositivity rates for HI against A/Indonesia/05/2005 at M12 and 24 were 39.8% and 35.7% in group A, 60.2% and 59.3% in group B and 61.3% and 66.7% in group C. The GMTs were lower compared with D42 but were higher than those observed at D21. The SPRs were in the range 27.7% - 43.5% at M12 and 10.7% - 40.0% at M24.

HI against A/Brisbane H1N1

Selected sera were also assayed for HI against A/Brisbane to explore whether the unexpected increase in NA against A/Vietnam strain in the Control group could possibly be due to intercurrent seasonal H1N1 influenza.

On D42 and at M6 several subjects in the Control group had developed HI antibodies against the A/Brisbane/59/2007 strain with some degree of correlation with the increase in NA titres against A/Vietnam. Group A subjects who were seropositive for NA against A/Vietnam at baseline more frequently showed A/Brisbane HI antibody titres of 10 and higher vs. subjects seronegative for NA against A/Vietnam at baseline.

Figure 4:

Synopsis Table 2: H5N1 HI antibodies against A/Indonesia/05/2005 for the different H5N1 vaccine formulations used in Phases A, B and C *(by age strata)*

	≥ 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
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	49	0.0	0.0	7.3	5.0	5.0	5.0	0.0	0.0	7.3						
PII(M12)	47	42.6	28.3	57.8	13.0	9.1	18.7	36.2	22.7	51.5	36.2	22.7	51.5	2.6	1.8	3.7
PII(M24)	47	40.4	26.4	55.7	10.1	7.7	13.4	10.6	3.5	23.1	10.6	3.5	23.1	2.0	1.5	2.7
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	41	0.0	0.0	8.6	5.0	5.0	5.0	0.0	0.0	8.6						
PII(M12)	36	36.1	20.8	53.8	10.5	7.0	15.8	19.4	8.2	36.0	17.6	6.8	34.5	1.9	1.3	2.8
PII(M24)	37	29.7	15.9	47.0	7.7	5.9	10.0	10.8	3.0	25.4	8.6	1.8	23.1	1.5	1.1	1.9
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	41	0.0	0.0	8.6	5.0	5.0	5.0	0.0	0.0	8.6						
PII(M12)	40	57.5	40.9	73.0	16.4	11.4	23.5	40.0	24.9	56.7	40.0	24.9	56.7	3.3	2.3	4.7
PII(M24)	39	71.8	55.1	85.0	22.7	15.2	33.7	48.7	32.4	65.2	48.7	32.4	65.2	4.5	3.0	6.7
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	45	0.0	0.0	7.9	5.0	5.0	5.0	0.0	0.0	7.9						
PII(M12)	43	62.8	46.7	77.0	15.0	11.1	20.1	16.3	6.8	30.7	16.3	6.8	30.7	3.0	2.2	4.0
PII(M24)	42	47.6	32.0	63.6	8.7	7.0	10.8	4.8	0.6	16.2	4.8	0.6	16.2	1.7	1.4	2.2
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	30	0.0	0.0	11.6	5.0	5.0	5.0	0.0	0.0	11.6						
PII(M12)	27	59.3	38.8	77.6	18.5	11.5	29.9	44.4	25.5	64.7	44.4	25.5	64.7	3.7	2.3	6.0
PII(M24)	26	69.2	48.2	85.7	27.5	16.1	47.0	53.8	33.4	73.4	53.8	33.4	73.4	5.5	3.2	9.4
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	36	0.0	0.0	9.7	5.0	5.0	5.0	0.0	0.0	9.7						
PII(M12)	35	62.9	44.9	78.5	20.4	13.4	31.1	42.9	26.3	60.6	42.9	26.3	60.6	4.1	2.7	6.2
PII(M24)	34	64.7	46.5	80.3	18.2	12.1	27.6	29.4	15.1	47.5	29.4	15.1	47.5	3.6	2.4	5.5

Neutralising antibody (NA) against A/Vietnam/1194/2004

NA titres were not assessed at these time points for Groups B and C and the data presented below are for Group A only.

Up to M24 98% of subjects in Group A and 50.0% of subjects in the Control group remained seropositive against A/Vietnam/1194/2004.

At M12 and 24 the GMTs for in Group A (211.0 and 269.9, respectively) were still higher than those observed on D21 (169.8). In the Control group the GMTs at M12 and 24 (31.3 and 42.6, respectively) were above the D0 value (21.1) but were lower than the D21 value (101.8). The SCRs at M12 and 24 were still 75.9% and 72.8%, respectively, for Group A compared to 22.2% and 30.4%, respectively, in the Control group.

No heterologous immune response against A/Indonesia/05/2005 was observed in the Control group at M12 or 24. In Group A the seropositivity rates were 96.4% and 97.6%, the GMTs were 156.6 and 168.1 and the SCRs were 88.3% and 92.4%, respectively. There were marked differences vs. the Control group for these parameters.

Figure 5:

Synopsis Table 3: Serum neutralising antibodies against A/Vietnam/1194/2004 for both vaccine groups in Phase A *(by age strata)*

		≥28 1/DIL			GMT				SCR		
			95% CI			95% CI				95% CI	
Timing	N	%	LL	UL	value	LL	UL	N	%	LL	UL
Control *Fluarix*™ - 3-5 years (Phase A)											
PRE	13	38.5	13.9	68.4	24.3	13.8	42.9	-	-	-	-
PII(M12)	14	42.9	17.7	71.1	35.4	16.7	74.9	13	23.1	5.0	53.8
PII(M24)	13	46.2	19.2	74.9	39.4	16.3	95.5	12	25.0	5.5	57.2
Control *Fluarix*™ - 6-9 years (Phase A)											
PRE	14	14.3	1.8	42.8	18.6	12.0	28.7	-	-	-	-
PII(M12)	14	28.6	8.4	58.1	27.6	13.4	56.9	14	21.4	4.7	50.8
PII(M24)	11	54.5	23.4	83.3	46.6	18.4	118.3	11	36.4	10.9	69.2
Half HA/Half AS03 - 3-5 years (Phase A)											
PRE	47	31.9	19.1	47.1	28.9	20.7	40.5	-	-	-	-
PII(M12)	47	97.9	88.7	99.9	238.9	186.1	306.6	45	82.2	67.9	92.0
PII(M24)	47	100	92.5	100	302.5	231.0	396.0	45	80.0	65.4	90.4
Half HA/Half AS03 - 6-9 years (Phase A)											
PRE	41	41.5	26.3	57.9	31.9	22.6	44.9	-	-	-	-
PII(M12)	36	94.4	81.3	99.3	179.4	126.1	255.3	34	67.6	49.5	82.6
PII(M24)	38	97.4	86.2	99.9	234.5	177.1	310.6	36	63.9	46.2	79.2

Cell-mediated immune response (CMI)

The MAH presented the available data from subsets of subjects according to age strata.

In Group A the frequency of CD4 T-cells producing IL-2 had increased by D21 in the H5N1 groups and by D42 there had been a further increase.

In the CMI samples taken at M6, 12 and 24 a high frequency of CD4 T-cells producing IL-2 was observed after in vitro re-stimulation with the H5N1 split antigen in the three H5N1 vaccine groups.

The frequency of H5N1-specific cytokine-positive CD4 T-cells producing IL-2 and IFN-γ but not IL-13 was high in these samples obtained from the H5N1 vaccine group.

No effect of vaccination on the frequency of cytokine-positive CD8 T-cells was apparent.

Comparable results were obtained after stimulation with a pool of peptides spanning the whole A/Vietnam/1194/2004 HA sequence; however, the effect was less pronounced.

Study D-Pan H5N1-010 in adults aged > 60 years

This is a phase II, randomised, multicentre, open study designed to evaluate the immunogenicity and safety of a single or double dose of the (pre)pandemic influenza vaccine H5N1 (A/Vietnam/1194/2004 strain, split virus formulation adjuvanted with AS03), given following a two-administration schedule on Days 0 and 21 in adults over 60 years of age, either healthy or with well-controlled underlying diseases. This study was designed based on the hypothesis that the elderly population might need higher dosages than younger adults to achieve a satisfactory immune response. The same antigen dosages were administered without adjuvant in control groups.

The persistence of the immune response was assessed 6, 12 and 24 months after the primary vaccination series, and the occurrence of SAEs was recorded during the entire study period.

Previous submissions of data from this study have been assessed within the Marketing Autrhorisations for Pandemrix and Prepandrix:

- The data to D51 were submitted in September 2008 to support a variation for Pandemrix (II/0005) and Prepandrix (II/0005) to add dose recommendations for the elderly. At the time of responding to the LOQ in April 2009 the MAH was also able to provide the available D180 data.
- In September 2010 the MAH submitted the available data to M24 as a FUM (Pandemrix FU2 010.1 and Prepandrix FU2 021.2). This annex report presented HI, NA and CMI responses along with safety data collected up to M24 for subjects in Belgium only. In the conclusions of the assessment report that assessor stated that there was no urgency to reflect these data in the SmPCs. In line with the co-circulated reports the assessor suggested that a single update on longer-term antibody could be made when the final data from study 038 became available (see next section for these data).

Therefore there are no new data submitted from D-Pan H5N1-010 in support of this variation since the same study report covering all available data up to M24 was already fully assessed. Details on the study design can be found in the assessments outlined above.

Persistence of the HI response against A/Vietnam/1194/2004 and A/Indonesia/05/2005

At M12 the seropositivity rates were 39.1% to 77.8% against A/Vietnam/1194/2004 and there was no further appreciable difference observed at M24 (45.8% to 70.4%). There was a trend for higher values in the AS03 adjuvanted vaccine group vs. the non-adjuvanted vaccine groups with only a small difference between the HA doses. HI titres against the heterologous A/Indonesia/05/2005 strain were much lower than for homologous virus at M12 and M24.

At M12 and M24, none of the CHMP or CBER criteria were still met against either strain except for the SCF against both strains in the 7.5/AS group at M12. Seroprotection rates were < 50% against homologous and < 30% against heterologous virus even in the adjuvanted vaccine groups.

Persistence of the SNA response against A/Vietnam/1194/2004 and A/Indonesia/05/2005

SNA was measured only for subsets in the adjuvanted vaccine groups.

At M24 all subjects were seropositive against A/Vietnam/1994/2004 while 89.8% and 96.3% were seropositive against A/Indonesia/05/2005. GMTs were also higher for the homologous vs. heterologous virus and were generally comparable between HA dose groups at M12 and at M24. The SCRs were comparable between HA dose groups against A/Vietnam/1994/2004 but higher in the 7.5/AS group against A/Indonesia/05/2005.

CMI at M12 and M24

There was a trend for a higher persistence of the CMI response in the 3.8/AS and 7.5/AS groups in terms of antigen-specific CD4 T-cells (ALL DOUBLES, CD40L, IL-2 and TNF-α) for A/Vietnam/1194/2004 at M12 and both strains at M24.

There was a negligible antigen-specific CD8 T-cell response in all vaccine groups at M12 and M24 with the assay used in this study.

Study D-Pan H5N1-038 in adults aged 18-60 years

D-Pan H5N1-038 was the final extension study of D-Pan H5N1-002/030, which has been included in the initial core dossier for the Pandemrix mock-up vaccine in 2007.

Further datasets have been assessed within subsequent post authorisation procedures.

CMI data from D-Pan H5N1-002 and -030 were submitted under a FUM in 2010.

D-Pan H5N1-038 was the extension from M12 onwards, which has been assessed as follows:

1. The M30 data from D-Pan H5N1-038 were reported and assessed under a FUM submitted in October 2010. This submission included safety and immunogenicity of a heterologous booster dose (as above) administered at M12 to a different subset of the study population as well as antibody persistence data from those who had been boosted at M6 and unboosted subjects assigned to receive a booster dose at M36. Following review of these data it was recommended that a single variation should be filed when the M42 data also became available.
2. The current submission concerns the data up to M42 and therefore includes the safety and immunogenicity of a booster dose (as above) at M36 as well as further antibody persistence data from the other study groups (i.e. boosted at M6 or M12). The study report is dated 13 May 2011 and it covers data accumulated up to 2 March 2011. The final report from this study will cover data to M48.

Further details of the study design are included in the above assessments.

The table that follows shows subject disposition up to M36 according to booster timed groups. For the M36 boost cohort only the mean age at boosting was 38 years (range 21-62 years), 48% were female subjects and all were Asian (58% were specifically described as East Asian).

Figure 6:

Number of subjects in H5N1-038 EXT 002 M36:	Total	Boosted at M6	Boosted at M12	Boosted at M36
Enrolled	837	216	186	435
Completed (at Month 42)		202	176	381
Safety (Total Vaccinated cohort; TVC)		216	185	390
Immunogenicity (according-to-protocol [ATP] cohort for immunogenicity)		210	180	387

HI data

In the subset boosted at M36 that provided a blood sample at ~D21 post-boost all three CHMP criteria were met based on HI titres against A/Indonesia/05/2005 (booster) and A/Vietnam/1994/2004 (primary) strains. In addition, the two CBER criteria were also fulfilled against both H5N1 strains.

There was a marked increase in HI GMTs and seropositivity rates from pre- to post-boost for both strains. The increment in GMTs was higher against the booster strain.

At M42 (i.e. approximately 6 months after the booster dose at M36) all CHMP and CBER criteria were still met for the H5N1 HI antibody response against both the A/Indonesia/05/2005 (booster) and A/Vietnam/1994/2004 (primary) vaccine strains.

Figure 7:

Synopsis Table 1: Seropositivity rates, GMTs, SPRs, Booster SCRs and Booster SCFs for H5N1 HI antibodies against A/Vietnam/1994/2004 and A/Indonesia/05/2005 for Month 36-boosted subjects (ATP cohort for immunogenicity for subjects boosted at Month 36)

	≥ 10 1/DIL				GMT			SPR			Booster SCR			Booster 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/1994/2004																
PII(M36)	387	42.1	37.1	47.2	10.5	9.5	11.6	16.3	12.7	20.3	-	-	-	-	-	-
PIII(M36+21D)	379	100	99.0	100	653.1	604.3	705.9	100	99.0	100	99.5	98.1	99.9	61.6	55.0	68.8
PIII(M42)	378	99.2	97.7	99.8	225.4	205.0	247.9	97.1	94.9	98.5	92.1	88.9	94.6	21.3	18.9	24.0
H5N1 HI Antibodies against A/Indonesia/05/2005																
PII(M36)	387	20.2	16.3	24.5	7.0	6.5	7.6	7.8	5.3	10.9	-	-	-	-	-	-
PIII(M36+21D)	379	100	99.0	100	877.5	809.1	951.6	100	99.0	100	99.7	98.5	100	123.8	112.1	136.8
PIII(M42)	378	99.2	97.7	99.8	263.5	238.3	291.3	97.6	95.5	98.9	96.6	94.2	98.2	37.1	33.1	41.6

Blood samples obtained at approximately 30 and 36 months after heterologous booster vaccination at M6 showed that GMTs were low. Against the booster strain only the SCF criteria were met up to M42 although the SCR criterion was still met at M36.

Figure 8:

Synopsis Table 2: Seropositivity rates, GMTs, SPRs, Booster SCRs and Booster SCFs for H5N1 HI antibodies against A/Vietnam/1994/2004 and A/Indonesia/05/2005 for subjects not boosted at Month 36 but boosted at Month 6 (ATP cohort for immunogenicity for subjects NOT boosted at Month 36 but boosted at Month 6)

	≥ 10 1/DIL				GMT			SPR			Booster SCR			Booster SCF		
Timing			95% CI			95% CI			95% CI			95% CI			95% CI	
	N	%	LL	UL	Value	LL	UL	%	LL	UL	%	LL	UL	Value	LL	UL
H5N1 HI Antibodies against A/Vietnam/1994/2004																
PII(M36)	208	71.6	65.0	77.7	24.3	20.6	28.6	43.3	36.4	50.3	13.5	9.1	18.9	1.3	1.1	1.6
PIII(M42)	201	68.7	61.8	75.0	20.1	17.3	23.5	39.3	32.5	46.4	10.9	7.0	16.1	1.1	0.9	1.3
H5N1 HI Antibodies against A/Indonesia/05/2005																
PII(M36)	208	69.2	62.5	75.4	24.5	20.6	29.1	50.0	43.0	57.0	43.8	36.9	50.8	3.8	3.2	4.5
PIII(M42)	201	63.2	56.1	69.9	17.8	15.2	20.9	34.8	28.3	41.8	29.4	23.2	36.2	2.8	2.4	3.2

For those boosted at M12 the samples obtained at about 24 and 30 moths post-boost showed HI titres that still met the CHMP criteria against the booster strain except for the SPR and M30.

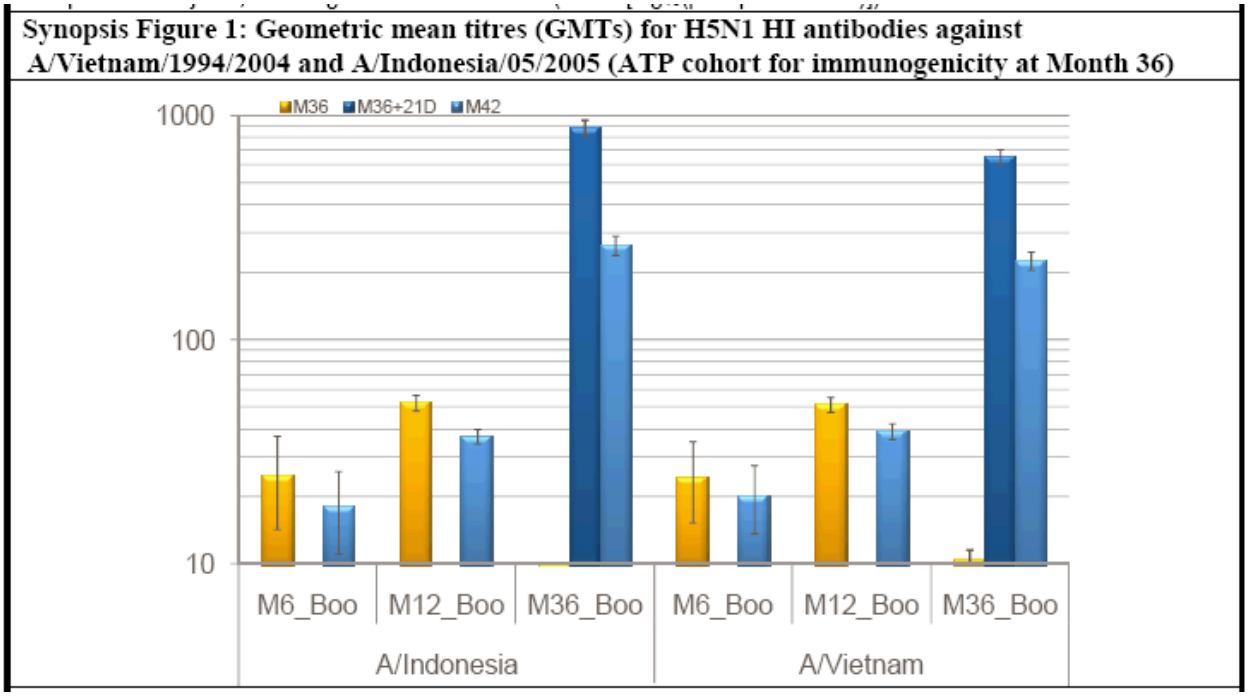
Figure 9:

Synopsis Table 3: Seropositivity rates, GMTs, SPRs, Booster SCRs and Booster SCFs for H5N1 HI antibodies against A/Vietnam/1994/2004 and A/Indonesia/05/2005 for subjects boosted at Month 12 (ATP cohort for immunogenicity for subjects NOT boosted at Month 36 but boosted at Month 12)

Timing	≥ 10 1/DIL				GMT			SPR			Booster SCR			Booster SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
	N	%	LL	UL	Value	LL	UL	%	LL	UL	%	LL	UL	Value	LL	UL
H5N1 HI Antibodies against A/Vietnam/1994/2004																
PII(M36)	178	85.4	79.3	90.2	51.2	42.3	62.0	68.0	60.6	74.8	47.7	40.0	55.4	4.5	3.7	5.5
PIII(M42)	176	84.7	78.5	89.6	39.0	32.6	46.6	62.5	54.9	69.7	40.6	33.1	48.4	3.4	2.8	4.1
H5N1 HI Antibodies against A/Indonesia/05/2005																
PII(M36)	178	82.6	76.2	87.8	52.4	42.3	65.1	70.8	63.5	77.3	66.9	59.3	73.8	8.6	6.9	10.7
PIII(M42)	176	81.3	74.7	86.7	37.0	30.3	45.2	57.4	49.7	64.8	52.4	44.6	60.1	6.0	4.9	7.4

Figure 10:

Synopsis Figure 1: Geometric mean titres (GMTs) for H5N1 HI antibodies against A/Vietnam/1994/2004 and A/Indonesia/05/2005 (ATP cohort for immunogenicity at Month 36)



Discussion on immunogenicity

H5N1-009/022/023

While the expected decrease in the H5N1 HI titres against A/Vietnam/1194/2004 was seen as time elapsed, there seemed to be a plateau effect from about M12 onwards. A heterologous HI immune response against A/Indonesia/05/2005 was also persistent. With the exception of a few subjects, no H5N1 HI immune response was observed in the Control group.

There was some persistence of the NA response against A/Vietnam and A/Indonesia up to M24 in Group A (from whom sera were assayed).

At M12 and at M24 the CMI data showed persistence of antigen-specific CD4 T-cells producing IL-2 and IFNγ in the H5N1 vaccine groups. This cytokine pattern is indicative of a Th0/Th1 profile rather than a

Th2 profile. There was no detectable effect of vaccination on the frequency of antigen-specific CD8 T-cells, which was also the observation in adult studies.

H5N1-010

The immunogenicity data up to M24 suggested a trend to higher remaining antibody levels in the groups that had received adjuvanted vaccine. However, the possible advantage for a double dose in the elderly was much less convincing at later time points and the difference may not be of any clinical significance.

It was of interest that the CMI data suggested that a double adjuvanted dose might have some advantage over a single adjuvanted dose in terms of GMs.

As noted in the longer term follow-up data from other studies there were very considerable decreases in antibody over time but the consequences for clinical protection are not known.

H5N1-038

A single-dose heterologous booster administration of the H5N1/AS03 vaccine at up to 36 months after a 2-dose primary immunisation series elicited robust HI responses against the priming and boosting strains. The marked responses to the booster dose despite the very low residual titres immediately pre-boosting strongly support all prior conclusions regarding the ability of the AS03-adjuvanted vaccine to effectively prime the immune system. HI titres waned after boosting but the M42 data for the groups that had been boosted at M6 and M12 suggested some degree of a plateau effect from M36 onwards.

Clinical Safety

H5N1 009/022/023

The incidence of unsolicited adverse events (AEs) reported between M6 and M24 post-vaccination in the adjuvanted vaccine groups was low and comparable to the Control groups.

Five unsolicited AEs that occurred up to M24 were consistent with the Adverse events of special interest (AESI) / potentially immune -mediated disorder (pIMD) definition and each of the individual preferred terms occurred in at most one subject in any vaccine group. These AESIs were:

- One subject in Group A and one in the Control group reported vitiligo and consulted a medical doctor. Both events were ongoing at the end of the study and assessed as being grade 1 in severity and not related to the vaccination.
- One subject in Group B had autoimmune hepatitis that was reported as an SAE (this case has been reported and investigated previously). One subject in the Control group had a diagnosis of type 1 diabetes mellitus with onset on Day 132.
- One subject in Group C had uveitis Day 8, which prompted an ER visit. The event was considered to be related to the vaccination and grade 3 in intensity. After 51 days, the subject had recovered with sequelae.

Serious adverse events (SAEs)

There were no SAEs reported before or between M6 and 24 in Group A.

One subject in Group B was diagnosed with autoimmune hepatitis 294 days after the first dose. This was of Grade 2 intensity and was considered to be related to vaccination. The outcome at Month 24 was 'recovering/resolving'. The subject had transaminases increased on D0. One subject in the Control group was hospitalised for type 1 diabetes mellitus.

One subject in Group C was hospitalised for a wound (onset 524 days after the second dose, Grade 3 in intensity and not related to vaccination). During the entire study period up to M24 three subjects had a single SAE (gastroenteritis, traumatic brain injury and wound).

There were no AEs leading to premature discontinuation between M6 and 24 and proportions with laboratory abnormalities at M12 and 24 were low. Laboratory findings (for selected parameters including ALT, AST, CREA, BUN, LDH and CPK) were not suggestive of clinically relevant alterations in the biochemistry profile from baseline.

H5N1-010

SAEs from M6 to M12

Nine subjects reported 12 non-fatal SAEs (2-4 per dose group). One SAE (right inferior lobar pneumonia undetermined cause: onset 299 days after last dose in 7.5/NoAS group) was considered causally related to vaccination by the investigator. At the M12 analysis data lock point, three SAEs were still ongoing (prostate cancer metastatic, schizophrenia and lung neoplasm malignant) while all other events had resolved (with or without sequelae).

SAEs from M12 to M24

Twenty-five subjects reported 29 non-fatal SAEs (2-9 per dose group). None was assessed as related to the vaccination. Five SAEs (breast cancer, cardiac failure acute, cardiac failure congestive, rectal cancer and polyneuropathy) were still ongoing at the M24. All other events had resolved (with or without sequelae).

There were no AESIs or pregnancies reported.

H5N1-038

Among subjects boosted at M36 the overall incidence of symptoms (solicited and unsolicited) during the 7-day post-vaccination period was 88.5%. Grade 3 or 4 symptoms (solicited and unsolicited) were observed in 9.7% of the subjects.

Pain at the injection site was the predominant solicited local AE (79.3%; see next table). Grade 3 pain was uncommon (4.4% of subjects). Other solicited local AEs (ecchymosis, induration, redness and swelling) were reported less frequently (from 0.3% to 11.4%).

The most frequently reported solicited general AEs were myalgia, fatigue and headache (60.9%, 56.0% and 35.8%, respectively). The frequency of grade 3 solicited general AEs ranged from 0.5% to 4.9%.

The percentage of subjects reporting at least one unsolicited AE was 21.8% (85 subjects). Unsolicited AE preferred terms were reported in less than 2.5% of the subjects. Grade 3 events, events considered related to vaccination as well as events with a medically attended visit were infrequent.

Figure 11: Percentage of subjects reporting the occurrence of unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-booster vaccination period (Total Vaccinated cohort for Subjects boosted at Month 36)

		Month 36-boosted subjects N = 390			
				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
At least one symptom		85	21.8	17.8	26.2
Ear and labyrinth disorders (10013993)	Tinnitus (10043882)	1	0.3	0.0	1.4
Eye disorders (10015919)	Chalazion (10008388)	1	0.3	0.0	1.4
	Choroiditis (10008792)	1	0.3	0.0	1.4
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	1	0.3	0.0	1.4
	Diarrhoea (10012735)	5	1.3	0.4	3.0
	Lip blister (10049307)	1	0.3	0.0	1.4
	Mouth ulceration (10028034)	1	0.3	0.0	1.4
	Nausea (10028813)	1	0.3	0.0	1.4
	Toothache (10044055)	1	0.3	0.0	1.4
General disorders and administration site conditions (10018065)	Asthenia (10003549)	1	0.3	0.0	1.4
	Axillary pain (10048750)	1	0.3	0.0	1.4
	Chest discomfort (10008469)	1	0.3	0.0	1.4
	Chest pain (10008479)	1	0.3	0.0	1.4
	Influenza like illness (10022004)	9	2.3	1.1	4.3
	Injection site anaesthesia (10022046)	1	0.3	0.0	1.4
	Injection site lymphadenopathy (10057665)	3	0.8	0.2	2.2
	Injection site pruritus (10022093)	7	1.8	0.7	3.7
	Injection site reaction (10022095)	1	0.3	0.0	1.4
	Injection site warmth (10022112)	1	0.3	0.0	1.4
	Local swelling (10024770)	1	0.3	0.0	1.4
	Malaise (10025482)	1	0.3	0.0	1.4
	Pain (10033371)	2	0.5	0.1	1.8
	Pyrexia (10037660)	1	0.3	0.0	1.4
	Thirst (10043458)	1	0.3	0.0	1.4
Infections and infestations (10021881)	Acute sinusitis (10001076)	1	0.3	0.0	1.4
	Gastroenteritis (10017888)	2	0.5	0.1	1.8
	Influenza (10022000)	2	0.5	0.1	1.8
	Nasopharyngitis (10028810)	8	2.1	0.9	4.0
	Skin infection (10040872)	1	0.3	0.0	1.4
	Upper respiratory tract infection (10046306)	5	1.3	0.4	3.0
Injury, poisoning and procedural complications (10022117)	Fall (10016173)	1	0.3	0.0	1.4
	Head injury (10019196)	1	0.3	0.0	1.4
	Muscle strain (10050031)	1	0.3	0.0	1.4
Metabolism and nutrition disorders (10027433)	Decreased appetite (10061428)	2	0.5	0.1	1.8
	Hypercholesterolaemia (10020603)	1	0.3	0.0	1.4

		Month 36-boosted subjects N = 390			
				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
Musculoskeletal and connective tissue disorders (10028395)	Arthralgia (10003239)	1	0.3	0.0	1.4
	Arthritis (10003246)	1	0.3	0.0	1.4
	Back pain (10003988)	1	0.3	0.0	1.4
	Bone pain (10006002)	1	0.3	0.0	1.4
	Neck pain (10028836)	2	0.5	0.1	1.8
	Osteoporosis (10031282)	1	0.3	0.0	1.4
	Plantar fasciitis (10035155)	1	0.3	0.0	1.4
Nervous system disorders (10029205)	Dizziness (10013573)	4	1.0	0.3	2.6
	Head discomfort (10019194)	1	0.3	0.0	1.4
	Headache (10019211)	2	0.5	0.1	1.8
Psychiatric disorders (10037175)	Insomnia (10022437)	1	0.3	0.0	1.4
Reproductive system and breast disorders (10038604)	Menopausal symptoms (10027304)	1	0.3	0.0	1.4
	Menstruation irregular (10027339)	1	0.3	0.0	1.4
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	2	0.5	0.1	1.8
	Epistaxis (10015090)	1	0.3	0.0	1.4
	Oropharyngeal pain (10068319)	4	1.0	0.3	2.6
	Rhinitis allergic (10039085)	2	0.5	0.1	1.8
	Rhinorrhoea (10039101)	8	2.1	0.9	4.0
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	3	0.8	0.2	2.2
	Pruritus (10037087)	1	0.3	0.0	1.4
	Rash (10037844)	2	0.5	0.1	1.8
	Rash generalised (10037858)	1	0.3	0.0	1.4
	Seborrhoeic dermatitis (10039793)	1	0.3	0.0	1.4
	Urticaria (10046735)	1	0.3	0.0	1.4
Vascular disorders (10047065)	Peripheral coldness (10034568)	1	0.3	0.0	1.4

Of 390 subjects boosted at M36 there were 12 subjects who reported 15 SAEs from M30 to M42. All SAEs resulted in hospitalisation and were considered to be unrelated to vaccination.

Twelve of the 401 subjects not boosted at M36 reported 16 SAEs from M30 to M42. One subject experienced an SAE leading to death (stab wound). All other events resulted in hospitalisation (14) or visit to a medical doctor (1). All 16 SAEs were considered to be unrelated to vaccination.

One subject boosted at M36 had a SAE between M30 to M42 leading to premature discontinuation. This SAE of joint dislocation was not considered related to vaccination.

From M30 to M42 five subjects boosted at M36 experienced an AESI. These concerned autoimmune thyroiditis (grade 1 AE, not related, onset before booster, recovering), hypoaesthesia (grade 2 SAE, not related, onset before booster, duration 129 days), optic neuritis (grade 2 SAE, not related, onset before booster, duration 47 days), urticaria (grade 2 AE, not related, onset 8 days after booster, duration 4 days) and a second case of urticaria (grade 1 AE, causally related, onset 95 days after booster, not recovered).

One subject not boosted at M36 experienced an AESI (systemic lupus erythematosus) 612 days after booster vaccination. This grade 1 AE was considered causally related to vaccination and was not recovered at the time of this analysis.

There were ten pregnancies reported for the study period up to the data lock point of 02 March 2011. All subjects were exposed to the study vaccine before conception. Pregnancy outcomes included live

births (8) and elective abortion (1); one pregnancy was ongoing. Note that this number included three cases of live births for subjects who were enrolled but did not receive any study vaccination.

Discussion on Safety

In study H5N1-009/022-/023, The incidence of AESIs and SAEs was low and comparable across the vaccine groups. No clinical pattern of biochemical abnormalities was apparent. No new safety concerns were raised but it should be noted that the AI hepatitis issue has been the subject of a separate thorough review.

The local and systemic solicited symptoms surrounding administration of the M36 booster dose in study H5N1-038 were in keeping with previously reported data in adults in the age range 18-60 years.

The AESIs included some cases of possible interest. The MAH recently submitted a PSUR on the H5N1/AS03 vaccines in which the cases will be further described and, as necessary, explored, during the assessment of the PSUR. If needed, the SmPC will be adjusted in a separate variation.

The safety data from study H5N1-010 did not raise any additional concern.

Overall, based on the new clinical safety data from the above three studies, no update of the Product Information was considered necessary.

3.3. Changes to the Product Information

The detailed changes can be found in the final approved highlighted SmPC attached to this report. Further to the assessment and the scientific discussions held at the CHMP no additional changes to the Product Information were requested.

3.4. Conclusions and Benefit / Risk Assessment

The CHMP concluded that the data reflect the cumulative experience of the AS03-adjuvanted vaccines and that there are no new concerns in view of immunogenicity. The inclusion of the longer-term data from these studies in the SmPC was considered appropriate.

In view of safety, no new concerns have arisen from these data that would require an update of the Product Information at this stage.

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 20 October 2011 the CHMP considered this Type II variation. to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to	II

	new quality, pre-clinical, clinical or pharmacovigilance data	

Update of section 5.1 'Pharmacodynamic Properties' of the SmPC to include persistence/booster data from

- Study H5N1-009/022/023 (conducted in children 3-9 years of age): Persistence Month 24
- Study H5N1-002/030/038 (conducted in adults 18-60 years of age): Persistence Month 36 & Booster given at Month 36
- Study H5N1-010 (in adults over 60 years of age): Persistence Month 24