Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemrix

Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)

Procedure No.: EMEA/H/C/000832/II/0051

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 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMA/CHMP/535380/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/000832/II/0051

Invented name/name:	Pandemrix
International non-proprietary name/common name:	Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)

Indication summary (as last approved):	prophylaxis of influenza
Marketing authorisation holder:	GlaxoSmithKline Biologicals S.A.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics To update sections 4.2 and 5.1 of the SmPC with haemagglutination inhibition (HI) antibody persistence results at month 12 after primary vaccination from studies D-Pan-H1N1-007 and D-Pan-H1N1-008, and neutralising antibody response data up to month 6 from study D-Pan-H1N1-008.
Rapporteur: Co-Rapporteur:	Ian Hudson Barbara van Zwieten-Boot
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	Summary of Product Characteristics

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

2. Steps taken for the assessment

Step	Step date
Submission date:	28 April 2011
Start of procedure:	22 May 2011
Rapporteur's preliminary assessment report circulated on:	27 May 2011
CHMP opinion:	21 July 2011

3. Scientific discussion

3.1. Introduction

Pandemrix is an adjuvanted vaccine against influenza caused by A H1N1v 2009 virus. It is supplied in two separate vials as a suspension (antigen) and emulsion (adjuvant) to mix for injection. The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

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

Pandemrix was granted Marketing Authorisation (MA) in the EU in May 2008, with use being restricted to subjects aged 18-60 years in section 4.2 of the summary of product characteristics (SmPC) due to lack of data outside of this age range. The granting of the initial Marketing Authorisation was based on a mock-up vaccine derived from A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14).

Following the onset of the H1N1v pandemic and the declaration of WHO Phase 6 in June 2009, the MAH applied for a variation (PU/0017) to change the pandemic vaccine strain composition from A/VietNam/1194/2004 H5N1-like strain (NIBRG-14) to A/California/7/2009 H1N1 strain (NYMC X-179A). The recommendation for the approval of the Pandemic Update PU/0017 was adopted by the CHMP on 24 September 2009. The MA under exceptional circumstances for the current H1N1v vaccine was granted by the European Commission on 29 September 2009.

Upon review of the MAH application, on 24 June 2010 the CHMP recommended to change the status of the MA outside the scope of Art. 14(8) of Regulation (EC) 726/2004 (switch from MA granted under "exceptional circumstances" into a full MA (SW/041)).

This variation aims to include the information on haemagglutination inhibition antibody persistence results at month 12 after primary vaccination from studies D-Pan-H1N1-007 and D-Pan-H1N1-008, and neutralising antibody response data up to month 6 from study D-Pan-H1N1-008.

The classification of this Type II variation is 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

To update sections 4.2 and 5.1 of the SmPC with haemagglutination inhibition (HI) antibody persistence results at month 12 after primary vaccination from studies D-Pan-H1N1-007 and D-Pan-H1N1-008, and neutralising antibody response data up to month 6 from study D-Pan-H1N1-008.

3.2. Clinical aspects

Rationale for the proposed change

The MAH committed in the in the Letter of Undertaking (LoU) dated 29 June 2010 to submit the following annex reports to the CHMP:

Area	Description	Due Date
Clinical	FUM: Study D-Pan H1N1-007 - Annex Report, Month 12	April 2011

Area	Description	Due Date
Clinical	FUM: Study D-Pan H1N1-008 - Annex Report, Month 12	April 2011

The above data provided antibody persistence results at month 12 and safety follow-up up to 12 months after primary vaccination, as well as neutralising antibody response data up to month 6 (in study D-Pan-H1N1-008).

The MAH now proposes to reflect these immunogenicity results in section 5.1 of the Pandemrix SmPC via the present type II variation.

Clinical Data

Study D-Pan-H1N1-007 (study 007)

D-PAN H1N1-007 was a study which aimed to demonstrate that two doses of vaccine containing 3.75 mcg HA derived from A/California/7/2009 (H1N1)v-like strain with AS03A results in an HI immune response to vaccine-homologous virus that meets or exceeds the CHMP criteria applied to seasonal influenza vaccines. It was conducted in 130 Belgian adults aged 18-60 years who have been randomised (1:1) with stratification by age (18-40, 41 to 50 and 51 to 60 years; 2:1:1) to receive:

- Group A: (N=64) two doses 21 days apart of HA (3.75µg) adjuvanted with AS03A = Pandemrix H1N1v as approved
- Group B: (N=66) two doses 21 days apart of HA 15 µg (derived from the same H1N1v strain) without adjuvant.

For further information on the study design, immunogenicity and safety data prior to month 12, please refer to variations II 023, II 038 and II 046.

Study D-PAN H1N1-008 (study 008)

This was a phase II, randomised, open-label, single centre study to evaluate the safety and immunogenicity of Pandemrix H1N1 following administration of one or two doses to healthy adults aged from the age of 18 years onwards. It aimed to demonstrate that vaccination with one dose of the H1N1 vaccine (A/California/7/2009 (H1N1)v-like strain) containing 3.75 mcg of HA adjuvanted with AS03A results in an HI immune response to the vaccine-homologous virus that meets or exceeds the EMA/CHMP guidance targets for seroconversion rate (SCR), seroprotection rate (SPR) and geometric mean fold rise (GMFR) at 21 days after vaccination in adults within the 18 to 60 years and above 60 years age strata. Study 008 allowed for comparison of one vs. two doses.

At the time of variation II 046 the applicant supplied HI and CMI (cell mediated immune response) data up to month 6.

For further information on the study design, immunogenicity and safety data prior to month 12, please refer to variations II 032, II 019 and II 046.

The new documentation includes NA data to month 6 from study 008 plus the HI data up to month 12 from both studies. The M12 samples were tested separately from D0 samples and therefore some degree of caution is required.

HI data to month 12

The majority of subjects in both studies were followed up at month 12 as shown below.

Table 1 Number of subjects enrolled and vaccinated and number of subjects excluded from ATP analyses at Month 12 in studies D-Pan-H1N1-007 and D-Pan-H1N1-008

Study	D-Pan-H1N1-007			D-Pan-H1N1-008					
Study group	Total	H1N1 +AS03	H1N1	Total		2-dose H1N1 + AS03		1-dose H1N1 + AS03	
Age category	18y-60y	18y-60y	18y-60y	18y-60y	>60y	18y-60y	>60y	18y-60y	>60y
Total vaccinated cohort	**130**	**64**	**66**	**120**	**120**	**68**	**70**	**52**	**50**
Administration of vaccine(s) forbidden in the protocol (code 1040)	3	3	0	0	0	0	0	0	0
ATP cohort for safety	**127**	**61**	**66**	**120**	**120**	**68**	**70**	**52**	**50**
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	0	0	0	0	0	0	0	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	2	1	1	0	0	0	0	0	0
Essential serological data missing (code 2100)	1	1	0	1	2	1	2	0	0
ATP cohort for persistence at Month 12	**124**	**59**	**65**	**119**	**118**	**67**	**68**	**52**	**50**

1. H1N1+AS03 = H1N1 antigen containing 3.75 µg of HA + $AS03_A$ adjuvant
2. H1N1 = H1N1 antigen containing 15µg of HA without adjuvant

Among all subjects aged 18-60 years in both studies who had received two doses of Pandemrix or unadjuvanted vaccine at D0 and D21 all CHMP HI criteria were still met at month 12 (M12). Among all subjects aged 18-60 years who received a single dose of Pandemrix in study 008 the M12 SPR rate was 65.4% although the SCR was 61.5% and the seroconversion factor SCF was 7.6.

In all subjects aged above 60 years who received either one or two doses of Pandemrix in study 008 the CHMP criteria were still met for SCR and SCF but not for SPR (54.4% in the 2-dose group and 44.0% in the 1-dose group). Values tended to be lower in subjects administered a single dose compared to two doses.

The tables below summarise these findings and also show results according to HI serostatus prior to vaccination. The M12 GMTs were generally higher in subjects seropositive at baseline, regardless of the number of vaccine doses administered and age category. In the overall population aged 18-60 years and above 60 years that received one or two doses of Pandemrix the CHMP criteria for SPR were met at Month 12 only for the subsets that had been seropositive at baseline. The SPR criterion was met in subjects seropositive or seronegative at baseline who received non-adjuvanted vaccine in study 007 but not in subjects in either group who were aged 41-60 years and seronegative on D0. All vaccine

groups in both studies met the SCR and SCF criteria regardless of baseline serostatus except the SCR for seronegative subjects aged > 60 years who received a single dose in study 008 (21.4%).

Table 2 **HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12 in study D-Pan-H1N1-007, overall and by initial serostatus (ATP cohort for persistence at Month 12)**

					≥10 1/DIL			GMT			SPR			SCR			SCF		
						95% CI			95% CI			95% CI			95% CI			95% CI	
Study group	Timing	Age stratum	Subgroup	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H1N1 + AS03$_A$	PII(M12)	All ages	S-	36	100	90.3	100	54.4	40.0	73.9	66.7	49.0	81.4	66.7	49.0	81.4	10.9	8.0	14.8
		18-60 years	S+	23	100	85.2	100	175.2	113.2	271.0	95.7	78.1	99.9	73.9	51.6	89.8	8.0	4.9	13.0
			Total	59	**100**	93.9	100	**85.8**	64.4	114.3	**78.0**	65.3	87.7	**69.5**	56.1	80.8	**9.7**	7.4	12.5
		18-40 years	S-	19	100	82.4	100	72.9	45.3	117.4	73.7	48.8	90.9	73.7	48.8	90.9	14.6	9.1	23.5
			S+	8	100	63.1	100	306.4	140.2	669.3	100	63.1	100	100	63.1	100	15.3	8.0	29.3
			Total	27	**100**	87.2	100	**111.6**	70.4	176.9	**81.5**	61.9	93.7	**81.5**	61.9	93.7	**14.8**	10.3	21.3
		41-60 years	S-	17	100	80.5	100	39.1	27.3	56.1	58.8	32.9	81.6	58.8	32.9	81.6	7.8	5.5	11.2
			S+	15	100	78.2	100	130.0	77.1	219.2	93.3	68.1	99.8	60.0	32.3	83.7	5.7	3.0	10.7
			Total	32	**100**	89.1	100	**68.7**	47.7	99.0	**75.0**	56.6	88.5	**59.4**	40.6	76.3	**6.7**	4.8	9.4
H1N1	PII(M12)	All ages	S-	38	92.1	78.6	98.3	56.1	39.3	80.1	76.3	59.8	88.6	76.3	59.8	88.6	11.2	7.9	16.0
		18-60 years	S+	27	100	87.2	100	164.2	103.9	259.5	96.3	81.0	99.9	63.0	42.4	80.6	5.4	3.5	8.3
			Total	65	**95.4**	87.1	99.0	**87.6**	64.7	118.8	**84.6**	73.5	92.4	**70.8**	58.2	81.4	**8.3**	6.2	11.0
		18-40 years	S-	18	100	81.5	100	106.9	73.9	154.7	100	81.5	100	100	81.5	100	21.4	14.8	30.9
			S+	14	100	76.8	100	297.2	164.2	537.8	100	76.8	100	64.3	35.1	87.2	7.1	3.3	15.3
			Total	32	**100**	89.1	100	**167.2**	116.4	240.3	**100**	89.1	100	**84.4**	67.2	94.7	**13.2**	8.7	20.1
		41-60 years	S-	20	85.0	62.1	96.8	31.4	19.5	50.6	55.0	31.5	76.9	55.0	31.5	76.9	6.3	3.9	10.1
			S+	13	100	75.3	100	86.6	48.8	153.9	92.3	64.0	99.8	61.5	31.6	86.1	4.0	2.7	6.1
			Total	33	**90.9**	75.7	98.1	**46.8**	31.7	69.2	**69.7**	51.3	84.4	**57.6**	39.2	74.5	**5.3**	3.8	7.3

Table 3 **HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12 in study D-Pan-H1N1-008 (ATP cohort for persistence at Month 12)**

					≥10 1/DIL			GMT			SPR			SCR			SCF		
						95% CI			95% CI			95% CI			95% CI			95% CI	
Study group	Timing	Age stratum	Subgroup	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H1N1 + AS03$_A$ 2-Dose schedule	PII(M12)	18-60 years	S-	43	100	91.8	100	61.3	44.2	84.9	69.8	53.9	82.8	69.8	53.9	82.8	12.3	8.8	17.0
			S+	24	100	85.8	100	182.1	132.7	250.0	95.8	78.9	99.9	83.3	62.6	95.3	7.8	5.4	11.3
			Total	67	**100**	94.6	100	**90.5**	69.4	118.1	**79.1**	67.4	88.1	**74.6**	62.5	84.5	**10.4**	8.1	13.4
		>60 years	S-	40	92.5	79.6	98.4	25.4	19.9	32.6	32.5	18.6	49.1	32.5	18.6	49.1	5.1	4.0	6.5
			S+	28	100	87.7	100	87.3	58.3	130.6	85.7	67.3	96.0	53.6	33.9	72.5	3.3	2.3	4.7
			Total	68	**95.6**	87.6	99.1	**42.3**	32.6	54.8	**54.4**	41.9	66.5	**41.2**	29.4	53.8	**4.3**	3.5	5.2
H1N1 + AS03$_A$ 1-Dose schedule	PI(M12)	18-60 years	S-	32	75.0	56.6	88.5	39.1	21.8	70.1	53.1	34.7	70.9	53.1	34.7	70.9	7.8	4.4	14.0
			S+	20	100	83.2	100	141.6	81.7	245.7	85.0	62.1	96.8	75.0	50.9	91.3	7.4	4.1	13.1
			Total	52	**84.6**	71.9	93.1	**64.2**	41.3	99.7	**65.4**	50.9	78.0	**61.5**	47.0	74.7	**7.6**	5.1	11.5
		>60 years	S-	28	67.9	47.6	84.1	15.2	9.5	24.2	21.4	8.3	41.0	21.4	8.3	41.0	3.0	1.9	4.8
			S+	22	100	84.6	100	61.2	39.7	94.6	72.7	49.8	89.3	40.9	20.7	63.6	2.7	1.7	4.3
			Total	50	**82.0**	68.6	91.4	**28.1**	19.4	40.6	**44.0**	30.0	58.7	**30.0**	17.9	44.6	**2.9**	2.1	4.0

Both studies showed an effect of age and in some age/baseline serostatus sub-groups the minimum criteria were not met. It was in the oldest subset in 007 that the benefit of adding AS03 was most evident. In 008 there was a benefit of two doses vs. one dose except for the subjects >70 years in whom no effect can really be discerned due to high baseline seropositivity, low numbers and the fact that subjects > 60 years who were seronegative at D0 had low HI titres at M12 even after two doses.

Appendix Table 1 **HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12 in study D-Pan-H1N1-007, by age subcategory and by initial serostatus (ATP cohort for persistence at Month 12)**

					≥10 1/DIL			GMT			SPR			SCR			SCF		
						95% CI			95% CI			95% CI			95% CI			95% CI	
Study group	Timing	Age stratum	Subgroup	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H1N1 + AS03$_A$	PII(M12)	41-50 years	S-	8	100	63.1	100	45.5	24.1	86.2	62.5	24.5	91.5	62.5	24.5	91.5	9.1	4.8	17.2
			S+	8	100	63.1	100	167.3	79.1	353.8	100	63.1	100	62.5	24.5	91.5	6.8	2.4	18.9
			Total	16	**100**	79.4	100	**87.3**	49.9	152.5	**81.3**	54.4	96.0	**62.5**	35.4	84.8	**7.8**	4.6	13.4
		51-60 years	S-	9	100	66.4	100	34.2	20.7	56.5	55.6	21.2	86.3	55.6	21.2	86.3	6.8	4.1	11.3
			S+	7	100	59.0	100	97.5	39.4	241.0	85.7	42.1	99.6	57.1	18.4	90.1	4.6	1.7	13.0
			Total	16	**100**	79.4	100	**54.1**	32.7	89.6	**68.8**	41.3	89.0	**56.3**	29.9	80.2	**5.8**	3.6	9.2
H1N1	PII(M12)	41-50 years	S-	7	100	59.0	100	48.8	23.9	99.7	71.4	29.0	96.3	71.4	29.0	96.3	9.8	4.8	19.9
			S+	9	100	66.4	100	122.2	59.1	252.7	100	66.4	100	66.7	29.9	92.5	4.9	3.0	7.9
			Total	16	**100**	79.4	100	**81.8**	48.8	136.9	**87.5**	61.7	98.4	**68.8**	41.3	89.0	**6.6**	4.4	9.9
		51-60 years	S-	13	76.9	46.2	95.0	24.8	12.9	47.6	46.2	19.2	74.9	46.2	19.2	74.9	5.0	2.6	9.5
			S+	4	100	39.8	100	40.0	25.2	63.4	75.0	19.4	99.4	50.0	6.8	93.2	2.6	0.9	7.4
			Total	17	**82.4**	56.6	96.2	**27.7**	16.8	45.6	**52.9**	27.8	77.0	**47.1**	23.0	72.2	**4.3**	2.5	7.2

Appendix Table 2 HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12 in study D-Pan-H1N1-008, by age subcategory and by initial serostatus (ATP cohort for persistence at Month 12)

					≥10 1/DIL			GMT			SPR			SCR			SCF		
						95% CI			95% CI			95% CI			95% CI			95% CI	
Study vaccine	Timing	Age stratum	Subgroup	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H1N1 + AS03A 2 Doses	PII(M12)	18-40 years	S-	18	100	81.5	100	72.6	47.3	111.6	88.9	65.3	98.6	88.9	65.3	98.6	14.5	9.5	22.3
			S+	14	100	76.8	100	249.7	176.6	353.0	100	76.8	100	78.6	49.2	95.3	8.0	4.4	14.4
			Total	32	**100**	89.1	100	**124.7**	87.8	177.1	**93.8**	79.2	99.2	**84.4**	67.2	94.7	**11.2**	7.9	15.9
		41-60 years	S-	25	100	86.3	100	54.2	33.3	88.3	56.0	34.9	75.6	56.0	34.9	75.6	10.8	6.7	17.7
			S+	10	100	69.2	100	117.1	68.9	198.7	90.0	55.5	99.7	90.0	55.5	99.7	7.5	4.5	12.4
			Total	35	**100**	90.0	100	**67.5**	46.0	99.3	**65.7**	47.8	80.9	**65.7**	47.8	80.9	**9.8**	6.8	14.1
		61-70 years	S-	23	95.7	78.1	99.9	28.6	21.0	39.1	34.8	16.4	57.3	34.8	16.4	57.3	5.7	4.2	7.8
			S+	17	100	80.5	100	72.3	42.7	122.4	82.4	56.6	96.2	52.9	27.8	77.0	3.3	2.2	5.0
			Total	40	**97.5**	86.8	99.9	**42.5**	31.2	57.9	**55.0**	38.5	70.7	**42.5**	27.0	59.1	**4.5**	3.5	5.8
		>70 years	S-	17	88.2	63.6	98.5	21.7	14.1	33.3	29.4	10.3	56.0	29.4	10.3	56.0	4.3	2.8	6.7
			S+	11	100	71.5	100	116.7	57.8	235.6	90.9	58.7	99.8	54.5	23.4	83.3	3.3	1.6	6.7
			Total	28	**92.9**	76.5	99.1	**42.0**	26.0	67.7	**53.6**	33.9	72.5	**39.3**	21.5	59.4	**3.9**	2.7	5.6
H1N1 + AS03A 1 Dose	PI(M12)	18-40 years	S-	15	80.0	51.9	95.7	62.1	24.5	157.4	73.3	44.9	92.2	73.3	44.9	92.2	12.4	4.9	31.5
			S+	12	100	73.5	100	184.8	95.5	357.8	100	73.5	100	91.7	61.5	99.8	10.4	5.4	20.0
			Total	27	**88.9**	70.8	97.6	**100.8**	55.5	183.3	**85.2**	66.3	95.8	**81.5**	61.9	93.7	**11.5**	6.6	20.0
		41-60 years	S-	17	70.6	44.0	89.7	26.0	12.1	56.1	35.3	14.2	61.7	35.3	14.2	61.7	5.2	2.4	11.2
			S+	8	100	63.1	100	95.0	31.4	287.7	62.5	24.5	91.5	50.0	15.7	84.3	4.4	1.4	13.9
			Total	25	**80.0**	59.3	93.2	**39.4**	20.8	74.4	**44.0**	24.4	65.1	**40.0**	21.1	61.3	**4.9**	2.7	8.9
		61-70 years	S-	19	73.7	48.8	90.9	14.6	8.6	25.0	21.1	6.1	45.6	21.1	6.1	45.6	2.9	1.7	5.0
			S+	14	100	76.8	100	53.9	28.5	102.0	64.3	35.1	87.2	35.7	12.8	64.9	2.6	1.5	4.7
			Total	33	**84.8**	68.1	94.9	**25.5**	16.2	40.0	**39.4**	22.9	57.9	**27.3**	13.3	45.5	**2.8**	1.9	4.1
		>70 years	S-	9	55.6	21.2	86.3	16.5	5.4	49.9	22.2	2.8	60.0	22.2	2.8	60.0	3.3	1.1	10.0
			S+	8	100	63.1	100	76.6	41.6	140.9	87.5	47.3	99.7	50.0	15.7	84.3	2.8	1.1	7.5
			Total	17	**76.5**	50.1	93.2	**34.0**	16.7	68.9	**52.9**	27.8	77.0	**35.3**	14.2	61.7	**3.1**	1.6	5.9

The analyses according to previous seasonal influenza vaccination history (next tables) showed that the GMTs at M12 were numerically higher in subjects who did not receive prior influenza vaccination in the preceding 3 seasons. However all CHMP criteria were still met subjects aged 18-60 years who received two doses of vaccine regardless of prior vaccination status. After a single dose of Pandemrix the SPR criteria were met in subjects with no prior influenza vaccination (82.1% in 18-60 years and 62.5% in > 60 years) but not in those with a pre-vaccination history (45.8% and 40.5%, respectively). However, only low numbers aged > 60 years were not previously vaccinated against influenza, which limits the interpretation of the comparisons.

Appendix Table 3 HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12, by history of influenza vaccination in study D-Pan-H1N1-007 (ATP cohort for persistence at Month 12)

				>= 10 1/DIL			GMT			SPR			SCR			SCF		
					95% CI			95% CI			95% CI			95% CI			95% CI	
Group	Sub-group	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H1N1+AS03	Pre-vacc FLU	PII(M12)	35	**100**	90.0	100	**68.9**	48.2	98.5	**71.4**	53.7	85.4	**60.0**	42.1	76.1	**7.2**	5.2	10.1
	No Pre-vacc FLU	PII(M12)	24	**100**	85.8	100	**118.1**	73.2	190.4	**87.5**	67.6	97.3	**83.3**	62.6	95.3	**14.7**	9.9	21.8
H1N1	Pre-vacc FLU	PII(M12)	26	**92.3**	74.9	99.1	**52.9**	32.9	85.3	**73.1**	52.2	88.4	**57.7**	36.9	76.6	**4.8**	3.5	6.5
	No Pre-vacc FLU	PII(M12)	39	**97.4**	86.5	99.9	**122.6**	84.4	178.2	**92.3**	79.1	98.4	**79.5**	63.5	90.7	**11.9**	8.1	17.6

Appendix Table 4 HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 12, by history of influenza vaccination in study D-Pan-H1N1-008 (ATP cohort for persistence at Month 12)

					>= 10 1/DIL			GMT			SPR			SCR			SCF		
						95% CI			95% CI			95% CI			95% CI			95% CI	
Group	Timing	Age category	Sub-group	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	%	LL	UL
H1N1 + AS03A 2 Doses	PII(M12)	18-60y	Pre-vacc FLU	40	**100**	91.2	100	**66.6**	47.1	94.3	**70.0**	53.5	83.4	**67.5**	50.9	81.4	**9.3**	6.9	12.8
			No Pre-vacc FLU	27	**100**	87.2	100	**142.5**	98.1	206.9	**92.6**	75.7	99.1	**85.2**	66.3	95.8	**12.2**	8.0	18.7
		>60y	Pre-vacc FLU	61	**95.1**	86.3	99.0	**42.1**	32.1	55.1	**55.7**	42.4	68.5	**42.6**	30.0	55.9	**4.3**	3.4	5.3
			No Pre-vacc FLU	7	**100**	59.0	100	**44.1**	12.4	156.3	**42.9**	9.9	81.6	**28.6**	3.7	71.0	**4.0**	1.9	8.6
H1N1 + AS03A 1 Dose		18-60y	Pre-vacc FLU	24	**70.8**	48.9	87.4	**30.8**	15.7	60.3	**45.8**	25.6	67.2	**41.7**	22.1	63.4	**4.1**	2.4	7.0
			No Pre-vacc FLU	28	**96.4**	81.7	99.9	**120.4**	72.7	199.3	**82.1**	63.1	93.9	**78.6**	59.0	91.7	**13.0**	7.4	22.7
		>60y	Pre-vacc FLU	42	**81.0**	65.9	91.4	**25.4**	17.2	37.5	**40.5**	25.6	56.7	**28.6**	15.7	44.6	**2.8**	2.0	3.8
			No Pre-vacc FLU	8	**87.5**	47.3	99.7	**47.6**	13.1	172.5	**62.5**	24.5	91.5	**37.5**	8.5	75.5	**3.7**	0.9	14.8

NA data to month 6 from study 008

The NA response was assessed in a subset of subjects at D0, 21, 42 and M6. The baseline seropositivity rates ranged from 64.7% to 77.3% but GMTs were low. At D21 there was evidence of a considerable NA increment even in the older subjects who were seronegative at baseline although GMTs and VRRs were higher in the baseline seropositives. At D42 it was clear that a second dose elicited a further increment in NA, again regardless of age and baseline status. At Month 6 the GMTs

were still significantly above baseline values and the overall data indicated some advantage for two doses over a single dose.

Table 4 **H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Month 6 in study D-Pan-H1N1-008 (ATP cohort for antibody persistence at Month 6, subset)**

					≥8 1/DIL			GMT			Vaccine response rate		
						95% CI			95% CI			95% CI	
Study group	Age stratum	Subgroup	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03A 2-Dose schedule	18-60 years	S-	PRE	6	**0.0**	0.0	45.9	**4.0**	4.0	4.0	-	-	-
			PI(21)	6	**83.3**	35.9	99.6	**195.6**	13.6	2816.8	**58.3**	27.7	84.8
			PII(D42)	6	**100**	54.1	100	**510.5**	122.4	2129.1	**91.7**	61.5	99.8
			PII(M6)	6	**83.3**	35.9	99.6	**96.8**	13.8	679.6	**83.3**	51.6	97.9
		S+	PRE	16	**100**	79.4	100	**17.9**	12.3	26.1	-	-	-
			PI(21)	16	**100**	79.4	100	**201.4**	97.0	418.4	**80.0**	44.4	97.5
			PII(D42)	16	**100**	79.4	100	**276.4**	139.0	549.7	**90.0**	55.5	99.7
			PII(M6)	16	**100**	79.4	100	**143.2**	83.2	246.3	**80.0**	44.4	97.5
		Total	PRE	22	**72.7**	49.8	89.3	**11.9**	8.0	17.8	-	-	-
			PI(21)	22	**95.5**	77.2	99.9	**199.8**	94.1	424.2	**68.2**	45.1	86.1
			PII(D42)	22	**100**	84.6	100	**326.8**	183.0	583.3	**90.9**	70.8	98.9
			PII(M6)	22	**95.5**	77.2	99.9	**128.7**	73.5	225.2	**81.8**	59.7	94.8
	>60 years	S-	PRE	5	**0.0**	0.0	52.2	**4.0**	4.0	4.0	-	-	-
			PI(21)	5	**100**	47.8	100	**71.5**	4.9	1052.9	**58.3**	27.7	84.8
			PII(D42)	5	**100**	47.8	100	**204.7**	27.6	1519.9	**91.7**	61.5	99.8
			PII(M6)	5	**100**	47.8	100	**77.0**	17.9	331.2	**58.3**	27.7	84.8
		S+	PRE	17	**100**	80.5	100	**25.7**	15.7	42.1	-	-	-
			PI(21)	17	**100**	80.5	100	**218.8**	113.0	423.8	**80.0**	44.4	97.5
			PII(D42)	17	**100**	80.5	100	**349.5**	215.1	567.9	**80.0**	44.4	97.5
			PII(M6)	17	**100**	80.5	100	**103.3**	58.5	182.6	**70.0**	34.8	93.3
		Total	PRE	22	**77.3**	54.6	92.2	**16.9**	10.1	28.1	-	-	-
			PI(21)	22	**100**	84.6	100	**169.7**	85.6	336.5	**68.2**	45.1	86.1
			PII(D42)	22	**100**	84.6	100	**309.5**	189.3	505.9	**86.4**	65.1	97.1
			PII(M6)	22	**100**	84.6	100	**96.7**	59.3	157.5	**63.6**	40.7	82.8

					≥8 1/DIL			GMT			Vaccine response rate		
						95% CI			95% CI			95% CI	
Study group	Age stratum	Subgroup	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03A 1-Dose schedule	18-60 years	S-	PRE	6	**0.0**	0.0	45.9	**4.0**	4.0	4.0	-	-	-
			PI(21)	6	**100**	54.1	100	**140.1**	21.5	911.6	**72.7**	39.0	94.0
			PI(D42)	6	**100**	54.1	100	**78.8**	16.2	383.0	**63.6**	30.8	89.1
			PI(M6)	6	**83.3**	35.9	99.6	**22.0**	5.3	91.0	**18.2**	2.3	51.8
		S+	PRE	11	**100**	71.5	100	**23.6**	11.2	50.0	-	-	-
			PI(21)	11	**100**	71.5	100	**241.2**	96.1	605.1	**66.7**	22.3	95.7
			PI(D42)	11	**100**	71.5	100	**184.6**	72.0	473.1	**66.7**	22.3	95.7
			PI(M6)	11	**100**	71.5	100	**90.9**	33.4	247.8	**66.7**	22.3	95.7
		Total	PRE	17	**64.7**	38.3	85.8	**12.6**	6.7	23.9	-	-	-
			PI(21)	17	**100**	80.5	100	**199.1**	92.3	429.7	**70.6**	44.0	89.7
			PI(D42)	17	**100**	80.5	100	**136.7**	64.8	288.6	**64.7**	38.3	85.8
			PI(M6)	17	**94.1**	71.3	99.9	**55.2**	24.7	123.3	**35.3**	14.2	61.7
	>60 years	S-	PRE	6	**0.0**	0.0	45.9	**4.0**	4.0	4.0	-	-	-
			PI(21)	6	**100**	54.1	100	**32.9**	7.9	136.0	**45.5**	16.7	76.6
			PI(D42)	6	**100**	54.1	100	**38.0**	13.3	109.1	**36.4**	10.9	69.2
			PI(M6)	6	**66.7**	22.3	95.7	**16.9**	4.8	60.2	**45.5**	16.7	76.6
		S+	PRE	12	**100**	73.5	100	**49.2**	24.6	98.1	-	-	-
			PI(21)	12	**100**	73.5	100	**133.0**	52.8	335.0	**14.3**	0.4	57.9
			PI(D42)	12	**100**	73.5	100	**131.0**	65.8	260.8	**14.3**	0.4	57.9
			PI(M6)	12	**100**	73.5	100	**128.2**	60.9	269.7	**28.6**	3.7	71.0
		Total	PRE	18	**66.7**	41.0	86.7	**21.3**	10.1	44.9	-	-	-
			PI(21)	18	**100**	81.5	100	**83.5**	38.8	179.4	**33.3**	13.3	59.0
			PI(D42)	18	**100**	81.5	100	**86.7**	48.0	156.7	**27.8**	9.7	53.5
			PI(M6)	18	**88.9**	65.3	98.6	**65.3**	30.8	138.4	**38.9**	17.3	64.3

While numbers in subsets are small, the next tables also suggest an advantage for two doses throughout the age range that was enrolled into study 008. In the younger cohort (18-60 years) the data indicate that two doses elicited higher titres than one dose in those with or without a history of prior influenza vaccination. The data cannot be interpreted for the older cohort due to low numbers without such a history.

Appendix Table 5 H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Month 6, by age subcategory in study D-Pan-H1N1-008 (ATP cohort for persistence at Month 6, subset)

				≥8 1/DIL			GMT			Vaccine response rate		
					95% CI			95% CI			95% CI	
Study group	Age stratum	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03$_A$ 2-Dose schedule	18-40 years	PRE	11	63.6	30.8	89.1	11.2	5.5	22.5	-	-	-
		PI(21)	11	90.9	58.7	99.8	244.7	60.2	994.5	72.7	39.0	94.0
		PII(D42)	11	100	71.5	100	398.6	161.2	985.6	100	71.5	100
		PII(M6)	11	90.9	58.7	99.8	127.2	43.2	374.3	81.8	48.2	97.7
	41-60 years	PRE	11	81.8	48.2	97.7	12.7	7.5	21.6	-	-	-
		PI(21)	11	100	71.5	100	163.2	69.6	382.3	63.6	30.8	89.1
		PII(D42)	11	100	71.5	100	267.9	112.0	640.6	81.8	48.2	97.7
		PII(M6)	11	100	71.5	100	130.2	72.4	234.2	81.8	48.2	97.7
	61-70 years	PRE	14	85.7	57.2	98.2	17.2	9.4	31.5	-	-	-
		PI(21)	14	100	76.8	100	110.1	56.7	214.1	57.1	28.9	82.3
		PII(D42)	14	100	76.8	100	247.5	152.5	401.5	78.6	49.2	95.3
		PII(M6)	14	100	76.8	100	67.9	45.1	102.4	50.0	23.0	77.0
	>70 years	PRE	8	62.5	24.5	91.5	16.3	5.1	52.3	-	-	-
		PI(21)	8	100	63.1	100	361.8	73.1	1789.5	87.5	47.3	99.7
		PII(D42)	8	100	63.1	100	457.8	136.1	1539.5	100	63.1	100
		PII(M6)	8	100	63.1	100	179.2	54.7	587.6	87.5	47.3	99.7

				≥8 1/DIL			GMT			Vaccine response rate		
					95% CI			95% CI			95% CI	
Study group	Age stratum	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03$_A$ 1-Dose schedule	18-40 years	PRE	9	55.6	21.2	86.3	8.3	4.3	16.0	-	-	-
		PI(21)	9	100	66.4	100	188.5	54.3	654.2	66.7	29.9	92.5
		PI(D42)	9	100	66.4	100	121.2	42.6	344.7	66.7	29.9	92.5
		PI(M6)	9	88.9	51.8	99.7	38.8	15.3	98.3	44.4	13.7	78.8
	41-60 years	PRE	8	75.0	34.9	96.8	20.3	5.9	69.9	-	-	-
		PI(21)	8	100	63.1	100	211.7	62.8	713.9	75.0	34.9	96.8
		PI(D42)	8	100	63.1	100	156.6	39.9	614.2	62.5	24.5	91.5
		PI(M6)	8	100	63.1	100	81.9	16.8	399.0	25.0	3.2	65.1
	61-70 years	PRE	12	66.7	34.9	90.1	15.1	7.6	30.0	-	-	-
		PI(21)	12	100	73.5	100	65.3	24.4	174.9	33.3	9.9	65.1
		PI(D42)	12	100	73.5	100	69.1	34.1	140.0	25.0	5.5	57.2
		PI(M6)	12	83.3	51.6	97.9	53.9	19.1	152.2	41.7	15.2	72.3
	>70 years	PRE	6	66.7	22.3	95.7	42.6	5.0	364.3	-	-	-
		PI(21)	6	100	54.1	100	136.2	27.4	676.5	33.3	4.3	77.7
		PI(D42)	6	100	54.1	100	136.7	34.5	542.4	33.3	4.3	77.7
		PI(M6)	6	100	54.1	100	95.9	25.4	362.9	33.3	4.3	77.7

Appendix Table 6 H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Month 6, by history of influenza vaccination in study D-Pan-H1N1-008 (ATP cohort for persistence at Month 6, subset)

					≥8 1/DIL			GMT			Vaccine response rate		
						95% CI			95% CI			95% CI	
Study group	Age stratum	Subgroup	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03$_A$ 2-Dose schedule	18-60 years	Pre-vacc FLU	PRE	14	78.6	49.2	95.3	12.9	7.6	22.0	-	-	-
			PI(21)	14	92.9	66.1	99.8	199.8	72.1	553.7	71.4	41.9	91.6
			PII(D42)	14	100	76.8	100	308.8	137.7	692.8	85.7	57.2	98.2
			PII(M6)	14	92.9	66.1	99.8	120.8	51.9	281.4	71.4	41.9	91.6
		No pre-vacc FLU	PRE	8	62.5	24.5	91.5	10.3	4.8	22.3	-	-	-
			PI(21)	8	100	63.1	100	199.9	48.6	821.4	62.5	24.5	91.5
			PII(D42)	8	100	63.1	100	360.7	130.9	993.9	100	63.1	100
			PII(M6)	8	100	63.1	100	143.6	68.7	300.3	100	63.1	100
	>60 years	Pre-vacc FLU	PRE	21	76.2	52.8	91.8	15.1	9.3	24.3	-	-	-
			PI(21)	21	100	83.9	100	163.7	80.0	334.9	71.4	47.8	88.7
			PII(D42)	21	100	83.9	100	304.7	181.9	510.4	90.5	69.6	98.8
			PII(M6)	21	100	83.9	100	99.4	59.7	165.5	66.7	43.0	85.4
		No pre-vacc FLU	PRE	1	100	2.5	100	181.0	-	-	-	-	-
			PI(21)	1	100	2.5	100	362.0	-	-	0.0	0.0	97.5
			PII(D42)	1	100	2.5	100	429.0	-	-	0.0	0.0	97.5
			PII(M6)	1	100	2.5	100	54.0	-	-	0.0	0.0	97.5

					≥8 1/DIL			GMT			Vaccine response rate		
						95% CI			95% CI			95% CI	
Study group	Age stratum	Subgroup	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
H1N1 + AS03$_A$ 1-Dose schedule	18-60 years	Pre-vacc FLU	PRE	5	40.0	5.3	85.3	6.6	2.7	15.9	-	-	-
			PI(21)	5	100	47.8	100	59.4	16.9	209.3	80.0	28.4	99.5
			PI(D42)	5	100	47.8	100	40.6	11.4	144.7	40.0	5.3	85.3
			PI(M6)	5	80.0	28.4	99.5	14.0	4.3	45.4	0.0	0.0	52.2
		No pre-vacc FLU	PRE	12	75.0	42.8	94.5	16.6	7.1	38.7	-	-	-
			PI(21)	12	100	73.5	100	329.6	136.0	798.5	66.7	34.9	90.1
			PI(D42)	12	100	73.5	100	226.7	98.0	524.3	75.0	42.8	94.5
			PI(M6)	12	100	73.5	100	97.7	39.6	241.1	50.0	21.1	78.9
	>60 years	Pre-vacc FLU	PRE	14	78.6	49.2	95.3	23.7	12.2	46.0	-	-	-
			PI(21)	14	100	76.8	100	76.4	32.1	181.7	28.6	8.4	58.1
			PI(D42)	14	100	76.8	100	86.8	47.5	158.5	28.6	8.4	58.1
			PI(M6)	14	100	76.8	100	82.1	42.1	160.1	42.9	17.7	71.1
		No pre-vacc FLU	PRE	4	25.0	0.6	80.6	14.7	0.2	917.7	-	-	-
			PI(21)	4	100	39.8	100	113.8	5.8	2225.3	50.0	6.8	93.2
			PI(D42)	4	100	39.8	100	86.6	4.8	1567.4	25.0	0.6	80.6
			PI(M6)	4	50.0	6.8	93.2	29.3	0.6	1455.2	25.0	0.6	80.6

Safety

The additional safety data concern only SAEs and AESIs up to Month 12 and biochemical parameters assessed at Day 364. There were no deaths reported up to M12 from either study.

In study 007 three subjects reported 3 SAEs. Two of these were reported between M6 and M12. None was considered by the investigators as causally related to vaccination and all had resolved at the data lock-point for the M12 analysis.

In study 008 up to M12 16 subjects had reported 29 SAEs, including 9 that were reported by 6 subjects between M6 and M12. None was considered by the investigator as related to vaccination. However, two subjects were withdrawn from the study due to SAEs – one had breast cancer and the other had multiple fractures and subdural hematoma following an accident.

No AESIs/pIMDs were reported in study 008. There was a single report in study 007 but this concerned a subject in the non-adjuvanted H1N1 group who developed uveitis 48 days after Dose 2. This was not considered as causally related and it resolved. The investigator reported the event was not autoimmune in origin.

In study 008 only there were clinical laboratory evaluations of ALT, AST, ALP, BUN, bilirubin and creatinine up to M12. The proportion of subjects with laboratory abnormalities was low in each study group and was not suggestive of clinically relevant alterations in the biochemistry profile from baseline.

3.3. Changes to the Product Information

The CHMP agreed with the changes proposed by the MAH for section 5.1 of the Pandemrix SmPC. However, the MAH was requested to also update the text in section 4.2 in accordance with the changes in section 5.1:

Section 4.2

Adults aged 18 years and older:

One dose of 0.5 ml at an elected date.

Immunogenicity data obtained at three weeks after one dose of Pandemrix (H1N1)v suggest that a single dose may be sufficient.

If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

See section 5.1 regarding immune responses to one and two doses of Pandemrix (H1N1)v, including antibody levels after 6 **and 12** months.

3.4. Overall conclusions and benefit / risk profile

The data to month 6 showed an advantage in terms of HI and CMI data for AS03-adjuvanted vaccine over plain HA in subjects aged 18-60 years when each was given for 2 doses 21 days apart in study 007. However, the most notable advantages for the adjuvanted vaccine in terms of HI were for those seronegative at baseline and over 40 years of age. At month 12 there was no discernible advantage for adjuvanted vs. non-adjuvanted vaccine except to a modest extent for the subgroup aged over 50 years.

There was an advantage in terms of HI data for two doses of adjuvanted vaccine over one dose as evident at M6 and to some extent also at M12 in study 008. The effect was detectable throughout the datasets (if only for selected parameters) but it was especially notable at M6 for those who were seronegative at baseline and aged > 60 years. The available SNA data at M6 also point to some

advantage for two doses. However, the M6 CMI data did not consistently suggest an advantage for two doses.

There are no effectiveness estimates for one vs. two doses in adults and it is not currently possible to discern whether the observed differences in HI response at M6 and M12 and the differences in SNA data at M6 have any implications for protection of adults, including the elderly. Therefore, while it can be observed that two doses are associated with higher HI and SNA titres at M6 (and for HI at M12) vs. one dose, the titres even after two doses are quite low in the elderly. If protection does not rely on circulating antibody but is driven by establishing immune memory then these data likely have little or no significance, but this is not known at present.

CHMP agreed that the findings should be stated in section 5.1 but it had no grounds to request any change to the dose recommendations in Section 4.2. Since public health decisions regarding dose regimens would likely take into account those least likely to respond and since routine baseline serological status determination is not feasible, CHMP agreed that the HI data should be mentioned for those who were sero-negative at baseline as well as overall.

4. Conclusion

On 21 July 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.