Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemrix

pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/2009 (h1n1)v like strain (x-179a)

Procedure No.: EMEA/H/C/000832/II/0046

Note

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

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2010
EMA/CHMP/797387/2010
Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000832/II/0046

Invented name/name:	Pandemrix
Common name:	pandemic 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 and Package Leaflet. To update sections 4.2 and 5.1 of the Summary of Product Characteristics to include persistence results and safety follow-up up to 6 months after primary vaccination from studies D-Pan H1N1-007 (adults 18-60) and D-pan H1N1-008 (adults 18-60 and >60).The MAH also took this opportunity to make a minor correction in the Package Leaflet (section 4).
Rapporteur:	Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2 and 5
Product Information affected:	SmPC and Package Leaflet (Attachment 1 - changes highlighted)

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2. Steps taken for the assessment

Step	Step date
Submission date:	30 September 2010
Start of procedure:	17 October 2010
Rapporteur's assessment report circulated on:	28 October 2010
CHMP opinion:	16 December 2010

3. Scientific discussion

3.1. Introduction

Pandemrix is an adjuvanted vaccine against influenza caused by A (H1N1)v 2009 virus. It is supplied in two separate vials as a suspension (antigen) and emulsion (adjuvant) for emulsion 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 Authorisations 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).

The scientific development was based on the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) and the guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03).

Following the onset of the (H1N1)v 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 used NYMC X-179A. The recommendation for the approval of the PU/0017 Pandemic Update was adopted by the CHMP on 24 September 2009. The marketing authorisation under exceptional circumstances for the current (H1N1)v vaccine was granted by the European Commission on 29 September 20.

In April 2010 the MAH applied to lift the Specific Obligations and to convert the MA granted under "exceptional circumstances" into a full MA (SW/041). On 24 June 2010 the CHMP recommended to change the status of the marketing authorisation outside the scope of Art. 14(8) of Regulation (EC) 726/2004.

Within this variation procedure (II/43), the MAH provided data from studies D-Pan H1N1-007 and 008 in this variation constitute documentation of safety and immunogenicity (Haemagglutination Inhibition (HI) and Cell mediated immune response (CMI) only) up to Month 6 in healthy adults aged from 18 to > 60 years.

The post-dose 1 and post-dose 2 data from each study were already assessed and added to the SmPC during the following preceding variations:

II/019 and II/032 – study D-Pan H1N1-007
II/023 and II/038 – study D-Pan H1N1-008
This variation has been submitted to fulfil the following follow-up measures (FUMs):
Study H1N1-007 Clinical Study Report, Month 6
Study H1N1-008 Clinical Study Report, Month 6

Type II-variation covered by this assessment:

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 Summary of Product Characteristics to include persistence results and safety follow-up up to 6 months after primary vaccination from studies D-Pan H1N1-007 (adults 18-60) and D-pan H1N1-008 (adults 18-60 and >60).The MAH also took this opportunity to make a minor correction in the Package Leaflet (section 4).

3.2. Clinical aspects

D-PAN H1N1-007

This is an ongoing study 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 $AS03_A$ = 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.

The vaccines administered were of the following content:

Study number	**Strain**	**HA dose (µg)***	**Adj dose****	**Dose volume**
D-Pan-H1N1-007	A/California/7/2009(H1N1)v-like 15 µg/ml + $AS03_A$	*3.75 µg (0.25 ml)*	$AS03_A$, (0.25 ml)	0.5 ml
	A/California/7/2009(H1N1)v-like 30 µg/mL	*15 µg (0.5 ml)*	-	0.5 ml

Study Design

The primary objective was to demonstrate that two doses of vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like strain with $AS03_A$ results in an HI immune response to vaccine-homologous virus that meets or exceeds the CHMP criteria applied to seasonal influenza vaccines.

The study is observer-blinded i.e. vaccine recipients and those responsible for the evaluation of any study endpoint are unaware of which vaccine was administered.

Blood samples for evaluation of HI antibody immune response were to be obtained prior to (Day 0) vaccination and at Days 21, 42, 182 and 364 after the first vaccination.

The HI data from days 0, 21 and 42 previously reported came from testing all sera in parallel. The month 6 (M6) samples were tested separately. The CMI data were generated using previously described methods.

Subsequent analyses will be performed after all data will become available for month 12.

Results up to month 6

The data lock point for the current report was 24 June 2010. Please see previous reports for the baseline demographics of the 130 subjects initially enrolled into this study. All except one subject, who was lost to follow up, completed the study up to M6 (day 182).

Four subjects were excluded from the ATP immunogenicity cohort because of non-compliance with the vaccination (1) or blood sampling (2) schedules or because of missing serological data.

The HI data are summarised below. Please note the pre-vaccination seropositivity rates as commented on in the prior assessment reports.

HI against vaccine-homologous virus up to Day 182 (ATP at D42 and D182)

				≥10 1/DIL			GMT			SPR			SCR			SCF		
					95% CI			95% CI			95% CI			95% CI			95% CI	
Grp.	**Age stratum**	**Timing**	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
H1N1 + AS03	**18-60 years**	PRE	60	**38.3**	26.1	51.8	**8.8**	7.0	11.1	**11.7**	4.8	22.6	**-**	-	-	**-**	-	-
		PI(D21)	60	**100**	94.0	100	**335.2**	250.1	449.2	**100**	94.0	100	**98.3**	91.1	100	**38.1**	28.6	50.7
		PII(D42)	59	**100**	93.9	100	**636.3**	520.9	777.3	**100**	93.9	100	**98.3**	90.9	100	**72.9**	55.4	95.9
		PII(D182)	59	**100**	93.9	100	**204.8**	161.5	259.8	**100**	93.9	100	**96.6**	88.3	99.6	**22.5**	18.0	28.2
	18-40 years	PRE	28	**28.6**	13.2	48.7	**7.4**	5.6	9.9	**7.1**	0.9	23.5	**-**	-	-	**-**	-	-
		PI(D21)	28	**100**	87.7	100	**458.2**	298.4	703.6	**100**	87.7	100	**100**	87.7	100	**61.7**	43.2	88.0
		PII(D42)	28	**100**	87.7	100	**790.0**	589.2	1059.3	**100**	87.7	100	**100**	87.7	100	**106.3**	79.8	141.6
		PII(D182)		**100**	87.2	100	**267.3**	184.8	386.8	**100**	87.2	100	**100**	87.2	100	**33.7**	25.6	44.3
	41-60 years	PRE	32	**46.9**	29.1	65.3	**10.2**	7.1	14.7	**15.6**	5.3	32.8	**-**	-	-	**-**	-	-
		PI(D21)	32	**100**	89.1	100	**255.0**	171.4	379.3	**100**	89.1	100	**96.9**	83.8	99.9	**25.0**	16.8	37.1
		PII(D42)	31	**100**	88.8	100	**523.4**	399.4	685.7	**100**	88.8	100	**96.8**	83.3	99.9	**51.8**	33.6	79.9
		PII(D182)	32	**100**	89.1	100	**163.6**	120.7	221.7	**100**	89.1	100	**93.8**	79.2	99.2	**16.0**	11.7	21.9
H1N1	**All ages -18-60 years**	PRE	66	**42.4**	30.3	55.2	**10.8**	8.1	14.4	**18.2**	9.8	29.6	**-**	-	-	**-**	-	-
		PI(D21)	66	**98.5**	91.8	100	**310.2**	218.8	439.7	**93.9**	85.2	98.3	**84.8**	73.9	92.5	**28.7**	20.0	41.2
		PII(D42)	66	**100**	94.6	100	**341.0**	259.9	447.3	**100**	94.6	100	**92.4**	83.2	97.5	**31.5**	23.1	43.2
		PII(D182)	61	**100**	94.1	100	**146.1**	108.5	196.7	**85.2**	73.8	93.0	**77.0**	64.5	86.8	**13.9**	10.2	18.9
	18-40 years	PRE	33	**45.5**	28.1	63.6	**13.1**	8.1	21.4	**24.2**	11.1	42.3	**-**	-	-	**-**	-	-
		PI(D21)	33	**100**	89.4	100	**588.5**	385.7	897.8	**97.0**	84.2	99.9	**90.9**	75.7	98.1	**44.8**	26.6	75.6
		PII(D42)	33	**100**	89.4	100	**570.3**	408.1	797.0	**100**	89.4	100	**93.9**	79.8	99.3	**43.4**	26.8	70.3
		PII(D182)		**100**	88.1	100	**273.9**	204.6	366.8	**100**	88.1	100	**89.7**	72.6	97.8	**22.1**	13.7	35.6
	41-60	PRE	33	**39.4**	22.9	57.9	**8.9**	6.6	12.1	**12.1**	3.4	28.2	**-**	-	-	**-**	-	-

				≥10 1/DIL			GMT			SPR			SCR			SCF		
					95% CI			95% CI			95% CI			95% CI			95% CI	
Grp.	**Age stratum**	**Timing**	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
	years																	
		PI(D21)	33	**97.0**	84.2	99.9	**163.5**	101.2	264.1	**90.9**	75.7	98.1	**78.8**	61.1	91.0	**18.4**	11.4	29.7
		PII(D42)	33	**100**	89.4	100	**203.9**	142.0	292.6	**100**	89.4	100	**90.9**	75.7	98.1	**22.9**	15.4	34.0
		PII(D182)	32	**100**	89.1	100	**82.6**	54.1	126.1	**71.9**	53.3	86.3	**65.6**	46.8	81.4	**9.1**	6.4	13.0

At D182 all subjects were seropositive but the GMTs were lower in the subgroups that had been seronegative at D0.

Table 1 **Seropositivity rates and GMTs for HI antibodies against A/California/7/2009 (ATP cohort for persistence at Day 182)**

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09 H1N1.HA Ab	H1N1+ AS03	S-	PII(D182)	35	35	100	90.0	100	140.7	109.8	180.4	40.0	905.0
		S+	PII(D182)	24	24	100	85.8	100	354.0	242.7	516.3	40.0	2560.0
		Total	PII(D182)	59	59	100	93.9	100	204.8	161.5	259.8	40.0	2560.0
	H1N1	S-	PII(D182)	35	35	100	90.0	100	97.4	65.9	144.1	14.0	905.0
		S+	PII(D182)	26	26	100	86.8	100	251.9	170.3	372.4	57.0	2560.0
		Total	PII(D182)	61	61	100	94.1	100	146.1	108.5	196.7	14.0	2560.0

All subjects in the adjuvanted vaccine group were seroprotected at D182. The SPR for subjects who were seronegative at D0 and received plain HA was 74.3% and those not seroprotected at D182 were all in the 41-60 years age group. There was an advantage for adjuvanted vaccine in each group regardless of baseline serostatus.

All CHMP criteria were met in the adjuvanted group at D182. In the plain HA group the SPR and SCR criteria were not met in the 51-60 years age stratum.

At D182, a persistent CD4 T-cell response was observed in both groups with a median CD4 T-cell expressing any pair of measured cytokine expression of 1306.5 per million T cells in the H1N1+AS03 group and 653.5 in the H1N1 group. The tables below show the results of stimulation with split peptide and HA peptide pool and subjects have been subdivided according to whether or not they had received a seasonal influenza vaccination in the 3 years preceding the study. Stimulation with split antigen suggested slightly higher responses in the groups that had not received prior seasonal influenza vaccination but there was no marked effect or consistent pattern noted when cells were stimulated with the peptide pool.

Table 2 **Descriptive Statistics on the frequency influenza-specific CD4 T-cells (per million CD4 T-cells) stimulated by split A (ATP cohort for persistence at Day 182)**

Immune marker	Group	Sub-group	Timing	N	Nmiss	GM	SD	Min	Q1	Median	Q3	Max
CD4.All dle bkg	H1N1 +AS03	Flu	PII(D182)	30	4	1220.83	708.41	353	960.0	1226.5	1720.0	3962
		NoFLU	PII(D182)	24	1	1391.52	858.40	453	993.5	1433.5	2033.0	4347
		Total	PII(D182)	54	5	1293.94	777.91	353	973.0	1306.5	1734.0	4347
	H1N1	Flu	PII(D182)	23	3	354.81	435.77	1	213.0	614.0	947.0	1427
		NoFLU	PII(D182)	29	6	571.50	322.18	89	480.0	654.0	774.0	1387
		Total	PII(D182)	52	9	462.86	373.70	1	373.5	653.5	853.5	1427
CD4.dle CD40L bkg	H1N1 +AS03	Flu	PII(D182)	30	4	1200.10	702.19	364	973.0	1186.5	1706.0	3949
		NoFLU	PII(D182)	24	1	1365.47	845.46	453	981.0	1426.5	2013.5	4280
		Total	PII(D182)	54	5	1270.97	768.31	364	973.0	1273.5	1720.0	4280
	H1N1	Flu	PII(D182)	23	3	363.78	427.09	1	227.0	587.0	907.0	1452
		NoFLU	PII(D182)	29	6	549.67	315.84	75	466.0	654.0	760.0	1334
		Total	PII(D182)	52	9	457.94	365.79	1	373.0	647.0	846.5	1452
CD4.dle IL-2 bkg	H1N1 +AS03	Flu	PII(D182)	30	4	977.77	640.72	238	800.0	953.0	1480.0	3660
		NoFLU	PII(D182)	24	1	1095.95	719.44	253	846.5	1080.0	1542.0	3600
		Total	PII(D182)	54	5	1028.64	674.23	238	814.0	1006.5	1480.0	3660
	H1N1	Flu	PII(D182)	23	3	215.21	311.03	1	120.0	404.0	640.0	1093
		NoFLU	PII(D182)	29	6	391.68	230.31	5	373.0	520.0	587.0	1013
		Total	PII(D182)	52	9	300.54	268.08	1	240.0	493.5	600.0	1093
CD4.dle INFg bkg	H1N1 +AS03	Flu	PII(D182)	30	4	729.18	393.87	146	612.0	786.0	1067.0	1999
		NoFLU	PII(D182)	24	1	783.40	655.27	174	612.0	800.0	1139.5	3294
		Total	PII(D182)	54	5	752.80	524.48	146	612.0	793.0	1093.0	3294
	H1N1	Flu	PII(D182)	23	3	197.46	246.41	1	147.0	306.0	494.0	1000
		NoFLU	PII(D182)	29	6	240.43	235.85	1	254.0	360.0	480.0	894
		Total	PII(D182)	52	9	220.38	240.19	1	160.0	333.5	492.5	1000
CD4.dle TNFa bkg	H1N1 +AS03	Flu	PII(D182)	30	4	812.07	557.94	66	666.0	1006.5	1346.0	2727
		NoFLU	PII(D182)	24	1	968.10	687.29	254	680.5	1013.5	1473.5	3493
		Total	PII(D182)	54	5	878.05	616.06	66	667.0	1006.5	1346.0	3493
	H1N1	Flu	PII(D182)	23	3	221.74	311.26	1	187.0	427.0	600.0	1040
		NoFLU	PII(D182)	29	6	356.01	277.93	26	294.0	433.0	560.0	1200
		Total	PII(D182)	52	9	288.75	290.40	1	240.5	430.0	580.0	1200

Table 3 **Descriptive Statistics on the frequency influenza-specific CD4 T-cells (per million CD4 T-cells) after stimulation with HA peptide pool (ATP cohort for persistence at Day 182**

Immune marker	Group	Sub-group	Timing	N	Nmiss	GM	SD	Min	Q1	Median	Q3	Max
CD4.All dle bkg	H1N1 +AS03	Flu	PII(D182)	30	4	705.69	349.18	253	454.0	800.0	1042.0	1493
		NoFLU	PII(D182)	24	1	740.32	404.34	267	579.5	707.0	1000.0	1865
		Total	PII(D182)	54	5	720.88	371.46	253	493.0	780.5	1042.0	1865
	H1N1	Flu	PII(D182)	23	3	602.15	282.35	320	427.0	640.0	774.0	1360
		NoFLU	PII(D182)	29	6	592.64	339.49	213	453.0	587.0	894.0	1527
		Total	PII(D182)	52	9	596.83	312.64	213	427.0	613.5	789.5	1527
CD4.dle CD40L bkg	H1N1 +AS03	Flu	PII(D182)	30	4	689.29	347.08	240	453.0	780.0	1054.0	1427
		NoFLU	PII(D182)	24	1	721.72	398.96	253	540.0	706.5	953.0	1830
		Total	PII(D182)	54	5	703.52	367.78	240	479.0	766.5	1029.0	1830
	H1N1	Flu	PII(D182)	23	3	597.39	267.95	306	413.0	627.0	774.0	1280
		NoFLU	PII(D182)	29	6	578.94	334.20	226	440.0	587.0	880.0	1512
		Total	PII(D182)	52	9	587.03	303.84	226	427.0	600.0	782.0	1512
CD4.dle IL-2 bkg	H1N1 +AS03	Flu	PII(D182)	30	4	462.22	293.19	1	360.0	667.0	827.0	1186
		NoFLU	PII(D182)	24	1	511.46	379.63	67	373.0	527.0	813.0	1569
		Total	PII(D182)	54	5	483.49	331.07	1	360.0	613.0	826.0	1569
	H1N1	Flu	PII(D182)	23	3	401.26	269.67	40	280.0	453.0	653.0	1080
		NoFLU	PII(D182)	29	6	388.22	304.84	40	280.0	440.0	653.0	1184
		Total	PII(D182)	52	9	393.94	287.06	40	280.0	446.5	653.0	1184
CD4.dle INFg bkg	H1N1 +AS03	Flu	PII(D182)	30	4	534.80	224.87	240	387.0	559.5	726.0	1013
		NoFLU	PII(D182)	24	1	480.12	314.16	199	326.0	439.0	653.5	1347
		Total	PII(D182)	54	5	509.77	265.93	199	346.0	499.5	707.0	1347
	H1N1	Flu	PII(D182)	23	3	463.04	225.44	186	347.0	466.0	662.0	1053
		NoFLU	PII(D182)	29	6	421.16	271.76	67	294.0	412.0	546.0	1163
		Total	PII(D182)	52	9	439.20	250.13	67	313.5	439.5	637.5	1163
CD4.dle TNFa bkg	H1N1 +AS03	Flu	PII(D182)	30	4	130.37	226.77	1	146.0	187.0	320.0	1160
		NoFLU	PII(D182)	24	1	135.63	142.10	1	120.0	226.5	321.0	507
		Total	PII(D182)	54	5	132.68	192.51	1	133.0	187.0	320.0	1160
	H1N1	Flu	PII(D182)	23	3	72.80	101.03	1	67.0	120.0	146.0	413
		NoFLU	PII(D182)	29	6	76.14	106.00	1	80.0	107.0	174.0	427
		Total	PII(D182)	52	9	74.64	102.88	1	67.0	113.5	166.5	427

The analyses are also shown for the total vaccinated cohort and the overall findings were comparable with those for the ATP cohort.

D-PAN H1N1-008

This is 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.

The study was initiated in September 2009 and is ongoing. Currently the data obtained up to D182 are reported with a data lock of 27 May 2010.

The primary objective was:

To demonstrate that vaccination with one dose of the H1N1 vaccine (A/California/7/2009 (H1N1)v-like strain) containing 3.75 μg of HA adjuvanted with $AS03_A$ results in an HI immune response to the vaccine-homologous virus that meets or exceeds the EMEA (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.

The secondary objectives were/ are:
To evaluate the HI immune response to the vaccine-homologous virus in terms of the EMEA (CHMP) guidance targets for pandemic vaccine at 21 days after the first dose of vaccine, as a function of the pre-vaccination serostatus, in each age stratum.

To assess whether vaccination with two doses of the H1N1 vaccine (A/California/7/2009 (H1N1)v-like strain) containing 3.75 μg of HA adjuvanted with $AS03_A$ results in an HI immune response to the vaccine-homologous virus that meets or exceeds the EMEA (CHMP) guidance targets for pandemic vaccine seroconversion rate (SCR), seroprotection rate (SPR), and geometric mean fold rise (GMFR) at 21 days after the second dose of H1N1 vaccine in adults within the 18 to 60 years and above 60 years age strata.

To describe (based on point estimates and 95% CIs) the persistence of the HI vaccine-homologous response against A/California/7/2009 (H1N1)v-like antigen at Days 42, 182 and 364 after one dose of H1N1 vaccine and at Days 182 and 364 after two doses of H1N1 vaccine in adults within the 18 to 60 years and above 60 years age strata.

To describe (based on point estimates and 95% CIs) the immunogenicity to A/California/7/2009 (H1N1)v-like antigen at Day 0, 21, 42, 182 and 364 in terms of neutralising antibodies in adults in a subset of subjects within the 18 to 60 years and above 60 years age strata.

To describe the safety of the vaccine regimens in terms of solicited adverse events (AEs), 7 days post-vaccination; unsolicited AEs, 21 or 84 days post-dose 1 and 63 days post-dose 2; AEs of specific interest (AESIs) for the entire study period, serious adverse events (SAEs) for the entire study period and biochemical parameters at Day 0, 21, 42, 182 and 364.

The vaccine comprised lot n° for H1N1 = DFLSA013A and lot n° for the adjuvant = AA03A209C.

The original design of this study was amended when the first results of study H1N1-021 became available. Thus, Groups 1 and 2 were defined as shown below. Both groups are to be followed up serologically to M12 to determine whether there is any advantage for two doses over a single dose in the longer term.

The study planned to enrol 240 subjects aged at least 18 years with allocation to two parallel vaccine groups (one or two doses) with a ratio of 1:1 as follows.

Group 1, referred to as Group A in the protocol: subjects received a single dose of the $AS03_A$-adjuvanted H1N1 candidate vaccine on Day 0 (but no second vaccination on Day 21).

Group 2, referred to as Group B in the protocol: subjects received two doses of the $AS03_A$-adjuvanted H1N1 candidate vaccine, administered on Days 0 and 21 (21-day interval).

Subjects were stratified according to age (18-40, 41-60, 61-75 and > 75 years) with a ratio of 1:1:1:1.

Results

As planned, the study enrolled 240 subjects (120 aged 18-60 years and 120 aged > 60 years), of which 238 completed the D182 visit and 236 subjects were included in the ATP immunogenicity cohort. Please see the previous assessment report for details of baseline demographics and prior seasonal influenza vaccination history.

The HI data collected over time are summarised below. It should be remembered that in this study the D0 and D21 samples were tested in a separate run from the D42 samples and it should be noted that the D182 samples were tested in isolation. Note the pre-vaccination HI seropositivity rates, as commented on previously.

HI against vaccine-homologous virus up to D182 (ATP)

				≥10 1/DIL			**GMT**			**SPR**			**SCR**			**SCF**		
					95% CI			**95% CI**			**95% CI**			**95% CI**			**95% CI**	
Group	**Age**	**Timing**	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
2-Dose	**18-60**	PRE	66*	**36.4**	24.9	49.1	**8.8**	7.0	10.9	**9.1**	3.4	18.7	**-**	-	-	**-**	-	-
		PI(D21)	66	**100**	94.6	100	**339.1**	258.6	444.8	**98.5**	91.8	100	**95.5**	87.3	99.1	**38.71**	29.10	51.51
		PII (D42)	66	**100**	94.6	100	**610.6**	507.9	734.0	**100**	94.6	100	**98.5**	91.8	100	**69.70**	53.79	90.32
		PII (D182)	67	**100**	94.6	100	**214.8**	169.8	271.8	**97.0**	89.6	99.6	**94.0**	85.4	98.3	**24.73**	19.31	31.67
	>60	PRE	67*	**41.8**	29.8	54.5	**10.3**	7.7	13.7	**9.0**	3.4	18.5	**-**	-	-	**-**	-	-
		PI(D21)	67	**100**	94.6	100	**142.7**	108.5	187.8	**88.1**	77.8	94.7	**79.1**	67.4	88.1	**13.86**	10.29	18.65
		PII(D42)	67	**100**	94.6	100	**345.8**	278.0	430.1	**98.5**	92.0	100	**94.0**	85.4	98.3	**33.57**	24.87	45.31
		PII (D182)	68	**100**	94.7	100	**108.7**	85.7	137.8	**89.7**	79.9	95.8	**76.5**	64.6	85.9	**10.45**	8.24	13.24
1-Dose	**18-60**	PRE	50*	**40.0**	26.4	54.8	**8.6**	6.8	10.8	**8.0**	2.2	19.2	**-**	-	-	**-**	-	-
		PI(D21)	50	**100**	92.9	100	**388.6**	262.0	576.2	**96.0**	86.3	99.5	**94.0**	83.5	98.7	**45.30**	30.32	67.68
		PI(D42)	50	**100**	92.9	100	**331.2**	220.7	497.1	**94.0**	83.5	98.7	**92.0**	80.8	97.8	**38.62**	25.96	57.45
		PI (D182)	51	**100**	93.0	100	**143.5**	96.6	213.0	**86.3**	73.7	94.3	**82.4**	69.1	91.6	**17.14**	11.83	24.84
	>60	PRE	49*	**42.9**	28.8	57.8	**9.7**	7.3	13.0	**10.2**	3.4	22.2	**-**	-	-	**-**	-	-
		PI(D21)	49	**95.9**	86.0	99.5	**129.3**	89.9	186.0	**85.7**	72.8	94.1	**77.6**	63.4	88.2	**13.32**	9.04	19.61
		PI(D42)	49	**98.0**	89.1	99.9	**117.1**	82.4	166.4	**87.8**	75.2	95.4	**79.6**	65.7	49	**42.9**	28.8	57.8
		PI (D182)	50	**92.0**	80.8	97.8	**51.6**	34.9	76.5	**56.0**	41.3	70.0	**42.0**	28.2	56.8	**5.31**	3.73	7.56

At M6 all subjects aged 18-60 years were seropositive but the SPR, SCR and SCF (as well as the GMT) were all numerically higher in the 2-dose group. All CHMP criteria were met in both dose groups.

In subjects aged > 60 years there was a much more clear advantage for 2 doses at Month 6. The SPR at M6 after a single dose was < 60% (i.e. was lower than the CHMP criterion).

The supplementary tables to the report also show the D182 data according to baseline HI serostatus.

					>= 10 1/DIL				>= 40 1/DIL				GMT		
							95% CI				95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Flu A/CAL/7/09 H1N1.HA Ab	grp 1	18-60y-	PII(D182)	43	43	100	91.8	100	41	95.3	84.2	99.4	154.9	114.7	209.2
		>60y-	PII(D182)	39	39	100	91.0	100	33	84.6	69.5	94.1	72.6	57.3	91.9
		18-60y+	PII(D182)	24	24	100	85.8	100	24	100	85.8	100	386.1	299.1	498.5
		>60y+	PII(D182)	29	29	100	88.1	100	28	96.6	82.2	99.9	186.9	126.4	276.5
	grp 2	18-60y-	PI(D182)	32	32	100	89.1	100	25	78.1	60.0	90.7	91.1	55.9	148.4
		>60y-	PI(D182)	28	24	85.7	67.3	96.0	9	32.1	15.9	52.4	28.6	17.0	48.1
		18-60y+	PI(D182)	19	19	100	82.4	100	19	100	82.4	100	308.6	176.9	538.2
		>60y+	PI(D182)	22	22	100	84.6	100	19	86.4	65.1	97.1	109.6	69.1	174.0

As shown above, the four subjects seronegative at D182 were aged 60 and seronegative at baseline and had received a single dose.

The SPRs at D182 were lower for subjects within each age group who were seronegative at baseline compared to those of the same age who were seropositive at baseline. This observation applied in both dose groups but SPRs were much lower at D182 in the single dose group vs. the 2-dose group.

In particular, only 9/28 (32%) subjects aged > 60 who were seronegative at baseline were still seroprotected at D182 after a single dose compared to 33/39 (85%) after two doses. There was a much smaller difference between one and two doses for those who were seropositive at baseline in this age group (97% vs. 86%).

Even among the younger subjects there was a perceptible advantage in terms of SPRs for two doses in those who were seronegative at baseline (95% vs. 78%) while all those seropositive at baseline were seroprotected at d182 after one or two doses.

The SCRs and SCFs at D182 still met the CHMP criteria by age at D182 regardless of baseline serostatus but differed by age and dose as shown below.

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
Flu A/CAL/7/09 H1N1.HA Ab	grp 1	18-60y-	43	41	95.3	84.2	99.4
		>60y-	39	33	84.6	69.5	94.1
		18-60y+	24	22	91.7	73.0	99.0
		>60y+	29	19	65.5	45.7	82.1
	grp 2	18-60y-	32	25	78.1	60.0	90.7
		>60y-	28	9	32.1	15.9	52.4
		18-60y+	19	17	89.5	66.9	98.7
		>60y+	22	12	54.5	32.2	75.6

				GMFR		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
Flu A/CAL/7/09 H1N1.HA Ab (1/DIL)	grp 1	18-60y-	43	30.98	22.93	41.85
		>60y-	39	14.52	11.46	18.39
		18-60y+	24	16.52	10.97	24.88
		>60y+	29	6.71	4.41	10.22
	grp 2	18-60y-	32	18.21	11.17	29.69
		>60y-	28	5.72	3.40	9.62
		18-60y+	19	15.47	8.33	28.75
		>60y+	22	4.84	2.94	7.98

Further analysis by age sub-groups (also from supplementary tables) suggested that differences between those aged 18-40 and 41-60 years were not very marked within each dose group except for the GMTs, which showed an approximate 2-fold difference.

The sub-groups aged 61-70 and >70 years also showed no marked difference within each dose group but each showed the effect of number of doses as described above.

					>= 10 1/DIL				>= 40 1/DIL				GMT		
							95% CI				95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Flu A/CAL/7/09 H1N1.HA Ab	18y-40y	18y-40y	PII(D182)	32	32	100	89.1	100	31	96.9	83.8	99.9	303.0	226.4	405.5
	41y-60y	41y-60y	PII(D182)	35	35	100	90.0	100	34	97.1	85.1	99.9	156.9	111.4	221.1
	61y-70y	61y-70y	PII(D182)	41	41	100	91.4	100	38	92.7	80.1	98.5	107.6	79.6	145.4
		>70y	PII(D182)	27	27	100	87.2	100	23	85.2	66.3	95.8	110.3	73.0	166.7
	grp 2	18y-40y	PI(D182)	27	27	100	87.2	100	24	88.9	70.8	97.6	212.0	121.8	369.0
		41y-60y	PI(D182)	24	24	100	85.8	100	20	83.3	62.6	95.3	92.5	53.4	160.1
		61y-70y	PI(D182)	33	30	90.9	75.7	98.1	17	51.5	33.5	69.2	45.8	28.1	74.7
		>70y	PI(D182)	17	16	94.1	71.3	99.9	11	64.7	38.3	85.8	65.2	31.8	133.8

When putting baseline serostatus and age into the same table (but noting small denominators) notable differences between one or two doses administered by age sub-group occurred among those who were seronegative at baseline.

					>= 10 1/DIL				>= 40 1/DIL				GMT		
							95% CI				95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Flu A/CAL/7/09 H1N1.HA Ab	grp 1	18-40y-	PII(D182)	18	18	100	81.5	100	17	94.4	72.7	99.9	209.3	141.0	310.8
		41-60y-	PII(D182)	25	25	100	86.3	100	24	96.0	79.6	99.9	124.7	80.8	192.5
		61-70y-	PII(D182)	23	23	100	85.2	100	21	91.3	72.0	98.9	76.5	57.6	101.6
		>70y-	PII(D182)	16	16	100	79.4	100	12	75.0	47.6	92.7	67.3	43.0	105.3
		18-40y+	PII(D182)	14	14	100	76.8	100	14	100	76.8	100	487.5	355.4	668.5
		41-60y+	PII(D182)	10	10	100	69.2	100	10	100	69.2	100	278.6	188.3	412.2
		61-70y+	PII(D182)	18	18	100	81.5	100	17	94.4	72.7	99.9	166.3	95.9	288.5
		>70y+	PII(D182)	11	11	100	71.5	100	11	100	71.5	100	226.3	123.3	415.3
	grp 2	18-40y-	PI(D182)	15	15	100	78.2	100	12	80.0	51.9	95.7	129.7	59.8	281.6
		41-60y-	PI(D182)	17	17	100	80.5	100	13	76.5	50.1	93.2	66.6	34.6	128.3
		61-70y-	PI(D182)	19	16	84.2	60.4	96.6	6	31.6	12.6	56.6	26.2	14.3	48.1
		>70y-	PI(D182)	9	8	88.9	51.8	99.7	3	33.3	7.5	70.1	34.3	10.2	114.6
		18-40y+	PI(D182)	12	12	100	73.5	100	12	100	73.5	100	391.8	184.5	832.2
		41-60y+	PI(D182)	7	7	100	59.0	100	7	100	59.0	100	204.9	77.3	543.0
		61-70y+	PI(D182)	14	14	100	76.8	100	11	78.6	49.2	95.3	97.5	48.8	194.7
		>70y+	PI(D182)	8	8	100	63.1	100	8	100	63.1	100	134.5	73.9	245.1

On D182 the median frequency of CD4 T-cells was 1277.0 and 746.5 in subjects aged 18-60 years and subjects aged >60 years respectively in Group 1. In Group 2 these frequencies were 660.0 and 563.0. Similar results were obtained after stimulation by a pool of peptides spanning the whole HA sequence.

No effect of vaccination on the frequency of cytokine-positive CD8 T-cells was apparent in the two age strata in Groups 1 and 2.

Table 29 **Descriptive Statistics on the frequency influenza-specific CD4 T-cells (per million CD4 T-cells) at visit 1 Day 0 and visit 4 Day 182 stimulated by split virus antigen (ATP cohort for persistence at Month 6)**

Immune marker	Group	Sub-group	Timing	N	Nmiss	GM	Mean	SD	Min	Q1	Median	Q3	Max
CD4.All dle bkg	grp 1	18y-60y	PRE	17	0	428.13	622.18	514.41	64	272.0	466.0	949.0	2051
			PII(D182)	15	2	1106.60	1327.07	768.58	347	720.0	1277.0	1880.0	3084
		>60y	PRE	17	1	230.98	357.76	274.08	1	240.0	307.0	352.0	1188
			PII(D182)	18	0	763.76	949.61	680.80	145	462.0	746.5	1160.0	3093
	grp 2	18y-60y	PRE	13	0	369.34	529.08	530.51	51	243.0	411.0	513.0	2102
			PI(D182)	12	1	814.50	1060.50	1013.08	307	550.0	660.0	1153.5	4021
		>60y	PRE	11	0	264.16	420.73	308.42	24	96.0	353.0	686.0	951
			PI(D182)	11	0	508.24	667.18	622.91	124	367.0	563.0	675.0	2452

Descriptive Statistics on the frequency influenza-specific CD4 T-cells (per million CD4 T-cells) at visit 1 Day 0 and visit 4 Day 182 stimulated by peptides (ATP cohort for persistence at Month 6)

Immune marker	Group	Sub-group	Timing	N	Nmiss	GM	Mean	SD	Min	Q1	Median	Q3	Max
CD4.All dle bkg	grp 1	18y-60y	PRE	17	0	35.07	98.41	96.29	1	14.0	69.0	171.0	271
			PII(D182)	15	2	1335.26	1418.60	518.58	800	1013.0	1227.0	1720.0	2398
		>60y	PRE	17	1	60.13	106.47	73.74	1	51.0	95.0	169.0	235
			PII(D182)	18	0	2157.47	2441.39	1431.09	958	1628.0	2239.5	2627.0	6689
	grp 2	18y-60y	PRE	13	0	64.91	125.00	130.92	1	41.0	97.0	140.0	502
			PI(D182)	12	1	1178.42	1356.92	656.98	310	1046.5	1406.5	1587.0	2797
		>60y	PRE	11	0	19.98	76.82	81.83	1	1.0	43.0	147.0	224
			PI(D182)	11	0	2759.84	3360.18	2483.00	813	1867.0	2781.0	4155.0	10021

Clinical Safety

Data to M6 from both studies

The safety and reactogenicity analysis for studies D-Pan-H1N1-007 and D-Pan-H1N1-008 was performed on the TVC and includes:

Unsolicited AEs reported up to D84
SAEs reported up to Day 182.

No deaths have been reported from either study up to D182 (Month 6).

In D-Pan-H1N1-007, one SAE (migraine reported by a 41 year old male in the non-adjuvanted H1N1 vaccine group) was reported which was considered as not related to vaccination by the investigator.

In study D-Pan-H1N1-008 11 subjects reported 12 SAEs up to Day 182. None of these SAEs were considered by the investigator as related to vaccination.

No AESIs or potential Immune-Mediated-Diseases (pIMDs) were reported during the study period up to D182 in either study.

There were no AEs leading to premature discontinuation from study D-Pan-H1N1-007. In study D-Pan-H1N1-008, one subject was withdrawn due to an SAE (diagnosed with breast cancer 116 days after Dose 2).

Across both studies, the overall incidence of AEs up to D84 was comparable between adjuvanted- and non-adjuvanted vaccines in study 007 (60.9% and 57.6%, respectively) and between 1-dose and 2-dose schedules in subjects aged 18-60 years in study 008 (75.0% and 66.2%, respectively). Subjects

aged >60 years displayed comparable rates of AEs in study 008 (60.0% and 65.7% in the 1-dose and 2-dose schedules, respectively).

There was no particular signal or clinical pattern of unsolicited AEs observed. Most seem very likely to reflect intercurrent illnesses.

Among adjuvanted vaccine recipients there were two cases of lymphadenopathy in study 007 and one in study 008 (2-dose schedule) plus one case in a plain HA recipient in study 007.

Incidences of grade 3 reports were generally comparable across groups.

Related events were reported at frequencies of 18.8% and 10.6% in adjuvanted and non-adjuvanted groups from study 007, and in 17.3% and 22.1% of subjects aged 18-60 from study 008. In the latter study, related AEs were reported by 14.0% of elderly subjects from the 1-dose schedule group and by 14.3% of elderly subjects from the 2-dose schedule group.

3.3 Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/ 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 section 4.2:
A statement in the sub-section on adults 18 years and older was included to refer to section 5.1 regarding immune responses to one and two doses of Pandemrix (H1N1)v, including antibody levels after 6 months, as the persistence data showed a different pattern in elderly than in adults.

SmPC section 5.1
This section was updated to also mention the baseline seronegative subsets for the 6-month persistence results and to present the data in tabulated format.

3.4 Results and Discussion

The CHMP agreed that the above data up to M6 from these studies show:

- An advantage in terms of HI and CMI data for Pandemrix over plain HA in subjects aged 18-60 years when each was given for 2 doses 21 days apart. 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.

- An advantage in terms of HI data for two doses of adjuvanted vaccine over one dose. The effect was detectable throughout the datasets (if only for selected parameters) but it was especially notable for those who were seronegative at baseline and aged > 60 years. However, the CMI data did not consistently suggest an advantage for two doses.

There are no SNA data available and no effectiveness estimates for one vs. two doses. It is not currently possible to discern whether the observed differences in HI response at M6 have implications for protection.

On this basis, the CHMP agreed that the findings should be reflected in section 5.1 but has no grounds to request any change to the dose recommendations in Section 4.2, besides a reference to section 5.1

in the sub-section on adults. Nevertheless, since public health decisions regarding dose regimens would likely take into account those least likely to respond and since routine baseline serostatus determination is not feasible it is recommended that the HI data should be mentioned for those who were seronegative at baseline as well as overall.

Overall there was no new safety concern raised by the additional safety data collected.

4. Conclusion

On 16 December 2010 the CHMP considered the following variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.