European Medicines Agency

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CHMP VARIATION ASSESSMENT REPORT

Invented name/Name: Pandemrix
International non-proprietary name/Common name: pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) a/california/7/2009 (H1N1)v like strain (X-179A)

TYPE II VARIATION: EMEA/H/C/000832/II/0019

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

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 (SPC) 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 declaration of the pandemic by the World Health Organisation (WHO), the MAH applied for a strain change to include the pandemic H1N1v strain.

The currently approved vaccine contains split influenza virus with a haemagglutinin content equivalent to 3.75 micrograms derived from A/California/7/2009 (H1N1)v-like strain (X-179A). The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

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

The MAH applied to update sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) for Pandemrix H1N1 to reflect newly available results from a clinical study in adults 18-60 years of age (D-PAN-H1N1-007, called "H1N1-007" in this report).

In submitting the above mentioned data from study H1N1-007 the MAH also fulfilled the Specific Obligation to provide an abridged report for: post dose 1 data from study H1N1-007 (adults 18-60 yrs-immunogenicity data+ solicited and unsolicited symptoms, SAEs).

1.2 Clinical aspects

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 haemagglutinin HA (3.75 µg) adjuvanted with AS03= 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 MAH provided for this variation a synoptic report of preliminary post-dose 1 immunogenicity results based on non-cleaned data from the total enrolled cohort. Subsequent analyses will be performed after data will become available for Day 42, Day 182 and Day 364 as part of specific obligations (SO) committed by the MAH in the Letter of Undertaking for the pandemic strain variation (PU-017).

1.2.1 Study design

The primary objective of the study is:
To demonstrate that two doses of vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like strain with ASO3 (Pandemrix (H1N1)) results in an HI immune response to vaccine-homologous virus that meets or exceeds the CHMP criteria applied to seasonal influenza vaccines.
Secondary: objectives are:

- To assess whether vaccination with Pandemrix (H1N1) results in an HI immune response to the vaccine-homologous virus that meets or exceeds CHMP guidance targets for pandemic vaccine seroconversion rate (SCR), seroprotection rate (SPR), and geometric mean fold rise (GMFR) 21 days after the first and the second dose of H1N1 vaccine in adults 18 to 60 years of age and within each age stratum (18 to 40 years and 41 to 60 years and within the 41-50 and 51-60 years substrata).

- To assess the immune response of the A/California/7/2009 (H1N1)v-like antigen containing 15 µg of HA in terms of vaccine-homologous virus HI response 21 days after each dose of H1N1 vaccine in adults 18 to 60 years of age and within each age stratum (18 to 40 years and 41-60 years and within the 41-50 and 51-60 years substrata).
- To describe (based on point estimates and 95% confidence intervals (CIs)) immunogenicity to vaccine-homologous A/California/7/2009 (H1N1)v-like antigen (both groups) in terms of HI at Day 0, 21, 42, 182 and 364 in adults 18-60 years of age and in each age stratum (18 to 40 years, 41-60 years and within the 41-50 and 51-60 years substrata)
- To describe (based on point estimates and 95% CIs) immunogenicity to A/California/7/2009 (H1N1)v-like antigen (both groups) at Day 0, 21, 42, 182 and 364 based on neutralizing antibodies in adults 18-60 years of age and in each of the age strata (18-40 years, 41-60 years and within the 41-50 and 51-60 years substrata).
- To describe the safety of the vaccine regimens in terms of solicited adverse events (AEs) 7 days post-vaccination, unsolicited AEs 21 days post-dose 1 and 63 days post-dose 2, AEs of specific interest (AESIs) for the entire study period, and serious adverse events (SAEs) for the entire study period in both treatment groups.

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

Blood samples for evaluation of haemagglutination inhibition (HI) antibody immune response are drawn prior to vaccination ("day 0") and at days 21, 42, 182 and 364 after the first vaccination.

HI antibody titres are measured based on the method described by the World Health Organization Collaborating Centre for Influenza, Centres for Disease Control, Atlanta, USA (1991) and modified according to *Stephenson et al. 2004*.

All HI assays are performed in duplicate in the same run. Assay variability is controlled by the use of control sera included in each run. The results obtained for the controls have to meet acceptance criteria. If the acceptance criteria are not fulfilled the assay run has to be repeated. Subjects with titres below the detection limit (1:10) are considered seronegative. A titre ≥ 1:40 is considered as seroprotective.

Descriptive analyses of the immune response in terms of HI antibodies are performed for each age group 18-40 years and 41-60 years as well as for the sub-strata of 41-50 years and 51-60 years.

The Total Vaccinated Cohort includes all vaccinated subjects for whom safety data are available. For the total analysis of immunogenicity, this includes vaccinated subjects of the immunogenicity subset for whom data concerning immunogenicity endpoint measures are available.

The “according-to-protocol” (ATP) cohort for analysis of immunogenicity includes all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) from the ATP cohort for safety for whom 2 doses are received and assay results are available for the blood sample taken 21 days after the second vaccine dose (i.e. at D42).

The analysis of immunogenicity presented in this variation procedure was performed on the total enrolled cohort in order to provide preliminary post dose 1 results based on non-cleaned data.

1.2.2 Results

Demography

The mean age at the time of the first vaccination was 38.6 +/- 13.78 years (mean +/- SD) for all subjects. Mean ages were 26.2 ± 6.40 years for subjects randomised to the 18-40 years age stratum and 51.0 ± 5.31 for subjects randomised to the 41-60 years age stratum. Females outnumbered males in this study.

Table 1: Number of subjects enrolled in study H1N1-007 (Total Enrolled cohort)

Number of subjects enrolled	H1N1+ ASO3	H1N1	Total
All ages – 18-60 years	64	66	130
18-40 years	32	33	65
41-60 years	32	33	65

Table 2: patient characteristics of subjects Enrolled in study H1N1-007

		All ages 18 -60 years					
		H1N1 +ASO3 N = 64		H1N1 N = 66		Total N = 130	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years)	Mean	39.1	-	38.2	-	38.6	-
	SD	13.53	-	14.10	-	13.78	-
	Median	40.5	-	40.5	-	40.5	-
	Minimum	19	-	18	-	18	-
	Maximum	60	-	60	-	60	-
Gender	Female	41	64.1	39	59.1	80	61.5
	Male	23	35.9	27	40.9	50	38.5
Ethnicity	White - Caucasian/ European heritage	64	100	65	98.5	129	99.2
	Asian - east asian heritage	0	0.0	1	1.5	1	0.8

Immunogenicity data

The HI humoral immune responses observed 21 days following the first dose of each vaccine formulation exceeded the CHMP criteria (seroconversion rate (SCR), seroconversion factor (SCF) and seroprotection rate (SPR)) and the FDA CBER criteria (lower limit of 95% CI of SCR and SPR) as shown in the table below. These criteria were also met in both age strata (18-40 years and 41-60 years). Supplementary tables show the criteria were also met in the two cohorts 41-50 and 51-60 years.

Table 3: HI antibody response against A/California/7/2009 (H1N1)v-like in study D-Pan-H1N1-007 (ATP cohort immunogenicity)

				≥10 1/DIL			GMT			SPR			SCR			SCF		
					95% CI			95% CI			95% CI			95% CI			95% CI	
Study group	**Age stratum**	**Timing**	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
H1N1 + $AS03_A$	**All ages -18-60 years**	PRE	64	**32.8**	21.6	45.7	**8.6**	6.9	10.9	**9.4**	3.5	19.3	-	-	-	-	-	-
		PI(D21)	61	**100**	94.1	100	**384.0**	285.1	517.1	**100**	94.1	100	**96.7**	88.7	99.6	**43.3**	31.8	59.0
	18-40 years	PRE	32	**21.9**	9.3	40.0	**7.1**	5.5	9.4	**6.3**	0.8	20.8	-	-	-	-	-	-
		PI(D21)	29	**100**	88.1	100	**561.2**	371.9	846.9	**100**	88.1	100	**100**	88.1	100	**75.7**	52.1	110.0
	41-60 years	PRE	32	**43.8**	26.4	62.3	**10.4**	7.1	15.2	**12.5**	3.5	29.0	-	-	-	-	-	-
		PI(D21)	32	**100**	89.1	100	**272.2**	180.5	410.6	**100**	89.1	100	**93.8**	79.2	99.2	**26.1**	17.1	39.8
H1N1	**All ages -18-60 years**	PRE	66	**42.4**	30.3	55.2	**10.7**	8.1	14.1	**18.2**	9.8	29.6	-	-	-	-	-	-
		PI(D21)	66	**98.5**	91.8	100	**331.9**	232.4	474.2	**93.9**	85.2	98.3	**84.8**	73.9	92.5	**31.0**	21.5	44.7
	18-40 years	PRE	33	**45.5**	28.1	63.6	**13.0**	8.1	20.9	**24.2**	11.1	42.3	-	-	-	-	-	-
		PI(D21)	33	**100**	89.4	100	**640.0**	423.8	966.5	**97.0**	84.2	99.9	**87.9**	71.8	96.6	**49.2**	29.1	83.4
	41-60 years	PRE	33	**39.4**	22.9	57.9	**8.8**	6.6	11.8	**12.1**	3.4	28.2	-	-	-	-	-	-
		PI(D21)	33	**97.0**	84.2	99.9	**172.2**	103.8	285.5	**90.9**	75.7	98.1	**81.8**	64.5	93.0	**19.5**	12.1	31.6

H1N1+ $AS03_A$ = H1N1 containing antigen-sparing dose of HA (3.75 µg) +$AS03_A$ adjuvant;
H1N1 = H1N1 containing higher dose HA antigen (15 µg) without adjuvant;
N = number of subjects with available results; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit;
PRE = Pre-vaccination at Day 0; PI(21) = Post-vaccination at Day 21;
SCR = Seroconversion rate defined as: For initially seronegative subjects, antibody titer ≥ 40 after vaccination; For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer; N = Number of subjects with pre- and post-vaccination results available; SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]); SPR = percentage of vaccinees with serum H1N1 HI antibody titer ≥1:40

HI responses were better in the younger age cohort (18-40 years) compared to the older cohort (41-60 years) although the difference is apparent only in terms of the geometric mean titres (GMTs). There was also a suggestion from the overall data that this effect of age was more marked in the group that received unadjuvanted vaccine compared to the AS03-adjuvanted group.

The amplitude of the HI immune responses observed at Day 21 with ASO3–adjuvanted vaccine was at least as high as with the non-adjuvanted vaccine formulation containing the higher antigen dose. HI responses were numerically better in the AS03-adjuvanted vaccine group in the older age cohort whereas there was not a difference in the younger subjects. For example, GMTs in the 18-40 years group were 561 in the AS03 group and 640 in the unadjuvanted group (and in each case much higher in those seropositive at baseline) whereas GMTs in those aged 51-60 years were 190.5 and 98 in respective groups, again with higher values in those already seropositive at baseline.

The supplementary tables below provide a further breakdown by age 18-40, 41-50 and 51-60 years including baseline serostatus.

At D0, 37.7% of the 130 subjects were already seropositive (titre ≥ 1:10) for HI antibodies against A/California/7/2009(H1N1) even though subjects were excluded from the study if they had clinically or virologically confirmed influenza within 6 months of D0. The seropositivity rates against A/California/7/2009 (H1N1) did not show a consistent trend to increase with age.

Table 4: Seropositive rates against A/California/7/2009 (H1N1) per age strata at D0

Age strata	Number seropositive subjects per age strata	Percentage of seropositive subjects in the study
18-40 years	22	33.8%
41-60 years	27	41.5%
41-50 years	17	53.1%
51-60 years	10	30.3%

In addition, before vaccination the overall seroprotection rates were up to 24% in the vaccine/age sub-groups but there was no consistent trend to higher rates with increasing age.

At D21 the overall data showed that GMTs were higher in those who had been seropositive at baseline and supplementary tables showed that this observation applied in each of the age cohorts 18-40, 41-50 and 51-60 years. However, these differences in GMTs did not have any appreciable effect on the SPRs according to baseline status in any age group among subjects that received the adjuvanted vaccine.

Table 5: Seropositivity rates and GMTs by pre-vaccination status (Total Enrolled cohort)

					≥ 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	**Group**	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Flu A/CAL/09.HA1 Ab	H1N1+ AS03	S-	PRE	43	0	0.0	0.0	8.2	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	40	40	100	91.2	100	283.6	199.7	402.7	40.0	2560.0
		S+	PRE	21	21	100	83.9	100	26.4	17.8	39.1	10.0	226.0
			PI(D21)	21	21	100	83.9	100	684.0	418.0	1119.3	57.0	5120.0
		Total	PRE	64	21	32.8	21.6	45.7	8.6	6.9	10.9	<10.0	226.0
			PI(D21)	61	61	100	94.1	100	384.0	285.1	517.1	40.0	5120.0
	H1N1	S-	PRE	38	0	0.0	0.0	9.3	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	38	37	97.4	86.2	99.9	216.1	136.6	342.1	<10.0	2560.0
		S+	PRE	28	28	100	87.7	100	30.1	20.0	45.3	10.0	320.0
			PI(D21)	28	28	100	87.7	100	594.2	354.1	997.2	40.0	7240.0
		Total	PRE	66	28	42.4	30.3	55.2	10.7	8.1	14.1	<10.0	320.0
			PI(D21)	66	65	98.5	91.8	100	331.9	232.4	474.2	<10.0	7240.0

The seroconversion rates (and the seroconversion factors (SCFs)) were slightly affected according to baseline status as would be expected. The overall rates are shown below.

Table 6: Seroconversion rate (SCR) at PI (D21) (Total Enrolled cohort)

					SCR			
							95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/09.HA1 Ab	H1N1+ AS03	S-	PI(D21)	40	40	100	91.2	100
		S+	PI(D21)	21	19	90.5	69.6	98.8
		Total	PI(D21)	61	59	96.7	88.7	99.6
	H1N1	S-	PI(D21)	38	34	89.5	75.2	97.1
		S+	PI(D21)	28	22	78.6	59.0	91.7
		Total	PI(D21)	66	56	84.8	73.9	92.5

In addition the data for the oldest cohort (aged 51-60 years) according to baseline status are shown below since this group had the lowest GMTs. These data demonstrate that the lower GMTs did not impact on satisfaction of CHMP criteria, which were exceeded in both vaccine groups regardless of baseline serostatus.

Table 7: SCF (Total Enrolled cohort, aged 51-60 years)

				SCF		
					95% CI	
Group	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
H1N1+ AS03	S-	PI(D21)	10	21.1	11.8	37.8
	S+	PI(D21)	6	19.1	3.0	121.6
	Total	PI(D21)	16	20.4	10.8	38.5
H1N1	S-	PI(D21)	13	14.4	6.0	34.1
	S+	PI(D21)	4	17.5	1.2	264.6
	Total	PI(D21)	17	15.0	7.2	31.7

Table 8: Seropositivity rates and GMTs (Total Enrolled cohort, aged 51-60 years)

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
	Group	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
	H1N1+ AS03	S-	PRE	10	0	0.0	0.0	30.8	5.0	5.0	5.0
			PI(D21)	10	10	100	69.2	100	105.7	59.1	189.0
		S+	PRE	6	6	100	54.1	100	26.6	8.0	88.9
			PI(D21)	6	6	100	54.1	100	508.6	124.3	2081.4
		Total	PRE	16	6	37.5	15.2	64.6	9.4	5.3	16.5
			PI(D21)	16	16	100	79.4	100	190.5	96.8	374.9
	H1N1	S-	PRE	13	0	0.0	0.0	24.7	5.0	5.0	5.0
			PI(D21)	13	12	92.3	64.0	99.8	71.8	30.2	170.7
		S+	PRE	4	4	100	39.8	100	15.4	5.4	43.7
			PI(D21)	4	4	100	39.8	100	269.1	40.9	1769.9
		Total	PRE	17	4	23.5	6.8	49.9	6.5	4.9	8.7
			PI(D21)	17	16	94.1	71.3	99.9	98.0	46.2	207.8

Table 9: SCRs (Total Enrolled cohort, aged 51-60 years)

				SCR			
						95% CI	
Group	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
H1N1+ AS03	S-	PI(D21)	10	10	100	69.2	100
	S+	PI(D21)	6	5	83.3	35.9	99.6
	Total	PI(D21)	16	15	93.8	69.8	99.8
H1N1	S-	PI(D21)	13	10	76.9	46.2	95.0
	S+	PI(D21)	4	3	75.0	19.4	99.4
	Total	PI(D21)	17	13	76.5	50.1	93.2

Table 10: SPRs (Total Enrolled cohort, aged 51-60 years)

				SPR			
						95% CI	
Group	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
H1N1+ AS03	S-	PRE	10	0	0.0	0.0	30.8
		PI(D21)	10	10	100	69.2	100
	S+	PRE	6	2	33.3	4.3	77.7
		PI(D21)	6	6	100	54.1	100
	Total	PRE	16	2	12.5	1.6	38.3
		PI(D21)	16	16	100	79.4	100
H1N1	S-	PRE	13	0	0.0	0.0	24.7
		PI(D21)	13	10	76.9	46.2	95.0
	S+	PRE	4	1	25.0	0.6	80.6
		PI(D21)	4	4	100	39.8	100
	Total	PRE	17	1	5.9	0.1	28.7
		PI(D21)	17	14	82.4	56.6	96.2

Of the 130 enrolled subjects, 49.2% reported having received at least one seasonal influenza vaccination in the previous three seasons. Analysis of the Day 21 HI antibody results showed no substantial impact of prior seasonal vaccination on the HI GMTs with baseline values between 8.0 and 11.5 and post-vaccination between 235.2 and 514.6. In addition, the SCRs, SCFs and SPRs did not seem to be affected within each vaccine group by previous seasonal vaccination and they all met the CHMP criteria regardless of vaccination history. This analysis was also shown in supplementary tables for the age strata and the same conclusions applied to HI responses according to pre-vaccination history.

Table 11: HI antibodies according to previous seasonal vaccination and by pre-vaccination status in study H1N1-007 (Total Enrolled cohort)

				SCR			SCF			SPR		
					95% CI			95% CI			95% CI	
Group	**Sub-group**	**Timing**	**N**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
H1N1-AS03	Pre-vacc FLU	Prevaccination	37	-	-	-	-	-	-	10.8	3.0	25.4
		PI(D21)	34	94.1	80.3	99.3	31.7	20.0	50.3	100	89.7	100
	No Pre-vacc FLU	Prevaccination	27	-	-	-	-	-	-	7.4	0.9	24.3
		PI(D21)	27	100	87.2	100	64.1	44.5	92.3	100	87.2	100
H1N1	Pre-vacc FLU	Prevaccination	27	-	-	-	-	-	-	22.2	8.6	42.3
		PI(D21)	27	81.5	61.9	93.7	20.4	12.0	34.7	92.6	75.7	99.1
	No Pre-vacc FLU	Prevaccination	39	-	-	-	-	-	-	15.4	5.9	30.5
		PI(D21)	39	87.2	72.6	95.7	41.4	25.2	68.0	94.9	82.7	99.4

Clinical safety

Post Dose 1 solicited and unsolicited symptoms based on the total enrolled cohort (non-cleaned data) have also been provided by the MAH for this variation. The four tables below summarise the reporting rates for local and general solicited symptoms in the week post-dose 1.

Table 12: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0- 6) post-vaccination period (Total Enrolled cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
H1N1+ AS03	64	59	92.2	82.7	97.4	64	37	57.8	44.8	70.1	64	56	87.5	76.8	94.4
H1N1	66	39	59.1	46.3	71.0	66	29	43.9	31.7	56.7	66	23	34.8	23.5	47.6

Table 13: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period (Total Enrolled cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
H1N1+ AS03	64	4	6.3	1.7	15.2	64	4	6.3	1.7	15.2	64	1	1.6	0.0	8.4
H1N1	66	2	3.0	0.4	10.5	66	2	3.0	0.4	10.5	66	0	0.0	0.0	5.4

Table 14: Symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period (Total Enrolled cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
H1N1+ AS03	64	58	90.6	80.7	96.5	64	33	51.6	38.7	64.2	64	56	87.5	76.8	94.4
H1N1	66	34	51.5	38.9	64.0	66	24	36.4	24.9	49.1	66	23	34.8	23.5	47.6

There were two general and one local symptom of grade 3 (on a scale of 1-3) considered to be related to vaccination.

More subjects reported solicited local symptoms with the ASO3 adjuvanted vaccine formulation. In particular, pain at the injection site (90.3% adjuvanted versus 37.1% unadjuvanted) was the predominant solicited local symptom in each vaccine group but was much more common with AS03. Swelling and redness were only reported with the adjuvanted formulation (6.5% and 1.6% respectively). Most reports of pain were Grade 1 on a scale of 1-3. There was only one report of grade 3 pain (after ASO3 adjuvanted vaccine) and no grade 3 redness or swelling was reported. Most local symptoms lasted 1-3 days.

Table 15: Percentage of doses followed by solicited local symptoms (all and Grade 3) during the 7-day post-Dose 1 period (Total enrolled cohort)

		H1N1+AS03					H1N1				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Pain	**All**	62	56	**90.3**	80.1	96.4	62	23	**37.1**	25.2	50.3
	Grade 3	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
Redness (mm)	**All**	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
	Grade 3	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
Swelling (mm)	**All**	62	4	**6.5**	1.8	15.7	62	0	**0.0**	0.0	5.8
	Grade 3	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8

Fatigue and muscle aches were the predominant solicited general symptoms in each vaccine group, followed by headache and joint pain. Higher incidences were noted with ASO3 vaccine for muscle aches (33.9% versus 11.3%), headache (27.4%% versus 17.7%) and joint pain (11.3% versus 6.5%). Fever (any above 380C) was not reported in any subject in either vaccine group. Grade 3 solicited general symptoms were infrequently reported (maximum one report per symptom type) in both vaccine groups.

Table 16: Percentage of doses followed by solicited general symptoms (Total enrolled cohort)

		H1N1+AS03					H1N1				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Post Dose 1											
Fatigue	**All**	62	21	**33.9**	22.3	47.0	62	18	**29.0**	18.2	41.9
	Grade 3	62	0	**0.0**	0.0	5.8	62	1	**1.6**	0.0	8.7
	Related	62	20	**32.3**	20.9	45.3	62	16	**25.8**	15.5	38.5
	Grade 3*Related	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
Headache	**All**	62	17	**27.4**	16.9	40.2	62	11	**17.7**	9.2	29.5
	Grade 3	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
	Related	62	15	**24.2**	14.2	36.7	62	8	**12.9**	5.7	23.9
	Grade 3*Related	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
Joint pain at other location	**All**	62	7	**11.3**	4.7	21.9	62	4	**6.5**	1.8	15.7
	Grade 3	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
	Related	62	7	**11.3**	4.7	21.9	62	3	**4.8**	1.0	13.5
	Grade 3*Related	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
Muscle aches	**All**	62	21	**33.9**	22.3	47.0	62	7	**11.3**	4.7	21.9
	Grade 3	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
	Related	62	21	**33.9**	22.3	47.0	62	5	**8.1**	2.7	17.8
	Grade 3*Related	62	1	**1.6**	0.0	8.7	62	0	**0.0**	0.0	5.8
Shivering	**All**	62	5	**8.1**	2.7	17.8	62	4	**6.5**	1.8	15.7
	Grade 3	62	0	**0.0**	0.0	5.8	62	1	**1.6**	0.0	8.7
	Related	62	5	**8.1**	2.7	17.8	62	2	**3.2**	0.4	11.2
	Grade 3*Related	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
Sweating	**All**	62	6	**9.7**	3.6	19.9	62	6	**9.7**	3.6	19.9
	Grade 3	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8
	Related	62	6	**9.7**	3.6	19.9	62	5	**8.1**	2.7	17.8
	Grade 3*Related	62	0	**0.0**	0.0	5.8	62	0	**0.0**	0.0	5.8

The incidence of unsolicited AEs after the first vaccine dose in the ASO3 adjuvanted H1N1 vaccine group and in the non-adjuvanted vaccine group was comparable (35.9% and 34.8%, respectively). Overall, unsolicited AEs reported after the first vaccination up Day 21 showed no particular signal or clinical pattern in any vaccine group.

Table 17: Global Summary of unsolicited signs and symptoms reported within the 21-day (Days 0-20) post-vaccination period (Total Enrolled cohort)

	Group		
	H1N1+ AS03	**H1N1**	**Total**
Number of subjects with at least one unsolicited symptom reported	23	23	46
Number of doses followed by at least one unsolicited symptom	23	23	46
Number of unsolicited symptoms classified by MedDRA Preferred Term*	30	28	58
Number of unsolicited symptoms reported	31	28	59

Upper respiratory tract infection, headache, rhinitis, oropharyngeal pain and diarrhoea were the most frequently reported unsolicited AEs in the ASO3 adjuvanted group and the non-adjuvanted group.

Two cases of lymphadenopathy were reported in the ASO3 adjuvanted H1N1 vaccine group versus zero in the non-adjuvanted study vaccine group.

The incidence of unsolicited AEs assessed as causally related to the vaccination by the investigator was relatively low and comparable in the two study groups (8%).

Table 18: Percentage of subjects with unsolicited AEs with causal relationship to vaccination, classified by MedDRA System Organ Class and Preferred Term, within the 21-day post-vaccination period at post Dose 1 in study H1N1-007 (Total Enrolled cohort)

		H1N1+ AS03 N = 64				**H1N1 N = 66**			
				95% CI				**95% CI**	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		***5***	***7.8***	***2.6***	***17.3***	***5***	***7.6***	***2.5***	***16.8***
---------- ( )	---------- ( )	0	0.0	0.0	5.6	1	1.5	0.0	8.2
Blood and lymphatic system disorders (10005329)	Lymphadenopathy (10025197)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	5.6	1	1.5	0.0	8.2
	Diarrhoea (10012735)	0	0.0	0.0	5.6	2	3.0	0.4	10.5
	Nausea (10028813)	2	3.1	0.4	10.8	1	1.5	0.0	8.2
General disorders and administration site conditions (10018065)	Feeling hot (10016334)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Oedema peripheral (10030124)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Musculoskeletal and connective tissue disorders (10028395)	Musculoskeletal stiffness (10052904)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Respiratory, thoracic and mediastinal disorders (10038738)	Oropharyngeal pain (10068319)	1	1.6	0.0	8.4	0	0.0	0.0	5.4

Five subjects in each study group (8%) reported at least one Grade 3 unsolicited AE. Among these, there was one case of Grade 3 lymphadenopathy reported following ASO3 adjuvanted H1N1 vaccine considered to be vaccine-related.

Table 19: Percentage of subjects with grade 3 unsolicited AEs classified by MedDRA System Organ Class and Preferred Term, within the 21-day post-vaccination period at post Dose 1 in study H1N1-007 (Total Enrolled cohort)

		H1N1+ AS03 N = 64				H1N1 N = 66			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		***5***	***7.8***	***2.6***	***17.3***	***5***	***7.6***	***2.5***	***16.8***
---------- ( )	---------- ( )	0	0.0	0.0	5.6	1	1.5	0.0	8.2
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Toothache (10044055)	0	0.0	0.0	5.6	1	1.5	0.0	8.2
	Vomiting (10047700)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
General disorders and administration site conditions (10018065)	Influenza like illness (10022004)	1	1.6	0.0	8.4	1	1.5	0.0	8.2
Infections and infestations (10021881)	Gastroenteritis (10017888)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Pharyngitis (10034835)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Upper respiratory tract infection (10046306)	1	1.6	0.0	8.4	1	1.5	0.0	8.2
Injury, poisoning and procedural complications (10022117)	Muscle strain (10050031)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Nervous system disorders (10029205)	Migraine (10027599)	0	0.0	0.0	5.6	1	1.5	0.0	8.2

Serious Adverse Events (SAEs)
No deaths were reported up to Day 21. One SAE, a case of migraine was reported, which was considered not related to vaccination. None of the AEs or SAE led to study withdrawal through Day 21.

Concomitant medication
The incidence of any concomitant medication received after the first dose in the AS03 adjuvanted vaccine group was within the same range as the incidence in the non-adjuvanted higher antigen dose group (35.9% and 30.3% of subjects, respectively). The incidence of any antipyretic medication in the adjuvanted and the non-adjuvanted vaccine group was 28.1% and 21.2%.

"Prophylactic" antipyretic medication was received by four subjects (6.3%) in the ASO3 adjuvanted H1N1 group and one subject (1.5%) in the non-adjuvanted higher antigen dose group. It is not clear why this was taken before a first dose. As already reported there were no subjects with a fever of 38^0C or above in this study. Since the majority did not take antipyretics before or after vaccination it seems unlikely that there would have been a substantial rate of fever even if no subject took an antipyretic.

Table 20: Incidence of concomitant medication during the 21-day post-Dose 1 period in study H1N1-007 (Total Enrolled cohort)

	H1N1+ AS03					H1N1				
				95% CI					95% CI	
	N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Any	64	23	**35.9**	24.3	48.9	66	20	**30.3**	19.6	42.9
Any antipyretic	64	18	**28.1**	17.6	40.8	66	14	**21.2**	12.1	33.0
Prophylactic antipyretic	64	4	**6.3**	1.7	15.2	66	1	**1.5**	0.0	8.2

1.3 Conclusion and benefit-risk assessment

The CHMP considered that the new data from study H1N1- 007 related to use of Pandemrix are in keeping with the results of study H1N1- 021 in which the vaccine used contained a slightly higher amount of HA and was included as preliminary data in the SPC for Pandemrix at the time of the granting of the pandemic strain variation (PU-017). Based on the data from study H1N1-007 the current SPC advice regarding the possibility of using a single dose in adults aged from 18-60 years is supported. The changes to the SPC to remove the references to data with the investigational formulation with a higher HA content from 4.2 and to replace the data in 5.1 from study H1N1-021 with those from H1N1-007 are supported.

In reaching this conclusion the CHMP took into account that the baseline serostatus of the subjects in study H1N1-007 was generally comparable with that observed in the subjects in study H1N1-021 (post day 21 results assessed within the pandemic strain variation PU-017) and that, although there was some difference in HI GMTs according to baseline serostatus, especially in the older subjects, there was no impact on satisfaction of the CHMP criteria.

The CHMP also took into account that the safety profile described with Pandemrix in study H1N1-007 is entirely in keeping with that described in H1N1-021 submitted earlier and also with the data for H5N1/AS03 vaccine, supporting the previous conclusions that the presence of the adjuvant is more influential than the HA content in terms of the reactogenicity profile.

Nevertheless, the CHMP reiterated that it remains possible that there could be advantages for a second dose. Even if the immediate HI response to Pandemrix is highly satisfactory across the entire age range 18-60 years there could be advantages for a second dose in terms of antibody persistence and also in terms of antibody against drifted variants. Indeed, the existing H5N1 data would suggest that this might be the case.

Therefore the NA data and the post-dose 2 HI and NA data are considered to be important even though all the current data support leaving the advice in the SPC as it stands.

Submission of the further data from this study is included in the Specific Obligations agreed during the assessment of the pandemic strain variation PU-017 and will be dealt with in sequential assessment reports.

The CHMP further concluded that the changes to the instructions for mixing and administration of the vaccine in the SPC and PL and the amendment to the Labelling (outer packaging) in line with these changes are acceptable and provide more clarity especially in view of administration of a half dose of the vaccine.

1.4 Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/Annex II/ Labelling/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.

SPC section 5.1 Pharmacodynamic properties
The table that presented the immune response to Pandemrix (H1N1) in adults aged 18-60 years from study H1N1-007 was updated to present the Seroprotection rate, Seroconversion rate and Seroconversion factor also for the subjects seronegative at baseline as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like	
	21 days after 1st dose	
	Total enrolled subjects N=61 [95% CI]	Seronegative subjects prior to vaccination N=40 [95% CI]
Seroprotection rate[1]	100% [94.1;100]	100% [91.2;100]
Seroconversion rate[2]	96.7% [88.7;99.6]	100% [91.2;100]
Seroconversion factor[3]	43.3 [31.8;59.0]	56.7 [39.9;80.5]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40; [2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Section 6.5 "Nature and contents of container"
In this section, the reference to "10 x 0.25 ml doses" was deleted to provide more clarity.

Section 6.6 "Special precautions for disposal and other handling"
The sub-section on Instructions for mixing and administration of the vaccine was revised in view of the recommendation to allow the reconstituted vial to reach room temperature before use and to give better guidance when a half dose of the vaccine (0.25 ml) is given. In addition, the recommendation to use one needle for withdrawal and one needle for injection was removed to accommodate different national recommendations on the use of multidose vials.
The PL and the Labelling of the outer packaging were revised in line with the changes in SPC sections 6.5 and 6.6.

In addition, Annex II was revised to reflect that the specific obligation regarding post-dose 1 data from Study H1N1-007 is now fulfilled and to reflect the current status of the Specific Obligations.

II. CONCLUSION

- On 22 October 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.