European Medicines Agency

London, 19 Novmeber 2009
Doc. Ref: EMEA/CHMP/763804/2009

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/0023

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

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 Authorisation 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 phase 6 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's) 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 and above (D-PAN-H1N1-008, called "H1N1-008" in this report).

In support of this variation the MAH has submitted a synoptic report of day 21 (D21) safety and immunogenicity data (HI only) from study H1N1-008

This variation has been submitted to fulfil the specific obligation SOB 051 for which the MAH committed to provide the post-dose 1 HI immunogenicity data (uncleaned) from this study to CHMP.

Further data will be submitted from this study at intervals as committed in the Letter of Undertaking for the pandemic strain variation (PU-017) and described in Annex II to the Opinion.

1.2 Clinical aspects

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.

Study Design and objectives
The original design of this study was amended when the first results of study H1N1-021 became available (for further details of this study, please refer to the Scientific Discussion of the pandemic strain variation PU-17). Thus, instead of administering two doses to all subjects in each age stratum one cohort will receive two doses as planned and the other will receive only a single dose. Both cohorts will then be followed up serologically at M6 and at M12 to determine whether there is any advantage for two doses over a single dose in the longer term.

The study was initiated in September 2009 and is ongoing. Currently only the data obtained up to D21 after a single dose of Pandemrix H1N1 are available. The MAH provides an abridged study report that covers the post-dose I immunogenicity results (i.e. at D21) after a single dose of 3.75 µg/$AS03_A$ together with data on reactogenicity, adverse events (AEs) and serious adverse events (SAEs).

The complete list of objectives for study D-Pan-H1N1-008 is detailed below. However, only the post Dose 1 (Day 21) results are available at this point.

The primary objective is:

- 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 pandemic vaccine seroconversion rate (SCR), seroprotection rate (SPR), and geometric mean fold rise (GMFR) at 21 days after the vaccination in adults within the 18 to 60 years and above 60 years age strata.

The secondary objectives 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 neutralizing 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 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.

The primary analysis was done on the total vaccinated cohort for each age stratum and overall.
The analysis of immunogenicity was done as a descriptive analysis of the humoral immune response overall and within each age stratum.

Results

As was planned, the study enrolled 240 subjects, including 120 aged 18-60 years and 120 aged > 60 years. Since all subjects received the first dose the total on which post-vaccination safety and immunogenicity data are reported at D21 is 240.

In the four age strata there were 59 aged 18-40 years, 61 aged 41-60, 75 aged 61-70 and 45 aged >70. The results have been shown according to these age groups and not according to the pre-defined strata at the time of randomisation. The age range per stratum was from 19-40 years, 42-60, 61 to 70 and 71 to 85 years. Within each cohort the percentage of each gender was variable but all values fell within 43-57%. All subjects were Caucasian.

As shown in the table, no subject had received vaccination for the 2009/10 season before study entry but the rate of prior vaccination on the two previous seasons increased with age. As expected, over 85% of those aged > 60 years had been vaccinated at least once since 2007.

History of influenza vaccination in the last 3 seasons by age strata (Total vaccinated cohort)

		18-40 N = 59		41-60 N = 61		61-70 N = 75		>70 N = 45	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
One season at least	Yes	23	39.0	41	67.2	64	85.3	41	91.1
	No	36	61.0	20	32.8	11	14.7	4	8.9
2007-2008	No	39	66.1	24	39.3	20	26.7	7	15.6
	YES	20	33.9	37	60.7	55	73.3	38	84.4
2008-2009	No	42	71.2	29	47.5	16	21.3	9	20.0
	YES	17	28.8	32	52.5	59	78.7	36	80.0
2009-2010	No	57	96.6	59	96.7	72	96.0	40	88.9
	YES	0	0.0	0	0.0	0	0.0	0	0.0
	N	2	3.4	2	3.3	3	4.0	5	11.1

- As shown below between 29-44% of subjects per age stratum were seropositive before the first dose but only 3-14% of subjects were seroprotected. There was no clear trend to increasing baseline seropositivity or seroprotection with age.
- At Day 21, all except two subjects aged 61-70 years were seropositive.
- The D21 **GMT** was significantly higher in subjects aged 18-40 compared to the older age strata. In the three older strata the GMT was numerically highest for those aged 41-60 years with no appreciable difference for the two cohorts aged > 60 years.
- The D21 **seroprotection rates** showed a trend to decrease with increasing age but the 95% CI all overlapped and the lowest rate observed exceeded 86%.
- Similarly the D21 **seroconversion rates** showed a trend to decrease with increasing age but the 95% CI all overlapped and the lowest rate observed exceeded 77%.
- The **seroconversion factors** decreased very markedly with increasing age with no overlap of 95% CI between the 18-40 and 41-60 years strata and no overlap in 95% CI between the 41-60 years and the two older strata. However, there was no appreciable difference between subjects in the 61-70 and >70 years strata. The lowest SCF exceeded 13.

Seropositivity rates and GMTs for HI antibody by age strata (Total vaccinated cohort)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
	Sub-group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
	18-40	PRE	59	26	44.1	31.2	57.6	9.99	7.78	12.83	<10.00	160.00
		PI(21)	59	59	100	93.9	100	**606.99**	465.37	791.72	28.00	5120.00
	41-60	PRE	61	18	29.5	18.5	42.6	7.31	6.15	8.69	<10.00	113.00
		PI(21)	61	61	100	94.1	100	**216.30**	157.96	296.19	10.00	2560.00
	61-70	PRE	75	32	42.7	31.3	54.6	9.49	7.52	11.98	<10.00	1280.00
		PI(21)	75	73	97.3	90.7	99.7	**128.09**	98.86	165.96	<10.00	1810.00
	>70	PRE	45	19	42.2	27.7	57.8	10.87	7.57	15.61	<10.00	640.00
		PI(21)	45	45	100	92.1	100	**151.58**	104.62	219.63	10.00	1810.00

Seroprotection rates (SPR) for HI antibody by age strata

					95% CI	
Sub-group	**Timing**	**N**	**n**	**%**	**LL**	**UL**
18-40	PRE	59	8	13.6	6.0	25.0
	PI(21)	59	58	**98.3**	90.9	100
41-60	PRE	61	2	3.3	0.4	11.3
	PI(21)	61	59	**96.7**	88.7	99.6
61-70	PRE	75	6	8.0	3.0	16.6
	PI(21)	75	66	**88.0**	78.4	94.4
>70	PRE	45	5	11.1	3.7	24.1
	PI(21)	45	39	**86.7**	73.2	94.9

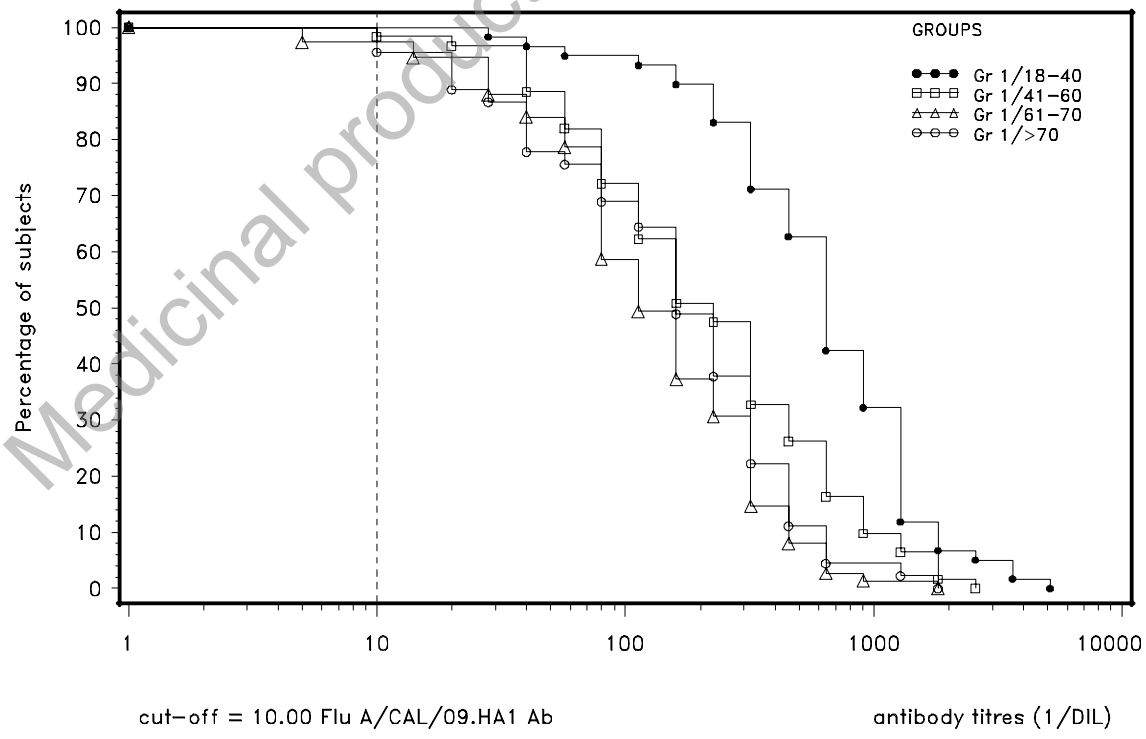
Seroconversion rate (SCR) for HI antibody by age strata

					95% CI	
Sub-group	**Timing**	**N**	**n**	**%**	**LL**	**UL**
18-40	PI(21)	59	56	**94.9**	85.9	98.9
41-60	PI(21)	61	58	**95.1**	86.3	99.0
61-70	PI(21)	75	60	**80.0**	69.2	88.4
>70	PI(21)	45	35	**77.8**	62.9	88.8

Seroconversion factor (SCF) for HI antibody by age strata

				95% CI	
Sub-group	**Timing**	**N**	**Value**	**LL**	**UL**
18-40	PI(21)	59	**60.77**	43.51	84.88
41-60	PI(21)	61	**29.59**	21.82	40.15
61-70	PI(21)	75	**13.49**	10.26	17.75
>70	PI(21)	45	**13.94**	9.24	21.05

The reverse cumulative distribution curve shown below demonstrates the marked separation between the youngest cohort and the three older cohorts, especially from around titres of around 1:160 upwards.



The MAH also provided an overview of HI responses according to baseline serostatus in various age sub-groups:

18-40 years

In this age group 33/59 subjects were seronegative at baseline. The D21 GMT was nearly two-fold higher in the subgroup that was seropositive at baseline but the SCF was about one third of that in the baseline seronegative subjects. SCRs were > 90% regardless of baseline serostatus and only 1/59 subjects was not seroprotected after a single dose.

41-60 years

In this age group 43/61 subjects were seronegative at baseline. The D21 GMT was >2-fold higher in the subgroup seropositive at baseline but the SCF was lower than that in the baseline seronegatives. SCRs were > 90% regardless of baseline serostatus and only 2/61 subjects were not seroprotected after a single dose.

61-70 years

In this age group 43/75 subjects were seronegative at baseline. The D21 GMT was close to 2-fold higher in the subgroup seropositive at baseline but the SCF was lower than that in the baseline seronegatives. SCRs were ~80% regardless of baseline serostatus. In baseline seronegatives 35/43 (81%) were seroprotected after a single dose compared to 31/32 (97%) of the baseline seropositives.

71-80 years

In this age group 23/40 subjects were seronegative at baseline. The D21 GMT was ~2.5-fold higher in the subgroup seropositive at baseline but the SCF was about one-third of that in the baseline seronegatives. SCRs were > 70% regardless of baseline serostatus. The D21 seroprotection rates were 19/23 (83%) for those seronegative at baseline and 16/17 (94%) for those seropositive at baseline.

>80 years

There were only five subjects in this age group, of which three were seronegative at baseline. The D21 GMT was >3-fold higher in the subgroup seropositive at baseline but the SCFs were comparable between subgroups. Overall 4/5 seroconverted. None of the five subjects was seroprotected before vaccination but 4/5 reached this cut-off (i.e. 80%) at D21.

The MAH further provided immunogenicity results for subjects aged < and > 60 years according to prior seasonal vaccination history (according to vaccination status and, for GMTs and SPRs, for baseline serostatus) as described below:

18-60 years

The data do not show an important effect of prior seasonal vaccination on HI responses at D21 after a single dose. However, those who were seronegative at baseline and had received seasonal vaccination had the lowest GMT and SPR at D21. It was therefore considered that some subjects in this sub-group do not respond so well in terms of HI to influenza vaccines. Nevertheless, the SPR was 93% in this sub-group.

> 60 years

The data show the same pattern as for the younger cohort, including in the sub-group that was seronegative at baseline but had received prior seasonal vaccination. Nevertheless, the SPR in this sub-group was 79%.

Clinical safety

The safety analysis was performed on the total vaccinated cohort of 240 subjects, for which all returned the symptom records.

As shown below, for total, general and local symptoms the reporting rates per subject decreased with increasing age and with no overlap of 95% between the youngest and the oldest strata. Almost all of these symptoms were considered to be related to vaccination.

Solicited and unsolicited symptoms reported during Days 0-6 post-vaccination by age strata (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Sub-group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
18-40	59	56	94.9	85.9	98.9	59	42	71.2	57.9	82.2	59	55	93.2	83.5	98.1
41-60	61	55	90.2	79.8	96.3	61	35	57.4	44.1	70.0	61	50	82.0	70.0	90.6
61-70	75	63	84.0	73.7	91.4	75	37	49.3	37.6	61.1	75	57	76.0	64.7	85.1
>70	45	29	64.4	48.8	78.1	45	16	35.6	21.9	51.2	45	25	55.6	40.0	70.4

Few symptoms were of Grade 3 and all of these were general symptoms (no local Grade 3 symptoms were reported in any age stratum). These also showed a trend to decrease with increasing age.

Incidence and nature of grade 3 symptoms by age strata

	Any symptom					General symptoms				
				95% CI					95% CI	
Sub-group	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
18-40	59	6	10.2	3.8	20.8	59	6	10.2	3.8	20.8
41-60	61	3	4.9	1.0	13.7	61	3	4.9	1.0	13.7
61-70	75	2	2.7	0.3	9.3	75	2	2.7	0.3	9.3
>70	45	0	0.0	0.0	7.9	45	0	0.0	0.0	7.9

As in other studies local pain was by far the most common solicited symptom, affecting almost all of the youngest cohort and more than half in all other cohorts but showing a decrease in incidence with increasing age. The vast majority of reports of pain were of grade 1 and none was Grade 3. Redness and swelling were each reported by < 12% of subjects per age cohort. Local symptoms lasted for a mean/median of 1-3 days.

Solicited local symptoms reported during the 7-day (Days 0-6) post-dose 1 vaccination period (Total vaccinated cohort)

		18-40					41-60				
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	59	55	93.2	83.5	98.1	61	50	82.0	70.0	90.6
	Grade 1	59	24	40.7	28.1	54.3	61	40	65.6	52.3	77.3
	Grade 2	59	31	52.5	39.1	65.7	61	10	16.4	8.2	28.1
	Grade 3	59	0	0.0	0.0	6.1	61	0	0.0	0.0	5.9
Redness (mm)	All	59	1	1.7	0.0	9.1	61	0	0.0	0.0	5.9
	[20.1 - 50.1[	59	1	1.7	0.0	9.1	61	0	0.0	0.0	5.9
	[50.1 - 100.1[	59	0	0.0	0.0	6.1	61	0	0.0	0.0	5.9
	[100.1 - ...	59	0	0.0	0.0	6.1	61	0	0.0	0.0	5.9
Swelling (mm)	All	59	7	11.9	4.9	22.9	61	4	6.6	1.8	15.9
	[20.1 - 50.1[	59	2	3.4	0.4	11.7	61	3	4.9	1.0	13.7
	[50.1 - 100.1[	59	5	8.5	2.8	18.7	61	1	1.6	0.0	8.8
	[100.1 - ...	59	0	0.0	0.0	6.1	61	0	0.0	0.0	5.9

		> 70					61 - 70				
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	45	24	53.3	37.9	68.3	75	54	72.0	60.4	81.8
	Grade 1	45	19	42.2	27.7	57.8	75	46	61.3	49.4	72.4
	Grade 2	45	5	11.1	3.7	24.1	75	8	10.7	4.7	19.9
	Grade 3	45	0	0.0	0.0	7.9	75	0	0.0	0.0	4.8
Redness (mm)	All	45	5	11.1	3.7	24.1	75	4	5.3	1.5	13.1
	[20.1 - 50.1[	45	4	8.9	2.5	21.2	75	3	4.0	0.8	11.2
	[50.1 - 100.1[	45	1	2.2	0.1	11.8	75	1	1.3	0.0	7.2
	[100.1 - ...	45	0	0.0	0.0	7.9	75	0	0.0	0.0	4.8
Swelling (mm)	All	45	4	8.9	2.5	21.2	75	8	10.7	4.7	19.9
	[20.1 - 50.1[	45	3	6.7	1.4	18.3	75	5	6.7	2.2	14.9
	[50.1 - 100.1[	45	1	2.2	0.1	11.8	75	3	4.0	0.8	11.2
	[100.1 - ...	45	0	0	0	7.9	75	0	0.0	0.0	4.8

The analysis of solicited general symptoms is shown by the two major age strata below, including Grade 3 report and vaccine-related reports. The MAH also provided similar analyses in the four age categories as above, which demonstrated a general decrease in incidence with increasing age.

Fatigue, headache and muscle aches predominated as in previous studies and in the H5N1 studies. Documented fever in these adults was reported by very few subjects. In general, the rates observed were also very much in keeping with those observed in the H5N1 studies in comparable age groups.

General symptoms lasted for a mean/median of 1-3 days.

Solicited general symptoms reported during the 7-day (Days 0-6) post-dose 1 (Total vaccinated cohort)

		18-60					>60				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	120	43	35.8	27.3	45.1	120	26	21.7	14.7	30.1
	Grade 1	120	28	23.3	16.1	31.9	120	20	16.7	10.5	24.6
	Grade 2	120	13	10.8	5.9	17.8	120	5	4.2	1.4	9.5
	Grade 3	120	2	1.7	0.2	5.9	120	1	0.8	0.0	4.6
	Rel	120	38	31.7	23.5	40.8	120	24	20.0	13.3	28.3
	Grade 1*Rel	120	26	21.7	14.7	30.1	120	18	15.0	9.1	22.7
	Grade 2*Rel	120	10	8.3	4.1	14.8	120	5	4.2	1.4	9.5
	Grade 3*Rel	120	2	1.7	0.2	5.9	120	1	0.8	0.0	4.6
Headache	All	120	44	36.7	28.1	45.9	120	22	18.3	11.9	26.4
	Grade 1	120	33	27.5	19.7	36.4	120	16	13.3	7.8	20.7
	Grade 2	120	10	8.3	4.1	14.8	120	6	5.0	1.9	10.6
	Grade 3	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	Rel	120	40	33.3	25.0	42.5	120	21	17.5	11.2	25.5
	Grade 1*Rel	120	31	25.8	18.3	34.6	120	15	12.5	7.2	19.8
	Grade 2*Rel	120	8	6.7	2.9	12.7	120	6	5.0	1.9	10.6
	Grade 3*Rel	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
Joint pain at other location	All	120	19	15.8	9.8	23.6	120	17	14.2	8.5	21.7
	Grade 1	120	10	8.3	4.1	14.8	120	10	8.3	4.1	14.8
	Grade 2	120	9	7.5	3.5	13.8	120	6	5.0	1.9	10.6
	Grade 3	120	0	0.0	0.0	3.0	120	1	0.8	0.0	4.6
	Rel	120	15	12.5	7.2	19.8	120	14	11.7	6.5	18.8
	Grade 1*Rel	120	9	7.5	3.5	13.8	120	8	6.7	2.9	12.7
	Grade 2*Rel	120	6	5.0	1.9	10.6	120	5	4.2	1.4	9.5
	Grade 3*Rel	120	0	0.0	0.0	3.0	120	1	0.8	0.0	4.6
Muscle aches	All	120	29	24.2	16.8	32.8	120	25	20.8	14.0	29.2
	Grade 1	120	15	12.5	7.2	19.8	120	18	15.0	9.1	22.7

		18-60					>60				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
	Grade 2	120	12	10.0	5.3	16.8	120	6	5.0	1.9	10.6
	Grade 3	120	2	1.7	0.2	5.9	120	1	0.8	0.0	4.6
	Rel	120	23	19.2	12.6	27.4	120	23	19.2	12.6	27.4
	Grade 1*Rel	120	13	10.8	5.9	17.8	120	16	13.3	7.8	20.7
	Grade 2*Rel	120	9	7.5	3.5	13.8	120	6	5.0	1.9	10.6
	Grade 3*Rel	120	1	0.8	0.0	4.6	120	1	0.8	0.0	4.6
Shivering	All	120	23	19.2	12.6	27.4	120	7	5.8	2.4	11.6
	Grade 1	120	14	11.7	6.5	18.8	120	6	5.0	1.9	10.6
	Grade 2	120	9	7.5	3.5	13.8	120	1	0.8	0.0	4.6
	Grade 3	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	Rel	120	20	16.7	10.5	24.6	120	7	5.8	2.4	11.6
	Grade 1*Rel	120	13	10.8	5.9	17.8	120	6	5.0	1.9	10.6
	Grade 2*Rel	120	7	5.8	2.4	11.6	120	1	0.8	0.0	4.6
	Grade 3*Rel	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
Sweating	All	120	19	15.8	9.8	23.6	120	6	5.0	1.9	10.6
	Grade 1	120	14	11.7	6.5	18.8	120	6	5.0	1.9	10.6
	Grade 2	120	4	3.3	0.9	8.3	120	0	0.0	0.0	3.0
	Grade 3	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	Rel	120	15	12.5	7.2	19.8	120	6	5.0	1.9	10.6
	Grade 1*Rel	120	11	9.2	4.7	15.8	120	6	5.0	1.9	10.6
	Grade 2*Rel	120	3	2.5	0.5	7.1	120	0	0.0	0.0	3.0
	Grade 3*Rel	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
		18-60					**>60**				
					95 % CI					**95 % CI**	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Temperature/(Axillary) (°C)	All	120	1	0.8	0.0	4.6	120	2	1.7	0.2	5.9
	[38.0 - 38.5[	120	0	0.0	0.0	3.0	120	2	1.7	0.2	5.9
	[38.5 - 39.0[	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	[39.0 - 40.1[	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	[40.1 - ...	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	Rel	120	1	0.8	0.0	4.6	120	1	0.8	0.0	4.6
	[38.0 - 38.5[*Rel	120	0	0.0	0.0	3.0	120	1	0.8	0.0	4.6
	[38.5 - 39.0[*Rel	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	[39.0 - 40.1[*Rel	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	[40.1 - ...*Rel	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0

Unsolicited AEs were reported by 44% of subjects aged < 60 years and by 26% aged > 60 years with corresponding rates for vaccine-related AEs of 20% and 12%. These were very mixed in nature and the majority were reported by only one or two subjects. The notable exception was nasopharyngitis, reported by 15 and 3 in respective age groups.

Pruritus was reported by two subjects and two reported rash, none of which was Grade 3 and one of each was considered vaccine-related. Lymphadenopathy does not appear to have been reported by any subject after the first dose. Ten subjects aged < 60 years and one aged > 60 years reported a Grade 3 unsolicited AE. These were mixed in nature and there was no discernable pattern.

No SAEs were reported up to D21 in this study.

The incidence of taking concomitant medications and of taking any antipyretic medication decreased with age across the four strata. It seems likely that most of the medications with an antipyretic effect were most likely taken for their analgesic effects (i.e. due to local pain, headaches and muscle aches) given the very low rates of fever.

Incidence of concomitant medication during the 21-day (Days 0-20) post-dose 1 (Total vaccinated cohort)

	18-60					>60				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	120	43	35.8	27.3	45.1	120	21	17.5	11.2	25.5
Any antipyretic	120	31	25.8	18.3	34.6	120	11	9.2	4.7	15.8
Prophylactic antipyretic	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0

II. Overall conclusion and benefit-risk assessment

This initial and abridged study report describes the preliminary safety and immunogenicity results following vaccination with Pandemrix (i.e. 3.75 µg HA +$AS03_A$) in adults aged from 18-60 years and over 60 years, with a good representation of subjects aged > 60 years (120) of which 45 were > 70 years although only five of these 45 subjects were aged > 80 years.

Based on the HI data at baseline the pre-vaccination seropositivity rates and seroprotection rates were in keeping with those observed in studies 021 and 007 in subjects aged 18-60 years. There was no clear trend to higher baseline rates with increasing age.

The CHMP criteria for HI responses were met in the initial analysis in the strata < 60 and > 60 years. The additional analyses by baseline serostatus, prior seasonal vaccination and detailed age strata that were provided by the MAH on request of the assessor also showed that in each analysis the three criteria were comfortably met, including the five subjects aged > 80 years, three of whom were seronegative at baseline.

The safety profile of Pandemrix H1N1 appears to be as seen with previously assessed studies (H1N1 021, H1N1-007) generally comparable with that reported with Pandemrix H5N1 in adults aged 18-60 years and in older subjects, in whom reporting rates were generally lower than in the younger cohort. There were no new safety issues raised by these data.

The CHMP considered that these preliminary data do not affect the current wording regarding use in subjects aged 18-60 years but the data could now be described as *limited* rather than *very limited* in the PI.

The new data in the elderly merit a cautious reflection in the SPC to allow the option of a single dose. It remains to be confirmed if it is possible to allow this even in those aged > 80 years based on the very limited data in this age group. It is clear from the data that GMTs decreased with age, as observed on previous studies with H5N1 and within the 18-60 years cohort with H1N1v versions of Pandemrix. However, and in contrast to the experience in this age group with H5N1 vaccine, all five subjects mounted an immune response. None of the five was seroprotected at baseline, although two were seropositive, but all were seropositive at D21 and four of the five were seroprotected. On this basis there does not seem to be any justification for setting an upper limit on the age at which a single dose may be an option although the limitations of the data must be clearly reflected in section 5.1.

Nevertheless, the CHMP reiterated that it remains possible that advantages for a second dose could exist. Even if the immediate HI response to Pandemrix is highly satisfactory in adults, including the elderly, there could be advantages for a second dose in terms of antibody persistence and also in terms of antibody against drifted variants. Indeed, the H5N1 data would suggest that this might be the case. Therefore the outstanding post-dose 1 NA data, the post-dose 2 HI and NA data and the antibody persistence data are still considered to be very important.

Submission of the further data from this study is included in the list of Specific Obligations and will be dealt with in sequential assessment reports.

1.4 Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/Annex II/ /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 4.2 -Posology and method of administration
The introductory paragraph was shortened and changed to be more concise. The sub-sections on adults and elderly were merged into one sub-section and revised to reflect that Immunogenicity data obtained at three weeks after administration of Pandemrix (H1N1) in clinical studies 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.

SPC section 4.4 -Special warnings and precautions for use
This section was revised to reflect that limited data available from clinical studies with Pandemrix (H1N1) in adults aged over 60 years and very limited data with Pandemrix (H1N1) or with a version of the vaccine containing H5N1 antigens in adults aged over 80 years.

SPC section 4.8 - Undesirable effects
A section was added to describe the safety data especially in adults >60 years of age from study H1N1-008

SPC section 5.1 Pharmacodynamic properties
This section was further revised to include data from study H1N1- 007 and H1N1-008 in a single table for adults aged 18-60 years. The study 008 data in subjects aged 60-71, 71-80 and 80+ years was included (by baseline serostatus) to show how many subjects were in each age stratum and a statement was included highlighting that no data are currently available on the neutralising antibody response.

SPC section 6.6 Special precautions for disposal and other handling
The text proposed by the MAH was considered acceptable. Further changes to the handling instructions have been assessed within variation II-25 adopted in parallel to this procedure.

The PL was updated accordingly.