European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 December 2009
Doc. Ref: EMA/CHMP/842790/2009

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/0034

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 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 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-α-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 post dose 1 efficacy and safety results from a clinical study on sequential administration of a licensed seasonal trivalent vaccine and Pandemrix administered in adults 61 years or above (D-PAN-H1N1-020).

In submitting the above-mentioned data from study 020 the MAH also fulfilled the Specific Obligation to provide an abridged report for: post dose 1 data from study D-PAN H1N1-020 (SOB 052).

1.2 Clinical aspects

Study 020
This is a randomised, single-blind study to evaluate the immunogenicity and safety of sequential administration of Fluarix and Pandemrix (H1N1) and *vice versa* in adults 61 years or above. The study is ongoing at six sites in Germany. The current abridged study report has a Data Lock Point of 18 November 2009 and is based on the HI data to D21 only.

Objectives are:

Primary
- To assess whether two doses of Pandemrix result in HI immune responses that meet or exceed the CHMP criteria at D42 when Fluarix has been administered at least 21 days before or not administered in subjects aged 61 years and older

Secondary
- To assess whether one dose of Fluarix results in an HI immune response that meets or exceeds for each vaccine strain at least one of the CHMP criteria at D21 when administered before or after Pandemrix (H1N1) in subjects aged 61 years and older
- To compare GMT ratios at D42 between groups who have and have not received Fluarix at least 3 weeks previously
- To compare GMT ratios at D21 after Fluarix given to subjects who have and have not received Pandemrix (H1N1)
- To assess the anti-H1N1 SCR, SPR and SCF at 6 and 12 months after vaccination
- To evaluate safety

Exploratory:

- To describe immunogenicity to the A/California/7/2009 (H1N1)v-like antigen at Day 0, Day 21 and Day 42 based on neutralising antibodies in each study group.

Healthy subjects aged > 60 years were randomised (1:1) to Groups A and B and vaccinated as follows:

- On Day -21, one dose of placebo was given to subjects in Group A and one dose of Fluarix was given to subjects in Group B
- On Day 0 all subjects received the first dose of Pandemrix (H1N1)
- On Day 21 all subjects received the second dose of Pandemrix but only the pre-vaccination HI results from the second dose (D21 sera) are currently available.
- On Day 42, one dose of Fluarix will be given to subjects in Group A and one dose of placebo will be given to subjects in Group B.

The placebo is a saline solution.

The data are presented for the total vaccinated cohort (TVC).
It was planned to enroll 144 subjects and 145 were actually enrolled. One vaccinated subject has since withdrawn consent; all others have completed to D21. The mean age was 69.4 years for the total vaccinated cohort (range 61-86 years; six subjects were aged > 80 years) and the male-female distribution was 49.7% versus 50.3%.

The majority of subjects had received seasonal influenza vaccine in each of the preceding winters with an imbalance between groups for overall rates (89% in Group A and 75% in Group B).

History of influenza vaccination in the previous 3 seasons (TVC)

		GROUP A N = 72		GROUP B N = 73		Total N = 145	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
At least one season	Yes	64	88.9	55	75.3	119	82.1
	No	8	11.1	18	24.7	26	17.9
Season 2006-2007	Yes	49	68.1	41	56.2	90	62.1
Season 2007-2008	Yes	49	68.1	49	67.1	98	67.6
Season 2008-2009	Yes	55	76.4	48	65.8	103	71.0

Immune response to Pandemrix (H1N1)

- At Day -21, 25/72 (34.7%) in Group A and 24/73 (32.9%) in Group B were seropositive vs. H1N1v but GMTs were low (8.5 and 7.8).
- At Day 0, 29/72 there were (40.3%) subjects seropositive in Group A (no Fluarix) compared to 54/72 (75%) in Group B (post-Fluarix) but GMTs remained low overall (8.9 and 14.3). There were only very small increases in GMTs from D-21 to D0 even in the subset in Group B that was seropositive at D-21.
- At D21, seropositivity rates were 100% in both groups with large increments in GMTs from D0 and final GMT values that were higher in the sub-groups that were seropositive at D-21. The 95% CI around the overall GMTs for groups A and B and between subsets in each group that were seropositive or seronegative at D-21 overlapped.

GMTs and seropositivity rates for HI against H1N1 by pre-vaccination status (TVC)

					>= 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/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	47	0	0.0	0.0	7.5	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	47	4	8.5	2.4	20.4	5.3	5.0	5.6	<10.0	10.0
			PII(D21)	47	47	100	92.5	100	103.5	76.2	140.5	10.0	1280.0
		S+	PI(D -21)	25	25	100	86.3	100	23.3	15.8	34.3	10.0	320.0
			PI(D0)	25	25	100	86.3	100	23.9	16.2	35.4	10.0	320.0
			PII(D21)	25	25	100	86.3	100	290.6	193.8	435.8	57.0	1280.0
		Total	PI(D -21)	72	25	34.7	23.9	46.9	8.5	6.9	10.6	<10.0	320.0
			PI(D0)	72	29	40.3	28.9	52.5	8.9	7.2	11.1	<10.0	320.0
			PII(D21)	72	72	100	95.0	100	148.1	113.6	193.1	10.0	1280.0
	GROUP B	S-	PI(D -21)	49	0	0.0	0.0	7.3	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	48	31	64.6	49.5	77.8	10.3	8.4	12.5	<10.0	57.0
			PII(D21)	48	48	100	92.6	100	91.7	67.2	125.0	14.0	905.0
		S+	PI(D -21)	24	24	100	85.8	100	19.1	13.7	26.7	10.0	226.0
			PI(D0)	24	23	95.8	78.9	99.9	27.8	19.0	40.7	<10.0	320.0
			PII(D21)	24	24	100	85.8	100	169.5	92.3	311.5	10.0	2560.0
		Total	PI(D -21)	73	24	32.9	22.3	44.9	7.8	6.5	9.3	<10.0	226.0
			PI(D0)	72	54	75.0	63.4	84.5	14.3	11.6	17.7	<10.0	320.0
			PII(D21)	72	72	100	95.0	100	112.5	84.3	150.3	10.0	2560.0

The following tables show the same data for the three age cohorts 61-70, 71-80 and >80 years.

In the 61-70 years age group there were 13/44 (29.5%) in Group A and 12/42 (28.6%) in Group B who were already seropositive at D-21 compared to 10/26 (38.5%) and 9/27 (33%) in the 71-80 years age group. Of the 6 subjects in the >80 years age group there were five already seropositive at D-21; the only seronegative subject was in Group B.
The tables show that D21 GMTs within each of Groups A and B were at least numerically higher in the subsets that were seropositive at D-21 with some trend for GMTs to decrease with increasing age from 61-80 years. GMTs in those aged > 80 years were higher because 5/6 were seropositive at D-21.

In the subjects aged 61-70 years who were seronegative at D-21 a dose of Fluarix (Group B) increased the seropositivity rate to 23/30 (77%) while 4/31 (13%) given placebo (Group A) became seropositive.

61-70 years of age

					>= 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/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	31	0	0.0	0.0	11.2	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	31	4	12.9	3.6	29.8	5.5	5.0	6.0	<10.0	10.0
			PII(D21)	31	31	100	88.8	100	127.9	87.8	186.4	10.0	1280.0
		S+	PI(D -21)	13	13	100	75.3	100	19.0	12.4	29.1	10.0	57.0
			PI(D0)	13	13	100	75.3	100	21.1	13.3	33.4	10.0	80.0
			PII(D21)	13	13	100	75.3	100	320.2	165.2	620.7	57.0	1280.0
		Total	PI(D -21)	44	13	29.5	16.8	45.2	7.4	6.0	9.2	<10.0	57.0
			PI(D0)	44	17	38.6	24.4	54.5	8.1	6.5	10.3	<10.0	80.0
			PII(D21)	44	44	100	92.0	100	167.7	119.4	235.6	10.0	1280.0
	GROUP B	S-	PI(D -21)	30	0	0.0	0.0	11.6	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	30	23	76.7	57.7	90.1	12.0	9.2	15.6	<10.0	57.0
			PII(D21)	30	30	100	88.4	100	97.3	64.6	146.5	14.0	640.0
		S+	PI(D -21)	12	12	100	73.5	100	15.4	11.1	21.3	10.0	40.0
			PI(D0)	12	11	91.7	61.5	99.8	22.4	13.5	37.4	<10.0	80.0
			PII(D21)	12	12	100	73.5	100	142.6	56.0	363.5	10.0	1810.0
		Total	PI(D -21)	42	12	28.6	15.7	44.6	6.9	5.8	8.3	<10.0	40.0
			PI(D0)	42	34	81.0	65.9	91.4	14.4	11.3	18.3	<10.0	80.0
			PII(D21)	42	42	100	91.6	100	108.5	74.5	158.2	10.0	1810.0

In subjects aged 71-80 years who were seronegative at D-21 the seropositivity rates at D0 were 8/17 (47%) after Fluarix and 0/16 after placebo.

71-80 years of age

					>= 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/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	16	0	0.0	0.0	20.6	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	16	0	0.0	0.0	20.6	5.0	5.0	5.0	<10.0	<10.0
			PII(D21)	16	16	100	79.4	100	68.7	40.9	115.4	10.0	453.0
		S+	PI(D -21)	10	10	100	69.2	100	35.9	16.1	80.2	10.0	320.0
			PI(D0)	10	10	100	69.2	100	33.6	14.7	76.4	10.0	320.0
			PII(D21)	10	10	100	69.2	100	242.7	123.1	478.3	57.0	1280.0
		Total	PI(D -21)	26	10	38.5	20.2	59.4	10.7	6.6	17.2	<10.0	320.0
			PI(D0)	26	10	38.5	20.2	59.4	10.4	6.5	16.7	<10.0	320.0
			PII(D21)	26	26	100	86.8	100	111.6	70.6	176.4	10.0	1280.0
	GROUP B	S-	PI(D -21)	18	0	0.0	0.0	18.5	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	17	8	47.1	23.0	72.2	8.1	6.0	11.1	<10.0	28.0
			PII(D21)	17	17	100	80.5	100	78.3	45.7	133.9	14.0	905.0
		S+	PI(D -21)	9	9	100	66.4	100	20.8	11.7	36.9	10.0	57.0
			PI(D0)	9	9	100	66.4	100	31.7	18.5	54.1	14.0	80.0
			PII(D21)	9	9	100	66.4	100	172.7	59.1	504.9	28.0	2560.0
		Total	PI(D -21)	27	9	33.3	16.5	54.0	8.0	5.9	11.0	<10.0	57.0
			PI(D0)	26	17	65.4	44.3	82.8	13.0	9.0	18.8	<10.0	80.0
			PII(D21)	26	26	100	86.8	100	102.9	63.1	168.0	14.0	2560.0

In subjects aged > 80 years the effect of Fluarix on D0 seropositivity rates cannot be discerned because there were only four subjects in Group B and three of these were already seropositive at D-21.

Above 80 years of age

					>= 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/7/09.HA1 Ab	GROUP A	S+	PI(D -21)	2	2	100	15.8	100	10.0	10.0	10.0	10.0	10.0
			PI(D0)	2	2	100	15.8	100	10.0	10.0	10.0	10.0	10.0
			PII(D21)	2	2	100	15.8	100	380.7	41.8	3464.3	320.0	453.0
		Total	PI(D -21)	2	2	100	15.8	100	10.0	10.0	10.0	10.0	10.0
			PI(D0)	2	2	100	15.8	100	10.0	10.0	10.0	10.0	10.0
			PII(D21)	2	2	100	15.8	100	380.7	41.8	3464.3	320.0	453.0
	GROUP B	S-	PI(D -21)	1	0	0.0	0.0	97.5	5.0	-	-	<10.0	<10.0
			PI(D0)	1	0	0.0	0.0	97.5	5.0	-	-	<10.0	<10.0
			PII(D21)	1	1	100	2.5	100	226.0	-	-	226.0	226.0
		S+	PI(D -21)	3	3	100	29.2	100	35.6	0.6	2079.5	10.0	226.0
			PI(D0)	3	3	100	29.2	100	44.7	0.5	3723.1	10.0	320.0
			PII(D21)	3	3	100	29.2	100	320.0	3.4	30453.9	80.0	2560.0
		Total	PI(D -21)	4	3	75.0	19.4	99.4	21.8	1.6	305.3	<10.0	226.0
			PI(D0)	4	3	75.0	19.4	99.4	25.9	1.4	468.4	<10.0	320.0
			PII(D21)	4	4	100	39.8	100	293.4	26.6	3229.3	80.0	2560.0

At Day 21, the HI immune responses **exceeded the CHMP and CBER regulatory acceptance criteria** for influenza vaccines in both groups.

However for all subjects (i.e. across all age cohorts and baseline serostatus) there were differences observed between Group A (Placebo-Pandemrix) and Group B (Fluarix-Pandemrix) as follows:

The observed **SCRs** were 88.9% for Group A and 65.3% for Group B with **non-overlapping** 95% CI. The difference between groups reflected the much lower SCR in the 54 Group B subjects who were seropositive at D0 compared to the 29 Group A subjects who were seropositive at D0.

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PII(D21)	43	38	88.4	74.9	96.1
		S+	PII(D21)	29	26	89.7	72.6	97.8
		Total	PII(D21)	72	64	88.9	79.3	95.1
	GROUP B	S-	PII(D21)	18	15	83.3	58.6	96.4
		S+	PII(D21)	54	32	59.3	45.0	72.4
		Total	PII(D21)	72	47	65.3	53.1	76.1

The **SCFs** were 16.6 and 7.9 with **non-overlapping** 95% CI. Again, the difference between groups reflected the much lower SCR in Group B subjects who were seropositive at D0. SCFs were also at least numerically lower in those seropositive vs. those seronegative at D0 in each of Groups A and B.

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab (1/DIL)	GROUP A	S-	PII(D21)	43	19.7	14.3	27.3
		S+	PII(D21)	29	12.8	8.5	19.1
		Total	PII(D21)	72	16.6	12.9	21.3
	GROUP B	S-	PII(D21)	18	23.0	12.6	42.3
		S+	PII(D21)	54	5.5	4.1	7.4
		Total	PII(D21)	72	7.9	5.8	10.6

At D-21 9/72 (12.5%) in Group A and 5/72 (6.9%) in Group B were seroprotected**.**

At D0, there was no increase in the numbers seroprotected in Group A but an additional six subjects in Group B (all of whom had been seropositive at D-21) had achieved a seroprotective HI antibody level following administration of Fluarix. Therefore 13/72 (18%) were seroprotected in Group B at D0.

The **D21 SPRs** were 93.1% in Group A and 86.1% in Group B with **overlapping** 95% CI.

Numerical differences in D21 SPRs between Groups A and B were observed in each of the subsets who were seronegative (88.4% vs. 83.3%) and seropositive (100% and 87%) at D-21 but the 95% CI overlapped for each subset comparison.

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	43	0	0.0	0.0	8.2
			PI(D0)	43	0	0.0	0.0	8.2
			PII(D21)	43	38	88.4	74.9	96.1
		S+	PI(D -21)	29	9	31.0	15.3	50.8
			PI(D0)	29	9	31.0	15.3	50.8
			PII(D21)	29	29	100	88.1	100
		Total	PI(D -21)	72	9	12.5	5.9	22.4
			PI(D0)	72	9	12.5	5.9	22.4
			PII(D21)	72	67	93.1	84.5	97.7
	GROUP B	S-	PI(D -21)	18	0	0.0	0.0	18.5
			PI(D0)	18	0	0.0	0.0	18.5
			PII(D21)	18	15	83.3	58.6	96.4
		S+	PI(D -21)	54	5	9.3	3.1	20.3
			PI(D0)	54	13	24.1	13.5	37.6
			PII(D21)	54	47	87.0	75.1	94.6
		Total	PI(D -21)	72	5	6.9	2.3	15.5
			PI(D0)	72	13	18.1	10.0	28.9
			PII(D21)	72	62	86.1	75.9	93.1

SCRs in the 61-70 and 71-80 years cohorts showed the same pattern of differences between Groups A and B and the subsets by D0 serostatus as reported above for the total population. The 95% CI did not overlap for the 61-70 years cohort but did overlap for the 71-80 years cohort. No pattern can be discerned for the six subjects aged > 80. In each cohort and subset SCRs were at least 45%.

61-70 years of age

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PII(D21)	27	25	92.6	75.7	99.1
		S+	PII(D21)	17	16	94.1	71.3	99.9
		Total	PII(D21)	44	41	93.2	81.3	98.6
	GROUP B	S-	PII(D21)	8	7	87.5	47.3	99.7
		S+	PII(D21)	34	21	61.8	43.6	77.8
		Total	PII(D21)	42	28	66.7	50.5	80.4

71-80 years of age

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PII(D21)	16	13	81.3	54.4	96.0
		S+	PII(D21)	10	8	80.0	44.4	97.5
		Total	PII(D21)	26	21	80.8	60.6	93.4
	GROUP B	S-	PII(D21)	9	7	77.8	40.0	97.2
		S+	PII(D21)	17	8	47.1	23.0	72.2
		Total	PII(D21)	26	15	57.7	36.9	76.6

Above 80 years of age

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S+	PII(D21)	2	2	100	15.8	100
		Total	PII(D21)	2	2	100	15.8	100
	GROUP B	S-	PII(D21)	1	1	100	2.5	100
		S+	PII(D21)	3	3	100	29.2	100
		Total	PII(D21)	4	4	100	39.8	100

SCFs also showed the same general pattern as reported above but the difference between Groups A and B and subsets according to D0 serostatus were really apparent only in the 61-70 years cohort with non-overlapping 95% CI between Group A and Group B and within the subsets seropositive at D0. In all cases SCFs exceeded 5.0.

61-70 years of age

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab (1/DIL)	GROUP A	S-	PII(D21)	27	24.4	16.1	37.1
		S+	PII(D21)	17	15.7	9.1	27.1
		Total	PII(D21)	44	20.6	14.9	28.5
	GROUP B	S-	PII(D21)	8	30.6	11.9	79.1
		S+	PII(D21)	34	5.4	3.6	8.2
		Total	PII(D21)	42	7.6	5.0	11.5

71-80 years of age

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab (1/DIL)	GROUP A	S-	PII(D21)	16	13.7	8.2	23.1
		S+	PII(D21)	10	7.2	3.8	13.7
		Total	PII(D21)	26	10.7	7.2	15.9
	GROUP B	S-	PII(D21)	9	16.6	5.9	46.4
		S+	PII(D21)	17	5.3	3.1	9.2
		Total	PII(D21)	26	7.9	4.7	13.2

Above 80 years of age

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab (1/DIL)	GROUP A	S+	PII(D21)	2	38.1	4.2	346.4
		Total	PII(D21)	2	38.1	4.2	346.4
	GROUP B	S-	PII(D21)	1	45.2	.	.
		S+	PII(D21)	3	7.2	4.4	11.6
		Total	PII(D21)	4	11.3	2.6	50.2

Regarding the SPRs:

In the 61-70 years age group there were 4/26 in Group A and 3/26 in Group B that were seroprotected at D-21. The SPR was increased at D0 only in Group B (8/42; 19%) and only among those already seropositive at D-21. The D21 SPRs were numerically lower in Group B regardless of D-21 serostatus but the 95% CI overlapped in each subset comparison.
In all cases the D21 SPR exceeded 85%.

In the 71-80 years age group there were 5/44 in Group A and 1/42 in Group B that were seroprotected at D-21. At D0 only one additional subject (in Group B who was seropositive at D-21) reached a seroprotective HI level. The D21 SPRs were numerically lower in Group B regardless of D-21 serostatus but the 95% CI overlapped in each subset comparison.
In all cases the D21 SPR exceeded 75%.

In subjects aged > 80 years only one of the six subjects was seroprotected at either D-21 or D0.
All six were seroprotected at D21.

61-70 years of age

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	27	0	0.0	0.0	12.8
			PI(D0)	27	0	0.0	0.0	12.8
			PII(D21)	27	25	92.6	75.7	99.1
		S+	PI(D -21)	17	5	29.4	10.3	56.0
			PI(D0)	17	5	29.4	10.3	56.0
			PII(D21)	17	17	100	80.5	100
		Total	PI(D -21)	44	5	11.4	3.8	24.6
			PI(D0)	44	5	11.4	3.8	24.6
			PII(D21)	44	42	95.5	84.5	99.4
	GROUP B	S-	PI(D -21)	8	0	0.0	0.0	36.9
			PI(D0)	8	0	0.0	0.0	36.9
			PII(D21)	8	7	87.5	47.3	99.7
		S+	PI(D -21)	34	1	2.9	0.1	15.3
			PI(D0)	34	8	23.5	10.7	41.2
			PII(D21)	34	29	85.3	68.9	95.0
		Total	PI(D -21)	42	1	2.4	0.1	12.6
			PI(D0)	42	8	19.0	8.6	34.1
			PII(D21)	42	36	85.7	71.5	94.6

71-80 years of age

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	GROUP A	S-	PI(D -21)	16	0	0.0	0.0	20.6
			PI(D0)	16	0	0.0	0.0	20.6
			PII(D21)	16	13	81.3	54.4	96.0
		S+	PI(D -21)	10	4	40.0	12.2	73.8
			PI(D0)	10	4	40.0	12.2	73.8
			PII(D21)	10	10	100	69.2	100
		Total	PI(D -21)	26	4	15.4	4.4	34.9
			PI(D0)	26	4	15.4	4.4	34.9
			PII(D21)	26	23	88.5	69.8	97.6
	GROUP B	S-	PI(D -21)	9	0	0.0	0.0	33.6
			PI(D0)	9	0	0.0	0.0	33.6
			PII(D21)	9	7	77.8	40.0	97.2
		S+	PI(D -21)	17	3	17.6	3.8	43.4
			PI(D0)	17	4	23.5	6.8	49.9
			PII(D21)	17	15	88.2	63.6	98.5
		Total	PI(D -21)	26	3	11.5	2.4	30.2
			PI(D0)	26	4	15.4	4.4	34.9
			PII(D21)	26	22	84.6	65.1	95.6

Immune response to Fluarix

The CHMP considered that the forthcoming comparison of the responses to Fluarix administered at D-21 compared to responses to Fluarix administered at D21 after a dose of Pandemrix H1N1 will be of special importance. The data that will allow this comparison are expected by 5 February 2010.

This section describes the responses to each of the strains in Fluarix. An analysis by age cohort will be examined when the comparison with D21 data is made.

In addition, as outlined in Annex II to the opinion, on 5 February 2010 the MAH will provide the D42 data from study 018 in which the two parallel vaccine groups are:

• F-PAN Group, one dose of Pandemrix H1N1 and one dose of Fluarix was given at Day 0 and one dose of Pandemrix H1N1 and one dose of placebo vaccine given at Day 21

• PAN-F Group, one dose of the Pandemrix H1N1 and one dose of placebo vaccine given at Day 0 and one dose of the H1N1 candidate vaccine and one dose of Fluarix at Day 21.

Thus far only the data to D21 (comparing one dose of Pandemrix with and without Fluarix) have been submitted from study 018, which showed no effect of co-administration on responses to H1N1v. The CHMP considered that this D42 data should provide additional insight into the possible effect of giving Fluarix after Pandemrix.

Study results from H1N1-020

At Day -21, despite the differences in previous seasonal vaccination histories, comparable proportions in Groups A and B were seropositive against:

- A/Brisbane (H1N1) [83.3% and 79.5%] and
- A/Uruguay (H3N2) [78.1% and 81.9%] and
- All subjects were seropositive for the B/Brisbane strain.

At Day 0

- HI responses against each of the three seasonal strains in **Group B** (vaccinated with Fluarix at D-21) exceeded all CHMP criteria for HI responses in adults older than 60 years with the exception of the SCR against B/Brisbane.
- **In Group B** the SCRs ranged from 26.4% to 50% and SCFs from 2.6 to 4.4 while the SPRs were 62.5% for A/Brisbane (H1N1), 86.1% for A/Uruguay (H3N2) and 100% for B/Brisbane.
- None of the CHMP criteria were met in **Group A** (who received placebo at D-21).

HI antibodies against A/Bri/59/07 (TVC)

					>= 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/Bri/59/07.HA1 Ab	GROUP A	S-	PI(D -21)	12	0	0.0	0.0	26.5	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	12	1	8.3	0.2	38.5	5.3	4.7	6.0	<10.0	10.0
		S+	PI(D -21)	60	60	100	94.0	100	27.1	22.7	32.4	10.0	320.0
			PI(D0)	60	60	100	94.0	100	26.5	22.2	31.7	10.0	320.0
		Total	PI(D -21)	72	60	83.3	72.7	91.1	20.5	16.6	25.2	<10.0	320.0
			PI(D0)	72	61	84.7	74.3	92.1	20.3	16.5	24.9	<10.0	320.0
	GROUP B	S-	PI(D -21)	15	0	0.0	0.0	21.8	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	15	15	100	78.2	100	63.4	26.5	151.8	10.0	2560.0
		S+	PI(D -21)	58	58	100	93.8	100	23.3	19.2	28.3	10.0	160.0
			PI(D0)	57	57	100	93.7	100	53.5	43.0	66.4	14.0	320.0
		Total	PI(D -21)	73	58	79.5	68.4	88.0	17.0	13.8	21.0	<10.0	160.0
			PI(D0)	72	72	100	95.0	100	55.4	43.7	70.3	10.0	2560.0

As shown in the tables below, the three CHMP criteria were not always met in subsets that were seronegative or already seropositive at D-21 against **A/Brisbane (H1N1).** Nevertheless, this is not required for seasonal influenza vaccines, which do not even have to meet all three criteria overall to be considered acceptable for the purposes of an annual strain change variation.

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Bri/59/07.HA1 Ab	GROUP A	S-	PI(D0)	12	0	0.0	0.0	26.5
		S+	PI(D0)	60	0	0.0	0.0	6.0
		Total	PI(D0)	72	0	0.0	0.0	5.0
	GROUP B	S-	PI(D0)	15	9	60.0	32.3	83.7
		S+	PI(D0)	57	14	24.6	14.1	37.8
		Total	PI(D0)	72	23	31.9	21.4	44.0

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/Bri/59/07.HA1 Ab (1/DIL)	GROUP A	S-	PI(D0)	12	1.1	0.9	1.2
		S+	PI(D0)	60	1.0	0.9	1.0
		Total	PI(D0)	72	1.0	0.9	1.0
	GROUP B	S-	PI(D0)	15	12.7	5.3	30.4
		S+	PI(D0)	57	2.3	1.9	2.8
		Total	PI(D0)	72	3.3	2.5	4.4

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Bri/59/07.HA1 Ab	GROUP A	S-	PI(D -21)	12	0	0.0	0.0	26.5
			PI(D0)	12	0	0.0	0.0	26.5
		S+	PI(D -21)	60	26	43.3	30.6	56.8
			PI(D0)	60	25	41.7	29.1	55.1
		Total	PI(D -21)	72	26	36.1	25.1	48.3
			PI(D0)	72	25	34.7	23.9	46.9
	GROUP B	S-	PI(D -21)	15	0	0.0	0.0	21.8
			PI(D0)	15	9	60.0	32.3	83.7
		S+	PI(D -21)	58	18	31.0	19.5	44.5
			PI(D0)	57	36	63.2	49.3	75.6
		Total	PI(D -21)	73	18	24.7	15.3	36.1
			PI(D0)	72	45	62.5	50.3	73.6

HI antibodies against A/Uru/07 (TVC)

					>= 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/Uru/07.HA3 Ab	GROUP A	S-	PI(D -21)	13	0	0.0	0.0	24.7	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	13	1	7.7	0.2	36.0	5.3	4.7	5.9	<10.0	10.0
		S+	PI(D -21)	59	59	100	93.9	100	41.6	31.8	54.5	10.0	320.0
			PI(D0)	59	58	98.3	90.9	100	39.9	30.5	52.3	<10.0	320.0
		Total	PI(D -21)	72	59	81.9	71.1	90.0	28.4	21.2	38.0	<10.0	320.0
			PI(D0)	72	59	81.9	71.1	90.0	27.7	20.8	36.9	<10.0	320.0
	GROUP B	S-	PI(D -21)	16	0	0.0	0.0	20.6	5.0	5.0	5.0	<10.0	<10.0
			PI(D0)	16	16	100	79.4	100	64.4	35.7	115.9	10.0	320.0
		S+	PI(D -21)	57	57	100	93.7	100	36.3	26.2	50.1	10.0	2560.0
			PI(D0)	56	55	98.2	90.4	100	118.1	86.7	160.7	<10.0	3620.0
		Total	PI(D -21)	73	57	78.1	66.9	86.9	23.5	17.1	32.2	<10.0	2560.0
			PI(D0)	72	71	98.6	92.5	100	103.2	78.5	135.5	<10.0	3620.0

As shown in the tables below, the three CHMP criteria were met in subsets that were seronegative or already seropositive at D-21 against **A/Uruguay (H3N2).**

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Uru/07.HA3 Ab	GROUP A	S-	PI(D0)	13	0	0.0	0.0	24.7
		S+	PI(D0)	59	0	0.0	0.0	6.1
		Total	PI(D0)	72	0	0.0	0.0	5.0
	GROUP B	S-	PI(D0)	16	12	75.0	47.6	92.7
		S+	PI(D0)	56	24	42.9	29.7	56.8
		Total	PI(D0)	72	36	50.0	38.0	62.0

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/Uru/07.HA3 Ab (1/DIL)	GROUP A	S-	PI(D0)	13	1.1	0.9	1.2
		S+	PI(D0)	59	1.0	0.9	1.0
		Total	PI(D0)	72	1.0	0.9	1.0
	GROUP B	S-	PI(D0)	16	12.9	7.1	23.2
		S+	PI(D0)	56	3.3	2.5	4.3
		Total	PI(D0)	72	4.4	3.3	5.9

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Uru/07.HA3 Ab	GROUP A	S-	PI(D -21)	13	0	0.0	0.0	24.7
			PI(D0)	13	0	0.0	0.0	24.7
		S+	PI(D -21)	59	36	61.0	47.4	73.5
			PI(D0)	59	35	59.3	45.7	71.9
		Total	PI(D -21)	72	36	50.0	38.0	62.0
			PI(D0)	72	35	48.6	36.7	60.7
	GROUP B	S-	PI(D -21)	16	0	0.0	0.0	20.6
			PI(D0)	16	12	75.0	47.6	92.7
		S+	PI(D -21)	57	25	43.9	30.7	57.6
			PI(D0)	56	50	89.3	78.1	96.0
		Total	PI(D -21)	73	25	34.2	23.5	46.3
			PI(D0)	72	62	86.1	75.9	93.1

The three CHMP criteria were met in subsets that were seronegative or already seropositive at D-21 against **B/Brisbane.**

HI antibodies against B/Bri/08 (TVC)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	**Group**	**Pre-vacc status**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
FluB/Bri/08.HA Ab	GROUP A	S+	PI(D -21)	72	72	100	95.0	100	121.1	100.3	146.0	10.0	1280.0
			PI(D0)	72	72	100	95.0	100	117.0	97.8	140.0	14.0	640.0
		Total	PI(D -21)	72	72	100	95.0	100	121.1	100.3	146.0	10.0	1280.0
			PI(D0)	72	72	100	95.0	100	117.0	97.8	140.0	14.0	640.0
	GROUP B	S+	PI(D -21)	73	73	100	95.1	100	134.9	107.6	169.1	28.0	1280.0
			PI(D0)	72	72	100	95.0	100	348.9	286.8	424.5	57.0	1810.0
		Total	PI(D -21)	73	73	100	95.1	100	134.9	107.6	169.1	28.0	1280.0
			PI(D0)	72	72	100	95.0	100	348.9	286.8	424.5	57.0	1810.0

As noted above all subjects were seropositive against B/Brisbane before receiving Fluarix or placebo. Indeed, almost all were already seroprotected. The SCR was not met but the SCF and SPR criteria were met at D0 in Group B.

					SCR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
FluB/Bri/08.HA Ab	GROUP A	S+	PI(D0)	72	1	1.4	0.0	7.5
		Total	PI(D0)	72	1	1.4	0.0	7.5
	GROUP B	S+	PI(D0)	72	19	26.4	16.7	38.1
		Total	PI(D0)	72	19	**26.4**	16.7	38.1

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
FluB/Bri/08.HA Ab (1/DIL)	GROUP A	S+	PI(D0)	72	1.0	0.9	1.0
		Total	PI(D0)	72	1.0	0.9	1.0
	GROUP B	S+	PI(D0)	72	2.6	2.1	3.2
		Total	PI(D0)	72	2.6	2.1	3.2

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
FluB/Bri/08.HA Ab	GROUP A	S+	PI(D -21)	72	69	95.8	88.3	99.1
			PI(D0)	72	69	95.8	88.3	99.1
		Total	PI(D -21)	72	69	95.8	88.3	99.1
			PI(D0)	72	69	95.8	88.3	99.1
	GROUP B	S+	PI(D -21)	73	69	94.5	86.6	98.5
			PI(D0)	72	72	100	95.0	100
		Total	PI(D -21)	73	69	94.5	86.6	98.5
			PI(D0)	72	72	100	95.0	100

Discussion on immunogenicity

Overall comparison between group A and B

Although pre-study exposure to seasonal vaccination was clearly higher in Group A than Group B the D-21 seropositivity rates against H1N1v were comparable between the two groups and very much as expected from the MAH's other studies in adults (i.e. about one third were seropositive at D-21).

At D0 subjects in Group B (who had received Fluarix at D-21) showed a marked increase in seropositivity rate against H1N1v (from 33% to 75%) but the GMTs showed virtually no change from D-21 to D0 and the seroprotection rate increased only from 7% to 18%.

At D21 after a dose of Pandemrix the subjects who had received Fluarix at D-21 (Group B) showed lower SCRs and SCFs overall compared to Group A. In each case the difference between Group A and Group B was driven by the much lower SCRs and SCFs in Group B subjects who were seropositive at D0. It is particularly notable that there was such a difference in SCFs since the D0 GMTs were not markedly different between Groups A and B.

The SPRs at D21 after a dose of Pandemrix were numerically lower in Group B overall and within each subset that had been seropositive or seronegative at D-21. However, the marked difference was between the subsets that had been seropositive at D-21 with 100% seroprotected at D21 in group A compared to 87% in Group B.

Despite the differences all the CHMP criteria were met at D21 in each of Groups A and B and regardless of pre-vaccination serostatus.
The results do suggest that exposure to Fluarix at three weeks before Pandemrix is given might result in lower HI responses to H1N1. However, since all the CHMP criteria are comfortably exceeded regardless of whether Fluarix was or was not given, the data do not indicate any need to preclude the administration of Pandemrix H1N1 when at least 3 weeks have elapsed after a dose of Fluarix. This finding could reasonably be extrapolated to administration of Pandemrix after other non-adjuvanted seasonal influenza vaccines.

There was a baseline imbalance in seasonal vaccine exposures over the last 3 years before study entry between Groups A and B. Although the D-21 HI seropositivity rates were comparable between Groups A and B despite this imbalance, it cannot be ruled out that some of the difference in the D21 responses to Pandemrix might be related to more extensive past exposure to seasonal influenza antigens in Group A compared to Group B resulting in a priming effect not detectable solely based on D-21 HI antibody status.

In this regard, the MAH did not provide analysis of responses according to prior vaccination history but the assessor considers that this would anyway not likely be helpful due to the high rates of any vaccination in the three preceding winters and the variability in exposure to different vaccine strains. The critical data are the responses by pre-Pandemrix HI serostatus plus the important analyses by age cohorts as described above.

Analysis by age cohort
The general pattern of responses according to Group and B and baseline or D0 serostatus applies also to the age cohorts 61-70 years and 71-80 years but the 95% CI more often overlap.

Most importantly, for each subset the D21 HI responses to H1N1v exceed the CHMP criteria for each of the three age cohorts. This finding supports the conclusion that there is no need to preclude administration of Pandemrix provided that at least 3 weeks have elapsed since administration of a non-adjuvanted seasonal influenza vaccine.

Immune response to Fluarix

The CHMP considered that the immune responses to a dose of Fluarix were satisfactory. The level of HI responses to the three strains suggest that the conclusions drawn regarding any prior effect of Fluarix on responses to Pandemrix should be generally valid.

Clinical safety

Safety following vaccination with Fluarix or Placebo at D-21

The overall comparisons between Group A (placebo) and Group B (Fluarix) in the four tables below indicate that the seasonal unadjuvanted vaccine was of low reactogenicity in this population of healthy subjects aged > 60 years. That is, overall rates were not markedly higher after Fluarix compared to placebo although there was more of a difference for local symptoms than for general symptoms.

Symptoms (solicited and unsolicited) reported during the 7-days post-vaccination

	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**
GROUP A	72	17	23.6	14.4	35.1	72	14	19.4	11.1	30.5	72	7	9.7	4.0	19.0
GROUP B	73	25	34.2	23.5	46.3	73	17	23.3	14.2	34.6	73	13	17.8	9.8	28.5

Grade 3 or 4 symptoms (solicited and unsolicited) reported during the 7-days post-vaccination

	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**
GROUP A	72	1	1.4	0.0	7.5	72	1	1.4	0.0	7.5	72	0	0.0	0.0	5.0
GROUP B	73	3	4.1	0.9	11.5	73	2	2.7	0.3	9.5	73	1	1.4	0.0	7.4

Symptoms causally related (solicited and unsolicited) reported during the 7-days post- vaccination

	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**
GROUP A	72	13	18.1	10.0	28.9	72	9	12.5	5.9	22.4	72	7	9.7	4.0	19.0
GROUP B	73	21	28.8	18.8	40.6	73	12	16.4	8.8	27.0	73	13	17.8	9.8	28.5

Grade 3 or 4 symptoms causally related (solicited and unsolicited) reported during the 7-days post-vaccination

	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**
GROUP A	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
GROUP B	73	2	2.7	0.3	9.5	73	1	1.4	0.0	7.4	73	1	1.4	0.0	7.4

Pain at the injection site was the most frequently reported solicited local symptom and was more common in Group B but none was Grade 3 and redness and swelling were reported at low rates.

Solicited local symptoms reported during the 7-days post-vaccination

		GROUP A					GROUP B				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	72	5	6.9	2.3	15.5	72	12	16.7	8.9	27.3
	Grade 1	72	4	5.6	1.5	13.6	72	10	13.9	6.9	24.1
	Grade 2	72	1	1.4	0.0	7.5	72	2	2.8	0.3	9.7
	Grade 3	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
Redness (mm)	All	72	2	2.8	0.3	9.7	72	1	1.4	0.0	7.5
	[20.1 - 50.1[	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	[50.1 - 100.1[	72	1	1.4	0.0	7.5	72	0	0.0	0.0	5.0
	[100.1 - ...	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
Swelling (mm)	All	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	[20.1 - 50.1[	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	[50.1 - 100.1[	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	[100.1 - ...	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0

Fatigue was the most frequently reported solicited general symptom following placebo (12.5%) while headache was the most common following Fluarix (13.9%). Related symptoms and Grade 3 adverse

symptoms were infrequent. Only one subject (in Group B) reported a fever, although this was above 39°C and was considered to be vaccine-related.

Solicited general symptoms reported during the 7-days post-vaccination

		GROUP A					GROUP B				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	72	9	12.5	5.9	22.4	72	7	9.7	4.0	19.0
	Grade 1	72	8	11.1	4.9	20.7	72	5	6.9	2.3	15.5
	Grade 2	72	0	0.0	0.0	5.0	72	2	2.8	0.3	9.7
	Grade 3	72	1	1.4	0.0	7.5	72	0	0.0	0.0	5.0
	Related	72	6	8.3	3.1	17.3	72	6	8.3	3.1	17.3
	Grade 1*Related	72	6	8.3	3.1	17.3	72	5	6.9	2.3	15.5
	Grade 2*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Grade 3*Related	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
Headache	All	72	5	6.9	2.3	15.5	72	10	13.9	6.9	24.1
	Grade 1	72	4	5.6	1.5	13.6	72	9	12.5	5.9	22.4
	Grade 2	72	1	1.4	0.0	7.5	72	1	1.4	0.0	7.5
	Grade 3	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	Related	72	3	4.2	0.9	11.7	72	8	11.1	4.9	20.7
	Grade 1*Related	72	3	4.2	0.9	11.7	72	7	9.7	4.0	19.0
	Grade 2*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Grade 3*Related	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
Joint pain at other location	All	72	7	9.7	4.0	19.0	72	2	2.8	0.3	9.7
	Grade 1	72	5	6.9	2.3	15.5	72	0	0.0	0.0	5.0
	Grade 2	72	1	1.4	0.0	7.5	72	1	1.4	0.0	7.5
	Grade 3	72	1	1.4	0.0	7.5	72	1	1.4	0.0	7.5
	Related	72	4	5.6	1.5	13.6	72	2	2.8	0.3	9.7
	Grade 1*Related	72	3	4.2	0.9	11.7	72	0	0.0	0.0	5.0
	Grade 2*Related	72	1	1.4	0.0	7.5	72	1	1.4	0.0	7.5
	Grade 3*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
Muscle aches	All	72	4	5.6	1.5	13.6	72	6	8.3	3.1	17.3
	Grade 1	72	4	5.6	1.5	13.6	72	4	5.6	1.5	13.6
	Grade 2	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Grade 3	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Related	72	3	4.2	0.9	11.7	72	5	6.9	2.3	15.5
	Grade 1*Related	72	3	4.2	0.9	11.7	72	4	5.6	1.5	13.6
	Grade 2*Related	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	Grade 3*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
Shivering	All	72	2	2.8	0.3	9.7	72	4	5.6	1.5	13.6
	Grade 1	72	2	2.8	0.3	9.7	72	3	4.2	0.9	11.7
	Grade 2	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	Grade 3	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Related	72	2	2.8	0.3	9.7	72	3	4.2	0.9	11.7
	Grade 1*Related	72	2	2.8	0.3	9.7	72	2	2.8	0.3	9.7
	Grade 2*Related	72	0	0.0	0.0	5.0	72	0	0.0	0.0	5.0
	Grade 3*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
Sweating	All	72	5	6.9	2.3	15.5	72	6	8.3	3.1	17.3
	Grade 1	72	5	6.9	2.3	15.5	72	3	4.2	0.9	11.7
	Grade 2	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Grade 3	72	0	0.0	0.0	5.0	72	2	2.8	0.3	9.7
	Related	72	3	4.2	0.9	11.7	72	4	5.6	1.5	13.6
	Grade 1*Related	72	3	4.2	0.9	11.7	72	2	2.8	0.3	9.7
	Grade 2*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5
	Grade 3*Related	72	0	0.0	0.0	5.0	72	1	1.4	0.0	7.5

There were 21 unsolicited AEs reported during the 21-day follow-up period post-Fluarix (13) or placebo (8) but no clinical pattern of events could be distinguished.

Safety following vaccination with H1N1 at D0

All subjects received a dose of Pandemrix H1N1 at D0. The four summary tables do not suggest that local or general reactogenicity was higher in the group that had received Fluarix compared to the group that had received Placebo at D-21.

Symptoms (solicited and unsolicited) reported during the 7-days post-vaccination

	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
GROUP A	71	51	71.8	59.9	81.9	71	30	42.3	30.6	54.6	71	47	66.2	54.0	77.0
GROUP B	71	48	67.6	55.5	78.2	71	28	39.4	28.0	51.7	71	42	59.2	46.8	70.7

Grade 3 or 4 symptoms (solicited and unsolicited) reported during the 7-days post-vaccination

	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
GROUP A	71	2	2.8	0.3	9.8	71	2	2.8	0.3	9.8	71	1	1.4	0.0	7.6
GROUP B	71	2	2.8	0.3	9.8	71	2	2.8	0.3	9.8	71	1	1.4	0.0	7.6

Symptoms causally related (solicited and unsolicited) reported during the 7-days post-vaccination

	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
GROUP A	71	51	71.8	59.9	81.9	71	29	40.8	29.3	53.2	71	47	66.2	54.0	77.0
GROUP B	71	46	64.8	52.5	75.8	71	23	32.4	21.8	44.5	71	42	59.2	46.8	70.7

Grade 3 or 4 symptoms causally related (solicited and unsolicited) reported during the 7-days post-vaccination

	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
GROUP A	71	2	2.8	0.3	9.8	71	2	2.8	0.3	9.8	71	1	1.4	0.0	7.6
GROUP B	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6

Pain at the injection site was the most frequently reported solicited local symptom with comparable rates between Groups A and B. Grade 3 pain was reported by one subject in each group. Redness was reported at comparable rates and swelling in 5.6% in group A and 14.1% in Group B.

Solicited local symptoms reported during the 7-days post-vaccination

		GROUP A					GROUP B				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	71	44	62.0	49.7	73.2	71	40	56.3	44.0	68.1
	Grade 1	71	34	47.9	35.9	60.1	71	30	42.3	30.6	54.6
	Grade 2	71	9	12.7	6.0	22.7	71	9	12.7	6.0	22.7
	Grade 3	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6
Redness (mm)	All	71	7	9.9	4.1	19.3	71	8	11.3	5.0	21.0
	[20.1 - 50.1[	71	5	7.0	2.3	15.7	71	4	5.6	1.6	13.8
	[50.1 - 100.1[	71	2	2.8	0.3	9.8	71	4	5.6	1.6	13.8
	[100.1 - ...	71	0	0.0	0.0	5.1	71	0	0.0	0.0	5.1
Swelling (mm)	All	71	4	5.6	1.6	13.8	71	10	14.1	7.0	24.4
	[20.1 - 50.1[	71	4	5.6	1.6	13.8	71	7	9.9	4.1	19.3
	[50.1 - 100.1[	71	0	0.0	0.0	5.1	71	3	4.2	0.9	11.9
	[100.1 - ...	71	0	0.0	0.0	5.1	71	0	0.0	0.0	5.1

Muscle ache was the most frequently reported solicited general symptom (21.1% in both groups). Grade 3 solicited general adverse events were infrequent in both groups. Only one subject (in Group B) had a fever and this was in the range 38.5-39°C but was not considered vaccine-related.

Solicited general symptoms reported during the 7-days post-vaccination period

		GROUP A					GROUP B				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	71	13	18.3	10.1	29.3	71	10	14.1	7.0	24.4
	Grade 1	71	9	12.7	6.0	22.7	71	4	5.6	1.6	13.8
	Grade 2	71	2	2.8	0.3	9.8	71	6	8.5	3.2	17.5
	Grade 3	71	2	2.8	0.3	9.8	71	0	0.0	0.0	5.1
	Related	71	12	16.9	9.0	27.7	71	8	11.3	5.0	21.0
	Grade 1*Related	71	9	12.7	6.0	22.7	71	3	4.2	0.9	11.9
	Grade 2*Related	71	2	2.8	0.3	9.8	71	5	7.0	2.3	15.7
	Grade 3*Related	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1
Headache	All	71	14	19.7	11.2	30.9	71	9	12.7	6.0	22.7
	Grade 1	71	12	16.9	9.0	27.7	71	5	7.0	2.3	15.7
	Grade 2	71	0	0.0	0.0	5.1	71	4	5.6	1.6	13.8
	Grade 3	71	2	2.8	0.3	9.8	71	0	0.0	0.0	5.1
	Related	71	14	19.7	11.2	30.9	71	8	11.3	5.0	21.0
	Grade 1*Related	71	12	16.9	9.0	27.7	71	5	7.0	2.3	15.7
	Grade 2*Related	71	0	0.0	0.0	5.1	71	3	4.2	0.9	11.9
	Grade 3*Related	71	2	2.8	0.3	9.8	71	0	0.0	0.0	5.1
Joint pain at other location	All	71	11	15.5	8.0	26.0	71	4	5.6	1.6	13.8
	Grade 1	71	9	12.7	6.0	22.7	71	3	4.2	0.9	11.9
	Grade 2	71	0	0.0	0.0	5.1	71	1	1.4	0.0	7.6
	Grade 3	71	2	2.8	0.3	9.8	71	0	0.0	0.0	5.1
	Related	71	8	11.3	5.0	21.0	71	4	5.6	1.6	13.8
	Grade 1*Related	71	7	9.9	4.1	19.3	71	3	4.2	0.9	11.9
	Grade 2*Related	71	0	0.0	0.0	5.1	71	1	1.4	0.0	7.6
	Grade 3*Related	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1
Muscle aches	All	71	15	21.1	12.3	32.4	71	15	21.1	12.3	32.4
	Grade 1	71	12	16.9	9.0	27.7	71	13	18.3	10.1	29.3
	Grade 2	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6
	Grade 3	71	2	2.8	0.3	9.8	71	1	1.4	0.0	7.6
	Related	71	13	18.3	10.1	29.3	71	14	19.7	11.2	30.9
	Grade 1*Related	71	11	15.5	8.0	26.0	71	12	16.9	9.0	27.7
	Grade 2*Related	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6
	Grade 3*Related	71	1	1.4	0.0	7.6	71	1	1.4	0.0	7.6
Shivering	All	71	4	5.6	1.6	13.8	71	8	11.3	5.0	21.0
	Grade 1	71	2	2.8	0.3	9.8	71	5	7.0	2.3	15.7
	Grade 2	71	1	1.4	0.0	7.6	71	3	4.2	0.9	11.9
	Grade 3	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1
	Related	71	4	5.6	1.6	13.8	71	4	5.6	1.6	13.8
	Grade 1*Related	71	2	2.8	0.3	9.8	71	2	2.8	0.3	9.8
	Grade 2*Related	71	1	1.4	0.0	7.6	71	2	2.8	0.3	9.8
	Grade 3*Related	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1
Sweating	All	71	4	5.6	1.6	13.8	71	7	9.9	4.1	19.3
	Grade 1	71	3	4.2	0.9	11.9	71	5	7.0	2.3	15.7
	Grade 2	71	0	0.0	0.0	5.1	71	2	2.8	0.3	9.8
	Grade 3	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1
	Related	71	3	4.2	0.9	11.9	71	3	4.2	0.9	11.9
	Grade 1*Related	71	2	2.8	0.3	9.8	71	2	2.8	0.3	9.8
	Grade 2*Related	71	0	0.0	0.0	5.1	71	1	1.4	0.0	7.6
	Grade 3*Related	71	1	1.4	0.0	7.6	71	0	0.0	0.0	5.1

There were 36 unsolicited AEs reported during the 21-day follow-up period with 17 in Group A (23.9%) and 19 in Group B (26.8%). No clinical pattern of events could be distinguished. Unsolicited AEs considered related to vaccination were reported by 11 (15.5%) and 6 (8.5%) in respective groups. Grade 3 unsolicited AEs were infrequent and none was considered related to vaccination.

Unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term, within 21 days follow-up

		GROUP A N = 71				GROUP B N = 71			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		17	23.9	14.6	35.5	19	26.8	16.9	38.6
---------- ( )	---------- ( )	2	2.8	0.3	9.8	5	7.0	2.3	15.7
Cardiac disorders (10007541)	Palpitations (10033557)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
Eye disorders (10015919)	Visual impairment (10047571)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
Gastrointestinal disorders (10017947)	Abdominal pain upper (10000087)	1	1.4	0.0	7.6	1	1.4	0.0	7.6
	Diarrhoea (10012735)	1	1.4	0.0	7.6	1	1.4	0.0	7.6
General disorders and administration site conditions (10018065)	Injection site pruritus (10022093)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
Infections and infestations (10021881)	Bronchitis (10006451)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Cystitis (10011781)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Nasopharyngitis (10028810)	8	11.3	5.0	21.0	5	7.0	2.3	15.7
	Pneumonia (10035664)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Tinea pedis (10043873)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
Injury, poisoning and procedural complications (10022117)	Contusion (10050584)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
	Radius fracture (10037802)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
Investigations (10022891)	Blood glucose decreased (10005555)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
Musculoskeletal and connective tissue disorders (10028395)	Arthralgia (10003239)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
	Back pain (10003988)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Pain in extremity (10033425)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
Nervous system disorders (10029205)	Dementia (10012267)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	1.4	0.0	7.6	1	1.4	0.0	7.6
Vascular disorders (10047065)	Hypertension (10020772)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Hypertensive crisis (10020802)	0	0.0	0.0	5.1	1	1.4	0.0	7.6
	Peripheral coldness (10034568)	1	1.4	0.0	7.6	0	0.0	0.0	5.1
	Thrombophlebitis (10043570)	1	1.4	0.0	7.6	0	0.0	0.0	5.1

Serious Adverse Events (SAEs) and AEs of special interest (AESI)

No AESIs were reported and no subject had withdrawn due to an AE up to time-point D21.

Four SAEs were reported by four subjects during the period covered by this report. One report of myalgia following Fluarix was considered as related to vaccination by the investigator.

SAEs during the entire follow-up period (Total Vaccinated Cohort)

		GROUP A N = 72				GROUP B N = 73			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		2	2.8	0.3	9.7	2	2.7	0.3	9.5
Injury, poisoning and procedural complications (10022117)	Lumbar vertebral fracture (10049947)	1	1.4	0.0	7.5	0	0.0	0.0	4.9
	Radius fracture (10037802)	1	1.4	0.0	7.5	0	0.0	0.0	4.9
	Spinal compression fracture (10041541)	0	0.0	0.0	5.0	1	1.4	0.0	7.4
Musculoskeletal and connective tissue disorders (10028395)	Myalgia (10028411)	0	0.0	0.0	5.0	1	1.4	0.0	7.4

Discussion on safety

The data post-Pandemrix were as expected from previous studies in this age group and do not indicate a higher rate of AEs when Pandemrix is given three weeks after Fluarix compared to three weeks after placebo.

1.3 Conclusions and Benefit / Risk Assessment

At 21 days after a first dose of Pandemrix (H1N1) all CHMP and CBER regulatory acceptance criteria were met regardless of whether or not Fluarix had been given three weeks previously. This conclusion also applied within each of the age cohorts 61-70 years, 71-80 years and over 80 years.

There was a detectable effect of prior Fluarix vaccination in terms of lower SCRs, SCFs and SPRs at D21 in the group that had received Fluarix compared to the group that had received Placebo at D-21. The 95% CI did not overlap for the SCRs and SCFs but did overlap for the SPRs. The same pattern was seen in each of the age cohorts 61-70 and 71-80 years. There were too few subjects aged > 80 years (and 5/6 were seropositive against H1N1v at D-21) for any conclusions to be drawn regarding any effect of prior Fluarix on responses to Pandemrix (H1N1).

The reactogenicity profile was comparable to that seen in other studies conducted in adults of this age group and there was no effect of prior Fluarix on the reactogenicity of Pandemrix (H1N1).

Overall, and despite the pattern of immune responses observed, the data suggest that there is unlikely to be a clinically important effect of prior vaccination with non-adjuvanted seasonal influenza vaccines on the safety or immunogenicity of Pandemrix in subjects aged > 60 years.

1.4 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:

- The PL was updated to better reflect the wording in section 4.5 of the SPC.