European Medicines Agency

London, 19 Novmeber 2009
Doc. Ref: EMEA/CHMP/763933/2009

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/0025

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.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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 section 4.5 of the Summary of Product Characteristics (SPC) for Pandemrix H1N1 to reflect the first preliminary results of study D-Pan-H1N1-018 (called "H1N1-018" in this report). This synoptic report of D21 safety and immunogenicity data (HI only) was assessed in the report on the specific obligation SOB 053 (circulated 10.11.09).

In support of this variation the MAH has submitted a synoptic report of day 21 (D21) safety and immunogenicity data (HI only) from study H1N1-018

The MAH also provided data from study 018 specific to subjects aged over 80 years and safety data by age strata that were requested following review of SOB 053.

In addition, as the potential impact of temperature of the rubber stopper is considered to be related to the appearance of coring the MAH also proposed to update section 6.6 of the SPC and section 6 of the Package Leaflet in view of the instructions for reconstituting the vaccine.

This variation has been submitted to fulfil SOB 053 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

FLU D-PAN H1N1-018

This is a phase II, randomised, observer-blind, 2 centre (Sweden) study to evaluate the immunogenicity, safety and reactogenicity of a two-dose schedule with Pandemrix H1N1 containing the AS03 adjuvant when co-administered with the seasonal 2009-2010 influenza vaccine Fluarix either at the time of the first or second Pandemrix H1N1 vaccination in elderly subjects aged 61 years and older.

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.

Both groups will then be followed up serologically at D42, M6 and at M12 to determine whether there is any advantage for two doses of Pandemrix H1N1 over a single dose in the longer term: to assess whether co-administration of two influenza vaccines has an effect on immunogenicity/safety of either vaccine and additionally to assess the immune response to Fluarix when administered with a second Pandemrix H1N1 vaccine.

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 in the PAN-F group and a dose of Fluarix co-administered with Pandemrix H1N1 in the F-PAN group are available. The MAH provided an abridged study report that covers the post-dose I immunogenicity results (i.e. at D21) together with data on reactogenicity, AEs and SAEs.

The complete list of objectives for study D-Pan-H1N1-018 is detailed below. However, only the post Dose 1 (Day 21) results are available at this point.

The co-primary objectives are:

• To assess whether vaccination with two doses of the H1N1 candidate vaccine results in an HI immune response to the vaccine-homologous virus that meets or exceeds the EMEA (CHMP) guidance targets for pandemic influenza vaccines (seroconversion rate (SCR), seroprotection rate (SPR), and seroconversion factor (SCF)) at 21 days after the second dose of H1N1 vaccine when co-administered with Fluarix either at the time of first or second vaccination in elderly subjects aged 61 years and older.

• To assess whether vaccination with one dose of Fluarix results in an HI immune response that meets or exceeds for each vaccine strain of the seasonal vaccine at least one of the EMEA (CHMP) guidance targets for seasonal influenza vaccines (SCR, and/or SPR and/or SCF) at 21 days after vaccination when co-administered with either the first or second dose of the H1N1 candidate vaccine in elderly subjects aged 61 years and older.

The secondary objectives are:

- To assess the immune response of two doses of the H1N1 candidate vaccine in terms of vaccine-homologous virus HI response 21 days after each dose of H1N1 vaccine when co-administered with Fluarix either at the time of first or second vaccination in elderly subjects aged 61 years and older.
- To assess the immune response of one dose of Fluarix in terms of HI response 21 days after vaccination when co-administered with either the first or second dose of the H1N1 candidate vaccine in elderly subjects aged 61 years and older.
- To assess the safety of the vaccine regimens in terms of solicited local and general 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) and serious adverse events (SAEs) for the entire study period.

The placebo used in the study was saline

The study planned to enrol 168 subjects aged at least 61 years (84 subjects in F-PAN group and 84 subjects in the PAN-F group and stratified by age; 112 in the 61-70 years stratum and 56 in the >70 years stratum) with allocation to two parallel vaccine groups. Subjects were to be stratified into two age strata (61-70 and > 70 years)

- The analyses reported thus far were performed on uncleaned data.
- 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

Demographics

As was planned, the study enrolled 168 subjects, including 112 aged 61-70 years and 56 aged > 70 years.

Within each vaccination cohort the percentage of gender was variable but all values fell within 50-56%. All subjects were Caucasian.

There is no information on whether any subject received vaccination for the 2009/10 season but the rate of prior vaccination in the individual three previous seasons ranged from 52.4% -73.8%.
More subjects in the PAN-F group had a history of previous influenza vaccination (82.1%) compared with the F-PAN group (72.6%).

History of influenza vaccination in the previous 3 seasons (Total vaccinated cohort)

		F-PAN N = 84		PAN-F N = 84		Total N = 168	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
At least one season	Yes	61	72.6	69	82.1	130	77.4
	No	23	27.4	15	17.9	38	22.6
Season 2006-2007	Yes	44	52.4	50	59.5	94	56.0
Season 2007-2008	Yes	49	58.3	59	70.2	108	64.3
Season 2008-2009	Yes	53	63.1	62	73.8	115	68.5

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix
N = Total number of subjects
n = number of subjects with influenza vaccination during the specified season
% = n / Number of subjects with available results x 100

Immune responses to Flu A/CAL/09 HA1.

- As shown below between 21.4-28% of subjects were seropositive in the F-PAN group compared with 37.5-39.3% in the PAN-F group.
- At Day 21, all except one subject aged >70 years in the F-PAN group were seropositive.
- The D21 **seroprotection rates** exceeded 87% in both vaccine cohorts. There was a trend for slightly lower rates in the F-PAN group but the 95% CI all overlapped and the lowest rate observed was 87.5%. There was no difference in SPR between the age groups.
- The D21 **seroconversion rates** were high and exceeded 87% in both vaccine cohorts and both age groups. There was a trend for marginally lower rates in the F-PAN group but the 95% CI all overlapped and the lowest rate observed was 87.5%. There was no difference in SCR between the age groups.
- The **seroconversion factors** decreased with increasing age but there was overlap in 95% CI between the two age groups. The lowest SCF exceeded 13.

Immune responses to FluA/Bri/07.HA1, Flu A/Uru/07.HA3 and FluB/Bri/08.HA

Baseline seropositivity for FluA/Bri/07.HA1, Flu A/Uru/07.HA3 and FluB/Bri/08.HA was very high in both vaccine cohorts, with a tendency for a higher level in the older groups (>70 yrs).

D21 seroprotection rates raged from 67.9% (in the >70 years for A/Bri/07) to 100% (both age cohorts for B/Bri/09)
Seroconversion rates were not met for those >70 years for H1N1 Brisbane, H3N1 or B/Brisbane
Seroconversion factor and seropositivity rates were satisfactory for both age strata.

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09.HA1, Flu A/Bri/07.HA1, Flu A/Uru/07.HA3 and FluB/Bri/08.HA by age strata (Total vaccinated cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/09.HA1 Ab	F-PAN	61-70Y	PRE	56	12	21.4	11.6	34.4	6.9	5.7	8.4	<10.0	80.0
			PI(D21)	56	56	100	93.6	100	155.0	112.9	213.0	14.0	2560.0
		>70Y	PRE	28	8	28.6	13.2	48.7	8.4	5.4	13.0	<10.0	453.0
			PI(D21)	28	27	96.4	81.7	99.9	111.8	73.7	169.8	<10.0	640.0
	PAN-F	61-70Y	PRE	56	21	37.5	24.9	51.5	8.2	6.6	10.2	<10.0	320.0
			PI(D21)	56	56	100	93.6	100	180.0	139.7	231.9	20.0	905.0
		>70Y	PRE	28	11	39.3	21.5	59.4	9.2	6.3	13.3	<10.0	160.0
			PI(D21)	28	28	100	87.7	100	146.8	103.8	207.5	40.0	453.0
Flu A/Bri/07.HA1 Ab	F-PAN	61-70Y	PRE	56	36	64.3	50.4	76.6	13.3	10.3	17.1	<10.0	113.0
			PI(D21)	56	56	100	93.6	100	59.4	44.8	78.8	10.0	640.0
		>70Y	PRE	28	24	85.7	67.3	96.0	20.7	14.9	29.0	<10.0	80.0
			PI(D21)	28	27	96.4	81.7	99.9	43.0	31.4	58.9	<10.0	113.0
	PAN-F	61-70Y	PRE	56	43	76.8	63.6	87.0	14.4	11.5	18.0	<10.0	80.0
		>70Y	PRE	28	25	89.3	71.8	97.7	19.7	14.1	27.5	<10.0	160.0
Flu A/Uru/07.HA3 Ab	F-PAN	61-70Y	PRE	56	35	62.5	48.5	75.1	15.3	11.3	20.8	<10.0	160.0
			PI(D21)	56	53	94.6	85.1	98.9	83.1	58.9	117.1	<10.0	905.0
		>70Y	PRE	28	24	85.7	67.3	96.0	25.0	17.0	36.7	<10.0	160.0
			PI(D21)	28	27	96.4	81.7	99.9	60.1	41.4	87.3	<10.0	320.0
	PAN-F	61-70Y	PRE	56	37	66.1	52.2	78.2	19.1	13.8	26.6	<10.0	320.0
		>70Y	PRE	28	20	71.4	51.3	86.8	20.7	12.5	34.5	<10.0	320.0
FluB/Bri/08.HA Ab	F-PAN	61-70Y	PRE	56	50	89.3	78.1	96.0	43.6	31.4	60.5	<10.0	905.0
			PI(D21)	56	56	100	93.6	100	249.8	206.0	302.9	57.0	1280.0
		>70Y	PRE	28	27	96.4	81.7	99.9	64.8	45.2	92.8	<10.0	453.0
			PI(D21)	28	28	100	87.7	100	210.2	154.4	286.2	57.0	1280.0
	PAN-F	61-70Y	PRE	56	56	100	93.6	100	96.3	78.2	118.6	20.0	640.0
		>70Y	PRE	28	28	100	87.7	100	166.1	119.4	230.9	20.0	640.0

Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09.HA1, Flu A/Bri/07.HA1, Flu A/Uru/07.HA3 and FluB/Bri/08.HA at visit 1 Day 0 and PI(D21) by age strata (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	61-70Y	PRE	56	3	5.4	1.1	14.9
			PI(D21)	56	49	87.5	75.9	94.8
		>70Y	PRE	28	3	10.7	2.3	28.2
			PI(D21)	28	26	92.9	76.5	99.1
	PAN-F	61-70Y	PRE	56	3	5.4	1.1	14.9
			PI(D21)	56	53	94.6	85.1	98.9
		>70Y	PRE	28	4	14.3	4.0	32.7
			PI(D21)	28	28	100	87.7	100
Flu A/Bri/07.HA1 Ab	F-PAN	61-70Y	PRE	56	13	23.2	13.0	36.4
			PI(D21)	56	39	69.6	55.9	81.2
		>70Y	PRE	28	10	35.7	18.6	55.9
			PI(D21)	28	19	67.9	47.6	84.1
	PAN-F	61-70Y	PRE	56	10	17.9	8.9	30.4
		>70Y	PRE	28	7	25.0	10.7	44.9
Flu A/Uru/07.HA3 Ab	F-PAN	61-70Y	PRE	56	17	30.4	18.8	44.1
			PI(D21)	56	44	78.6	65.6	88.4
		>70Y	PRE	28	13	46.4	27.5	66.1
			PI(D21)	28	22	78.6	59.0	91.7
	PAN-F	61-70Y	PRE	56	22	39.3	26.5	53.2
		>70Y	PRE	28	9	32.1	15.9	52.4
FluB/Bri/08.HA Ab	F-PAN	61-70Y	PRE	56	36	64.3	50.4	76.6
			PI(D21)	56	56	100	93.6	100
		>70Y	PRE	28	21	75.0	55.1	89.3
			PI(D21)	28	28	100	87.7	100
	PAN-F	61-70Y	PRE	56	51	91.1	80.4	97.0
		>70Y	PRE	28	27	96.4	81.7	99.9

Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09.HA1, Flu A/Bri/07.HA1, Flu A/Uru/07.HA3 and FluB/Bri/08.HA at PI(D21) by age strata (Total vaccinated cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	61-70Y	PI(D21)	56	49	87.5	75.9	94.8
		>70Y	PI(D21)	28	25	89.3	71.8	97.7
	PAN-F	61-70Y	PI(D21)	56	52	92.9	82.7	98.0
		>70Y	PI(D21)	28	26	92.9	76.5	99.1
Flu A/Bri/07.HA1 Ab	F-PAN	61-70Y	PI(D21)	56	28	50.0	36.3	63.7
		>70Y	PI(D21)	28	3	10.7	2.3	28.2
Flu A/Uru/07.HA3 Ab	F-PAN	61-70Y	PI(D21)	56	30	53.6	39.7	67.0
		>70Y	PI(D21)	28	6	21.4	8.3	41.0
FluB/Bri/08.HA Ab	F-PAN	61-70Y	PI(D21)	56	33	58.9	45.0	71.9
		>70Y	PI(D21)	28	8	28.6	13.2	48.7

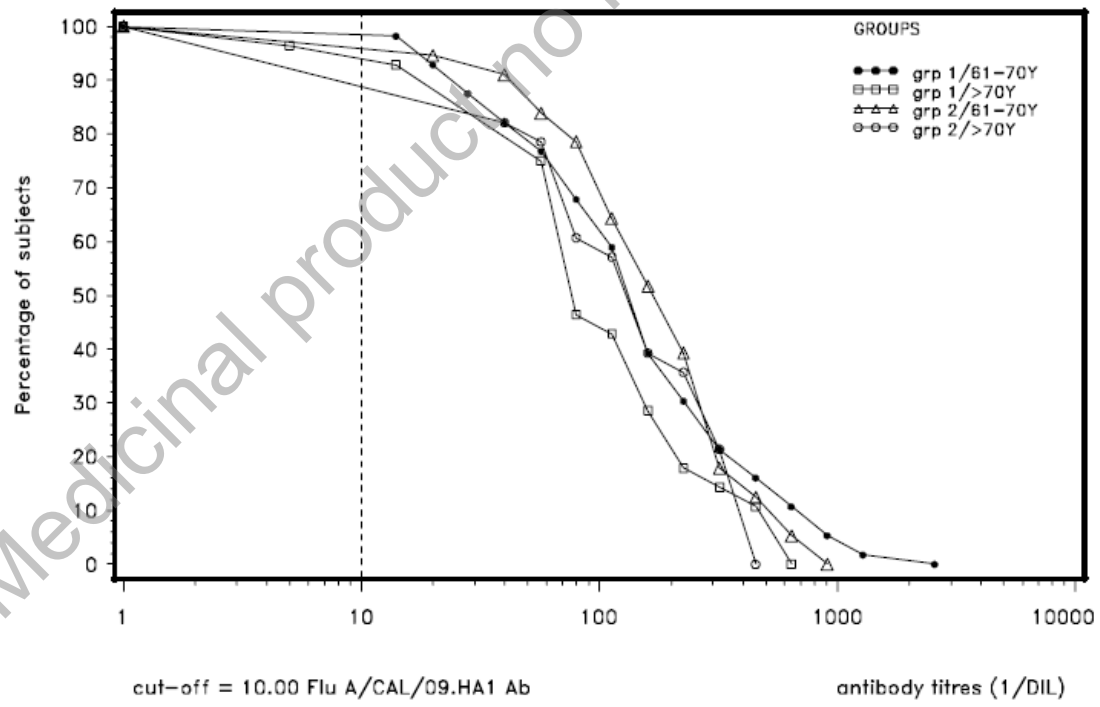
Seroconversion factor (SCF) for HI antibody titer at PI(D21) by age strata (Total vaccinated cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	F-PAN	61-70Y	PI(D21)	56	22.4	16.5	30.2
		>70Y	PI(D21)	28	13.3	9.0	19.7
	PAN-F	61-70Y	PI(D21)	56	22.0	16.7	29.0
		>70Y	PI(D21)	28	16.0	10.3	24.9

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/Bri/07.HA1 Ab (1/DIL)	F-PAN	61-70Y	PI(D21)	56	4.5	3.5	5.8
		>70Y	PI(D21)	28	2.1	1.6	2.7
Flu A/Uru/07.HA3 Ab (1/DIL)	F-PAN	61-70Y	PI(D21)	56	5.4	3.9	7.6
		>70Y	PI(D21)	28	2.4	1.8	3.2
FluB/Bri/08.HA Ab (1/DIL)	F-PAN	61-70Y	PI(D21)	56	5.7	4.1	7.9
		>70Y	PI(D21)	28	3.2	2.2	4.7

The reverse cumulative distribution curve shown below demonstrates similar results in both vaccine cohorts and both age groups.

Reverse cumulative distribution curve (PI (D21)) of anti-HI antibody titer against A/California/7/2009(H1N1)v-like strain 21 days after dose 1 by age-strata (Total vaccinated cohort)



grp 1 = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
grp 2 = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix
61-70Y = Subjects aged between and including 61 years to 70 years
>70Y = Subjects aged more than 70 years

The D21 responses to responses to FluA/Bri/07.HA1H1N1 according to baseline serostatus are shown below for the 2 vaccination cohorts.
The D21 seroprotection rates are higher in those who are seropositive at baseline, but the lowest rate observed exceeded 85%.

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09.HA1 by pre-vaccination serostatus (Total vaccinated cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vaccination status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	64	0	0.0	0.0	5.6	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	64	63	98.4	91.6	100	113.7	86.1	150.2	<10.0	1280.0
		S+	PRE	20	20	100	83.2	100	25.9	15.4	43.3	10.0	453.0
			PI(D21)	20	20	100	83.2	100	264.7	161.0	435.2	57.0	2560.0
		Total	PRE	84	20	23.8	15.2	34.3	7.4	6.1	9.0	<10.0	453.0
			PI(D21)	84	83	98.8	93.5	100	139.1	108.2	178.6	<10.0	2560.0
	PAN-F	S-	PRE	52	0	0.0	0.0	6.8	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	52	52	100	93.2	100	140.1	110.0	178.4	20.0	453.0
		S+	PRE	32	32	100	89.1	100	20.2	14.8	27.5	10.0	320.0
			PI(D21)	32	32	100	89.1	100	226.3	160.1	319.9	40.0	905.0
		Total	PRE	84	32	38.1	27.7	49.3	8.5	7.1	10.2	<10.0	320.0
			PI(D21)	84	84	100	95.7	100	168.2	137.5	205.7	20.0	905.0

Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09.HA1 at visit 1 Day 0 and at PI (D21) by pre-vaccination serostatus (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	64	0	0.0	0.0	5.6
			PI(D21)	64	55	85.9	75.0	93.4
		S+	PRE	20	6	30.0	11.9	54.3
			PI(D21)	20	20	100	83.2	100
		Total	PRE	84	6	7.1	2.7	14.9
			PI(D21)	84	75	89.3	80.6	95.0
	PAN-F	S-	PRE	52	0	0.0	0.0	6.8
			PI(D21)	52	49	94.2	84.1	98.8
		S+	PRE	32	7	21.9	9.3	40.0
			PI(D21)	32	32	100	89.1	100
		Total	PRE	84	7	8.3	3.4	16.4
			PI(D21)	84	81	96.4	89.9	99.3

Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) by pre-vaccination serostatus (Total vaccinated cohort)

					SCR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PI(D21)	64	55	85.9	75.0	93.4
		S+	PI(D21)	20	19	95.0	75.1	99.9
		Total	PI(D21)	84	74	88.1	79.2	94.1
	PAN-F	S-	PI(D21)	52	49	94.2	84.1	98.8
		S+	PI(D21)	32	29	90.6	75.0	98.0
		Total	PI(D21)	84	78	92.9	85.1	97.3

Seroconversion factor (SCF) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) by pre-vaccination serostatus (Total vaccinated cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Pre-vaccination status	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	F-PAN	S-	PI(D21)	64	22.7	17.2	30.0
		S+	PI(D21)	20	10.2	6.8	15.4
		Total	PI(D21)	84	18.8	14.8	23.9
	PAN-F	S-	PI(D21)	52	28.0	22.0	35.7
		S+	PI(D21)	32	11.2	7.4	17.0
		Total	PI(D21)	84	19.8	15.7	25.0

This data shows that CHMP criteria were met regardless of baseline serostatus and regardless of whether there was co-administration with Fluarix with the first dose of Pandemrix H1N1.

The data was also provided by age 61-70/70+ AND by baseline serostatus.

Age 61-70 yrs

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09.HA1 for Subjects aged between and including 61 years to 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vaccination status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	44	0	0.0	0.0	8.0	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	44	44	100	92.0	100	130.3	91.6	185.3	14.0	1280.0
		S+	PRE	12	12	100	73.5	100	23.0	13.6	39.0	10.0	80.0
			PI(D21)	12	12	100	73.5	100	293.6	146.3	589.2	57.0	2560.0
		Total	PRE	56	12	21.4	11.6	34.4	6.9	5.7	8.4	<10.0	80.0
			PI(D21)	56	56	100	93.6	100	155.0	112.9	213.0	14.0	2560.0
	PAN-F	S-	PRE	35	0	0.0	0.0	10.0	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	35	35	100	90.0	100	139.3	103.1	188.4	20.0	453.0
		S+	PRE	21	21	100	83.9	100	18.6	12.8	27.2	10.0	320.0
			PI(D21)	21	21	100	83.9	100	275.8	181.4	419.4	40.0	905.0
		Total	PRE	56	21	37.5	24.9	51.5	8.2	6.6	10.2	<10.0	320.0
			PI(D21)	56	56	100	93.6	100	180.0	139.7	231.9	20.0	905.0

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix

Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09.HA1 at visit 1 Day 0 and at PI (D21) for Subjects aged between and including 61 years to 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	44	0	0.0	0.0	8.0
			PI(D21)	44	37	84.1	69.9	93.4
		S+	PRE	12	3	25.0	5.5	57.2
			PI(D21)	12	12	100	73.5	100
		Total	PRE	56	3	5.4	1.1	14.9
			PI(D21)	56	49	87.5	75.9	94.8
	PAN-F	S-	PRE	35	0	0.0	0.0	10.0
			PI(D21)	35	32	91.4	76.9	98.2
		S+	PRE	21	3	14.3	3.0	36.3
			PI(D21)	21	21	100	83.9	100
		Total	PRE	56	3	5.4	1.1	14.9
			PI(D21)	56	53	94.6	85.1	98.9

Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) for Subjects aged between and including 61 years to 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SCR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PI(D21)	44	37	84.1	69.9	93.4
		S+	PI(D21)	12	12	100	73.5	100
		Total	PI(D21)	56	49	87.5	75.9	94.8
	PAN-F	S-	PI(D21)	35	32	91.4	76.9	98.2
		S+	PI(D21)	21	20	95.2	76.2	99.9
		Total	PI(D21)	56	52	92.9	82.7	98.0

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix

Seroconversion factor (SCF) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) for Subjects aged between and including 61 years to 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Pre-vaccination status	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	F-PAN	S-	PI(D21)	44	26.1	18.3	37.1
		S+	PI(D21)	12	12.8	7.6	21.4
		Total	PI(D21)	56	22.4	16.5	30.2
	PAN-F	S-	PI(D21)	35	27.9	20.6	37.7
		S+	PI(D21)	21	14.8	8.7	25.2
		Total	PI(D21)	56	22.0	16.7	29.0

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix

For the age group 61-70 years all 3 CHMP criteria are met regardless of baseline serostatus.

Age >70 years

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09.HA1 for Subjects aged more than 70 years by prevaccination serostatus (Total vaccinated cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vaccination status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	20	0	0.0	0.0	16.8	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	20	19	95.0	75.1	99.9	84.3	53.6	132.7	<10.0	320.0
		S+	PRE	8	8	100	63.1	100	30.8	9.0	105.2	10.0	453.0
			PI(D21)	8	8	100	63.1	100	226.5	93.2	550.8	57.0	640.0
		Total	PRE	28	8	28.6	13.2	48.7	8.4	5.4	13.0	<10.0	453.0
			PI(D21)	28	27	96.4	81.7	99.9	111.8	73.7	169.8	<10.0	640.0
	PAN-F	S-	PRE	17	0	0.0	0.0	19.5	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	17	17	100	80.5	100	141.6	90.3	222.0	40.0	453.0
		S+	PRE	11	11	100	71.5	100	23.4	12.5	43.9	10.0	160.0
			PI(D21)	11	11	100	71.5	100	155.2	81.4	295.9	40.0	453.0
		Total	PRE	28	11	39.3	21.5	59.4	9.2	6.3	13.3	<10.0	160.0
			PI(D21)	28	28	100	87.7	100	146.8	103.8	207.5	40.0	453.0

Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09.HA1 at visit 1 Day 0 and at PI (D21) for Subjects aged more than 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	20	0	0.0	0.0	16.8
			PI(D21)	20	18	90.0	68.3	98.8
		S+	PRE	8	3	37.5	8.5	75.5
			PI(D21)	8	8	100	63.1	100
		Total	PRE	28	3	10.7	2.3	28.2
			PI(D21)	28	26	92.9	76.5	99.1
	PAN-F	S-	PRE	17	0	0.0	0.0	19.5
			PI(D21)	17	17	100	80.5	100
		S+	PRE	11	4	36.4	10.9	69.2
			PI(D21)	11	11	100	71.5	100
		Total	PRE	28	4	14.3	4.0	32.7
			PI(D21)	28	28	100	87.7	100

Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) for Subjects aged more than 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SCR			
							95% CI	
Strain	Group	Pre-vaccination status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PI(D21)	20	18	90.0	68.3	98.8
		S+	PI(D21)	8	7	87.5	47.3	99.7
		Total	PI(D21)	28	25	89.3	71.8	97.7
	PAN-F	S-	PI(D21)	17	17	100	80.5	100
		S+	PI(D21)	11	9	81.8	48.2	97.7
		Total	PI(D21)	28	26	92.9	76.5	99.1

Seroconversion factor (SCF) for HI antibodies against Flu A/CAL/09.HA1 at PI (D21) for Subjects aged more than 70 years by pre-vaccination serostatus (Total vaccinated cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Pre-vaccination status	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	F-PAN	S-	PI(D21)	20	16.9	10.7	26.5
		S+	PI(D21)	8	7.3	3.4	15.9
		Total	PI(D21)	28	13.3	9.0	19.7
	PAN-F	S-	PI(D21)	17	28.3	18.1	44.4
		S+	PI(D21)	11	6.6	3.5	12.5
		Total	PI(D21)	28	16.0	10.3	24.9

For the age group >70 years all 3 CHMP criteria are met for responses to H1N1 regardless of baseline serostatus.

Immune responses to Fluarix

The response to Fluarix by age showed that SCR was not met in those >70yrs for H1N1Brisbane, H3N1 or B/Brisbane, but other criteria were met and so the responses passed the minimal CHMP criteria for the age group.

Adults aged >80 years.

There were five subjects aged over 80 years in this study. For responses to Flu A/Cal/09 HAI the following were noted in them:

- At baseline one of the five subjects (in the F-PAN group) was seropositive and this subject was also seroprotected.
- At D21 all subjects in both vaccine cohorts were seropositive and seroprotected.
- All subjects seroconverted.
- The seroconversion factors exceeded the minimum requirement in both groups.

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09.HA1 Ab for subjects aged > 80 years (Total cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	2	0	0.0	0.0	84.2	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	2	2	100	15.8	100	113.1	1.4	9248.7	80.0	160.0
		S+	PRE	1	1	100	2.5	100	113.0	-	-	113.0	113.0
			PI(D21)	1	1	100	2.5	100	453.0	-	-	453.0	453.0
		Total	PRE	3	1	33.3	0.8	90.6	14.1	0.2	1237.2	<10.0	113.0
			PI(D21)	3	3	100	29.2	100	179.7	20.6	1570.2	80.0	453.0
	PAN-F	S-	PRE	2	0	0.0	0.0	84.2	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	2	2	100	15.8	100	56.6	0.7	4624.3	40.0	80.0
		Total	PRE	2	0	0.0	0.0	84.2	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	2	2	100	15.8	100	56.6	0.7	4624.3	40.0	80.0

1. F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
2. PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix

Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09.HA1 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PI(D21)	2	2	100	15.8	100
		S+	PI(D21)	1	1	100	2.5	100
		Total	PI(D21)	3	3	100	29.2	100
	PAN-F	S-	PI(D21)	2	2	100	15.8	100
		Total	PI(D21)	2	2	100	15.8	100

Seroconversion factor (SCF) for HI antibodies against Flu A/CAL/09.HA1 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	F-PAN	S-	PI(D21)	2	22.6	0.3	1849.7
		S+	PI(D21)	1	4.0	.	.
		Total	PI(D21)	3	12.7	0.9	175.8
	PAN-F	S-	PI(D21)	2	11.3	0.1	924.9
		Total	PI(D21)	2	11.3	0.1	924.9

Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09.HA1 Ab at visit 1 Day 0 and at PI (D21) for subjects aged > 80 years (Total cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	F-PAN	S-	PRE	2	0	0.0	0.0	84.2
			PI(D21)	2	2	100	15.8	100
		S+	PRE	1	1	100	2.5	100
			PI(D21)	1	1	100	2.5	100
		Total	PRE	3	1	33.3	0.8	90.6
			PI(D21)	3	3	100	29.2	100
	PAN-F	S-	PRE	2	0	0.0	0.0	84.2
			PI(D21)	2	2	100	15.8	100
		Total	PRE	2	0	0.0	0.0	84.2
			PI(D21)	2	2	100	15.8	100

Immune responses to Flu A/Bri/07 HAI

All subjects were seropositive at baseline and two of the three in the F-Pan group were already seroprotected, which greatly limits any interpretation of the data for this age group. No subject seroconverted and the SCF was 1.3 while all three were seroprotected after Fluarix.

Seropositivity rates and GMTs for HI antibodies against Flu A/Bri/07.HA1 Ab for subjects aged > 80 years (Total cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/Bri/07.HA1 Ab	F-PAN	S+	PRE	3	3	100	29.2	100	50.4	6.9	368.0	20.0	80.0
			PI(D21)	3	3	100	29.2	100	63.5	23.5	171.6	40.0	80.0
		Total	PRE	3	3	100	29.2	100	50.4	6.9	368.0	20.0	80.0
			PI(D21)	3	3	100	29.2	100	63.5	23.5	171.6	40.0	80.0
	PAN-F	S+	PRE	2	2	100	15.8	100	19.8	0.2	1618.5	14.0	28.0
		Total	PRE	2	2	100	15.8	100	19.8	0.2	1618.5	14.0	28.0

Seroprotection rates (SPR) for HI antibodies against Flu A/Bri/07.HA1 Ab at visit 1 Day 0 and at PI (D21) for subjects aged > 80 years (Total cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/Bri/07.HA1 Ab	F-PAN	S+	PRE	3	2	66.7	9.4	99.2
			PI(D21)	3	3	100	29.2	100
		Total	PRE	3	2	66.7	9.4	99.2
			PI(D21)	3	3	100	29.2	100
	PAN-F	S+	PRE	2	0	0.0	0.0	84.2
		Total	PRE	2	0	0.0	0.0	84.2

Seroconversion rate (SCR) for HI antibodies against Flu A/Bri/07.HA1 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/Bri/07.HA1 Ab	F-PAN	S+	PI(D21)	3	0	0.0	0.0	70.8
		Total	PI(D21)	3	0	0.0	0.0	70.8

Seroconversion factor (SCF) for HI antibodies against Flu A/Bri/07.HA1 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/Bri/07.HA1 Ab (1/DIL)	F-PAN	S+	PI(D21)	3	1.3	0.5	3.4
		Total	PI(D21)	3	1.3	0.5	3.4

For responses to Flu A/Uru/07.HA3 the following were noted

All were seropositive at baseline and two of the three in the F-Pan group were already seroprotected. After Fluarix all three were seroprotected, one seroconverted and the SCF was 2.8.

Seropositivity rates and GMTs for HI antibodies against Flu A/Uru/07.HA3 Ab for subjects aged > 80 years (Total cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/Uru/07.HA3 Ab	F-PAN	S+	PRE	3	3	100	29.2	100	40.0	7.1	223.8	20.0	80.0
			PI(D21)	3	3	100	29.2	100	113.1	47.8	267.5	80.0	160.0
		Total	PRE	3	3	100	29.2	100	40.0	7.1	223.8	20.0	80.0
			PI(D21)	3	3	100	29.2	100	113.1	47.8	267.5	80.0	160.0
	PAN-F	S+	PRE	2	2	100	15.8	100	19.8	0.2	1618.5	14.0	28.0
		Total	PRE	2	2	100	15.8	100	19.8	0.2	1618.5	14.0	28.0

Seroprotection rates (SPR) for HI antibodies against Flu A/Uru/07.HA3 Ab at visit 1 Day 0 and at PI (D21) for subjects aged > 80 years (Total cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/Uru/07.HA3 Ab	F-PAN	S+	PRE	3	2	66.7	9.4	99.2
			PI(D21)	3	3	100	29.2	100
		Total	PRE	3	2	66.7	9.4	99.2
			PI(D21)	3	3	100	29.2	100
	PAN-F	S+	PRE	2	0	0.0	0.0	84.2
		Total	PRE	2	0	0.0	0.0	84.2

Seroconversion rate (SCR) for HI antibodies against Flu A/Uru/07.HA3 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/Uru/07.HA3 Ab	F-PAN	S+	PI(D21)	3	1	33.3	0.8	90.6
		Total	PI(D21)	3	1	33.3	0.8	90.6

Seroconversion factor (SCF) for HI antibodies against Flu A/Uru/07.HA3 Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/Uru/07.HA3 Ab (1/DIL)	F-PAN	S+	PI(D21)	3	2.8	0.6	12.5
		Total	PI(D21)	3	2.8	0.6	12.5

Immune responses to FluB/Bri/08.HA

All were seropositive and seroprotected at baseline. No subject seroconverted after Fluarix and the SCF was 2.0.

Seropositivity rates and GMTs for HI antibodies against FluB/Bri/08.HA Ab for subjects aged > 80 years (Total cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
FluB/Bri/08.HA Ab	F-PAN	S+	PRE	3	3	100	29.2	100	100.8	37.3	272.4	80.0	160.0
			PI(D21)	3	3	100	29.2	100	201.6	74.6	544.8	160.0	320.0
		Total	PRE	3	3	100	29.2	100	100.8	37.3	272.4	80.0	160.0
			PI(D21)	3	3	100	29.2	100	201.6	74.6	544.8	160.0	320.0
	PAN-F	S+	PRE	2	2	100	15.8	100	160.0	160.0	160.0	160.0	160.0
		Total	PRE	2	2	100	15.8	100	160.0	160.0	160.0	160.0	160.0

Seroprotection rates (SPR) for HI antibodies against FluB/Bri/08.HA Ab at visit 1 Day 0 and at PI (D21) for subjects aged > 80 years (Total cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
FluB/Bri/08.HA Ab	F-PAN	S+	PRE	3	3	100	29.2	100
			PI(D21)	3	3	100	29.2	100
		Total	PRE	3	3	100	29.2	100
			PI(D21)	3	3	100	29.2	100
	PAN-F	S+	PRE	2	2	100	15.8	100
		Total	PRE	2	2	100	15.8	100

Seroconversion rate (SCR) for HI antibodies against FluB/Bri/08.HA Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
FluB/Bri/08.HA Ab	F-PAN	S+	PI(D21)	3	0	0.0	0.0	70.8
		Total	PI(D21)	3	0	0.0	0.0	70.8

Seroconversion factor (SCF) for HI antibodies against FluB/Bri/08.HA Ab at PI (D21) for subjects aged > 80 years (Total cohort)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
FluB/Bri/08.HA Ab (1/DIL)	F-PAN	S+	PI(D21)	3	2.0	2.0	2.0
		Total	PI(D21)	3	2.0	2.0	2.0

Responses to Pandemrix

The data show that all 3 CHMP criteria were met for responses to H1N1 in the 5 subjects >80years regardless of baseline serostatus.

Responses to Fluarix

It is difficult to interpret data on 5 subject >80 years due to the very high pre-vaccination seropositivity and seroprotection rates, which limited the detectable HI responses to vaccination.

Overall the responses to Fluarix in the total >70 year group met minimal CHMP criteria for seasonal influenza vaccines.

The additional safety analysis provided data according to age 61-70 years and >70 years as requested. All subjects returned their symptom records. As shown below, in both vaccine groups the rates of local symptoms were lower in the older age group. Overall the data did not consistently suggest higher rates of local or general symptoms on co-administration vs. Pandemrix alone.

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

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	61-70Y	56	45	80.4	67.6	89.8	56	27	48.2	34.7	62.0	56	44	78.6	65.6	88.4
	>70Y	28	16	57.1	37.2	75.5	28	9	32.1	15.9	52.4	28	15	53.6	33.9	72.5
PAN-F	61-70Y	56	50	89.3	78.1	96.0	56	20	35.7	23.4	49.6	56	48	85.7	73.8	93.6
	>70Y	28	21	75.0	55.1	89.3	28	12	42.9	24.5	62.8	28	19	67.9	47.6	84.1

A comparison of local symptoms following vaccination with Fluarix and Pandemrix was provided. This demonstrated that Pandemrix H1N1 was associated with very much higher rates of local reactions compared with Fluarix as was expected from all previously reported data. Local reactions were less common in the older age group with both vaccines.

Incidence and nature of local symptoms (solicited and unsolicited) reported for each vaccine during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		FLUARIXVACCINE					FLUD-PANH1N1AS03A					PLACEBO				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	61-70Y	56	16	28.6	17.3	42.2	56	44	78.6	65.6	88.4	0	0	0.0	0.0	0.0
	>70Y	28	4	14.3	4.0	32.7	28	15	53.6	33.9	72.5	0	0	0.0	0.0	0.0
PAN-F	61-70Y	0	0	0.0	0.0	0.0	56	48	85.7	73.8	93.6	56	4	7.1	2.0	17.3
	>70Y	0	0	0.0	0.0	0.0	28	18	64.3	44.1	81.4	28	7	25.0	10.7	44.9

Grade 3 symptoms were seen in two subjects in the 61-70 year age group, one general reaction in the F-Pan group and one local reaction in the Pan-F group that was considered vaccine-related.

Pain was by far the most common local symptom. Local reactions were less common in those >70 years with the exception of swelling in the PAN-F group where 25% of those >70 years had swelling compared with 16.1% of those in the 61-70 years group. In the F-Pan group the rates of local swelling were similar in both age groups.

General symptoms were lower in those >70 years compared with the 61-70 year group. No grade 3 systemic reactions were seen in those >70 years and no temperatures above 38oC were seen in either age group. As for the total cohort in study 018 general symptoms were not higher in those who received co-administration of Fluarix compared with those in the PAN-F group alone.

Conclusions and Benefit / Risk Assessment

The abridged study report submitted for this procedure describes the preliminary safety and immunogenicity results following vaccination with Pandemrix H1N1 (i.e. 3.75 µg HA +$AS03_A$) co-administered either with Fluarix (F-PAN group) or with saline (PAN-F group) in adults aged >60 years, with a good representation of subjects aged 61-70 years (112) and 56 subjects >70 years. The oldest subject was 85 years.

On assessment of the immunogenicity of Pandemrix H1N1 (whether administered alone or co-administered with Fluarix) the HI data at baseline, the pre-vaccination seropositivity rates and D21 seroprotection rates were in keeping with those observed in study 008 in those aged >60 years.

The CHMP criteria for HI responses were very easily met in the initial analysis in the strata 61-70 years and >70 yrs. The additional analyses by baseline serostatus, prior seasonal vaccination and age strata also showed that in each analysis the three criteria were comfortably met for H1N1.

Further analyses of the data from five subjects aged > 80 years of age and a breakdown of safety into the two age groups (61-70 and > 70 years) for study 018 were provided. These showed that the immunogenicity of Pandemrix in subjects aged > 80 resulted in all seroprotected at D21 compared to only one at baseline and the SCR and SCF CHMP criteria were also met. These data supplement and agree with the results reported from five subjects aged > 80 years in study 008 (see II/023) and do not suggest any interference from co-administration with Fluarix.

Responses to Fluarix were considered difficult to interpret in this small number of elderly subjects due to the baseline seropositivity rates. However in study 018 the responses to Fluarix in the entire age cohort >70 years met the minimal CHMP criteria for seasonal influenza vaccines.

The co-administration of Fluarix did not impact on the immunogenicity of Pandemrix H1N1. For Fluarix the responses passed minimal CHMP criteria for seasonal flu vaccine in this age group.

The MAH provided safety data divided into age groups (61-70 years and >70 years). The data show that local reactions occurred much more often at the Pandemrix injection site compared to the Fluarix injection site, as was expected from all previous experience with AS03-adjuvanted influenza vaccines. The rates for local and systemic reactions tend to be lower in those >70 years and Grade 3 reactions occurred in only two subjects.

The safety profile of Pandemrix H1N1 when co-administered with Fluarix is comparable to that seen with Pandemrix H1N1 (with saline placebo), and also appears to be comparable with that reported in study 008 in the older age groups. No difference in the safety profile of Pandemrix H1N1 was seen between the two vaccine groups. This suggests that co-administration of Pandemrix with Fluarix has a similar safety profile (local and systemic, solicited and unsolicited) to that seen with Pandemrix H1N1 vaccination alone. Overall, there were no new safety issues raised by these data.

The additional information provided in this report supports the co-administration of seasonal flu vaccine and Pandemrix H1N1. Further data will provide information on whether there are any differences in immunogenicity between co-administration of Fluarix with the first or second dose of Pandemrix H1N1.

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 4.5 - Interaction with other medicinal products and other forms of interaction

This section has been revised to reflect that the seasonal vaccine used in the study was Fluarix, and that co-administration was not associated with higher rates of local or systemic reactions compared to administration of Pandemrix alone.

SPC section 6.6 -Special precautions for disposal and other handling

This section was updated to clarify that the reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed (including rubber particles from the stopper), discard the vaccine.

The PL is updated accordingly.