European Medicines Agency

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CHMP VARIATION ASSESSMENT REPORT

Invented name/Name: Pandemrix
International non-proprietary name/Common name: pandemic influenza vaccine (H1N!) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179a)

TYPE II VARIATION: EMEA/H/C/000832/II/0032

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 2 efficacy and safety results from a clinical study in adults 18-60 years of age (D-PAN-H1N1-007).

In submitting the above mentioned data from study 010 the MAH also fulfilled the Specific Obligation to provide an abridged report for: post dose 2 data from study D-PAN H1N1-007 (SO2 50.1).

In addition, this procedure discusses data in young adults 10-17 years of age who have received a single adult dose in study H1N1- 010., while the data in children 3-9 years of age from this trial are being discussed in variation II-33.

Study H1N1010 provided post-dose 1 data with the adult dose in subjects aged 10-17 years. Since these data in subjects aged 10-17 years from study H1N1- 010 are pertinent to the use of adult doses, the CHMP considered that the information on use of the adult dose in subjects aged 10-17 years including the newly available safety data from this population should be added to the SPC and PL .

The data on administration of an adult dose to children 3-9 years of age in study H1N1-010 are under separate assessment within the scope of variation II-33.

1.2 Clinical aspects

D-PAN H1N1-007

This is an ongoing study in 130 Belgian adults aged 18-60 years who have been randomised (1:1) with stratification by age (18-40, 41 to 50 and 51 to 60 years; 2:1:1) to receive:

- Group A: (N=64) two doses 21 days apart of HA (3.75µg) adjuvanted with $AS03_A$ = Pandemrix H1N1v as approved
- Group B: (N=66) two doses 21 days apart of HA 15 µg (derived from the same H1N1v strain) without adjuvant.

The vaccines are of the following content:

Composition and vaccine formulations used in D-Pan-H1N1-007

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

HA : haemagglutinin

$AS03_A$: GSK Biologicals' proprietary adjuvant containing the oil–in-water SB62 emulsion, consisting of an oil phase containing DL-α-tocopherol and squalene, and an aqueous phase containing the non-ionic detergent Tween 80

The primary objective is to demonstrate that two doses of vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like strain with AS03A results in an HI immune response to vaccine-homologous virus that meets or exceeds the CHMP criteria applied to seasonal influenza vaccines.

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

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

HI antibody is determined in GSK Biologicals' central laboratory (SSW, Dresden, Germany) using standardised procedures with adequate controls validated by GSK Biologicals as previously described.

The data from days 0, 21 and 42 reported below originate from testing of all sera in parallel. This means that the D0 and D21 data differ slightly from those previously reported in variation II-019 as a result of assay variability. This PI is therefore updated with these values in section 5.1

The synoptic report included in the submission also provided data on cell-mediated immunity (CMI). Subsequent analyses will be performed after all data will become available for Day 182 and Day 364.

Results reported as of 19 November 2009

The mean age at the time of the first vaccination was 38.6 ± 13.78 years (mean ± SD) for all subjects. Mean ages were 26.2 ± 6.40 years for subjects randomised to the 18-40 years age stratum and 51.0 ± 5.31 for subjects randomised to the 41-60 years age stratum. Females outnumbered males in this study. Of the 130 enrolled, 129 subjects received the second dose and one subject was lost to follow-up.

Subjects who received study vaccine doses (Total vaccinated cohort)

	H1N1+AS03 N = 64		H1N1 N = 66		Total N = 130	
Total number of doses received	n	%	n	%	n	%
1	1	1.6	0	0.0	1	0.8
2	63	98.4	66	100	129	99.2
Any	64	100	66	100	130	100

At Day 0 overall seropositivity rates were 38.3% and 42.4% in the two vaccine groups and Geometric Mean Titer (GMT) values were 8.8 and 10.8. All subjects were seropositive at Day 42. In the

H1N1+AS03a group there was a clear increase in the GMT from D21 to D42 regardless of baseline HI serostatus.

Seropositivity rates and GMTs for HI antibodies (ATP cohort for immunogenicity)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
H1N1+AS03	S-	PRE	37	0	0.0	0.0	9.5	5.0	5.0	5.0	<10.0	<10.0
		PI(D21)	37	37	100	90.5	100	234.9	167.6	329.3	40.0	1280.0
		PII(D42)	37	37	100	90.5	100	566.7	445.4	721.0	80.0	1810.0
	S+	PRE	23	23	100	85.2	100	21.9	14.9	32.0	10.0	160.0
		PI(D21)	23	23	100	85.2	100	593.8	369.0	955.4	57.0	5120.0
		PII(D42)	22	22	100	84.6	100	773.2	537.6	1112.1	160.0	5120.0
	Total	PRE	60	23	38.3	26.1	51.8	8.8	7.0	11.1	<10.0	160.0
		PI(D21)	60	60	100	94.0	100	335.2	250.1	449.2	40.0	5120.0
		PII(D42)	59	59	100	93.9	100	636.3	520.9	777.3	80.0	5120.0
H1N1	S-	PRE	38	0	0.0	0.0	9.3	5.0	5.0	5.0	<10.0	<10.0
		PI(D21)	38	37	97.4	86.2	99.9	204.8	130.4	321.7	<10.0	2560.0
		PII(D42)	38	38	100	90.7	100	254.9	188.5	344.8	40.0	1810.0
	S+	PRE	28	28	100	87.7	100	30.8	20.0	47.4	10.0	453.0
		PI(D21)	28	28	100	87.7	100	544.9	328.9	902.7	40.0	7240.0
		PII(D42)	28	28	100	87.7	100	505.9	314.9	812.9	40.0	5120.0
	Total	PRE	66	28	42.4	30.3	55.2	10.8	8.1	14.4	<10.0	453.0
		PI(D21)	66	65	98.5	91.8	100	310.2	218.8	439.7	<10.0	7240.0
		PII(D42)	66	66	100	94.6	100	341.0	259.9	447.3	40.0	5120.0

At Day 42, HI responses in subjects from both study groups exceeded all the CHMP criteria. In the H1N1+AS03A group the SCR was 98.3%, the SCF was 72.9 and the SPR was 100.0%. For GMTs, SCR and SCF a general trend towards lower estimates in the unadjuvanted group was observed.

As shown in the tables below the CHMP criteria were also met in each of the sub-groups according to HI baseline serostatus. The SCFs in the AS03-adjuvanted vaccine group showed increases from D21 to D42 regardless of baseline serostatus. In the unadjuvanted group there was an increase only in those seronegative at baseline, reflecting the modest increase in GMT observed in this subset.

Seroprotection rates (SPR) for HI antibodies (ATP cohort for immunogenicity)

						95% CI	
Group	Pre-vacc status	Timing	N	n	%	LL	UL
H1N1+AS03	S-	PRE	37	0	0.0	0.0	9.5
		PI(D21)	37	37	100	90.5	100
		PII(D42)	37	37	100	90.5	100
	S+	PRE	23	7	30.4	13.2	52.9
		PI(D21)	23	23	100	85.2	100
		PII(D42)	22	22	100	84.6	100
	Total	PRE	60	7	11.7	4.8	22.6
		PI(D21)	60	60	100	94.0	100
		PII(D42)	59	59	100	93.9	100
H1N1	S-	PRE	38	0	0.0	0.0	9.3
		PI(D21)	38	34	89.5	75.2	97.1
		PII(D42)	38	38	100	90.7	100
	S+	PRE	28	12	42.9	24.5	62.8
		PI(D21)	28	28	100	87.7	100
		PII(D42)	28	28	100	87.7	100
	Total	PRE	66	12	18.2	9.8	29.6
		PI(D21)	66	62	93.9	85.2	98.3
		PII(D42)	66	66	100	94.6	100

Seroconversion factor (SCF) for HI antibodies (ATP cohort for immunogenicity)

					95% CI	
Group	Sub-group	Timing	N	Value	LL	UL
H1N1+AS03	S-	PI(D21)	37	47.0	33.5	65.9
		PII(D42)	37	113.3	89.1	144.2
	S+	PI(D21)	23	27.2	16.2	45.4
		PII(D42)	22	34.7	21.1	56.8
	Total	PI(D21)	60	38.1	28.6	50.7
		PII(D42)	59	72.9	55.4	95.9
H1N1	S-	PI(D21)	38	41.0	26.1	64.3
		PII(D42)	38	51.0	37.7	69.0
	S+	PI(D21)	28	17.7	9.9	31.5
		PII(D42)	28	16.4	9.5	28.4
	Total	PI(D21)	66	28.7	20.0	41.2
		PII(D42)	66	31.5	23.1	43.2

Seroconversion rate (SCR) for HI antibodies (ATP cohort for immunogenicity)

					SCR			
							95% CI	
	Group	Sub-group	Timing	N	n	%	LL	UL
	H1N1+AS03	S-	PI(D21)	37	37	100	90.5	100
			PII(D42)	37	37	100	90.5	100
		S+	PI(D21)	23	22	95.7	78.1	99.9
			PII(D42)	22	21	95.5	77.2	99.9
		Total	PI(D21)	60	59	98.3	91.1	100
			PII(D42)	59	58	98.3	90.9	100
	H1N1	S-	PI(D21)	38	34	89.5	75.2	97.1
			PII(D42)	38	38	100	90.7	100
		S+	PI(D21)	28	22	78.6	59.0	91.7
			PII(D42)	28	23	82.1	63.1	93.9
		Total	PI(D21)	66	56	84.8	73.9	92.5
			PII(D42)	66	61	92.4	83.2	97.5

The MAH provided the HI responses by age strata 18-40 and 41-60 years and baseline serostatus. The CHMP criteria were met in both age strata in both vaccine groups and regardless of baseline serostatus. However, the GMTs after each dose were lower in the older age stratum.

HI responses at D21 and D42 by age strata 18-40 and 41-60 years

		≥10 1/DIL			**GMT**			**SPR**			**SCR**			**SCF**		
			95% CI			**95% CI**			**95% CI**			**95% CI**			**95% CI**	
Timing	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Group H1N1 + AS03A Overall																
PRE	60	38.3	26.1	51.8	8.8	7.0	11.1	11.7	4.8	22.6	-	-	-	-	-	-
PI(D21)	60	100	94.0	100	335.2	250.1	449.2	100	94.0	100	98.3	91.1	100	38.1	28.6	50.7
PII(D42)	59	100	93.9	100	636.3	520.9	777.3	100	93.9	100	98.3	90.9	100	72.9	55.4	95.9
18-40 years stratum																
PRE	28	28.6	13.2	48.7	7.4	5.6	9.9	7.1	0.9	23.5	-	-	-	-	-	-
PI(D21)	28	100	87.7	100	561.2	371.9	846.9	100	87.7	100	100	87.7	100	61.7	43.2	88.0
PII(D42)	28	100	87.7	100	790.0	589.2	1059.3	100	87.7	100	100	87.7	100	106.3	79.8	141.6
41-60 years stratum																
PRE	32	46.9	29.1	65.3	10.2	7.1	14.7	15.6	5.3	32.8	-	-	-	-	-	-
PI(D21)	32	100	89.1	100	255.0	171.4	379.3	100	89.1	100	96.9	83.8	99.9	25.0	16.8	37.1
PII(D42)	31	100	88.8	100	523.4	399.4	685.7	100	88.8	100	96.8	83.3	99.9	51.8	33.6	79.9
Group H1N1 Overall																
PRE	66	42.4	30.3	55.2	10.8	8.1	14.4	18.2	9.8	29.6	-	-	-	-	-	-
PI(D21)	66	98.5	91.8	100	310.2	218.8	439.7	93.9	85.2	98.3	84.8	73.9	92.5	28.7	20.0	41.2
PII(D42)	66	100	94.6	100	341.0	259.9	447.3	100	94.6	100	92.4	83.2	97.5	31.5	23.1	43.2
18-40 years stratum																
PRE	33	45.5	28.1	63.6	13.1	8.1	21.4	24.2	11.1	42.3	-	-	-	-	-	-
PI(D21)	33	100	89.4	100	588.5	385.7	897.8	97.0	84.2	99.9	90.9	75.7	98.1	44.8	26.6	75.6
PII(D42)	33	100	89.4	100	570.3	408.1	797.0	100	89.4	100	93.9	79.8	99.3	43.4	26.8	70.3
41-60 years stratum																
PRE	33	39.4	22.9	57.9	8.9	6.6	12.1	12.1	3.4	28.2	-	-	-	-	-	-
PI(D21)	33	97.0	84.2	99.9	163.5	101.2	264.1	90.9	75.7	98.1	78.8	61.1	91.0	18.4	11.4	29.7
I(D42)	33	100	89.4	100	203.9	142.0	292.6	100	89.4	100	90.9	75.7	98.1	22.9	15.4	34.0

The MAH also provided the HI responses by age strata 18-40, 41-50 and 51-60 years by baseline serostatus. The CHMP criteria were met in all age strata in both vaccine groups and regardless of baseline serostatus. However, the GMTs after each dose were almost always lowest in the oldest of these three age strata.

Similar analyses were provided according to history of influenza vaccination and again this had no impact on meeting CHMP criteria in any age stratum.

The oldest group (51-60 years) generally showed the lowest responses as outlined in the tables below in which results are presented according to baseline serostatus. The responses in this group also met the CHMP criteria.

Seropositivity rates and GMTs (ATP age stratum 51-60)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
H1N1+AS03	S-	PRE	9	0	0.0	0.0	33.6	5.0	5.0	5.0	<10.0	<10.0
		PI(D21)	9	9	100	66.4	100	100.8	49.8	204.0	40.0	640.0
		PII(D42)	9	9	100	66.4	100	419.0	191.0	919.2	80.0	1280.0
	S+	PRE	7	7	100	59.0	100	21.0	8.1	54.4	10.0	160.0
		PI(D21)	7	7	100	59.0	100	353.7	107.2	1166.7	57.0	1810.0
		PII(D42)	6	6	100	54.1	100	678.0	322.6	1424.8	226.0	1810.0
H1N1	S-	PRE	13	0	0.0	0.0	24.7	5.0	5.0	5.0	<10.0	<10.0
		PI(D21)	13	12	92.3	64.0	99.8	73.9	31.8	171.7	<10.0	1280.0
		PII(D42)	13	13	100	75.3	100	133.0	73.3	241.2	40.0	1280.0
	S+	PRE	4	4	100	39.8	100	15.4	5.4	43.7	10.0	40.0
		PI(D21)	4	4	100	39.8	100	269.1	40.9	1769.9	80.0	1280.0
		PII(D42)	4	4	100	39.8	100	226.3	54.5	939.8	80.0	640.0

SPR (ATP age stratum 51-60)

Strain	Group	Pre-vacc status	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	H1N1+AS03	S-	PRE	9	0	0.0	0.0	33.6
			PI(D21)	9	9	100	66.4	100
			PII(D42)	9	9	100	66.4	100
		S+	PRE	7	2	28.6	3.7	71.0
			PI(D21)	7	7	100	59.0	100
			PII(D42)	6	6	100	54.1	100
		Total	PRE	16	2	12.5	1.6	38.3
			PI(D21)	16	16	100	79.4	100
			PII(D42)	15	15	100	78.2	100
	H1N1	S-	PRE	13	0	0.0	0.0	24.7
			PI(D21)	13	10	76.9	46.2	95.0
			PII(D42)	13	13	100	75.3	100
		S+	PRE	4	1	25.0	0.6	80.6
			PI(D21)	4	4	100	39.8	100
			PII(D42)	4	4	100	39.8	100
		Total	PRE	17	1	5.9	0.1	28.7
			PI(D21)	17	14	82.4	56.6	96.2
			PII(D42)	17	17	100	80.5	100

SCR (ATP age stratum 51-60)

Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/09.HA1 Ab	H1N1+AS03	S-	PI(D21)	9	9	100	66.4	100
			PII(D42)	9	9	100	66.4	100
		S+	PI(D21)	7	6	85.7	42.1	99.6
			PII(D42)	6	5	83.3	35.9	99.6
		Total	PI(D21)	16	15	93.8	69.8	99.8
			PII(D42)	15	14	93.3	68.1	99.8
	H1N1	S-	PI(D21)	13	10	76.9	46.2	95.0
			PII(D42)	13	13	100	75.3	100
		S+	PI(D21)	4	3	75.0	19.4	99.4
			PII(D42)	4	3	75.0	19.4	99.4
		Total	PI(D21)	17	13	76.5	50.1	93.2
			PII(D42)	17	16	94.1	71.3	99.9

SCF (ATP age stratum 51-60)

Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/09.HA1 Ab (1/DIL)	H1N1+AS03	S-	PI(D21)	9	20.2	10.0	40.8
			PII(D42)	9	83.8	38.2	183.8
		S+	PI(D21)	7	16.9	4.1	70.0
			PII(D42)	6	30.2	7.0	130.3
		Total	PI(D21)	16	18.6	9.9	35.1
			PII(D42)	15	55.7	27.9	111.2
	H1N1	S-	PI(D21)	13	14.8	6.4	34.3
			PII(D42)	13	26.6	14.7	48.2
		S+	PI(D21)	4	17.5	1.2	264.6
			PII(D42)	4	14.7	1.5	148.8
		Total	PI(D21)	17	15.4	7.4	31.9
			PII(D42)	17	23.1	13.2	40.6

Neutralising antibodies

Neutralising antibodies (NA) at Day 0, day 21 and day 42 have been evaluated on a subset of 28 subjects from the AS03 group and 30 subjects from the unadjuvanted vaccine group at Viroclinics laboratory. The Viroclinics NA assay is known to be less sensitive than GSK's. The differences are likely due to assay protocol specificities, such as the short incubation time (1h) of the mix serum/virus/cells.

NA seropositivity rates at D0 were imbalanced at 28.6% in the AS03 group and 56.7% in the non-adjuvanted vaccine group and in each group showed a trend to increase with age. At D21 rates increased to 96.4% and 97.6% for adjuvanted and non-adjuvanted groups, respectively, and to 100% for both groups post-dose 2.

GMTs were low at Day 0 but D21 GMTs were 152.3 (adjuvanted group) and 89.9 (non-adjuvanted group) with a further increase at D42 (243.8 and 144.9). Seroconversion rates reached 75.0% and 73.3% post-dose 1 but were 96.9% vs. 76.7% at D42

The analysis by age strata showed an overall trend to a lower response to each vaccine with increasing age. Results in the youngest and oldest stratum also showed a larger difference between adjuvanted and non-adjuvanted vaccine groups with increasing age but the results for the 8 subjects aged 41-50 years did not show this difference.

Cell mediated immune response (CMI)
The CD4 T-cell response observed after dose 2 was markedly higher in the H1N1 + $AS03_A$ group as compared to the H1N1 group. A consistent trend for a further increase in the CD4 T-cell response was observed from D21 to D42 in the H1N1 + $AS03_A$ group, whatever the antigen used for stimulation in vitro (split antigen or HA peptide pool). A smaller increase was observed after stimulation with the HA peptide pool in the H1N1 group.

There was no detectable effect of vaccination on the frequency of antigen-specific CD8 T-cells with the assay method used.

H1N1-010 - post dose 1 HI data in subjects aged 10-17 years

D-PAN H1N1-010 is an ongoing study that commenced on 10 September 2009 at five study sites in Spain.

The study planned to enrol 200 subjects aged 3-17 years with stratification by age groups 3-5, 6-9 and 10 to 17 years in a ratio of 1:1:2.

All subjects were to receive two doses of Pandemrix three weeks apart, given into the deltoid muscle of the non-dominant arm. The vaccine comprised the following content and lots:

Composition and lot numbers of vaccine formulations used in D-Pan-H1N1-010

Study number	Strain	HA dose (µg)*	Adjuvant dose**	Injected volume	Vaccine lot	
					Antigen container	Adjuvant container
D-Pan-H1N1-010	A/California/7/2009(H1N1)v-like	*3.75 µg (0.25 mL)*	$AS03_A$, (0.25 mL)	0.5 mL	DFLSA013A	AA03A209C

HA : haemagglutinin
$AS03_A$: GSK Biologicals' proprietary adjuvant containing the oil–in-water SB62 emulsion, consisting of an oil phase containing DL- -tocopherol and squalene, and an aqueous phase containing the non-ionic detergent Tween 80

The sequential co-primary objectives are:
- To evaluate whether the humoral immune response after two doses meets or exceeds the CHMP criteria (as applied to adults age 18-60 years and to seasonal influenza vaccines) at day 42 in children aged 3 to 17 years.
- To evaluate superiority in terms of HI response to a 6-month booster compared to the D42 response. The criteria for success require a lower limit of the two-sided 95% confidence interval (CI) for the geometric mean titer (GMT) ratio (at seven days after a 6-month booster after 2-dose primary vaccination / 21 days after the first dose) > 2.0.

The secondary objectives are:
- To assess HI responses at D21, D42 and M6
- To assess HI responses 7 days, six months and one year after the booster
- To describe the response by age strata
- To describe the NA response at each time point in a subset of sera
- To evaluate safety in terms of selected biochemistry safety parameters at Day 0, 21, 42, at Month 6, and Month 6 + 7 days.
- To evaluate safety and reactogenicity after each dose in terms of 7-day solicited local and general symptoms, unsolicited AEs, medically attended AEs (MAEs), AEs of specific interests (AESIs) or potential Immune Mediated Diseases (pIMDs) and SAEs

Exploratory objectives include evaluation of the CMI response and immune responses to drifted variants. Also, to describe the occurrence of lab-confirmed (H1N1)v cases (including drifted variant cases) during the entire study period.

HI antibody is determined in GSK Biologicals' central laboratory (SSW, Dresden, Germany) as previously described.

The Total Vaccinated cohort and ATP cohort are defined as in all other GSK studies.
The analysis of immunogenicity presented in this summary was performed on the TVC in order to provide preliminary post Dose 1 results based on non-cleaned data.

Study Results -post dose 1 in 10-17 year old subjects (full adult dose) :

Overall, there were 100 subjects in the 10-17 years group. Of these, 97 subjects completed the trial. For the three non-completers in the 10-17 years group parental consent for participation was withdrawn and the reason for withdrawal was not due to an AE.
The mean age at the time of the first vaccination was 13.3 years. Females slightly outnumbered males in this study as outlined in the table below

Demography: age (in years) at vaccination dose by gender (Total vaccinated cohort)

Sub-group	Sex	N	N with age	MEAN	SD	MIN	MAX
10-17Y	F	61	61	13.6	2.43	10	17
	M	39	39	12.9	1.83	10	17
	Total	100	100	13.3	2.23	10	17

A history of seasonal influenza vaccine was obtained from 11/89 subjects aged 10-17 years.

The D0 HI seropositivity rate was 39% in the 10-17 years age group, resembling that reported in adults aged 18-60 years in studies 007 and 008. At D21 all subjects were seropositive. The highest GMT was noted in the 10-17 years age group (699.7) and GMT values increased with age.

H1N1 HI Antibodies against A/California/7/2009 (H1N1) - 10 to 17 years age stratum

		>=10 1/DIL			GMT			SPR			SCR#			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
PRE	100	39.0	29.4	49.3	10.9	8.4	14.2	17.0	10.2	25.8	-	-	-	-	-	-
PI(D21	97	100	96.3	100	699.7	583.7	838.8	100	96.3	100	96.9	91.2	99.4	69.0	54.9	86.7

In adolescents from 10-17 years the baseline status was comparable with that observed in adults in studies H1N1-007 and H1N1-008. The GMT reported in study 010 in this age group closely resembles that reported at D21 in subjects aged 18-40 years in studies 007 and 008 (561 and 607).

SCR at PI (D21) in subjects aged 10-17 years

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09.HA1 Ab	H1N1+ASO3A	10-17Y	PI(21)	97	94	96.9	91.2	99.4

SCF at PI (D21) in subjects aged 10-17 years

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	H1N1+ASO3A	10-17Y	PI(21)	97	69.0	54.9	86.7

SPR at PI (D21) in subjects aged 10-17 years

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	H1N1 + ASO3	10-17Y	PRE	100	17	17.0	10.2	25.8
			PI(21)	97	97	100	96.3	100

Clinical Safety

Study H1N1-007

The four tables below summarise the reporting rates for total, Grade 3 and vaccine-related (all and Grade 3) local and general solicited symptoms after each dose, per dose and per subject. These rates did not increase after the second dose compared to the first dose in either vaccine group. However, the higher rates in the adjuvanted vaccine group compared to the unadjuvanted vaccine group were maintained after dose 1 and dose 2.

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

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H1N1+AS03	64	59	92.2	82.7	97.4	64	37	57.8	44.8	70.1	64	57	89.1	78.8	95.5
	H1N1	66	40	60.6	47.8	72.4	66	29	43.9	31.7	56.7	66	23	34.8	23.5	47.6
Dose 2	H1N1+AS03	63	57	90.5	80.4	96.4	63	36	57.1	44.0	69.5	63	56	88.9	78.4	95.4
	H1N1	66	31	47.0	34.6	59.7	66	23	34.8	23.5	47.6	66	20	30.3	19.6	42.9
Overall/dose	H1N1+AS03	127	116	91.3	85.0	95.6	127	73	57.5	48.4	66.2	127	113	89.0	82.2	93.8
	H1N1	132	71	53.8	44.9	62.5	132	52	39.4	31.0	48.3	132	43	32.6	24.7	41.3
Overall/subject	H1N1+AS03	64	62	96.9	89.2	99.6	64	44	68.8	55.9	79.8	64	61	95.3	86.9	99.0
	H1N1	66	49	74.2	62.0	84.2	66	37	56.1	43.3	68.3	66	32	48.5	36.0	61.1

Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H1N1+AS03	64	5	7.8	2.6	17.3	64	5	7.8	2.6	17.3	64	1	1.6	0.0	8.4
	H1N1	66	2	3.0	0.4	10.5	66	2	3.0	0.4	10.5	66	0	0.0	0.0	5.4
Dose 2	H1N1+AS03	63	3	4.8	1.0	13.3	63	3	4.8	1.0	13.3	63	2	3.2	0.4	11.0
	H1N1	66	4	6.1	1.7	14.8	66	4	6.1	1.7	14.8	66	0	0.0	0.0	5.4
Overall/dose	H1N1+AS03	127	8	6.3	2.8	12.0	127	8	6.3	2.8	12.0	127	3	2.4	0.5	6.7
	H1N1	132	6	4.5	1.7	9.6	132	6	4.5	1.7	9.6	132	0	0.0	0.0	2.8
Overall/subject	H1N1+AS03	64	8	12.5	5.6	23.2	64	8	12.5	5.6	23.2	64	3	4.7	1.0	13.1
	H1N1	66	6	9.1	3.4	18.7	66	6	9.1	3.4	18.7	66	0	0.0	0.0	5.4

Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H1N1+AS03	64	58	90.6	80.7	96.5	64	33	51.6	38.7	64.2	64	57	89.1	78.8	95.5
	H1N1	66	34	51.5	38.9	64.0	66	23	34.8	23.5	47.6	66	23	34.8	23.5	47.6
Dose 2	H1N1+AS03	63	57	90.5	80.4	96.4	63	33	52.4	39.4	65.1	63	56	88.9	78.4	95.4
	H1N1	66	30	45.5	33.1	58.2	66	21	31.8	20.9	44.4	66	20	30.3	19.6	42.9
Overall/dose	H1N1+AS03	127	115	90.6	84.1	95.0	127	66	52.0	42.9	60.9	127	113	89.0	82.2	93.8
	H1N1	132	64	48.5	39.7	57.3	132	44	33.3	25.4	42.1	132	43	32.6	24.7	41.3
Overall/subject	H1N1+AS03	64	62	96.9	89.2	99.6	64	41	64.1	51.1	75.7	64	61	95.3	86.9	99.0
	H1N1	66	45	68.2	55.6	79.1	66	32	48.5	36.0	61.1	66	32	48.5	36.0	61.1

Incidence and nature of grade 3 symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H1N1+AS03	64	3	4.7	1.0	13.1	64	3	4.7	1.0	13.1	64	1	1.6	0.0	8.4
	H1N1	66	0	0.0	0.0	5.4	66	0	0.0	0.0	5.4	66	0	0.0	0.0	5.4
Dose 2	H1N1+AS03	63	3	4.8	1.0	13.3	63	3	4.8	1.0	13.3	63	2	3.2	0.4	11.0
	H1N1	66	2	3.0	0.4	10.5	66	2	3.0	0.4	10.5	66	0	0.0	0.0	5.4
Overall/dose	H1N1+AS03	127	6	4.7	1.8	10.0	127	6	4.7	1.8	10.0	127	3	2.4	0.5	6.7
	H1N1	132	2	1.5	0.2	5.4	132	2	1.5	0.2	5.4	132	0	0.0	0.0	2.8
Overall/subject	H1N1+AS03	64	6	9.4	3.5	19.3	64	6	9.4	3.5	19.3	64	3	4.7	1.0	13.1
	H1N1	66	2	3.0	0.4	10.5	66	2	3.0	0.4	10.5	66	0	0.0	0.0	5.4

Pain at the injection site was the most frequently reported solicited adverse event but was more than twice as common in the adjuvanted vaccine group compared to the non-adjuvanted vaccine group. No increase in pain was observed after dose 2 as compared to after dose 1 in either group. Grade 3 pain was infrequent in the H1N1 + AS03A group and was not reported in the H1N1 group.

Swelling and redness were observed at much lower frequencies than pain in the H1N1 + AS03A group and were not observed after either dose in the H1N1 group.

Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		H1N1+AS03					H1N1				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	All	63	57	90.5	80.4	96.4	65	23	35.4	23.9	48.2
	Grade 1	63	56	88.9	78.4	95.4	65	23	35.4	23.9	48.2
	Grade 2	63	19	30.2	19.2	43.0	65	1	1.5	0.0	8.3
	Grade 3	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
Redness (mm)	All	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	[20.1 - 50.1[	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	[50.1 - 100.1[	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	[100.1 - ...	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
Swelling (mm)	All	63	5	7.9	2.6	17.6	65	0	0.0	0.0	5.5
	[20.1 - 50.1[	63	4	6.3	1.8	15.5	65	0	0.0	0.0	5.5
	[50.1 - 100.1[	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
	[100.1 - ...	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
Dose 2											
Pain	All	62	56	90.3	80.1	96.4	66	20	30.3	19.6	42.9
	Grade 1	62	55	88.7	78.1	95.3	66	20	30.3	19.6	42.9
	Grade 2	62	18	29.0	18.2	41.9	66	2	3.0	0.4	10.5
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
Redness (mm)	All	62	3	4.8	1.0	13.5	66	0	0.0	0.0	5.4
	[20.1 - 50.1[	62	3	4.8	1.0	13.5	66	0	0.0	0.0	5.4
	[50.1 - 100.1[	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[100.1 - ...	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
Swelling (mm)	All	62	9	14.5	6.9	25.8	66	0	0.0	0.0	5.4
	[20.1 - 50.1[	62	9	14.5	6.9	25.8	66	0	0.0	0.0	5.4
	[50.1 - 100.1[	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[100.1 - ...	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4

The table below shows the symptoms reported after dose 2, which display the higher rates for each in the adjuvanted group as was observed after dose 1. The frequency of Grade 3 solicited general symptoms after the second dose did not exceed two subjects per symptom (3.2%).

While the total of solicited and unsolicited general symptoms reported after dose 2 was not higher than after dose 1 in either vaccine group the rates for individual solicited symptoms in the H1N1 + AS03A group after dose 1 and dose 2 showed a clear trend for higher reactogenicity after dose 2. The rates after doses 1 and 2 respectively were: fatigue (34.9 vs. 45.2%), headache (27 vs. 35.5%), muscle aches (31.7% after both doses), sweating (9.5 vs. 19.4%), joint pain at other location (11.1 vs. 21%) and shivering (9.5% vs. 17.7%). Symptoms persisted for 1-3 days in almost all cases although prolonged fatigue was reported occasionally.

Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		H1N1+AS03					H1N1				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 2											
Fatigue	All	62	28	45.2	32.5	58.3	66	13	19.7	10.9	31.3
	Grade 1	62	25	40.3	28.1	53.6	66	13	19.7	10.9	31.3
	Grade 2	62	9	14.5	6.9	25.8	66	6	9.1	3.4	18.7
	Grade 3	62	2	3.2	0.4	11.2	66	2	3.0	0.4	10.5
	Related	62	27	43.5	31.0	56.7	66	13	19.7	10.9	31.3
	Grade 1*Related	62	25	40.3	28.1	53.6	66	13	19.7	10.9	31.3
	Grade 2*Related	62	8	12.9	5.7	23.9	66	6	9.1	3.4	18.7
	Grade 3*Related	62	2	3.2	0.4	11.2	66	2	3.0	0.4	10.5
Headache	All	62	22	35.5	23.7	48.7	66	9	13.6	6.4	24.3
	Grade 1	62	18	29.0	18.2	41.9	66	8	12.1	5.4	22.5
	Grade 2	62	8	12.9	5.7	23.9	66	1	1.5	0.0	8.2
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	Related	62	20	32.3	20.9	45.3	66	8	12.1	5.4	22.5
	Grade 1*Related	62	18	29.0	18.2	41.9	66	8	12.1	5.4	22.5
	Grade 2*Related	62	6	9.7	3.6	19.9	66	0	0.0	0.0	5.4
	Grade 3*Related	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
Joint pain at other location	All	62	13	21.0	11.7	33.2	66	4	6.1	1.7	14.8
	Grade 1	62	12	19.4	10.4	31.4	66	4	6.1	1.7	14.8
	Grade 2	62	3	4.8	1.0	13.5	66	1	1.5	0.0	8.2
	Grade 3	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	13	21.0	11.7	33.2	66	4	6.1	1.7	14.8
	Grade 1*Related	62	12	19.4	10.4	31.4	66	4	6.1	1.7	14.8
	Grade 2*Related	62	3	4.8	1.0	13.5	66	1	1.5	0.0	8.2
	Grade 3*Related	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
Muscle aches	All	62	23	37.1	25.2	50.3	66	7	10.6	4.4	20.6
	Grade 1	62	22	35.5	23.7	48.7	66	7	10.6	4.4	20.6
	Grade 2	62	8	12.9	5.7	23.9	66	0	0.0	0.0	5.4
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	Related	62	23	37.1	25.2	50.3	66	6	9.1	3.4	18.7
	Grade 1*Related	62	22	35.5	23.7	48.7	66	6	9.1	3.4	18.7
	Grade 2*Related	62	8	12.9	5.7	23.9	66	0	0.0	0.0	5.4
	Grade 3*Related	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
Shivering	All	62	11	17.7	9.2	29.5	66	3	4.5	0.9	12.7
	Grade 1	62	8	12.9	5.7	23.9	66	2	3.0	0.4	10.5
	Grade 2	62	5	8.1	2.7	17.8	66	2	3.0	0.4	10.5

		H1N1+AS03					H1N1				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
	Grade 3	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	11	17.7	9.2	29.5	66	2	3.0	0.4	10.5
	Grade 1*Related	62	8	12.9	5.7	23.9	66	1	1.5	0.0	8.2
	Grade 2*Related	62	5	8.1	2.7	17.8	66	2	3.0	0.4	10.5
	Grade 3*Related	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
Sweating	All	62	12	19.4	10.4	31.4	66	7	10.6	4.4	20.6
	Grade 1	62	12	19.4	10.4	31.4	66	7	10.6	4.4	20.6
	Grade 2	62	3	4.8	1.0	13.5	66	1	1.5	0.0	8.2
	Grade 3	62	1	1.6	0.0	8.7	66	0	0.0	0.0	5.4
	Related	62	12	19.4	10.4	31.4	66	6	9.1	3.4	18.7
	Grade 1*Related	62	12	19.4	10.4	31.4	66	6	9.1	3.4	18.7
	Grade 2*Related	62	3	4.8	1.0	13.5	66	1	1.5	0.0	8.2
	Grade 3*Related	62	1	1.6	0.0	8.7	66	0	0.0	0.0	5.4
Temperature/(Axillary) (°C)	All	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[38 - 38.5[	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[38.5 - 39[	62	1	1.6	0.0	8.7	66	0	0.0	0.0	5.4
	[39 - 40.1[	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	[40.1 - ...	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[38 - 38.5[*Related	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	[38.5 - 39[*Related	62	1	1.6	0.0	8.7	66	0	0.0	0.0	5.4
	[39 - 40.1[*Related	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	[40.1 - ...*Related	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4

No subjects reported any fever after dose 1 and there were only two subjects with any fever after the second dose of adjuvanted vaccine. Three subjects in the adjuvanted group reported taking a prophylactic antipyretic before the first dose but no subject in either group took prophylactic antipyretics before the second dose.

The frequency of subjects reporting at least one unsolicited adverse event within the total 42-day period was comparable between groups (53.1% in H1N1 + AS03A and 48.5% in H1N1). These reports were very varied in nature but included three and one subjects in respective groups with lymphadenopathy, two and none with injection site lymphadenopathy and 10 (15.6%) and 2 (3%) with rhinitis although rates of URTI overall were comparable.

All unsolicited AEs	Group		
	H1N1+AS03	H1N1	Total
Number of subjects with at least one unsolicited symptom reported	34	32	66
Number of doses followed by at least one unsolicited symptom	46	39	85
Number of unsolicited symptoms classified by MedDRA Preferred Term*	67	50	117
Number of unsolicited symptoms reported	68	51	119

Grade 3 unsolicited AEs were reported by 10.9% and 12.1% in the two groups.

Grade 2 unsolicited AEs	Group		
	H1N1+AS03	H1N1	Total
Number of subjects with at least one unsolicited symptom reported	7	8	15
Number of doses followed by at least one unsolicited symptom	7	8	15
Number of unsolicited symptoms classified by MedDRA Preferred Term*	9	9	18
Number of unsolicited symptoms reported	9	9	18

The unsolicited AEs considered to be related to vaccination are shown in the table below and included four of the three reports of lymphadenopathy. Two Grade 3 unsolicited AEs considered as related to vaccination were reported in the H1N1 + AS03A group. These were reports of influenza-like illness and malaise.

Percentage reporting the occurrence of unsolicited adverse events with causal relationship to vaccination, within the 42-day post-vaccination period (Total vaccinated cohort)

		H1N1+AS03 N = 64				H1N1 N = 66			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		12	18.8	10.1	30.5	7	10.6	4.4	20.6
Blood and lymphatic system disorders (10005329)	Lymphadenopathy (10025197)	2	3.1	0.4	10.8	1	1.5	0.0	8.2
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	5.6	1	1.5	0.0	8.2
	Abdominal pain upper (10000087)	0	0.0	0.0	5.6	2	3.0	0.4	10.5
	Diarrhoea (10012735)	0	0.0	0.0	5.6	2	3.0	0.4	10.5
	Nausea (10028813)	3	4.7	1.0	13.1	1	1.5	0.0	8.2
General disorders and administration site conditions (10018065)	Feeling hot (10016334)	2	3.1	0.4	10.8	0	0.0	0.0	5.4
	Influenza like illness (10022004)	2	3.1	0.4	10.8	0	0.0	0.0	5.4
	Injection site lymphadenopathy (10057665)	2	3.1	0.4	10.8	0	0.0	0.0	5.4
	Injection site reaction (10022095)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Malaise (10025482)	2	3.1	0.4	10.8	0	0.0	0.0	5.4
Infections and infestations (10021881)	Rhinitis (10039083)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Psychiatric disorders (10037175)	Insomnia (10022437)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	1.6	0.0	8.4	0	0.0	0.0	5.4
	Oropharyngeal pain (10068319)	3	4.7	1.0	13.1	0	0.0	0.0	5.4

No AESIs or SAEs were reported up to time-point D42 in the adjuvanted vaccine group while one SAE of migraine was reported in the non-adjuvanted vaccine group.

There have been no withdrawals due to AEs or SAEs thus far and no pregnancies.

Study H1N1-007

Safety data were provided following the first and second adult doses in subjects aged from 10-17 years. The reporting rates for local and general solicited and unsolicited symptoms in this age group were generally comparable with rates observed in young adults as above but mostly slightly lower for individual symptoms. However, rates of local and general solicited symptoms showed a consistent trend to be higher after the second dose compared to the first dose.

In the subjects aged 10-17 years, incidences after the first and second dose were 49.0% and 54.9% for headache, 44.9% and 54.9% for fatigue and 35.7% and 51.6% for myalgia. The respective incidences of any fever were 17.3% and 24.2%. but only one subject had a fever > 39°C (after the second dose).

Conclusions and Benefit / Risk Assessment

The new data relating to administration of a second dose of Pandemrix H1N1 in study 007 are in keeping with the results of study 021 in which the vaccine used contained a slightly higher amount of HA.

The baseline serostatus of the Belgian subjects in study 007 was generally comparable with that observed in German subjects in study 021 and, although there was some difference in HI GMTs according to baseline serostatus, especially in the older subjects, there was no impact on satisfaction of the CHMP criteria after the first or second doses. Based on these data the current SPC advice regarding the use of a single dose in adults aged from 18-60 years is supported subject to the caveats regarding the unknown longer-term benefit that might be afforded by a second dose.

The HI data reported for D42 in study 007 can be directly compared with those reported in the tables above from D0 and D21 since all samples were run in parallel to avoid any effect of assay variability on interpretation of the findings. Re-run of the D0 and D21 samples did not have a marked effect on the data previously reported at these time points in variation II-019.

Importantly, data from re-run of the sera confirmed that all CHMP criteria were already met at D21 in each age stratum and regardless of baseline serostatus or prior seasonal influenza vaccination history. There was a clear increment in GMT from D21 to D42 in the adjuvanted vaccine group only and GMTs after each dose showed a trend to decrease with increasing age. The findings were consistent with those reported after the second dose in study H1N1-021 (using a higher dose of HA) as already reported in the assessment of FU2.020.

The limited NA data available from a subset of subjects and derived from an assay performed at Viroclinics showed a baseline imbalance in seropositivity rates. Responses appeared to be generally greater in the AS03 group, including the results by age strata although the responses in the 8 subjects aged 41-50 years were somewhat anomalous. These results must be viewed with some caution but they do demonstrate a good increment in NA titres in the AS03 group after one dose and overall a further increment after the second dose.

The report to D42 from study 007 also indicates that the CD4 T-cell response observed 21 days after dose 2 was higher in the H1N1 + $AS03_A$ group compared to the H1N1 group and there were increments from D21 to D42 in the adjuvanted vaccine group regardless of the mode of testing. As observed in the H5N1 studies, there was no effect of vaccination on the CD8 response but this issue has been explored and discussed previously and will not be revisited specifically with regard to H1N1.

The safety profile described with Pandemrix H1N1 in study 007 was generally comparable with that observed after first and second doses in study 021, supporting the previous conclusions that the presence of the adjuvant is much more influential than the HA content in terms of the reactogenicity profile. However, in study 021 there was no consistent trend for higher rates of reporting solicited general symptoms after the second dose although this was observed in study 007 for most symptoms.

Although the current SPC recommends only a single dose in adults aged 18-60 years the option of a second dose is left open and therefore the CHMP proposed that the data relevant to the second dose should have been added to sections 4.8 (as a brief mention) and 5.1 (tabulated) of the SPC (see the Annex 1).

While this variation proposed to update the SPC only with the post-dose 2 data from study 007 in adults the MAH simultaneously provided post-dose 1 data from study 010 with the adult dose in subjects aged 10-17 years.

Since these data from study 010 (filed as part of variation II/033) are pertinent to the use of adult doses, and since the current SPC already recommends dosing of subjects aged 10-17 years in accordance with the adult dose recommendation, the CHMP agreed to add the information on use of the adult dose and the safety data in subjects age 10-17 years to the SPC and PL in this variation.

Overall the HI responses to a single adult dose in subjects aged 10-17 years generally resemble those in young adults. In addition, in the table proposed in section 5.1 of the SPC the MAH showed the HI responses separately for children aged 10-17 years who were seronegative at baseline. As expected, these data show satisfactory responses in this subset that far exceeded the CHMP criteria applied to adults. In addition, the safety profile of the first and second adult doses in subjects aged 10-17 years was generally comparable with that observed after each dose in young adults. In subjects aged 10-17 years there were increments in local as well as general solicited symptoms with the second dose compared to the first dose whereas in young adults general symptoms increased with the second dose. On this basis the CHMP considered that it is very reasonable that the SPC should continue to recommend a single adult dose from 10 years upwards

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:

- Sections 4.2, 4.4, 4.8 and 5.1 of the SPC were updated to reflect information from study H1N1-009 in the subgroup of 10-17 year old subjects. In this respect, section 4.2 and 4.4 were updated to inform that data in this age group are now available, and to delete the recommendation in section 4.2 that the choice of dose for this age group should take into account the available data on safety and immunogenicity in adults and in children aged from 3-9 years for this reason.
- Section 4.8 was updated to reflect that in 10-17 year old subjects no increased reactogenicity after the second dose was observed, however gastro-intestinal symptoms and shivering were reported at higher rates in the children aged 10-17 years than previously reported for other age groups. Furthermore it was added that after the second dose there were higher rates of most general solicited symptoms (such as fatigue, headache, arthralgia, shivering, sweating and fever) compared to the first dose in adults.
- Annex II was updated to reflect the current status of the Specific Obligations and availability of further data as agreed by CHMP.
- The PL was updated in section 4 to reflect the revised SPC section 4.