European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP VARIATION ASSESSMENT REPORT

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

TYPE II VARIATION: EMEA/H/C/000832/II/0033

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.

This variation initially proposed to update the SPC and PL with the post-dose 1 immunogenicity and the post-dose 1+2 safety data from study 010 in children aged 3-17 years who have received two adult doses of Pandemrix (H1N1).

However, the CHMP requested post-dose 1 HI and safety data in children aged 3-9 years who have received a half adult dose of Pandemrix (H1N1) in study H1N1-023 during the procedure.

The CHMP considered that changes could only be made to the current SPC regarding children aged 3-9 years until these additional data have been reviewed and assessed, which has been done during this procedure.

However, study 010 also 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 010 are pertinent to the use of adult doses, it was agreed that the information on use of the adult dose in subjects aged 10-17 years have been added to the SPC and PL in the variation II/032 that received a positive Opinion in December 2009.

In submitting the above mentioned data from study H1N1-010 the MAH also fulfilled the Specific Obligation "to provide an abridged report for a post dose 2 abridged report from study D-PAN H1N1-010" (SOB 057). In addition the MAH took the opportunity to update Annex II with the current status of Specific Obligations

Study H1N1-010 provided also 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 information on use of the adult dose in subjects aged 10-17 years including the newly available safety data from this population was added to the SPC and PL previously in variation II/32.

3.1 Clinical aspects

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-α-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 (TVC) and according-to-protocol (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.

Results reported as of 18 November 2009

There were 210 subjects aged 3 to 17 years enrolled and vaccinated, including 53 in the 3-5 years group, 57 in the 6-9 years group and 100 in the 10-17 years group.

Of these, 207 subjects completed (53, 57 and 97 in respective age groups). 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 9.2 years. Females slightly outnumbered males in this study (44% vs. 56%).

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

Sub-group	Sex	N	N with age	MEAN	SD	MIN	MAX
3-5Y	F	31	31	3.5	0.68	3	5
	M	22	22	3.5	0.74	3	5
	Total	53	53	3.5	0.70	3	5
6-9Y	F	25	25	7.2	1.27	6	9
	M	32	32	7.6	1.10	6	9
	Total	57	57	7.5	1.18	6	9
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
Overall	F	117	117	9.5	4.80	3	17
	M	93	93	8.9	4.01	3	17
	Total	210	210	9.2	4.47	3	17

A history of seasonal influenza vaccine was obtained from 7/46 aged 3-5 years, 6/51 aged 6-9 years and 11/89 aged 10-17 years.

- At Day 0, the observed seropositivity rate for HI antibodies against the A/California strain across all age groups was 21.9%.
- 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.
- The D0 seropositivity rate was 12% in the 6-9 years age stratum and no subject was seropositive in the 3-5 years group.
- The D0 GMTs did not exceed 10.9.

At D21 all subjects were seropositive. The highest GMT was noted in the oldest group (699.7) and GMT values increased with age.

Seropositivity rates and GMTs by age-strata (Total vaccinated cohort)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
	3-5Y	PRE	53	0	0.0	0.0	6.7	5.0	5.0	5.0	<10.0	<10.0
		PI(21)	50	50	100	92.9	100	249.3	211.8	293.4	80.0	905.0
	6-9Y	PRE	57	7	12.3	5.1	23.7	6.5	5.3	8.0	<10.0	160.0
		PI(21)	54	54	100	93.4	100	368.5	287.4	472.3	80.0	2560.0
	10-17Y	PRE	100	39	39.0	29.4	49.3	10.9	8.4	14.2	<10.0	905.0
		PI(21)	97	97	100	96.3	100	699.7	583.7	838.8	80.0	5120.0
	Overall	PRE	210	46	21.9	16.5	28.1	7.8	6.8	9.0	<10.0	905.0
		PI(21)	201	201	100	98.2	100	455.6	399.9	519.1	80.0	5120.0

H1N1 HI Antibodies against A/California/7/2009 (H1N1)																
		≥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
Overall																
PRE	210	21.9	16.5	28.1	7.8	6.8	9.0	10.0	6.3	14.9	-	-	-	-	-	-
PI(D21)	201	100	98.2	100	455.6	399.9	519.1	100	98.2	100	98.5	95.7	99.7	60.2	52.9	68.4
3 to 5 years stratum																
PRE	53	0.0	0.0	6.7	5.0	5.0	5.0	0.0	0.0	6.7	-	-	-	-	-	-
PI(D21)	50	100	92.9	100	249.3	211.8	293.4	100	92.9	100	100	92.9	100	49.9	42.4	58.7
6 to 9 years stratum																
PRE	57	12.3	5.1	23.7	6.5	5.3	8.0	7.0	1.9	17.0	-	-	-	-	-	-
PI(D21)	54	100	93.4	100	368.5	287.4	472.3	100	93.4	100	100	93.4	100	55.9	46.1	67.9
10 to 17 years stratum																
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

As shown above, at Day 21 the overall HI responses exceeded the CHMP and CBER regulatory acceptance criteria for seasonal influenza vaccines for adults. The observed HI SCR was 98.5% (range from 96.9 to 100% in the three age cohorts), SCF was 60.2 (range from 49.9 to 69.1 per cohort) and SPR was 100%.

When viewed by age stratum, four children aged 6-9 years and 17 aged 10-17 years were seroprotected at D0 compared to all children in each stratum seroprotected at D21.

The D21 SCRs were 100% in the two younger strata and 97% in the 10-17 years group while SCFs were 50, 56 and 69 in ascending age strata.

The MAH also supplied the data according to age cohorts **3-9 years** and **10-17 years** for comparison with the SPC recommendations according to these age groups.

As shown in the four tables below the only difference between these two age cohorts was in the final GMTs, being twice as high in the older children. In subjects aged 10-17 years the GMT after a single full adult dose was comparable with that observed in young adults.

Seropositivity rates and GMTs by age-strata 3-9 years and 10-17 years and overall

					>= 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/7/09.HA1 Ab	H1N1 + ASO3	3-9Y	PRE	110	7	6.4	2.6	12.7	5.7	5.1	6.4	<10.0	160.0
			PI(21)	104	104	100	96.5	100	305.3	262.0	355.9	80.0	2560.0
		10-17Y	PRE	100	39	39.0	29.4	49.3	10.9	8.4	14.2	<10.0	905.0
			PI(21)	97	97	100	96.3	100	699.7	583.7	838.8	80.0	5120.0
		Overall	PRE	210	46	21.9	16.5	28.1	7.8	6.8	9.0	<10.0	905.0
			PI(21)	201	201	100	98.2	100	455.6	399.9	519.1	80.0	5120.0

SCR at PI (D21) by age-strata 3-9 years and 10-17 years and overall

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09.HA1 Ab	H1N1+ASO3A	3-9Y	PI(21)	104	104	100	96.5	100
		10-17Y	PI(21)	97	94	96.9	91.2	99.4
		Overall	PI(21)	201	198	98.5	95.7	99.7

SCF at PI (D21) by age-strata 3-9 years and 10-17 years and overall

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	H1N1+ASO3A	3-9Y	PI(21)	104	52.9	46.7	60.0
		10-17Y	PI(21)	97	69.0	54.9	86.7
		Overall	PI(21)	201	60.2	52.9	68.4

SPR at PI (D21) stratified by 3-9 years and 10-17 years and overall (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09.HA1 Ab	H1N1 + ASO3	3-9Y	PRE	110	4	3.6	1.0	9.0
			PI(21)	104	104	100	96.5	100
		10-17Y	PRE	100	17	17.0	10.2	25.8
			PI(21)	97	97	100	96.3	100
		Overall	PRE	210	21	10.0	6.3	14.9
			PI(21)	201	201	100	98.2	100

Post-dose 1 HI data in children aged 3-9 years (half adult dose) from study H1N1-023

D-PAN H1N1-023 is a phase III, non-randomised, open-label study to evaluate the safety and immunogenicity of a prime-boost schedule of Pandemrix H1N1 (using 1.9 µg HA and $AS03_B$ i.e. half adult doses) administered to subjects aged 3 to 17 years. The full study design is summarised in the figure. Currently the MAH reports only the safety and immunogenicity data observed up to D21 of the study from blood sampling group 1 (BS 1). However, in addition to the request specifically for the data in children aged 3-9 years to verify the current SPC recommendations the MAH also provides the data for the older cohort of 10-17 years.

The study planned to randomised children (total 232 in 1:1 ratios) to one of the two blood sampling schedules:

- BS1 = Day 0, Day 21, Day 42 and Month 6 for schedule 1
- BS2 = Day 42, Month 6, Month 6+7 days and Month 12 for schedule 2.

Randomisation was to be stratified by age in a ratio 1:1:2 for 3 to 5 years, 6 to 9 years and 10 to 17 years. All subjects will receive two doses of Pandemrix H1N1 containing 1.9 µg of HA antigen and $AS03_B$ on days 0 and 21 plus a booster dose at Month 6.

The study has actually enrolled 122 subjects into each of the blood sampling schedule groups, comprising a total of 61 aged 3-5 years, 65 aged 6-9 years and 118 aged 10-17 years. Five subjects withdrew between D0 and D21 due to the withdrawal of the consent (3), non-serious AEs (1) and in one case for unknown reasons.

For the total vaccinated cohort from the BS1 group the details of ages at the time of enrolment and gender per age stratum are as shown below.

		H1N1BS1							
		3-5Y N = 31		6-9Y N = 31		10-17Y N = 60		Overall N = 122	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years)	Mean	4.1	-	7.3	-	12.8	-	9.2	-
	SD	0.91	-	1.09	-	2.12	-	4.09	-
	Median	4.0	-	7.0	-	13.0	-	9.0	-
	Minimum	3	-	6	-	10	-	3	-
	Maximum	5	-	9	-	17	-	17	-
Gender	Female	13	41.9	18	58.1	25	41.7	56	45.9
	Male	18	58.1	13	41.9	35	58.3	66	54.1

The HI data are currently reported at D0 and D21 for the BS1 group.

The MAH provided a full summary of the data by and across the three age strata and also according to baseline serostatus.

Despite the high seasonal influenza vaccination rates the baseline HI seropositivity rates were low in children aged 3-5 years (10%) and 6-9 years (3%) but one third (20/60) aged 10-17 years were already seropositive at D0. Only one child aged 3-9 years was seroprotected at baseline compared to 7/60 (12%) aged 10-17 years.

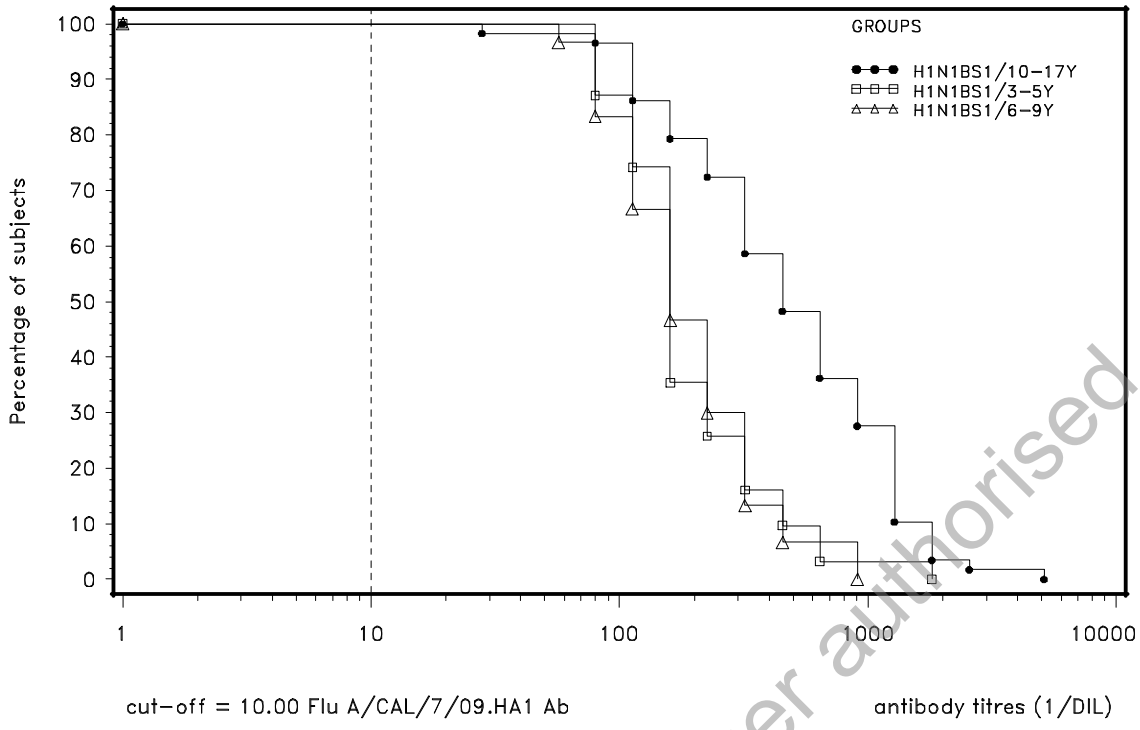
The HI response at D21 greatly exceeded all three CHMP criteria applied to young adults for seasonal influenza vaccinations.

In the 3-9 years strata all children seroconverted and were seroprotected at D21 regardless of their baseline serostatus. In each of the 3-5 and 6-9 years strata the GMT was higher and the SCF was lower in the subsets seropositive at baseline.

A single half adult dose was also highly immunogenic in the stratum aged 10-17 years. Only one subject was not seroprotected and two had not seroconverted at D21. The GMT was higher and the SCF was lower for the subset seropositive at baseline and in each case the 95% CI did not overlap with those for the baseline seronegative subset.

The GMTs were comparable between the 3-5 and 6-9 years strata within each subset according to baseline serostatus. These GMTs were much lower than those observed in children aged 10-17 years in the corresponding subsets and the 95% CI did not overlap for any comparison. The reverse cumulative distribution (RCD) curve shown below demonstrates the difference between age strata. However, this figure shows that the divergence in curves becomes apparent only from titres of 1:160 upwards.

Reverse cumulative distribution curve (PI (D21)) (Total vaccinated cohort)



In each age stratum and in each subset according to baseline serostatus the GMTs at D21 were lower than the corresponding GMTs observed after a single adult dose in study 010.

History of seasonal influenza vaccination

Approximately half of the children in each age stratum of the BS1 group had a history of seasonal influenza vaccination.

The MAH provided tabulations of D0 and D21 HI data according to history of seasonal influenza vaccination in order to confirm that the results at D21 may be extrapolated to other populations with much lower prior exposure to seasonal vaccination.

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09.HA1 Ab stratified by age-strata 3-5 years, 6-9 years and 10-17 years and overall - by previous history for Flu vaccination since birth (Total vaccinated cohort)

H1N1BS1					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	FLU_HIST	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09.HA1 Ab	YES	3-5Y	PRE	15	3	20.0	4.3	48.1	6.9	4.4	10.9	<10.0	113.0
			PI(21)	15	15	100	78.2	100	216.0	135.8	343.5	80.0	1810.0
		6-9Y	PRE	16	0	0.0	0.0	20.6	5.0	5.0	5.0	<10.0	<10.0
			PI(21)	15	15	100	78.2	100	188.1	119.7	295.5	57.0	905.0
		10-17Y	PRE	28	12	42.9	24.5	62.8	11.7	7.1	19.5	<10.0	640.0
			PI(21)	27	27	100	87.2	100	418.8	271.2	646.8	28.0	1810.0
		Overall	PRE	59	15	25.4	15.0	38.4	8.1	6.2	10.7	<10.0	640.0
			PI(21)	57	57	100	93.7	100	285.0	217.4	373.6	28.0	1810.0
	NO	3-5Y	PRE	15	0	0.0	0.0	21.8	5.0	5.0	5.0	<10.0	<10.0
			PI(21)	16	16	100	79.4	100	178.3	132.1	240.5	80.0	640.0
		6-9Y	PRE	15	1	6.7	0.2	31.9	5.5	4.5	6.7	<10.0	20.0
			PI(21)	15	15	100	78.2	100	192.4	140.4	263.8	80.0	453.0
		10-17Y	PRE	32	8	25.0	11.5	43.4	8.8	5.6	13.7	<10.0	640.0
			PI(21)	31	31	100	88.8	100	541.1	380.6	769.3	113.0	5120.0

H1N1BS1					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	FLU_HIST	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
		Overall	PRE	62	9	14.5	6.9	25.8	6.8	5.4	8.7	<10.0	640.0
			PI(21)	62	62	100	94.2	100	316.4	248.7	402.5	80.0	5120.0

Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09.HA1 Ab stratified by age-strata 3-5 years, 6-9 years and 10-17 years and overall - by history for Flu vaccination in the last three seasons (Total vaccinated cohort)

H1N1BS1					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	FLU_HIST	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09.HA1 Ab	YES	3-5Y	PRE	13	2	15.4	1.9	45.4	5.7	4.7	7.0	<10.0	14.0
			PI(21)	13	13	100	75.3	100	187.7	127.3	276.8	80.0	640.0
		6-9Y	PRE	13	0	0.0	0.0	24.7	5.0	5.0	5.0	<10.0	<10.0
			PI(21)	12	12	100	73.5	100	142.6	100.0	203.3	57.0	320.0
		10-17Y	PRE	21	8	38.1	18.1	61.6	12.8	6.5	25.0	<10.0	640.0
			PI(21)	20	20	100	83.2	100	348.7	202.8	599.7	28.0	1810.0
		Overall	PRE	47	10	21.3	10.7	35.7	7.9	5.7	10.8	<10.0	640.0
			PI(21)	45	45	100	92.1	100	229.7	172.1	306.6	28.0	1810.0
	NO	3-5Y	PRE	17	1	5.9	0.1	28.7	6.0	4.1	8.9	<10.0	113.0
			PI(21)	18	18	100	81.5	100	201.5	138.0	294.3	80.0	1810.0
		6-9Y	PRE	18	1	5.6	0.1	27.3	5.4	4.6	6.4	<10.0	20.0
			PI(21)	18	18	100	81.5	100	230.6	161.4	329.6	80.0	905.0
		10-17Y	PRE	39	12	30.8	17.0	47.6	8.8	6.1	12.8	<10.0	640.0
			PI(21)	38	38	100	90.7	100	568.4	420.1	769.1	113.0	5120.0
		Overall	PRE	74	14	18.9	10.7	29.7	7.2	5.8	8.9	<10.0	640.0
			PI(21)	74	74	100	95.1	100	354.7	283.9	443.2	80.0	5120.0

While the GMTs were variable, and for the table according to vaccination within three seasons suggested higher GMTs in those with no such history (but all 95% CI overlapped), the SCFs met the minimum required.

Discussion on immunogenicity

The CHMP considered that the extrapolation of the CHMP and CBER criteria in adults to the responses to a pandemic vaccine in children and adolescents carries several uncertainties.

Nevertheless, in the children and adolescents from 10-17 years the baseline status was comparable with that observed in adults in studies 007 and 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).

Overall the HI responses 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. On this basis the CHMP considers that it is very reasonable that the SPC should continue to recommend a single adult dose from 10 years upwards.

In children aged 3-9 years the SPC currently (following II/028) recommends one or two half adult doses given at least 3 weeks apart based on the safety and immunogenicity data obtained previously with H5N1/AS03 in children in this same age range and taking into account the post-dose 2 safety data from study 009 and the reported safety experience thus far in older children during routine use.

The CHMP highlighted that in the H5N1/AS03 study children did not mount an immune response to the first dose of either half or full adult doses. The immune response to the second dose against the H5N1 vaccine strain was comparable for HI and NA between the half and full adult dose groups. Therefore the H5N1 data cannot be considered supportive in assessing whether one or two half adult doses would be suitable for children aged 3-9 years but suggest that there may not be a marked difference between the two.

The HI data against H1N1v suggest a very robust immune response to a single adult dose in children aged 3-9 years. The data in this age group after a single half adult dose has also been provided during the procedure and also provided a sufficient immune response that exceeded the CHMP criteria.

The CHMP agrees with the MAH that it would not be appropriate based on current evidence, and taking into account the safety data reported below, to recommend the alternative of a single adult dose in children aged from 3-9 years at this time.

The D21 data after a half adult dose in children aged 3-9 years from study H1N1-023 has also been provided during the procedure.

In the 10-17 years age group the HI data from study 023 suggest that a single half adult dose might well be sufficient. However, the MAH considers that the benefit for a half vs. full adult dose in terms of adverse reactions is limited and therefore proposes to maintain the current recommendation for a single full adult dose at least until such time that more data are available (i.e. microneutralisation assay results, persistence results and heterologous immune response data). Meanwhile the MAH proposes to amend section 5.1 of the SPC to include a table that directly compares the D21 HI data from study 023 with those from study 010. The CHMP agrees with this proposal (see the Annex).

In the 3-9 years age group the HI data from study 023 also suggest that a single half adult dose might be sufficient although the absence of additional serological data as outlined above limits the confidence that can be placed in the results. Nevertheless, the data lend support to the current dose recommendation in the SPC for this age group, which was made on grounds of caution following the reactogenicity observed after the second half adult dose in children aged 6-35 months in study H1N1-009 (variation II/028) and also taking into account the safety of the first adult dose in children aged 3-9 years reported from study 010. On these grounds, the post-dose 2 safety data from study 023 will be revealing since they may or may not confirm that reactogenicity in children aged 3-9 years is higher after the second half adult dose as was seen in children aged 6-35 months.

Meanwhile, with higher GMTs after a full adult dose in study 010 vs a half adult dose in study 023 in this age group it is pertinent to note that the post-dose 1 rates of local reactions were higher for children aged 3-5 and 6-9 years in study 010 vs study 023 and that rates of general reactions were higher in study 010 for the 6-9 years stratum. Overall, the assessor does not consider that current evidence indicates any merit in changing the dose recommendations for children aged 3-9 years. It can be agreed that the additional safety data from study 023 should replace the data relating to the H5N1 vaccine in section 4.8 of the SPC and the post-dose 1 HI data from study 023 should appear in section 5.1.

The baseline seropositivity rates in study 023 were low in children aged 3-9 years despite the fact that about half had received prior seasonal influenza vaccination. However, it cannot be ruled out that a proportion of these children could have been primed even though they had no detectable HI at D0. The submission does not provide the HI responses according to influenza vaccination history In particular the GMTs and SCFs are required since the SPRs and SCRs were anyway at or near 100%. The assessor considers that these tabulations should be provided before reaching a final opinion on this variation in order to confirm that the results at D21 may be extrapolated to other populations with much lower prior exposure to seasonal vaccination.

The MAH further provided results of D0 and D21 HI data according to history of seasonal influenza vaccination which confirmed that the results at D21 may be extrapolated to other populations with much lower prior exposure to seasonal vaccination.

Concerning the MAH's plans to obtain NA data after half and full adult doses in children, the submission of homologous neutralising antibody (NA) response in at least one third of the subjects at each sampled time point in all paediatric studies (D-Pan-H1N1-009, D-Pan-H1N1-010, D-Pan-H1N1-012 and D-Pan-H1N1-023) will be further discussed within the follow up to the respective Specific Obligation (SOB 049).

Clinical Safety

H1N1-010

Local and systemic symptoms after the first dose of Pandemrix (H1N1)

Reporting rates for local and general symptoms were lower in the youngest age group and comparable between the two older age cohorts. Most symptoms were considered to be vaccine-related.

Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day 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
H1N1+ASO3A	3-5Y	53	48	90.6	79.3	96.9	53	29	54.7	40.4	68.4	53	44	83.0	70.2	91.9
	6-9Y	57	56	98.2	90.6	100	57	41	71.9	58.5	83.0	57	54	94.7	85.4	98.9
	10-17Y	100	92	92.0	84.8	96.5	100	71	71.0	61.1	79.6	100	92	92.0	84.8	96.5
	Overall	210	196	93.3	89.1	96.3	210	141	67.1	60.3	73.5	210	190	90.5	85.7	94.1

The rate of Grade 3 local symptoms increased with age but there was no age-related trend for Grade 3 general symptoms.

Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day 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
H1N1+ASO3A	3-5Y	53	6	11.3	4.3	23.0	53	4	7.5	2.1	18.2	53	3	5.7	1.2	15.7
	6-9Y	57	8	14.0	6.3	25.8	57	4	7.0	1.9	17.0	57	6	10.5	4.0	21.5
	10-17Y	100	22	22.0	14.3	31.4	100	8	8.0	3.5	15.2	100	15	15.0	8.6	23.5
	Overall	210	36	17.1	12.3	22.9	210	16	7.6	4.4	12.1	210	24	11.4	7.5	16.5

Across all age groups, pain at the injection site was the most frequent reported solicited local adverse event with rates that increased with age. The highest reporting of Grade 3 pain (8.2%) was also in the 10-17 years group. The median durations of injection site pain of any grade and of Grade 3 were 3 days and 1 day, respectively. Any and Grade 3 swelling and redness were reported less frequently than pain and only swelling appeared to be more common in the oldest stratum.

Incidence of solicited local symptoms reported during the 7-days post-vaccination period

		H1N1+ASO3A														
		3-5Y					6-9Y					10-17Y				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	53	40	75.5	61.7	86.2	57	54	94.7	85.4	98.9	98	91	92.9	85.8	97.1
	Grade 3	53	2	3.8	0.5	13.0	57	3	5.3	1.1	14.6	98	8	8.2	3.6	15.5
Redness (mm)	All (> 0 mm)	53	15	28.3	16.8	42.3	57	14	24.6	14.1	37.8	98	21	21.4	13.8	30.9
	> 50 mm	53	0	0.0	0.0	6.7	57	2	3.5	0.4	12.1	98	6	6.1	2.3	12.9
Swelling (mm)	All (> 0 mm)	53	18	34.0	21.5	48.3	57	16	28.1	17.0	41.5	98	41	41.8	31.9	52.2
	> 50 mm	53	1	1.9	0.0	10.1	57	3	5.3	1.1	14.6	98	6	6.1	2.3	12.9

The reported incidence of general solicited symptoms was lower than for local symptoms. The majority of general symptoms resolved within 1-2 days. Across all age groups, the incidence of grade 3 solicited general symptoms was low and did not exceed 4.1%.

In the 3-5 years group the most frequently reported solicited general symptoms were loss of appetite, irritability and fever, each reported with an incidence of 26.4%. One subject in the 3-5 years age group reported grade 3 fever.

In the 6-9 years and 10-17 years groups the pattern of general symptoms more closely resembled that in adults but rates were mostly lower, the most frequently reported general symptom being headache.

Incidence of solicited general symptoms reported during the 7-day post-vaccination period

		3-5Y					6-9Y					10-17Y				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	All	53					57	9	**15.8**	7.5	27.9	98	26	**26.5**	18.1	36.4
	Grade 3	53					57	0	0.0	0.0	6.3	98	1	1.0	0.0	5.6
	Related	53					57	8	14.0	6.3	25.8	98	26	26.5	18.1	36.4
	Grade 3*Related	53					57	0	0.0	0.0	6.3	98	1	1.0	0.0	5.6
Diarrhoea	All	53	2	**3.8**	0.5	13.0	57					98				
	Grade 3	53	0	0.0	0.0	6.7	57					98				
	Related	53	1	1.9	0.0	10.1	57					98				
	Grade 3*Related	53	0	0.0	0.0	6.7	57					98				
Drowsiness	All	53	11	**20.8**	10.8	34.1	57					98				
	Grade 3	53	0	0.0	0.0	6.7	57					98				
	Related	53	8	15.1	6.7	27.6	57					98				
	Grade 3*Related	53	0	0.0	0.0	6.7	57					98				
Fatigue	All	53					57	21	**36.8**	24.4	50.7	98	44	**44.9**	34.8	55.3
	Grade 3	53					57	1	1.8	0.0	9.4	98	4	4.1	1.1	10.1
	Related	53					57	20	35.1	22.9	48.9	98	40	40.8	31.0	51.2
	Grade 3*Related	53					57	1	1.8	0.0	9.4	98	4	4.1	1.1	10.1
Gastrointestinal	All	53					57	13	**22.8**	12.7	35.8	98	12	**12.2**	6.5	20.4
	Grade 3	53					57	2	3.5	0.4	12.1	98	1	1.0	0.0	5.6
	Related	53					57	9	15.8	7.5	27.9	98	6	6.1	2.3	12.9
	Grade 3*Related	53					57	2	3.5	0.4	12.1	98	1	1.0	0.0	5.6
Headache	All	53					57	25	**43.9**	30.7	57.6	98	48	**49.0**	38.7	59.3
	Grade 3	53					57	2	3.5	0.4	12.1	98	3	3.1	0.6	8.7
	Related	53					57	24	42.1	29.1	55.9	98	41	41.8	31.9	52.2
	Grade 3*Related	53					57	2	3.5	0.4	12.1	98	2	2.0	0.2	7.2
Irritability	All	53	14	**26.4**	15.3	40.3	57					98				
	Grade 3	53	0	0.0	0.0	6.7	57					98				
	Related	53	10	18.9	9.4	32.0	57					98				
	Grade 3*Related	53	0	0.0	0.0	6.7	57					98				
Loss of appetite	All	53	14	**26.4**	15.3	40.3	57					98				
	Grade 3	53	0	0.0	0.0	6.7	57					98				
	Related	53	8	15.1	6.7	27.6	57					98				
	Grade 3*Related	53	0	0.0	0.0	6.7	57					98				

		3-5Y					6-9Y					10-17Y				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Myalgia	All	53					57	15	**26.3**	15.5	39.7	98	35	**35.7**	26.3	46.0
	Grade 3	53					57	2	3.5	0.4	12.1	98	2	2.0	0.2	7.2
	Related	53					57	13	22.8	12.7	35.8	98	34	34.7	25.4	45.0
	Grade 3*Related	53					57	2	3.5	0.4	12.1	98	2	2.0	0.2	7.2
Shivering	All	53	5	**9.4**	3.1	20.7	57	7	**12.3**	5.1	23.7	98	19	**19.4**	12.1	28.6
	Grade 3	53	0	0.0	0.0	6.7	57	0	0.0	0.0	6.3	98	0	0.0	0.0	3.7
	Related	53	2	3.8	0.5	13.0	57	4	7.0	1.9	17.0	98	14	14.3	8.0	22.8
	Grade 3*Related	53	0	0.0	0.0	6.7	57	0	0.0	0.0	6.3	98	0	0.0	0.0	3.7
Sweating	All	53	4	**7.5**	2.1	18.2	57	2	**3.5**	0.4	12.1	98	8	**8.2**	3.6	15.5
	Grade 3	53	0	0.0	0.0	6.7	57	0	0.0	0.0	6.3	98	0	0.0	0.0	3.7
	Related	53	1	1.9	0.0	10.1	57	1	1.8	0.0	9.4	98	5	5.1	1.7	11.5
	Grade 3*Related	53	0	0.0	0.0	6.7	57	0	0.0	0.0	6.3	98	0	0.0	0.0	3.7
Temperature/(Axillary) (°C)	All	53	14	**26.4**	15.3	40.3	57	13	**22.8**	12.7	35.8	98	17	**17.3**	10.4	26.3
	[39.1 - ...	53	1	**1.9**	0.0	10.1	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
	Related	53	8	**15.1**	6.7	27.6	57	10	**17.5**	8.7	29.9	98	14	**14.3**	8.0	22.8
	[39.1 - ...*Related	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7

The rate of any fever decreased slightly with increasing age. The rate in the oldest stratum was higher than observed in adults but there were no fevers over 39°C. Only one child (in the 3-5 years group) received prophylactic antipyretic medication in this study.

Local and systemic symptoms after the second dose of Pandemrix (H1N1)

The MAH also provided preliminary safety data after the second adult dose administered to children aged from 3-17 years in study H1N1-010 in the Clinical Summary and Overview submitted with variation II/033. The discussion that follows compares the reactogenicity of first and second doses.

As shown in the table on the next page the rates of ***solicited local symptoms*** showed an almost consistent trend for higher local reactogenicity after the second dose, the only exception being swelling in the 3-5 years age group. Only pain showed a trend to be higher in older children but this may reflect the ability of older children to complain.

Grade 3 pain was reported by 6.3% and 12.6% of subjects after the first and second dose, respectively. The incidence of grade 3 pain at post Dose 1 was highest in the 10-17 years age group (8.2%) and at post Dose 2 it was highest in the 6-9 years age group (14.3%).

Swelling and redness were reported at lower frequencies. Incidence of redness was 24.0% post Dose 1 with 3.8% of grade 3 intensity, and 30.7% post Dose 2 with 4.0% of grade 3 intensity. Incidence of swelling was 36.1% post Dose 1 with 4.8% of grade 3 intensity and 46.2% post Dose 2 with 2.5% of grade 3 intensity. After the second dose, the frequency of swelling tended to be lower in younger children aged 3- 5 years (30.8%) compared to children aged 6-9 years and 10-17 years (46.4% and 54.9%).

Percentage of doses followed by solicited local symptoms during the 7-day post-Dose 1 and Post Dose 2 period, including those of grade 3 intensity in study D-Pan-H1N1-010 (Total vaccinated cohort)

Study vaccine		H1N1 + AS03$_A$																			
Age category		All ages, 3-17 years					3-5 years					6-9 years					10-17 years				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
		Dose 1																			
Pain	All	208	185	**88.9**	83.9	92.9	53	40	**75.5**	61.7	86.2	57	54	**94.7**	85.4	98.9	98	91	**92.9**	85.8	97.1
	Grade 3	208	13	**6.3**	3.4	10.5	53	2	**3.8**	0.5	13.0	57	3	**5.3**	1.1	14.6	98	8	**8.2**	3.6	15.5
Redness	All	208	50	**24.0**	18.4	30.4	53	15	**28.3**	16.8	42.3	57	14	**24.6**	14.1	37.8	98	21	**21.4**	13.8	30.9
	Grade 3	208	8	**3.8**	1.7	7.4	53	0	**0.0**	0.0	6.7	57	2	**3.5**	0.4	12.1	98	6	**6.1**	2.3	12.9
Swelling	All	208	75	**36.1**	29.5	43.0	53	18	**34.0**	21.5	48.3	57	16	**28.1**	17.0	41.5	98	41	**41.8**	31.9	52.2
	Grade 3	208	10	**4.8**	2.3	8.7	53	1	**1.9**	0.0	10.1	57	3	**5.3**	1.1	14.6	98	6	**6.1**	2.3	12.9
		Dose 2																			
Pain	All	199	187	**94.0**	89.7	96.8	52	44	**84.6**	71.9	93.1	56	54	**96.4**	87.7	99.6	91	89	**97.8**	92.3	99.7
	Grade 3	199	25	**12.6**	8.3	18.0	52	5	**9.6**	3.2	21.0	56	8	**14.3**	6.4	26.2	91	12	**13.2**	7.0	21.9
Redness	All	199	61	**30.7**	24.3	37.6	52	18	**34.6**	22.0	49.1	56	18	**32.1**	20.3	46.0	91	25	**27.5**	18.6	37.8
	Grade 3	199	8	**4.0**	1.8	7.8	52	4	**7.7**	2.1	18.5	56	2	**3.6**	0.4	12.3	91	2	**2.2**	0.3	7.7
Swelling	All	199	92	**46.2**	39.2	53.4	52	16	**30.8**	18.7	45.1	56	26	**46.4**	33.0	60.3	91	50	**54.9**	44.2	65.4
	Grade 3	199	5	**2.5**	0.8	5.8	52	2	**3.8**	0.5	13.2	56	1	**1.8**	0.0	9.6	91	2	**2.2**	0.3	7.7

H1N1 + AS03$_A$ = H1N1 vaccine containing 3.75 µg HA (A/California/7/2009 (H1N1) v-like, adjuvanted with AS03$_A$

Grade 3 pain = severe pain that prevents normal activity (age 6-17 years)/ spontaneously painful, cries when limb is moved (age 3-5 years)

Grade 3 redness/swelling = largest surface diameter >50mm

N= number of subjects with at least one documented dose

n/%= number/percentage of subjects reporting at least once the symptom when the intensity is maximum

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Solicited general symptoms in children aged 3- 5 years were fever, irritability/fussiness, drowsiness, sweating, shivering, diarrhoea/vomiting and loss of appetite, and in older children aged 6-17 years were fatigue, headache, gastrointestinal symptoms, arthralgia, myalgia, shivering, sweating, and fever.

The number and percentage of doses followed by solicited general symptoms within the 7 day post-vaccination period after the first and after the second vaccine dose are presented in the table that follows by age category.

In children aged 3-5 years, fever was the predominant solicited general symptom (26.4% and 48.1% after the first and second dose, respectively), followed by loss of appetite (26.4% and 40.4%), drowsiness (20.8% and 32.7%) and irritability (26.4% and 28.8%), with a trend for higher incidences after the second dose compared to incidences after the first dose. Grade 3 solicited general symptoms after the first dose were infrequent (e.g. there was only one report of Grade 3 fever). After the second dose, solicited general symptoms of Grade 3 intensity were reported at higher incidences (5.8% for irritability and loss of appetite, 3.8% for fever and drowsiness and 1.9% for shivering).

In subjects aged 6 to 17 years old, fatigue, headache and myalgia were the most frequently reported symptoms. A trend for a higher incidence of general symptoms post Dose 2 compared to post Dose 1 was also observed in this age group.

In children aged 6-9 years, respective incidences after the first and second dose were 43.9% and 44.6% for headache, 36.8% and 51.8% for fatigue and 26.3% and 28.6% for myalgia.

In children 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 fever after the first and second dose were 22.8% and 33.9% in the 6-9 years age category and 17.3% and 24.2% in the 10-17 years category, which tends to be lower than in the younger age category aged 3-5 years (26.4% and 48.1% after the first and second dose, respectively).

The incidence of Grade 3 solicited general symptoms after the first dose was low and did not exceed 4.1%. An overall higher incidence of Grade 3 general symptoms was noted after the second dose, with the highest frequency observed for headache (7.1%) in the group aged 6-9 years.

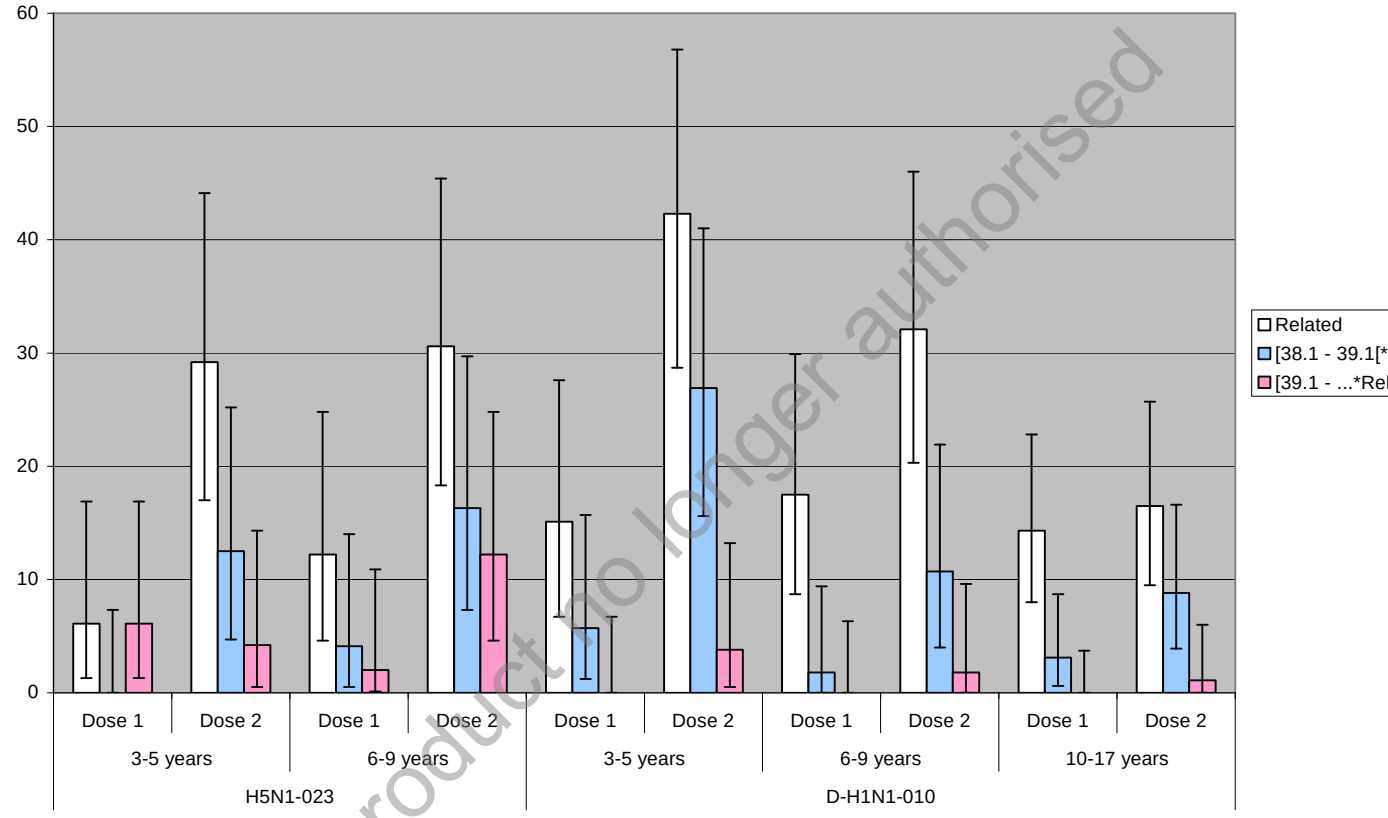
Solicited general symptoms during the 7-day period after each dose

Study vaccine		H1N1+ASO3$_A$														
Age category		3-5 years					6-9 years					10-17 years				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
		Dose 1														
Arthralgia	All						57	9	**15.8**	7.5	27.9	98	26	**26.5**	18.1	36.4
	Grade 3						57	0	**0.0**	0.0	6.3	98	1	**1.0**	0.0	5.6
	Related						57	8	**14.0**	6.3	25.8	98	26	**26.5**	18.1	36.4
	Grade 3*Related						57	0	**0.0**	0.0	6.3	98	1	**1.0**	0.0	5.6
Fatigue	All						57	21	**36.8**	24.4	50.7	98	44	**44.9**	34.8	55.3
	Grade 3						57	1	**1.8**	0.0	9.4	98	4	**4.1**	1.1	10.1
	Related						57	20	**35.1**	22.9	48.9	98	40	**40.8**	31.0	51.2
	Grade 3*Related						57	1	**1.8**	0.0	9.4	98	4	**4.1**	1.1	10.1
Gastrointestinal	All						57	13	**22.8**	12.7	35.8	98	12	**12.2**	6.5	20.4
	Grade 3						57	2	**3.5**	0.4	12.1	98	1	**1.0**	0.0	5.6
	Related						57	9	**15.8**	7.5	27.9	98	6	**6.1**	2.3	12.9
	Grade 3*Related						57	2	**3.5**	0.4	12.1	98	1	**1.0**	0.0	5.6
Headache	All						57	25	**43.9**	30.7	57.6	98	48	**49.0**	38.7	59.3
	Grade 3						57	2	**3.5**	0.4	12.1	98	3	**3.1**	0.6	8.7
	Related						57	24	**42.1**	29.1	55.9	98	41	**41.8**	31.9	52.2
	Grade 3*Related						57	2	**3.5**	0.4	12.1	98	2	**2.0**	0.2	7.2
Myalgia	All						57	15	**26.3**	15.5	39.7	98	35	**35.7**	26.3	46.0
	Grade 3						57	2	**3.5**	0.4	12.1	98	2	**2.0**	0.2	7.2
	Related						57	13	**22.8**	12.7	35.8	98	34	**34.7**	25.4	45.0
	Grade 3*Related						57	2	**3.5**	0.4	12.1	98	2	**2.0**	0.2	7.2
Diarrhoea/vomiting	All	53	2	**3.8**	0.5	13.0										
	Grade 3	53	0	**0.0**	0.0	6.7										
	Related	53	1	**1.9**	0.0	10.1										
	Grade 3*Related	53	0	**0.0**	0.0	6.7										
Drowsiness	All	53	11	**20.8**	10.8	34.1										
	Grade 3	53	0	**0.0**	0.0	6.7										
	Related	53	8	**15.1**	6.7	27.6										
	Grade 3*Related	53	0	**0.0**	0.0	6.7										
Irritability	All	53	14	**26.4**	15.3	40.3										
	Grade 3	53	0	**0.0**	0.0	6.7										
	Related	53	10	**18.9**	9.4	32.0										
	Grade 3*Related	53	0	**0.0**	0.0	6.7										
Loss of appetite	All	53	14	**26.4**	15.3	40.3										
	Grade 3	53	0	**0.0**	0.0	6.7										
	Related	53	8	**15.1**	6.7	27.6										
	Grade 3*Related	53	0	**0.0**	0.0	6.7										
Shivering	All	53	5	**9.4**	3.1	20.7	57	7	**12.3**	5.1	23.7	98	19	**19.4**	12.1	28.6
	Grade 3	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
	Related	53	2	**3.8**	0.5	13.0	57	4	**7.0**	1.9	17.0	98	14	**14.3**	8.0	22.8
	Grade 3*Related	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
Sweating	All	53	4	**7.5**	2.1	18.2	57	2	**3.5**	0.4	12.1	98	8	**8.2**	3.6	15.5
	Grade 3	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
	Related	53	1	**1.9**	0.0	10.1	57	1	**1.8**	0.0	9.4	98	5	**5.1**	1.7	11.5
	Grade 3*Related	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7

Study vaccine		H1N1+ASO3A														
Age category		3-5 years					6-9 years					10-17 years				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
		Dose 2														
Arthralgia	All						56	12	**21.4**	11.6	34.4	91	33	**36.3**	26.4	47.0
	Grade 3						56	1	**1.8**	0.0	9.6	91	1	**1.1**	0.0	6.0
	Related						56	12	**21.4**	11.6	34.4	91	31	**34.1**	24.5	44.7
	Grade 3*Related						56	1	**1.8**	0.0	9.6	91	1	**1.1**	0.0	6.0
Fatigue	All						56	29	**51.8**	38.0	65.3	91	50	**54.9**	44.2	65.4
	Grade 3						56	3	**5.4**	1.1	14.9	91	5	**5.5**	1.8	12.4
	Related						56	28	**50.0**	36.3	63.7	91	48	**52.7**	42.0	63.3
	Grade 3*Related						56	3	**5.4**	1.1	14.9	91	5	**5.5**	1.8	12.4
Gastrointestinal	All						56	9	**16.1**	7.6	28.3	91	10	**11.0**	5.4	19.3
	Grade 3						56	0	**0.0**	0.0	6.4	91	0	**0.0**	0.0	4.0
	Related						56	8	**14.3**	6.4	26.2	91	6	**6.6**	2.5	13.8
	Grade 3*Related						56	0	**0.0**	0.0	6.4	91	0	**0.0**	0.0	4.0
Headache	All						56	25	**44.6**	31.3	58.5	91	50	**54.9**	44.2	65.4
	Grade 3						56	4	**7.1**	2.0	17.3	91	5	**5.5**	1.8	12.4
	Related						56	25	**44.6**	31.3	58.5	91	49	**53.8**	43.1	64.4
	Grade 3*Related						56	4	**7.1**	2.0	17.3	91	4	**4.4**	1.2	10.9
Myalgia	All						56	16	**28.6**	17.3	42.2	91	47	**51.6**	40.9	62.3
	Grade 3						56	1	**1.8**	0.0	9.6	91	2	**2.2**	0.3	7.7
	Related						56	16	**28.6**	17.3	42.2	91	44	**48.4**	37.7	59.1
	Grade 3*Related						56	1	**1.8**	0.0	9.6	91	2	**2.2**	0.3	7.7
Diarrhoea/vomiting	All	52	6	**11.5**	4.4	23.4										
	Grade 3	52	0	**0.0**	0.0	6.8										
	Related	52	3	**5.8**	1.2	15.9										
	Grade 3*Related	52	0	**0.0**	0.0	6.8										
Drowsiness	All	52	17	**32.7**	20.3	47.1										
	Grade 3	52	2	**3.8**	0.5	13.2										
	Related	52	15	**28.8**	17.1	43.1										
	Grade 3*Related	52	2	**3.8**	0.5	13.2										
Irritability	All	52	15	**28.8**	17.1	43.1										
	Grade 3	52	3	**5.8**	1.2	15.9										
	Related	52	14	**26.9**	15.6	41.0										
	Grade 3*Related	52	3	**5.8**	1.2	15.9										
Loss of appetite	All	52	21	**40.4**	27.0	54.9										
	Grade 3	52	3	**5.8**	1.2	15.9										
	Related	52	17	**32.7**	20.3	47.1										
	Grade 3*Related	52	3	**5.8**	1.2	15.9										
Shivering	All	52	6	**11.5**	4.4	23.4	56	14	**25.0**	14.4	38.4	91	27	**29.7**	20.5	40.2
	Grade 3	52	1	**1.9**	0.0	10.3	56	0	**0.0**	0.0	6.4	91	1	**1.1**	0.0	6.0
	Related	52	5	**9.6**	3.2	21.0	56	13	**23.2**	13.0	36.4	91	25	**27.5**	18.6	37.8
	Grade 3*Related	52	1	**1.9**	0.0	10.3	56	0	**0.0**	0.0	6.4	91	1	**1.1**	0.0	6.0
Sweating	All	52	6	**11.5**	4.4	23.4	56	7	**12.5**	5.2	24.1	91	8	**8.8**	3.9	16.6
	Grade 3	52	0	**0.0**	0.0	6.8	56	0	**0.0**	0.0	6.4	91	0	**0.0**	0.0	4.0
	Related	52	4	**7.7**	2.1	18.5	56	4	**7.1**	2.0	17.3	91	7	**7.7**	3.1	15.2
	Grade 3*Related	52	0	**0.0**	0.0	6.8	56	0	**0.0**	0.0	6.4	91	0	**0.0**	0.0	4.0

The data for fevers are summarised in the table and figure below, which provides estimates of any fever, 38.1-39.1°C and over 39.1°C. The figure also compares the findings to administration of two full doses of H5N1/AS03 as previously reported from study 023. These data clearly show that there is an increment in fever rates after the second dose of Pandemrix H1N1 in each age group but fever rates after the first dose are comparable across age groups whereas rates after the second dose decrease with increasing age.

		N	n	3-5	LL	UL	N	n	6-9	LL	UL	N	n	10-17	LL	UL
DOSE 1																
Fever(Axillary) (°C)	**All**	53	14	**26.4**	15.3	40.3	57	13	**22.8**	12.7	35.8	98	17	**17.3**	10.4	26.3
	>39°C	53	1	**1.9**	0.0	10.1	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
	Related	53	8	**15.1**	6.7	27.6	57	10	**17.5**	8.7	29.9	98	14	**14.3**	8.0	22.8
	>39°C *Related	53	0	**0.0**	0.0	6.7	57	0	**0.0**	0.0	6.3	98	0	**0.0**	0.0	3.7
DOSE 2																
Fever(Axillary) (°C)	**All**	52	25	**48.1**	34.0	62.4	56	19	**33.9**	21.8	47.8	91	22	**24.2**	15.8	34.3
	>39°C	52	2	**3.8**	0.5	13.2	56	1	**1.8**	0.0	9.6	91	1	**1.1**	0.0	6.0
	Related	52	22	**42.3**	28.7	56.8	56	18	**32.1**	20.3	46.0	91	15	**16.5**	9.5	25.7
	>39°C *Related	52	2	**3.8**	0.5	13.2	56	1	**1.8**	0.0	9.6	91	1	**1.1**	0.0	6.0



In addition, the table on the next page provides a side by side comparison of the solicited general symptom rates **considered related to vaccination** after each dose and by age strata.

This table also demonstrates the clear trend for increases for most symptoms with the second dose. Rates for any related fever are lower and more comparable across age strata after the first dose compared to the second dose, where there is a trend to decreasing fever rates with increasing age. Even in the youngest children the rate is not as high as seen in the children aged <3 years after the second half adult dose.

Incidence of solicited general symptoms <u>related to vaccination</u>, all and of grade 3 intensity, reported during the 7-day (Days 0-6) post Dose 1 and post Dose 2 periods in study D-Pan-H1N1-010 (Total vaccinated cohort)

		3-5 years						6-9 years						10-17 years					
		Dose 1			Dose 2			Dose 1			Dose 2			Dose 1			Dose 2		
		N=53			N=52			N=57			N=56			N=98			N=91		
			95% CI			95% CI			95% CI			95% CI			95% CI			95% CI	
Symptom	**Type**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Arthralgia	Related							**14.0**	6.3	25.8	**21.4**	11.6	34.4	**26.5**	18.1	36.4	**34.1**	24.5	44.7
	Grade 3*Related							**0.0**	0.0	6.3	**1.8**	0.0	9.6	**1.0**	0.0	5.6	**1.1**	0.0	6.0
Diarrhoea	Related	**1.9**	0.0	10.1	**5.8**	1.2	15.9												
	Grade 3*Related	**0.0**	0.0	6.7	**0.0**	0.0	6.8												
Drowsiness	Related	**15.1**	6.7	27.6	**28.8**	17.1	43.1												
	Grade 3*Related	**0.0**	0.0	6.7	**3.8**	0.5	13.2												
Fatigue	Related							**35.1**	22.9	48.9	**50.0**	36.3	63.7	**40.8**	31.0	51.2	**52.7**	42.0	63.3
	Grade 3*Related							**1.8**	0.0	9.4	**5.4**	1.1	14.9	**4.1**	1.1	10.1	**5.5**	1.8	12.4
Gastrointestinal	Related							**15.8**	7.5	27.9	**14.3**	6.4	26.2	**6.1**	2.3	12.9	**6.6**	2.5	13.8
	Grade 3*Related							**3.5**	0.4	12.1	**0.0**	0.0	6.4	**1.0**	0.0	5.6	**0.0**	0.0	4.0
Headache	Related							**42.1**	29.1	55.9	**44.6**	31.3	58.5	**41.8**	31.9	52.2	**53.8**	43.1	64.4
	Grade 3*Related							**3.5**	0.4	12.1	**7.1**	2.0	17.3	**2.0**	0.2	7.2	**4.4**	1.2	10.9
Irritability	Related	**18.9**	9.4	32.0	**26.9**	15.6	41.0												
	Grade 3*Related	**0.0**	0.0	6.7	**5.8**	1.2	15.9												
Loss of appetite	Related	**15.1**	6.7	27.6	**32.7**	20.3	47.1												
	Grade 3*Related	**0.0**	0.0	6.7	**5.8**	1.2	15.9												
Myalgia	Related							**22.8**	12.7	35.8	**28.6**	17.3	42.2	**34.7**	25.4	45.0	**48.4**	37.7	59.1
	Grade 3*Related							**3.5**	0.4	12.1	**1.8**	0.0	9.6	**2.0**	0.2	7.2	**2.2**	0.3	7.7
Shivering	Related	**3.8**	0.5	13.0	**9.6**	3.2	21.0	**7.0**	1.9	17.0	**23.2**	13.0	36.4	**14.3**	8.0	22.8	**27.5**	18.6	37.8
	Grade 3*Related	**0.0**	0.0	6.7	**1.9**	0.0	10.3	**0.0**	0.0	6.3	**0.0**	0.0	6.4	**0.0**	0.0	3.7	**1.1**	0.0	6.0
Sweating	Related	**1.9**	0.0	10.1	**7.7**	2.1	18.5	**1.8**	0.0	9.4	**7.1**	2.0	17.3	**5.1**	1.7	11.5	**7.7**	3.1	15.2
	Grade 3*Related	**0.0**	0.0	6.7	**0.0**	0.0	6.8	**0.0**	0.0	6.3	**0.0**	0.0	6.4	**0.0**	0.0	3.7	**0.0**	0.0	4.0
Temperature/(Axillary) (°C)	Related	**15.1**	6.7	27.6	**42.3**	28.7	56.8	**17.5**	8.7	29.9	**32.1**	20.3	46.0	**14.3**	8.0	22.8	**16.5**	9.5	25.7
	[39.1 - ...*Related	**0.0**	0.0	6.7	**3.8**	0.5	13.2	**0.0**	0.0	6.3	**1.8**	0.0	9.6	**0.0**	0.0	3.7	**1.1**	0.0	6.0

AEs after the 1st dose

Overall 26.2% reported at least one unsolicited AE with the highest rate in the youngest cohort.

Unsolicited adverse events reported within the 21-day post-vaccination period (TVC)

	3-5Y	6-9Y	10-17Y	Overall
Number of subjects with at least one unsolicited symptom reported	18	15	22	55
Number of unsolicited symptoms classified by MedDRA Preferred Term*	26	17	30	73
Number of unsolicited symptoms reported	27	17	32	76

		3-5Y N = 53				6-9Y N = 57				10-17Y N = 100				Overall N = 210			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		18	34.0	21.5	48.3	15	26.3	15.5	39.7	22	22.0	14.3	31.4	55	26.2	20.4	32.7

No specific clinical pattern of unsolicited AEs could be identified in the different age groups. The most frequently reported unsolicited AE was upper respiratory tract infection. There was one case of urticaria reported in a child in the 6-9 years group but this does not seem to have been considered related to vaccination. The proportion of unsolicited AEs resulting in a medically attended visit decreased with increasing age.

Unsolicited AEs with medically attended visit (TVC)

		3-5Y N = 53				6-9Y N = 57				10-17Y N = 100				Overall N = 210			
				95% CI				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		16	30.2	18.3	44.3	6	10.5	4.0	21.5	8	8.0	3.5	15.2	30	14.3	9.9	19.8

The percentage of events considered by the investigator to be related to vaccination was low (2.9% across all age groups) and there were none in the youngest age stratum.

Unsolicited AEs with causal relationship within the 21-day post-vaccination period (TVC)

		3-5Y N = 53				6-9Y N = 57				10-17Y N = 100				Overall N = 210			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		0	0.0	0.0	6.7	3	5.3	1.1	14.6	3	3.0	0.6	8.5	6	2.9	1.1	6.1
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	1	0.5	0.0	2.6
	Vomiting (10047700)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	1	0.5	0.0	2.6
General disorders and administration site conditions (10018065)	Axillary pain (10048750)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	1	1.0	0.0	5.4	2	1.0	0.1	3.4
	Injection site nodule (10057880)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	1	0.5	0.0	2.6
	Malaise (10025482)	0	0.0	0.0	6.7	0	0.0	0.0	6.3	1	1.0	0.0	5.4	1	0.5	0.0	2.6
Psychiatric disorders (10037175)	Insomnia (10022437)	0	0.0	0.0	6.7	0	0.0	0.0	6.3	1	1.0	0.0	5.4	1	0.5	0.0	2.6

Grade 3 unsolicited AEs were infrequent (maximum 5.7% in the 3-5 years group). Two grade 3 events considered related to vaccination were reported in one subject only (in the 6-9 years group). As shown in the tables above and below this was the child who had abdominal pain and vomiting.

Grade 3 unsolicited adverse events within the 21-day post-vaccination period (TVC)

		H1N1+ASO3A															
		3-5Y N = 53				6-9Y N = 57				10-17Y N = 100				Overall N = 210			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		3	5.7	1.2	15.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	4	1.9	0.5	4.8
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	1	0.5	0.0	2.6
	Vomiting (10047700)	0	0.0	0.0	6.7	1	1.8	0.0	9.4	0	0.0	0.0	3.6	1	0.5	0.0	2.6
Infections and infestations (10021881)	Ear infection (10014011)	1	1.9	0.0	10.1	0	0.0	0.0	6.3	0	0.0	0.0	3.6	1	0.5	0.0	2.6
	Laryngitis (10023874)	1	1.9	0.0	10.1	0	0.0	0.0	6.3	0	0.0	0.0	3.6	1	0.5	0.0	2.6
	Otitis externa (10033072)	1	1.9	0.0	10.1	0	0.0	0.0	6.3	0	0.0	0.0	3.6	1	0.5	0.0	2.6

The overall incidence of unsolicited AEs resulting in a medically attended visit was 14.3%, with more cases in the youngest age stratum 3-5 years (30.2%) than the two older strata (10.5% in 6-9 years and 8.0% in 10-17 years).

No AESIs/pIMDs or SAEs were reported up to time-point D21.

There have been no withdrawals due to adverse events, no SAEs and no pregnancies.

Statistical analysis of selected serum biochemistry safety parameters was not available at the time of finalization of this report. However, a review of the raw data of the available serum biochemistry has been done and no safety signal was detected. Statistical analysis will be provided as soon as available.

Breakdown of fevers in children aged 3-9 years

The total fever rate increased in all age strata from dose 1 to dose 2. Rates of fever over 38°C in the age group for which an adult dose is recommended (10-17 years) showed a modest increase from dose 1 to dose 2 and only one subject had a fever 39.1°C after the second dose.

It should be noted that a single adult dose is the standard recommendation for children aged 10-17 years and that a half adult dose is the current recommendation in the age group 3-9 years of age and that administration of a second dose is left open.

The largest increase in fevers over 38°C from dose 1 to dose 2 was observed in the youngest age stratum (3-5 years) with a smaller difference for the 6-9 years group. Even here only two subjects aged 3-5 and one subject aged 6-9 years had fever over 39.1°C after the second dose.

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The safety data have also been summarised by age strata.

Overall, the reporting rates for all, local and general symptoms did not show a consistent trend to increase or decrease with age but rates for Grade 3 symptoms increased with age, mainly reflecting the local symptom data and higher rates of reporting pain and swelling in the oldest children (see third table below).

Symptoms (solicited and unsolicited) reported during the 7-days post-dose 1 (TVC)

		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
H1N1AD	3-5Y	61	45	73.8	60.9	84.2	61	35	57.4	44.1	70.0	61	40	65.6	52.3	77.3
	6-9Y	65	45	69.2	56.6	80.1	65	27	41.5	29.4	54.4	65	43	66.2	53.4	77.4
	10-17Y	118	96	81.4	73.1	87.9	118	74	62.7	53.3	71.4	118	90	76.3	67.6	83.6
	Overall	244	186	76.2	70.4	81.4	244	136	55.7	49.3	62.1	244	173	70.9	64.8	76.5

Grade 3 symptoms (solicited and unsolicited) reported during the 7-days post-dose 1 (TVC)

		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
H1N1AD	3-5Y	61	5	8.2	2.7	18.1	61	4	6.6	1.8	15.9	61	2	3.3	0.4	11.3
	6-9Y	65	9	13.8	6.5	24.7	65	4	6.2	1.7	15.0	65	6	9.2	3.5	19.0
	10-17Y	118	24	20.3	13.5	28.7	118	14	11.9	6.6	19.1	118	13	11.0	6.0	18.1
	Overall	244	38	15.6	11.3	20.7	244	22	9.0	5.7	13.3	244	21	8.6	5.4	12.9

Solicited local symptoms reported during the 7-days post-dose 1 (TVC)

		H1N1AD														
		3-5Y					6-9Y					10-17Y				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	60	36	60.0	46.5	72.4	65	41	63.1	50.2	74.7	118	87	73.7	64.8	81.4
	Grade 1	60	28	46.7	33.7	60.0	65	20	30.8	19.9	43.4	118	31	26.3	18.6	35.2
	Grade 2	60	6	10.0	3.8	20.5	65	17	26.2	16.0	38.5	118	47	39.8	30.9	49.3
	Grade 3	60	2	3.3	0.4	11.5	65	4	6.2	1.7	15.0	118	9	7.6	3.5	14.0
Redness (mm)	All	60	16	26.7	16.1	39.7	65	15	23.1	13.5	35.2	118	27	22.9	15.7	31.5
	[0.1 - 20.1[	60	14	23.3	13.4	36.0	65	11	16.9	8.8	28.3	118	19	16.1	10.0	24.0
	[20.1 - 50.1[	60	2	3.3	0.4	11.5	65	3	4.6	1.0	12.9	118	8	6.8	3.0	12.9
	[50.1 - ...	60	0	0.0	0.0	6.0	65	1	1.5	0.0	8.3	118	0	0.0	0.0	3.1
Swelling (mm)	All	60	13	21.7	12.1	34.2	65	15	23.1	13.5	35.2	118	35	29.7	21.6	38.8
	[0.1 - 20.1[	60	8	13.3	5.9	24.6	65	9	13.8	6.5	24.7	118	22	18.6	12.1	26.9
	[20.1 - 50.1[	60	5	8.3	2.8	18.4	65	4	6.2	1.7	15.0	118	8	6.8	3.0	12.9
	[50.1 - ...	60	0	0.0	0.0	6.0	65	2	3.1	0.4	10.7	118	5	4.2	1.4	9.6

The tables on the three following pages summarise all the solicited general symptom data for each age stratum, noting that the range of solicited symptoms differed between the 3-5 years and the two older strata.

Headache, myalgia and shivering were reported more often in the 10-17 years stratum compared to the 6-9 years group.

Rates of fever above 38.5ºC were low in each stratum (all and related) and highest in the 3-5 years group (but still < 10%).

Solicited general symptoms during the 7-days post-dose 1 by age strata (TVC)

		3-5Y				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Diarrhoea	All	60	6	10.0	3.8	20.5
	Grade 3	60	1	1.7	0.0	8.9
	Rel	60	3	5.0	1.0	13.9
	Grade 3*Rel	60	1	1.7	0.0	8.9
Drowsiness	All	60	15	25.0	14.7	37.9
	Grade 3	60	1	1.7	0.0	8.9
	Rel	60	14	23.3	13.4	36.0
	Grade 3*Rel	60	1	1.7	0.0	8.9
Irritability	All	60	12	20.0	10.8	32.3
	Grade 3	60	1	1.7	0.0	8.9
	Rel	60	12	20.0	10.8	32.3
	Grade 3*Rel	60	1	1.7	0.0	8.9
Loss of appetite	All	60	13	21.7	12.1	34.2
	Grade 3	60	0	0.0	0.0	6.0
	Rel	60	12	20.0	10.8	32.3
	Grade 3*Rel	60	0	0.0	0.0	6.0
Shivering	All	60	9	15.0	7.1	26.6
	Grade 3	60	0	0.0	0.0	6.0
	Rel	60	8	13.3	5.9	24.6
	Grade 3*Rel	60	0	0.0	0.0	6.0
Sweating	All	60	7	11.7	4.8	22.6
	Grade 3	60	0	0.0	0.0	6.0
	Rel	60	6	10.0	3.8	20.5
	Grade 3*Rel	60	0	0.0	0.0	6.0
Temperature/(Axillary) (°C)	All	60	19	31.7	20.3	45.0
	[37.5 - 38.1[	60	13	21.7	12.1	34.2
	[38.1 - 38.6[	60	1	1.7	0.0	8.9
	[38.6 - 39.1[	60	4	6.7	1.8	16.2
	[39.1 - 39.6[	60	1	1.7	0.0	8.9
	[39.6 - 40.1[	60	0	0.0	0.0	6.0
	[40.1 - ...	60	0	0.0	0.0	6.0
	Rel	60	16	26.7	16.1	39.7
	[37.5 - 38.1[*Rel	60	10	16.7	8.3	28.5
	[38.1 - 38.6[*Rel	60	1	1.7	0.0	8.9
	[38.6 - 39.1[*Rel	60	4	6.7	1.8	16.2
	[39.1 - 39.6[*Rel	60	1	1.7	0.0	8.9
	[39.6 - 40.1[*Rel	60	0	0.0	0.0	6.0
	[40.1 - ...*Rel	60	0	0.0	0.0	6.0

		6-9Y				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	All	65	10	15.4	7.6	26.5
	Grade 3	65	0	0.0	0.0	5.5
	Rel	65	10	15.4	7.6	26.5
	Grade 3*Rel	65	0	0.0	0.0	5.5
Fatigue	All	65	19	29.2	18.6	41.8
	Grade 3	65	1	1.5	0.0	8.3
	Rel	65	18	27.7	17.3	40.2
	Grade 3*Rel	65	1	1.5	0.0	8.3
Gastrointestinal	All	65	12	18.5	9.9	30.0
	Grade 3	65	1	1.5	0.0	8.3
	Rel	65	9	13.8	6.5	24.7
	Grade 3*Rel	65	1	1.5	0.0	8.3
Headache	All	65	14	21.5	12.3	33.5
	Grade 3	65	2	3.1	0.4	10.7
	Rel	65	14	21.5	12.3	33.5
	Grade 3*Rel	65	2	3.1	0.4	10.7
Myalgia	All	65	11	16.9	8.8	28.3
	Grade 3	65	0	0.0	0.0	5.5
	Rel	65	11	16.9	8.8	28.3
	Grade 3*Rel	65	0	0.0	0.0	5.5
Shivering	All	65	8	12.3	5.5	22.8
	Grade 3	65	0	0.0	0.0	5.5
	Rel	65	7	10.8	4.4	20.9
	Grade 3*Rel	65	0	0.0	0.0	5.5
Sweating	All	65	5	7.7	2.5	17.0
	Grade 3	65	0	0.0	0.0	5.5
	Rel	65	4	6.2	1.7	15.0
	Grade 3*Rel	65	0	0.0	0.0	5.5
Temperature/(Axillary) (°C)	All	65	10	15.4	7.6	26.5
	[37.5 - 38.1[	65	6	9.2	3.5	19.0
	[38.1 - 38.6[	65	3	4.6	1.0	12.9
	[38.6 - 39.1[	65	0	0.0	0.0	5.5
	[39.1 - 39.6[	65	1	1.5	0.0	8.3
	[39.6 - 40.1[	65	0	0.0	0.0	5.5
	[40.1 - ...	65	0	0.0	0.0	5.5
	Rel	65	8	12.3	5.5	22.8
	[37.5 - 38.1[*Rel	65	5	7.7	2.5	17.0
	[38.1 - 38.6[*Rel	65	3	4.6	1.0	12.9
	[38.6 - 39.1[*Rel	65	0	0.0	0.0	5.5
	[39.1 - 39.6[*Rel	65	0	0.0	0.0	5.5
	[39.6 - 40.1[*Rel	65	0	0.0	0.0	5.5
	[40.1 - ...*Rel	65	0	0.0	0.0	5.5

		10-17Y				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	All	118	12	10.2	5.4	17.1
	Grade 3	118	2	1.7	0.2	6.0
	Rel	118	11	9.3	4.7	16.1
	Grade 3*Rel	118	1	0.8	0.0	4.6
Fatigue	All	118	38	32.2	23.9	41.4
	Grade 3	118	3	2.5	0.5	7.3
	Rel	118	33	28.0	20.1	37.0
	Grade 3*Rel	118	2	1.7	0.2	6.0
Gastrointestinal	All	118	17	14.4	8.6	22.1
	Grade 3	118	4	3.4	0.9	8.5
	Rel	118	13	11.0	6.0	18.1
	Grade 3*Rel	118	3	2.5	0.5	7.3
Headache	All	118	50	42.4	33.3	51.8
	Grade 3	118	8	6.8	3.0	12.9
	Rel	118	42	35.6	27.0	44.9
	Grade 3*Rel	118	7	5.9	2.4	11.8
Myalgia	All	118	27	22.9	15.7	31.5
	Grade 3	118	2	1.7	0.2	6.0
	Rel	118	26	22.0	14.9	30.6
	Grade 3*Rel	118	1	0.8	0.0	4.6
Shivering	All	118	26	22.0	14.9	30.6
	Grade 3	118	1	0.8	0.0	4.6
	Rel	118	24	20.3	13.5	28.7
	Grade 3*Rel	118	1	0.8	0.0	4.6
Sweating	All	118	10	8.5	4.1	15.0
	Grade 3	118	1	0.8	0.0	4.6
	Rel	118	9	7.6	3.5	14.0
	Grade 3*Rel	118	1	0.8	0.0	4.6
Temperature/(Axillary) (°C)	All	118	12	10.2	5.4	17.1
	[37.5 - 38.1[	118	9	7.6	3.5	14.0
	[38.1 - 38.6[	118	1	0.8	0.0	4.6
	[38.6 - 39.1[	118	0	0.0	0.0	3.1
	[39.1 - 39.6[	118	2	1.7	0.2	6.0
	[39.6 - 40.1[	118	0	0.0	0.0	3.1
	[40.1 - ...	118	0	0.0	0.0	3.1
	Rel	118	8	6.8	3.0	12.9
	[37.5 - 38.1[*Rel	118	6	5.1	1.9	10.7
	[38.1 - 38.6[*Rel	118	0	0.0	0.0	3.1
	[38.6 - 39.1[*Rel	118	0	0.0	0.0	3.1
	[39.1 - 39.6[*Rel	118	2	1.7	0.2	6.0
	[39.6 - 40.1[*Rel	118	0	0.0	0.0	3.1
	[40.1 - ...*Rel	118	0	0.0	0.0	3.1

Numbers with unsolicited symptoms are summarised below. URTI predominated. The single reports of rash and urticaria were not considered to be vaccine-related. Only two subjects (aged 10-17 years) had a Grade 3 unsolicited symptom (upper respiratory tract infection in one).

Global Summary of unsolicited adverse events reported within the 21-day (Days 0-20) post dose 1 period (Total vaccinated cohort)

	Group			
	H1N1AD			
	3-5Y	6-9Y	10-17Y	Overall
Number of subjects with at least one unsolicited symptom reported	26	11	23	60
Number of doses followed by at least one unsolicited symptom	26	11	23	60
Number of unsolicited symptoms classified by MedDRA Preferred Term*	34	15	28	77
Number of unsolicited symptoms reported	34	16	28	78

Two subjects had SAEs – a case of fracture and a case of UTI.

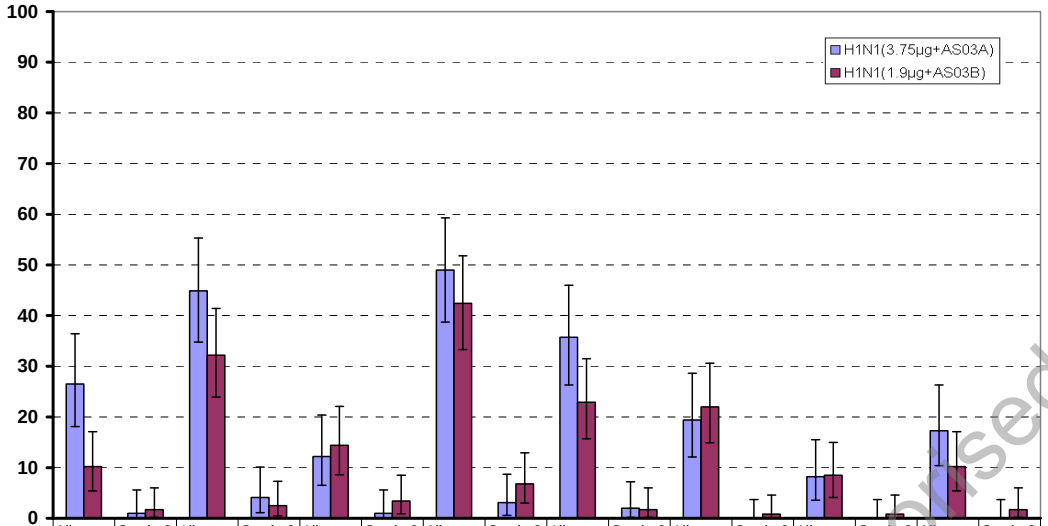
The data from study 023 for children aged 3-5 years and aged 6-9 years have been summarised by the MAH in the table below and compared with the data in these same age groups reported with half adult doses of D-Pan H5N1. Such comparisons between different studies must be viewed with caution. Nevertheless, almost all the comparisons of post-dose 1 data between studies suggest that the H1N1 version of the vaccine is more reactogenic than the H5N1 version and this observation applies for both the 3-5 years and 6-9 years strata.

Solicited symptoms with causal relationship to vaccination after one or two half adult doses of specified AS03-adjuvanted vaccine

Symptom	D-Pan H1N1-023 post dose 1		D-Pan H5N1-009 post dose 1		D-Pan H5N1-009 post dose 1 and post dose 2 per dose frequencies	
	3-5 years	6-9 years	3-5 years	6-9 years	3-5 years	6-9 years
Pain	60.0%	63.1%	51.0%	76.5%	48.5%	68.0%
Redness	26.7%	23.1%	9.8%	9.8%	10.9%	13.0%
Swelling	21.7%	23.1%	11.8%	5.9%	11.9%	14.0%
Shivering	13.3%	10.8%	2.0%	3.9%	1.0%	4.0%
Sweating	10.0%	6.2%	3.9%	3.9%	-	-
Fever >38°C	10.0%	4.6%	5.9%	2.0%	4.0%	2.0%
Fever >39°C	1.7%	0.0%	3.9%	0.0%	2.0%	0.0%
Vomiting	NA	NA	3.9%	NA	-	-
Diarrhoea	5.0%	NA	NA	NA	-	-
Drowsiness	23.3%	NA	7.8%	NA	7.9%	-
Irritability	20.0%	NA	11.8%	NA	7.9%	-
Loss of appetite	20.0%	NA	9.8%	NA	6.9%	-
Arthralgia	NA	15.4%	NA	7.8%	-	-
Myalgia	NA	16.9%	NA	11.8%	-	-
Fatigue	NA	27.7%	NA	11.8%	-	-
Gastrointestinal	NA	13.8%	NA	11.8%	-	-
Headache	NA	21.5%	NA	21.6%	-	-

In addition, the MAH has compared the solicited general symptoms reported after the first half adult dose in study 023 for the 10-17 years age stratum with corresponding data after a full adult dose in study 010 in the figure below. Only rates of arthralgia, fatigue and myalgia show a notable possible advantage for use of a half adult dose in this age range.

Solicited general symptoms after a first half or full adult dose in children aged 10-17 years



	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3
	Arthralgia		Fatigue		Gastrointestinal		Headache		Myalgia		Shivering		Sweating		Fever	
	10-17y															
3.75µg+AS03A	26.5	1	44.9	4.1	12.2	1	49	3.1	35.7	2	19.4	0	8.2	0	17.3	0
1.9µg+AS03B	10.2	1.7	32.2	2.5	14.4	3.4	42.4	6.8	22.9	1.7	22	0.8	8.5	0.8	10.2	1.7

A similar comparison is made in the table for solicited symptoms considered to be related to vaccination. These data suggest an advantage for a half adult dose in rates of pain, swelling, arthralgia, fatigue and myalgia but the frequency categories are the same except for arthralgia.

Solicited symptoms with causal relationship to vaccination after a first half or full adult dose in children aged 10-17 years

Symptom	**D-Pan-H1N1-023 (half dose)**	**D-Pan-H1N1-010 (full dose)**
	%	**%**
Pain	73.7%	92.9%
Redness (mm)	22.9%	21.4%
Swelling (mm)	29.7%	41.8%
Arthralgia	9.3%	26.5%
Fatigue	28.0%	40.8%
Gastrointestinal	11.0%	6.1%
Headache	35.6%	41.8%
Myalgia	22.0%	34.7%
Shivering	20.3%	14.3%
Sweating	7.6%	5.1%
Temperature/(Axillary) (°C) > 38°C	0%	3.1%
Temperature/(Axillary) (°C) > 39°C	1.7%	0%

Discussion on safety

The safety data indicate that a first adult dose of Pandemrix H1N1 results in approximately the same safety profile between children aged 10-17 years and young adults. If an authority chose to administer a second dose to this age group, as would be covered as an option by the SPC, the safety profile would not preclude this possibility. Therefore the data raise no particular concerns in this age group.

In the children aged 3-9 years the safety profile associated with a first adult dose could be considered acceptable. However, the second dose is clearly much more reactogenic and results in much higher rates of fevers. In this context it should be noted that some of the spontaneous reports of febrile convulsion have occurred in children aged 5-6 years. Therefore the safety profile would not preclude the option of a single adult dose in this age group. However, the situation that would apply of an authority were to give a second dose would likely raise concerns comparable to those recently discussed by CHMP in context of a second half adult dose in children aged 6-35 months.

The MAH further provided an analysis of fevers according to any, over 38^0 C, over 38.5^0 C and over 39^0 C for each age stratum and after each dose during the procedure.

The further breakdown in fevers was considered informative but it was not considered to have further implications for the SPC. It should be noted that for the 10-17 years age group in whom a single adult dose is the standard recommendation section 4.8 of the SPC currently states:

> *"Another clinical study evaluated the reactogenicity in children 10 to 17 years of age who received two doses of 0.5 ml of Pandemrix H1N1. No increased reactogenicity after the second dose was observed."*

Given the fact that fever over 39.1^0C occurred after a second dose in only one subject and since febrile convulsions are not a feature of children aged over 10 years the CHMP considered that there is no need to change this statement.

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 4.8 and 5.1 of the SPC were updated to reflect information from study H1N1-023.
- Information on results in 10-17 year old subjects were initially proposed within this procedure, but have already been included in variation II-32, including related changes in section 4.2. and 4.4.
- Section 4.8 was revised to present the safety data in different age categories more clearly, and a comparison of 3-5 and 6-9 year old children was added. In addition, information on the frequency of adverse events after the 2^{nd} (full) dose (an increase in injection site reactions and general symptoms after the second dose compared to the first dose) was included.
- In section 5.1 the information on H5N1 results was summarised and the more detailed description of the H5N1 data was replaced with H1N1 data. A statement was included that additional data from the H5N1 studies can be found in the Product Information of Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals. Furthermore, the section on data in 3-17 year old subjects was splitted into one section on 10-17 and one on 3-9 years of age. Information on half dose vs full dose immunogenicity results in 10-17 year old subjects was also added.
- The PL was updated accordingly.
- In addition, Annex II was updated to reflect the current status of SOBS as agreed by the CHMP during its January 2010 plenary meeting.

Conclusions and Benefit / Risk Assessment

This variation initially proposed to update the SPC and PL with the post-dose 1 immunogenicity and the post-dose 1+2 safety data from study 010 in children aged 3-17 years who had received two adult doses of Pandemrix (H1N1).

Study 010 provided post-dose 1 safety and HI data following a single adult dose in subjects aged 10-17 years that supported the current SPC recommendations for this age group and the relevant data were added to the SPC and PL at the time of concluding variation II/032. While the HI data now

reported from study 023 with a half adult dose in this age group suggest that this might be sufficient there is no important safety advantage for the half adult dose and in the absence of further immunogenicity data there is no reason to amend the current posology for this age group. However, it is agreed that the HI data should be added to the SPC.

During the procedure post-dose 1 HI and safety data in children aged 3-9 years who had received a half adult dose of Pandemrix H1N1 in study 023 have been provided.

The data from study 023 after a half adult dose and from study 010 after a full adult dose have demonstrated a very robust HI response to a single dose of Pandemrix in children from 3-9 years with an advantage for the adult dose only in terms of GMTs and hence SCFs. The safety profiles associated with the first half or full adult doses were broadly acceptable but there was some advantage for a half adult dose in children aged 3-5 and 6-9 years. Overall, there seems no reason to amend the current posology for children aged 3-9 years but the CHMP agreed to add safety and HI data to the SPC as indicated in the Annex.

IV. CONCLUSION

On 20 January 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.