European Medicines Agency
Evaluation of Medicines for Human Use

London, 3 December 2009
Doc. Ref: EMA/CHMP/815870/2009

CHMP VARIATION ASSESSMENT REPORT

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

TYPE II VARIATION: EMEA/H/C/000832/II/0028

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

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Pandemrix was granted Marketing Authorisation in the EU in May 2008, with use being restricted to subjects aged 18-60 years in section 4.2 of the summary of product characteristics (SPC) due to lack of data outside of this age range. The granting of the initial Marketing Authorisation was based on a mock-up vaccine derived from A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14).

Following the declaration of the pandemic phase 6 by the World Health Organisation (WHO), the MAH applied for a strain change to include the pandemic H1N1v strain.

The currently approved vaccine contains split influenza virus with a haemagglutinin content equivalent to 3.75 micrograms derived from A/California/7/2009 (H1N1)v-like strain (X-179A).
The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

The vaccine also contains the marketing authorisation holder's (MAH's) proprietary adjuvant AS03, which is composed of squalene, DL-alpha-tocopherol and polysorbate 80.

The MAH applied to update sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) for Pandemrix H1N1 to reflect newly available post-dose 2- results from a clinical study in children 6 -35 months of age (D-PAN-H1N1-009, called "H1N1-009" in this report).
Furthermore, preliminary safety data from study D-Pan-H1N1—010 in 3-17 year old children and available post-marketing spontaneous reporting data were assessed for this variation.

This variation has been submitted to fulfil the specific obligation SOB 056.1 for which the MAH committed to provide safety and HI immunogenicity data (uncleaned) post dose 2 (half dose) from this study to CHMP.

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

1.2 Clinical aspects

FLU D-PAN H1N1-009

This is a phase II, randomised, open-label, multicentre study to evaluate the safety and immunogenicity of Pandemrix H1N1 following a homologous prime-boost schedule in children aged 6 to 35 months. The study was initiated in September 2009 and is ongoing at five study sites in Spain.

The study planned to enrol 204 children aged 6 to 35 months with allocation to two parallel vaccine groups in a ratio of 1:1 (i.e. to receive the full 3.75 µg/$AS03_A$ or half 1.9 µg/$AS03_B$ adult dose). Subjects were to be stratified into three age strata (6 to 11 months, 12 to 23 months, and 24 to 35 months) with a ratio of 1:1:1. Enrolment was to occur in three steps:

- Step 1: Open enrolment of 51 subjects into vaccine group 1.9 µg/$AS03_B$. There were to be 17 enrolled into each age stratum.
- Step 2: Open-label, randomised enrolment of 102 subjects in a 1:1 randomisation ratio between vaccine group 1.9 µg/$AS03_B$ and vaccine group 3.75 µg/$AS03_A$
- Step 3: Open enrolment of 51 subjects into vaccine group 3.75 µg/$AS03_A$.

The sequential co-primary objectives are:

- To evaluate superiority in terms of vaccine homologous haemagglutination inhibition (HI) antibody response after a booster dose of Pandemrix administered at 6 months following a two-dose primary series with 3.75 µg/AS03$_A$ vaccine compared to the response after the first dose.
- To evaluate superiority in terms of vaccine homologous haemagglutination inhibition (HI) antibody response after a booster dose of Pandemrix administered at 6 months following a two-dose primary series with 1.9 µg/AS03$_B$ vaccine compared to the response after the first dose.

The secondary objectives are:

Immunogenicity

- To assess HI responses at 21 days after the 1st and the 2nd dose primary vaccinations and after the booster at Month 6 in each vaccine group.
- To assess HI GMTs, SCRs, SPRs and SCFs seven days, six months and one year after the booster dose.
- To describe the antibody responses in the three age strata used for enrolment in this study.
- To describe the neutralising antibodies at each time point in a subset of sera.

Safety

- To evaluate safety in terms of selected biochemistry safety parameters (ALT, AST, BILI, BUN and CREA) on Day 0, Day 21, Day 42, at Month 6 and Month 6+7 Days.
- To evaluate post-primary and post-boost safety and reactogenicity in terms of 7-day solicited local and general symptoms and the 21-day post Dose 1, 62-day post Dose 2 and 30-day post-booster dose unsolicited AEs.
- To describe medically-attended events (MAEs), adverse events of specific interest (AESIs) or potential Immune-Mediated-Diseases (pIMDs) and SAEs during the whole study period.

Exploratory

- To evaluate the cell-mediated immune (CMI) response in terms of the expression of T-helper 1 (Th1) and T-helper 2 (Th2) markers in a sub-cohort of 60 subjects at each time point.
- To describe immunogenicity to any emergent drifted variant from A/California/7/2009 (H1N1)v-like antigen in terms of HI on Day 0, Day 21 and Day 42 in all subjects and neutralising antibodies on Day 0, Day 21 and Day 42 in a subset of subjects. This analysis will depend on the emergence of such a drifted strain and on the availability of adequate testing reagents.

Vaccination was to occur on Day 0 and Day 21 with administration IM into the anterolateral part of the thigh for subjects below 12 months of age at entry and into the deltoid for older children.

Results

The data that triggered this variation application refer to children from Step 1 and 2. Safety data are now available from children as shown in the table. The total available safety data now comprise:

i) Administration of one and two doses of 1.9 µg/AS03$_B$ (i.e. half the adult dose of HA and of AS03 in 0.25 ml volume)
   - Data after the first dose in the initial cohort were already reported (N=51; see II/025).
   - Data after the second dose are now reported from this initial cohort (N=51).
   - Data after a first dose are also reported for a second cohort (N=53).

ii) Administration of the first dose of 3.75 µg/AS03$_A$ (i.e. one adult dose in 0.5 ml volume) to a third cohort of children (N=53). The plan to administer a second dose is on hold for the present time.

Study Phase	1.9µg + AS03B	3.75µg + AS03A
Step1	51 subjects dose 1 51 subjects dose 2	0
Step 2	53 subjects dose 1	53 subjects dose 1
Total available	104 subjects dose 1 51 subjects dose 2	53 subjects dose 1

Immunogenicity data from the additional children enrolled since the data from the first cohort of 51 were reported are not yet available.

However, the MAH has submitted HI data post-dose 1 and post-dose 2 from the 51 children in the initial cohort plus neutralising antibody (NA) data from a subset of the sera obtained after the first dose in this initial cohort of 51 children.

Immunogenicity data

The table below summarises the immunogenicity data overall and by age strata as reported from the first cohort of 51 subjects, assessed in variation II/025 and already included in section 5.1 of the SmPC. At Day 0 only three subjects (all in the 6-11 month stratum) were seropositive and 2/3 were seroprotected.

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	6-11 months		12-23 months[4]	24-35 months[4]
	Total enrolled subjects N=17 [95% CI]	Seronegative subjects prior to vaccination N=14 [95% CI]	Total enrolled subjects N=17 [95% CI]	Total enrolled subjects N=16 [95% CI]
Seroprotection rate[1]	100% [80.5;100]	100% [76.8;100]	100% [80.5;100]	100% [79.4;100]
Seroconversion rate[2]	94.1% [71.3;99.9]	100% [76.8;100]	100% [80.5;100]	100% [79.4;100]
Seroconversion factor[3]	44.4 [24.1;81.5]	70.67 [51.91;96.20]	76.9 [55.7;106.1]	53.8 [40.7;71.1]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.
[4]all subjects seronegative prior to vaccination

On November 27th the MAH officially filed this variation with inclusion of statistical tables that compare the HI responses in the initial cohort of 51 subjects after doses 1 and 2. Tables are provided for the total cohort and for the three age strata.

The GMTs showed very marked increases overall and in each of the three age strata from D21 to D42.

TABLE 1 Seropositivity rates and GMTs for HI antibodies against A/California/7/2009(H1N1) (Total vaccinated cohort)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
A/California /7/2009(H1 N1)	Gr 1	PRE	51	3	5.9	1.2	16.2	5.97	4.74	7.51	<10.00	320.00
		PI(D21)	50	50	100	92.9	100	340.64	278.73	416.31	57.00	3620.00
		PII(D42)	50	50	100	92.9	100	1939.99	1687.75	2229.94	640.00	5120.00

TABLE 5 Seropositivity rates and GMTs for HI antibodies against A/California/7/2009(H1N1) (Total vaccinated cohort)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
A/California /7/2009(H1 N1)	Gr 1	6-11M	PRE	17	3	17.6	3.9	43.4	8.50	4.19	17.24	<10.00	320.00
			PI(D21)	17	17	100	80.5	100	376.88	238.23	596.23	57.00	3620.00
			PII(D42)	17	17	100	80.5	100	1895.40	1478.61	2404.09	640.00	3620.00
		12-23M	PRE	17	0	0.0	0.0	19.5	5.00	5.00	5.00	<10.00	<10.00
			PI(D21)	17	17	100	80.5	100	384.46	278.61	530.51	160.00	1280.00
			PII(D42)	16	16	100	79.4	100	1890.21	1410.18	2533.65	905.00	5120.00
		24-35M	PRE	17	0	0.0	0.0	19.5	5.00	5.00	5.00	<10.00	<10.00
			PI(D21)	16	16	100	79.4	100	269.04	203.70	355.34	113.00	640.00
			PII(D42)	17	17	100	80.5	100	2045.61	1603.50	2609.62	905.00	3620.00

Seroprotection rates were already 100% in each age stratum at D21 and therefore also at D42 in each age stratum.

TABLE 6 Seroprotection rates (SPR) for HI antibodies against A/California/7/2009(H1N1) at visit 1 Day 0, visit 2 Day 21 and visit 3 Day 42 (Total vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/California/7/2009(H1N1)	Gr 1	6-11M	PRE	17	2	11.8	1.5	36.4
			PI(D21)	17	17	100	80.5	100
			PII(D42)	17	17	100	80.5	100
		12-23M	PRE	17	0	0.0	0.0	19.5
			PI(D21)	17	17	100	80.5	100
			PII(D42)	16	16	100	79.4	100
		24-35M	PRE	17	0	0.0	0.0	19.5
			PI(D21)	16	16	100	79.4	100
			PII(D42)	17	17	100	80.5	100

The single child who had not seroconverted at D21 had done so by D42.

TABLE 7 Seroconversion rate (SCR) for HI antibodies against A/California/7/2009(H1N1) and Flu A/CAL/7/09.HA1 Ab at visit 2 Day 21 and visit 3 Day 42 (Total vaccinated cohort)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09.HA1 Ab	Gr 1	6-11M	PI(D21)	17	16	94.1	71.3	99.9
			PII(D42)	17	17	100	80.5	100
		12-23M	PI(D21)	17	17	100	80.5	100
			PII(D42)	16	16	100	79.4	100
		24-35M	PI(D21)	16	16	100	79.4	100
			PII(D42)	17	17	100	80.5	100

Following the increments observed in the GMTs the SCFs exceeded at least 200 at D42 in each age stratum. As with the GMTs the increments increased with increasing age.

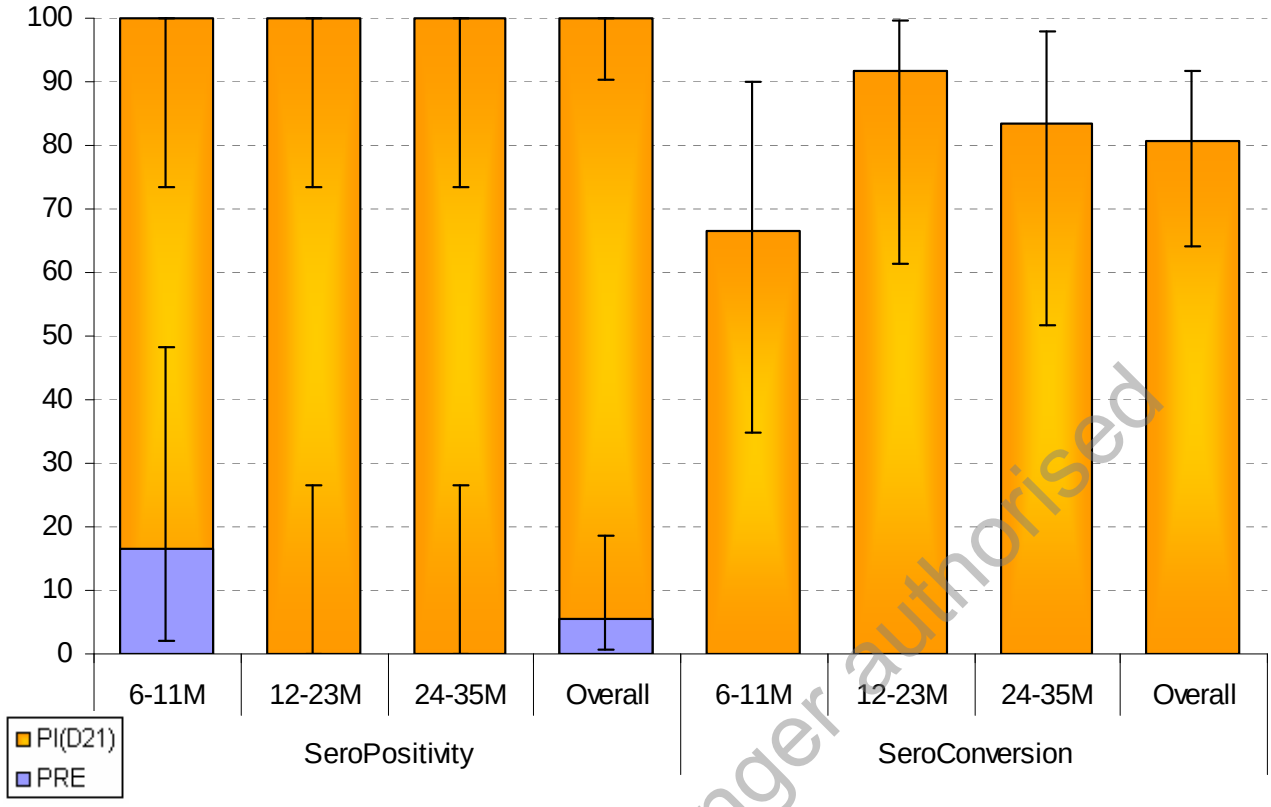
TABLE 8 Seroconversion factor (SCF) for HI antibody titer at each post-vaccination time point (Total vaccinated cohort)

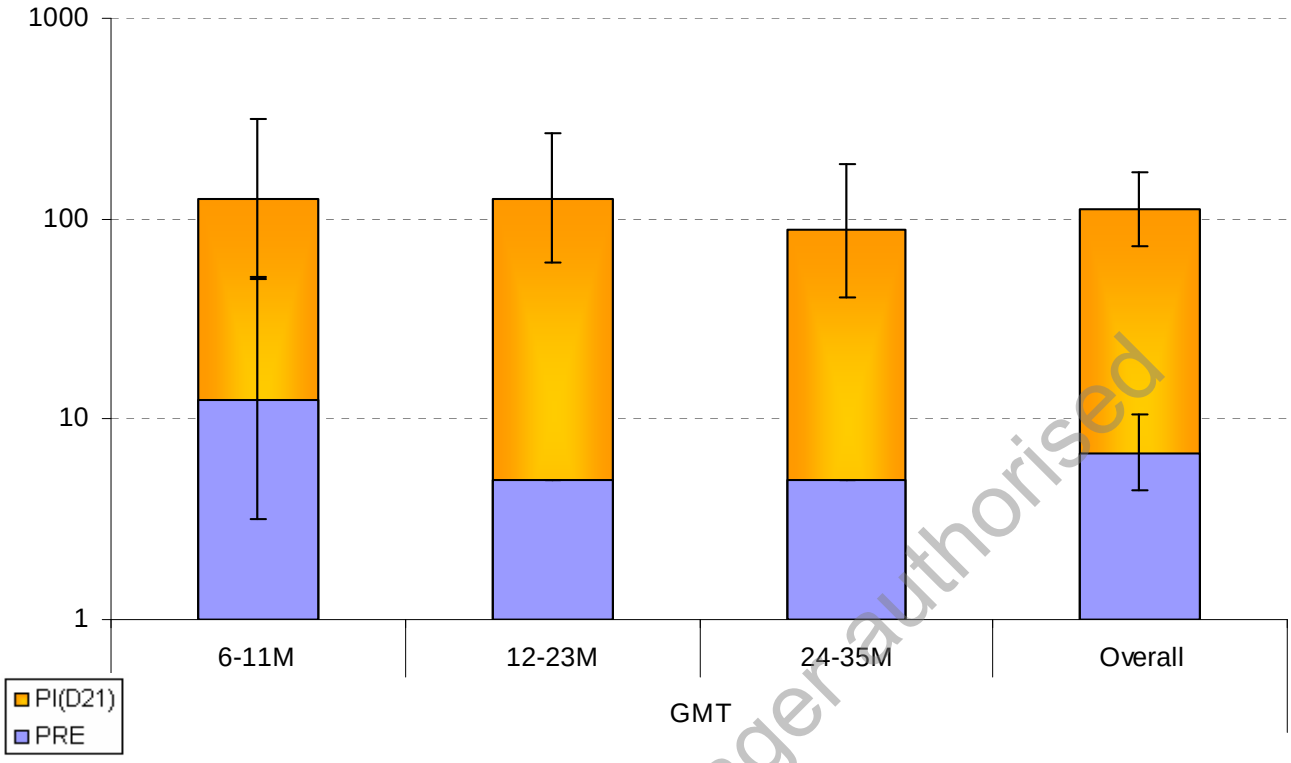
					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	Gr 1	6-11M	PI(D21)	17	44.36	24.14	81.55
			PII(D42)	17	221.94	102.58	480.17
		12-23M	PI(D21)	17	76.89	55.72	106.10
			PII(D42)	16	378.04	282.04	506.73
		24-35M	PI(D21)	16	53.81	40.74	71.07
			PII(D42)	17	409.12	320.70	521.92

The MAH does not yet have an in-house neutralising antibody (NA) assay up and running. Post-dose 1 sera (N=36) from the first cohort of 51 children to receive a half adult dose in this study were sent to CDC (Atlanta, USA) for determination of neutralising antibody titres. It should be noted that this assay is not of the same general design as that used by the MAH to determine NA against H5N1 in previous studies and therefore the titres obtained cannot be compared with results from the H5N1 studies in any age group.

The number of sera tested from each age stratum and the NA seroconversion rates are shown below. As shown in the figure below no children aged 12 months or above were seropositive before vaccination while 2/12 (17 %) were seropositive in the 6-11 months age group, probably reflecting maternal antibody. Seroconversion rates (defined as a 4-fold rise and reaching at least 1:40) were from 66.7% (8/12) in the 6-11 months age stratum to 91.7% (11/12) and 83.3% (10/12) in the two older strata. The GMTs were comparable across the three age strata.

			Seroconversion		
	N	n	%	LL	UL
All	36	29	80.6	64	91.8
6-11M	12	8	66.7	34.9	90.1
12-23M	12	11	91.7	61.5	99.8
24-35M	12	10	83.3	51.6	97.9





Discussion on immunogenicity

The immunogenicity data show a very marked increment in HI GMT after the second half adult dose. However, with all children already seroprotected and all but one seroconverted after the first half adult dose there was no discernible effect of the second half adult dose on SPR or SCR at D42. As already pointed out in II//025 it is not known if the CHMP criteria are of any relevance to this age group and therefore the potential benefits of a very large increase in GMT with a second half adult dose cannot be interpreted in terms of what this may mean for protective efficacy.

The limited NA data, based on the CDC assay, indicate that at least 2/3 children seroconverted after a first half adult dose and all were seropositive at D21. The response was lowest in the children aged 6-11 months. These data support a conclusion that there is a marked immune response to a first half adult dose but suggest that a second half adult dose may potentially provide a major increment in NA.

On the basis of these data alone it is not possible to conclude that a single half adult dose would provide optimal protection against clinical disease in children aged 6-35 months but at the same time it cannot be ruled out that a single half adult dose may be sufficient.

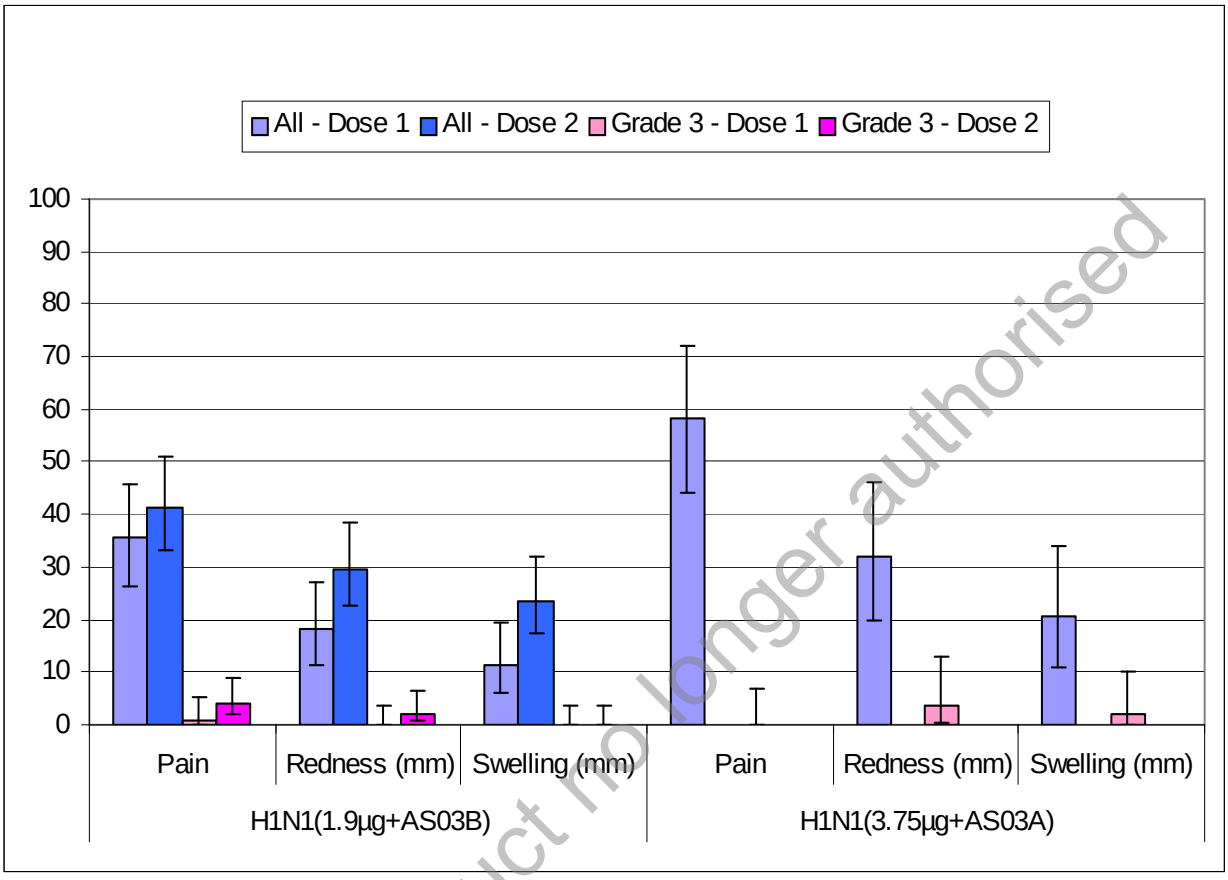
Clinical safety

The safety analysis based on the initial cohort after the first half adult dose provided the summary data shown in the two tables below. It should be noted that no child over 2 years of age had a fever and no child had a fever over 39^0C while only 3/51 had a fever over 38^0C. The risk of fever appeared to decrease with increasing age.

These results should be viewed in the light of the fact that the diary cards indicated that no prophylactic antipyretics were administered for the first dose.

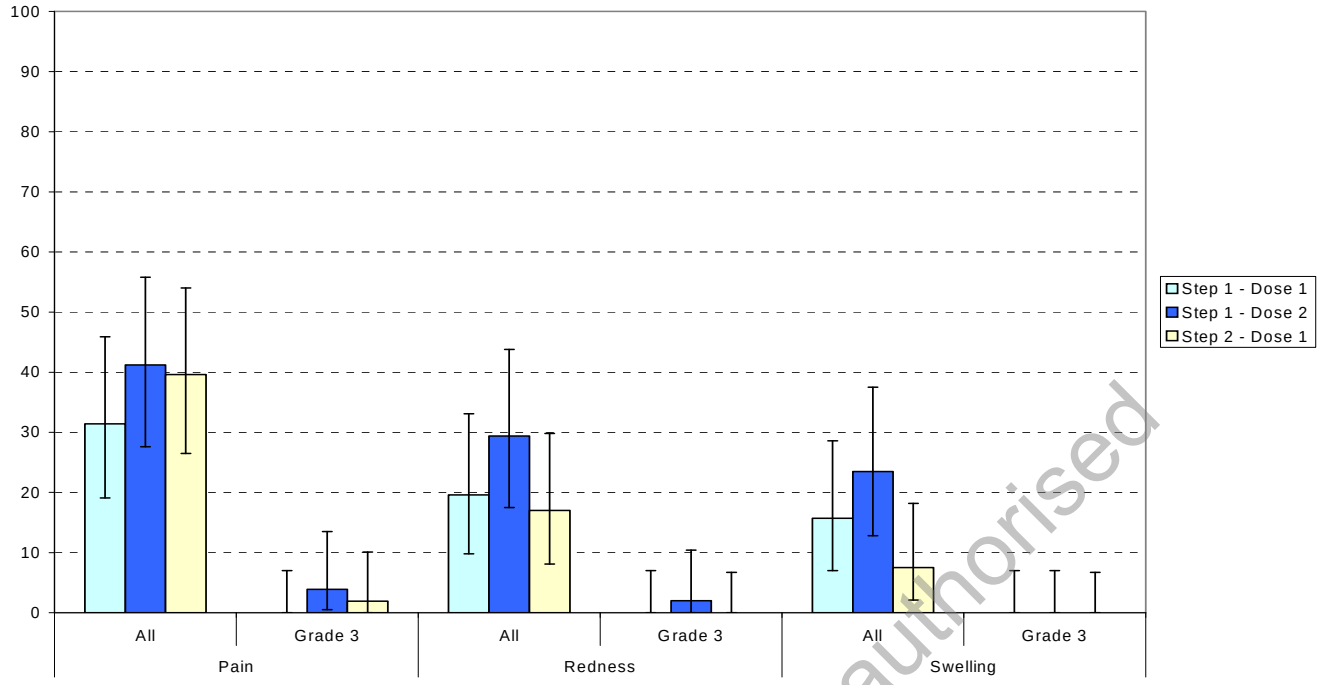
After the second half adult dose in the initial 51 subjects the rates of each of pain, redness and swelling (all and Grade 3) were higher compared to the first half adult dose based on a total dataset of 104 subjects (51 from the initial cohort and 53 from the second cohort).

The figure below also shows the post-dose 1 data for the 53 subjects who have received a first vaccination with the full adult dose. This was associated with higher rates of pain than after the first or second of the half adult doses but the rates of redness and swelling were comparable with the second half adult dose. Administration of a second adult dose to these 53 subjects is currently on hold.



The MAH also compared local reactogenicity between the initial and second cohorts after the first half adult dose and in the same figure below these rates are compared with the data after the second half adult dose.

These data show that after the first half adult dose the rate of pain was anyway higher in the second cohort compared to the initial cohort but comparable with that after the second half adult dose. In contrast the rates of redness and swelling were slightly lower after the first half adult dose in the second cohort to be vaccinated compared with the initial cohort and lower than rates reported after the second half adult dose.



In the statistical tabulations of safety the rates of local reactions are shown after the first and second doses by age stratum.

The most comparable data are those for the 51 subjects who have received two half adult doses.
The three tables below show the data for this initial cohort after the first and second half adult doses. The MAH also provided data for the total after a first and total after second half adult doses plus the data by age stratum after a first full adult dose.

For local reactions (first table below) the rates of pain must be interpreted in the ability of subjects to express pain as opposed to parents suspecting pain. That is, reporting rates go up with age, which may correlate with ability of subjects to verbalise complaints.

Redness and swelling are more objective and after the first dose it was mainly those aged 12-23 months who were affected but rates went down in this age group after the second dose while they increased in the other two strata.

In the additional 53 children who received a half adult dose and the 53 that received a full adult dose in step 2 the rates of local reactions were highest in the 12-23 month group and, as shown in the figures above, higher after a full adult dose.

The second and third tables below show the general symptoms after first and second half adult doses in the initial cohort of 51 children. After the first dose drowsiness, irritability and loss of appetite were reported most often in the youngest cohort. There were 8 children with any fever of which 5 were aged 6-11 months and 3 were aged 12-23 months.

As shown in the figures that follow, the rates of all general symptoms increased after the second dose and the tables demonstrate that this was observed in each age stratum such that rates of drowsiness, irritability and loss of appetite were not only higher but more comparable across the age strata after the second half adult dose. Fever rates were highest in the youngest cohort, in which 15/17 children had any fever compared to 10/17 in each of the other two cohorts. In addition, the rate of fever $\geq 38.5^{0}$C was highest in the 6-11 months stratum (6/17; 4/17 in each of the other age cohorts). There were only three children with fever $\geq 39^{0}$C, one aged 6-11 months and two aged 24-35 months.

Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following dose 1 and dose 2 and overall (Total vaccinated cohort, subjects only from step 1)

		1_9HN																			
		6-11m					12-23m					24-35m					whole cohort				
					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	17	4	23.5	6.8	49.9	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1	51	16	31.4	19.1	45.9
	Grade 1	17	4	23.5	6.8	49.9	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1	51	16	31.4	19.1	45.9
	Grade 2	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Redness (mm)	All	17	2	11.8	1.5	36.4	17	8	47.1	23.0	72.2	17	0	0.0	0.0	19.5	51	10	19.6	9.8	33.1
	[0.1 - 20.1[	17	1	5.9	0.1	28.7	17	5	29.4	10.3	56.0	17	0	0.0	0.0	19.5	51	6	11.8	4.4	23.9
	[20.1 - 50.1[	17	1	5.9	0.1	28.7	17	3	17.6	3.8	43.4	17	0	0.0	0.0	19.5	51	4	7.8	2.2	18.9
	[50.1 - ...	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Swelling (mm)	All	17	0	0.0	0.0	19.5	17	7	41.2	18.4	67.1	17	1	5.9	0.1	28.7	51	8	15.7	7.0	28.6
	[0.1 - 20.1[	17	0	0.0	0.0	19.5	17	5	29.4	10.3	56.0	17	0	0.0	0.0	19.5	51	5	9.8	3.3	21.4
	[20.1 - 50.1[	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	17	1	5.9	0.1	28.7	51	3	5.9	1.2	16.2
	[50.1 - ...	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Dose 2																					
Pain	All	17	5	29.4	10.3	56.0	17	5	29.4	10.3	56.0	17	11	64.7	38.3	85.8	51	21	41.2	27.6	55.8
	Grade 1	17	5	29.4	10.3	56.0	17	5	29.4	10.3	56.0	17	8	47.1	23.0	72.2	51	18	35.3	22.4	49.9
	Grade 2	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	51	1	2.0	0.0	10.4
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	51	2	3.9	0.5	13.5
Redness (mm)	All	17	4	23.5	6.8	49.9	17	6	35.3	14.2	61.7	17	5	29.4	10.3	56.0	51	15	29.4	17.5	43.8
	[0.1 - 20.1[	17	3	17.6	3.8	43.4	17	5	29.4	10.3	56.0	17	3	17.6	3.8	43.4	51	11	21.6	11.3	35.3
	[20.1 - 50.1[	17	1	5.9	0.1	28.7	17	1	5.9	0.1	28.7	17	1	5.9	0.1	28.7	51	3	5.9	1.2	16.2
	[50.1 - ...	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	51	1	2.0	0.0	10.4
Swelling (mm)	All	17	4	23.5	6.8	49.9	17	5	29.4	10.3	56.0	17	3	17.6	3.8	43.4	51	12	23.5	12.8	37.5
	[0.1 - 20.1[	17	2	11.8	1.5	36.4	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	51	7	13.7	5.7	26.3
	[20.1 - 50.1[	17	2	11.8	1.5	36.4	17	2	11.8	1.5	36.4	17	1	5.9	0.1	28.7	51	5	9.8	3.3	21.4
	[50.1 - ...	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0

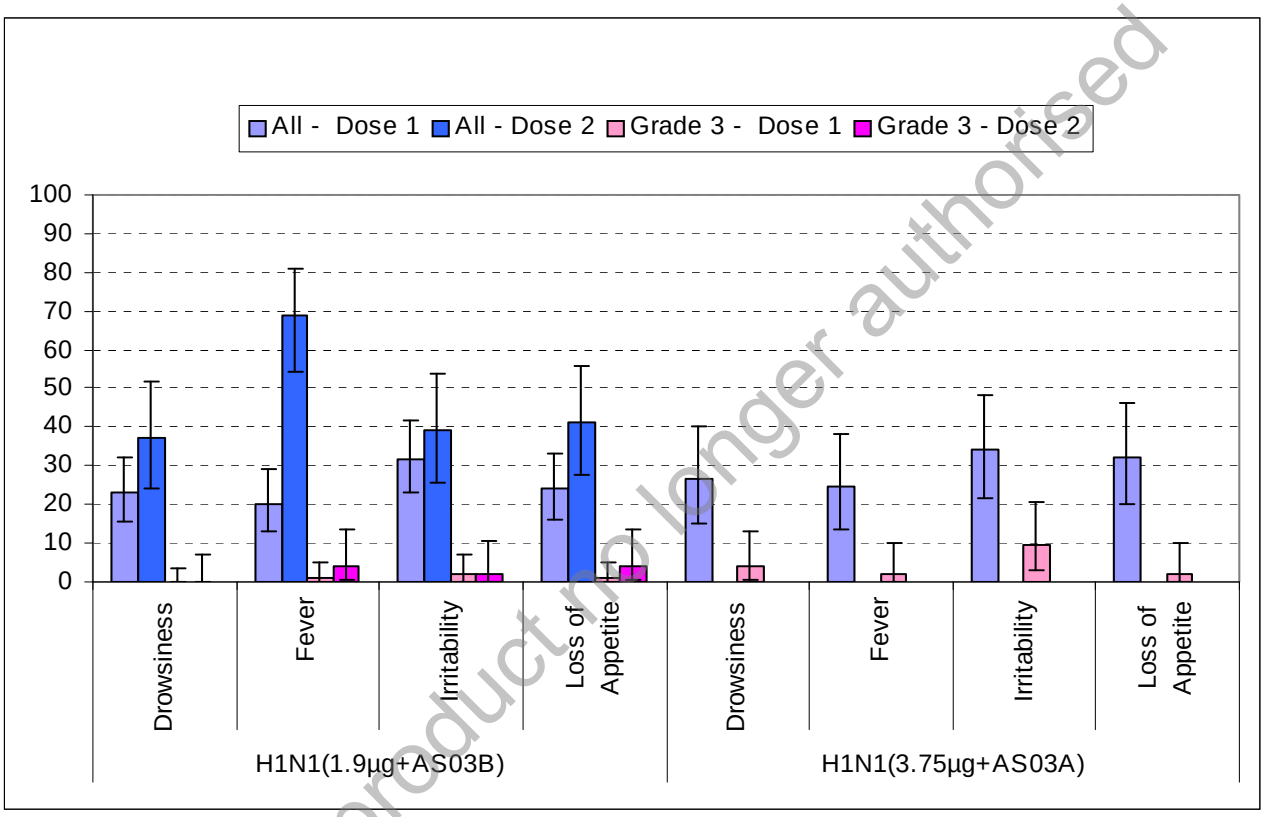
Table 1 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following dose 1 and 2 and overall (Total vaccinated cohort, subjects only from step 1)

		1_9HN																			
		6-11m					12-23m					24-35m					whole cohort				
					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																					
Drowsiness	All	17	3	17.6	3.8	43.4	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	51	8	15.7	7.0	28.6
	Grade 1	17	3	17.6	3.8	43.4	17	3	17.6	3.8	43.4	17	1	5.9	0.1	28.7	51	7	13.7	5.7	26.3
	Grade 2	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	51	1	2.0	0.0	10.4
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Rel	17	2	11.8	1.5	36.4	17	1	5.9	0.1	28.7	17	1	5.9	0.1	28.7	51	4	7.8	2.2	18.9
	Grade 1*Rel	17	2	11.8	1.5	36.4	17	1	5.9	0.1	28.7	17	1	5.9	0.1	28.7	51	4	7.8	2.2	18.9
	Grade 2*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Grade 3*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Irritability	All	17	7	41.2	18.4	67.1	17	6	35.3	14.2	61.7	17	1	5.9	0.1	28.7	51	14	27.5	15.9	41.7
	Grade 1	17	5	29.4	10.3	56.0	17	4	23.5	6.8	49.9	17	1	5.9	0.1	28.7	51	10	19.6	9.8	33.1
	Grade 2	17	1	5.9	0.1	28.7	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	51	3	5.9	1.2	16.2
	Grade 3	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	Rel	17	4	23.5	6.8	49.9	17	6	35.3	14.2	61.7	17	1	5.9	0.1	28.7	51	11	21.6	11.3	35.3
	Grade 1*Rel	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9	17	1	5.9	0.1	28.7	51	8	15.7	7.0	28.6
	Grade 2*Rel	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	51	2	3.9	0.5	13.5
	Grade 3*Rel	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
Loss of appetite	All	17	5	29.4	10.3	56.0	17	2	11.8	1.5	36.4	17	2	11.8	1.5	36.4	51	9	17.6	8.4	30.9
	Grade 1	17	5	29.4	10.3	56.0	17	1	5.9	0.1	28.7	17	2	11.8	1.5	36.4	51	8	15.7	7.0	28.6
	Grade 2	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Rel	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	51	5	9.8	3.3	21.4
	Grade 1*Rel	17	3	17.6	3.8	43.4	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	4	7.8	2.2	18.9
	Grade 2*Rel	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	Grade 3*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Temperature/(Axillary) (°C)	All	17	5	29.4	10.3	56.0	17	3	17.6	3.8	43.4	17	0	0.0	0.0	19.5	51	8	15.7	7.0	28.6
	[37.5 - 38[	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	51	5	9.8	3.3	21.4
	[38 - 38.5[	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	2	3.9	0.5	13.5
	[38.5 - 39[	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	[39 - 39.5[	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	[39.5 - 40[	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Rel	17	5	29.4	10.3	56.0	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	51	7	13.7	5.7	26.3
	[37.5 - 38[*Rel	17	3	17.6	3.8	43.4	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	4	7.8	2.2	18.9
	[38 - 38.5[*Rel	17	2	11.8	1.5	36.4	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	2	3.9	0.5	13.5
	[38.5 - 39[*Rel	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	[39 - 39.5[*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	[39.5 - 40[*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0

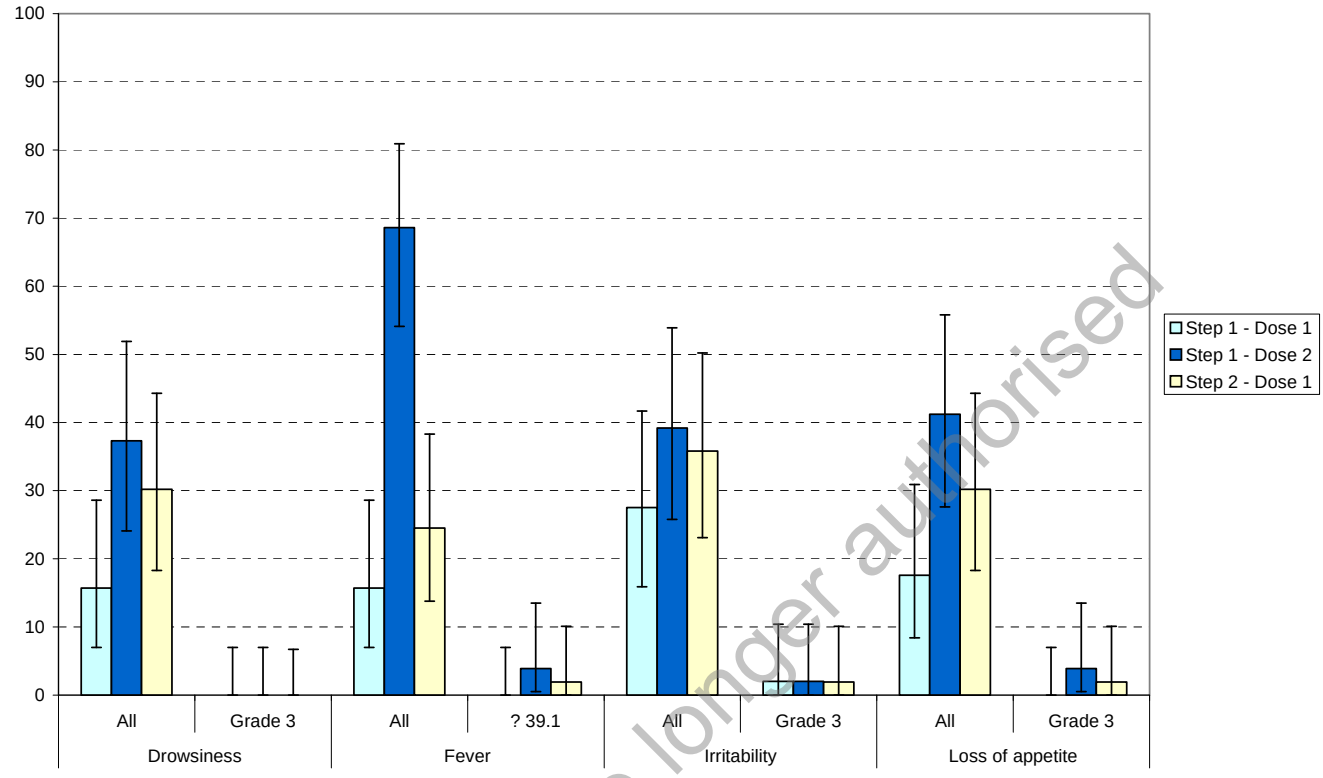
Dose 2																				
Drowsiness	All	17	6	35.3	14.2	61.7	17	7	41.2	18.4	67.1	17	6	35.3	14.2	61.7	51	19	37.3	24.1	51.9
	Grade 1	17	6	35.3	14.2	61.7	17	4	23.5	6.8	49.9	17	6	35.3	14.2	61.7	51	16	31.4	19.1	45.9
	Grade 2	17	0	0.0	0.0	19.5	17	3	17.6	3.8	43.4	17	0	0.0	0.0	19.5	51	3	5.9	1.2	16.2
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
	Rel	17	6	35.3	14.2	61.7	17	6	35.3	14.2	61.7	17	6	35.3	14.2	61.7	51	18	35.3	22.4	49.9
	Grade 1*Rel	17	6	35.3	14.2	61.7	17	3	17.6	3.8	43.4	17	6	35.3	14.2	61.7	51	15	29.4	17.5	43.8
	Grade 2*Rel	17	0	0.0	0.0	19.5	17	3	17.6	3.8	43.4	17	0	0.0	0.0	19.5	51	3	5.9	1.2	16.2
	Grade 3*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0
Irritability	All	17	8	47.1	23.0	72.2	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1	51	20	39.2	25.8	53.9
	Grade 1	17	3	17.6	3.8	43.4	17	1	5.9	0.1	28.7	17	3	17.6	3.8	43.4	51	7	13.7	5.7	26.3
	Grade 2	17	5	29.4	10.3	56.0	17	4	23.5	6.8	49.9	17	3	17.6	3.8	43.4	51	12	23.5	12.8	37.5
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	51	1	2.0	0.0	10.4
	Rel	17	7	41.2	18.4	67.1	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1	51	19	37.3	24.1	51.9
	Grade 1*Rel	17	3	17.6	3.8	43.4	17	1	5.9	0.1	28.7	17	3	17.6	3.8	43.4	51	7	13.7	5.7	26.3
	Grade 2*Rel	17	4	23.5	6.8	49.9	17	4	23.5	6.8	49.9	17	3	17.6	3.8	43.4	51	11	21.6	11.3	35.3
	Grade 3*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	1	5.9	0.1	28.7	51	1	2.0	0.0	10.4
Loss of appetite	All	17	7	41.2	18.4	67.1	17	6	35.3	14.2	61.7	17	8	47.1	23.0	72.2	51	21	41.2	27.6	55.8
	Grade 1	17	3	17.6	3.8	43.4	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9	51	10	19.6	9.8	33.1
	Grade 2	17	4	23.5	6.8	49.9	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	51	9	17.6	8.4	30.9
	Grade 3	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	51	2	3.9	0.5	13.5
	Rel	17	6	35.3	14.2	61.7	17	6	35.3	14.2	61.7	17	8	47.1	23.0	72.2	51	20	39.2	25.8	53.9
	Grade 1*Rel	17	3	17.6	3.8	43.4	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9	51	10	19.6	9.8	33.1
	Grade 2*Rel	17	3	17.6	3.8	43.4	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	51	8	15.7	7.0	28.6
	Grade 3*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	51	2	3.9	0.5	13.5
Temperature/(Axillary) (°C)	All	17	15	88.2	63.6	98.5	17	10	58.8	32.9	81.6	17	10	58.8	32.9	81.6	51	35	68.6	54.1	80.9
	[37.5 - 38[	17	5	29.4	10.3	56.0	17	4	23.5	6.8	49.9	17	1	5.9	0.1	28.7	51	10	19.6	9.8	33.1
	[38 - 38.5[	17	4	23.5	6.8	49.9	17	2	11.8	1.5	36.4	17	5	29.4	10.3	56.0	51	11	21.6	11.3	35.3
	[38.5 - 39[	17	5	29.4	10.3	56.0	17	4	23.5	6.8	49.9	17	2	11.8	1.5	36.4	51	11	21.6	11.3	35.3
	[39 - 39.5[	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	51	2	3.9	0.5	13.5
	[39.5 - 40[	17	1	5.9	0.1	28.7	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	1	2.0	0.0	10.4
	Rel	17	12	70.6	44.0	89.7	17	8	47.1	23.0	72.2	17	10	58.8	32.9	81.6	51	30	58.8	44.2	72.4
	[37.5 - 38[*Rel	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9	17	1	5.9	0.1	28.7	51	8	15.7	7.0	28.6
	[38 - 38.5[*Rel	17	4	23.5	6.8	49.9	17	1	5.9	0.1	28.7	17	5	29.4	10.3	56.0	51	10	19.6	9.8	33.1
	[38.5 - 39[*Rel	17	5	29.4	10.3	56.0	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	51	10	19.6	9.8	33.1
	[39 - 39.5[*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	2	11.8	1.5	36.4	51	2	3.9	0.5	13.5
	[39.5 - 40[*Rel	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	17	0	0.0	0.0	19.5	51	0	0.0	0.0	7.0

On comparing the total cohort results between doses and recruitment cohorts, again the greatest concern is clearly the rate of fever (and especially fever based on axillary temperature ≥38.5°C) after the second half adult dose compared to the first half adult dose. The rate of any fever increased from 16% after the first to 69% after the second half adult dose in the initial cohort of 51 subjects. Rates for other general symptoms showed smaller and less worrying increases. Nevertheless, rates of Grade 3 general symptoms (including Grade 3 fever defined as axillary temperature > 39°C) remained low.

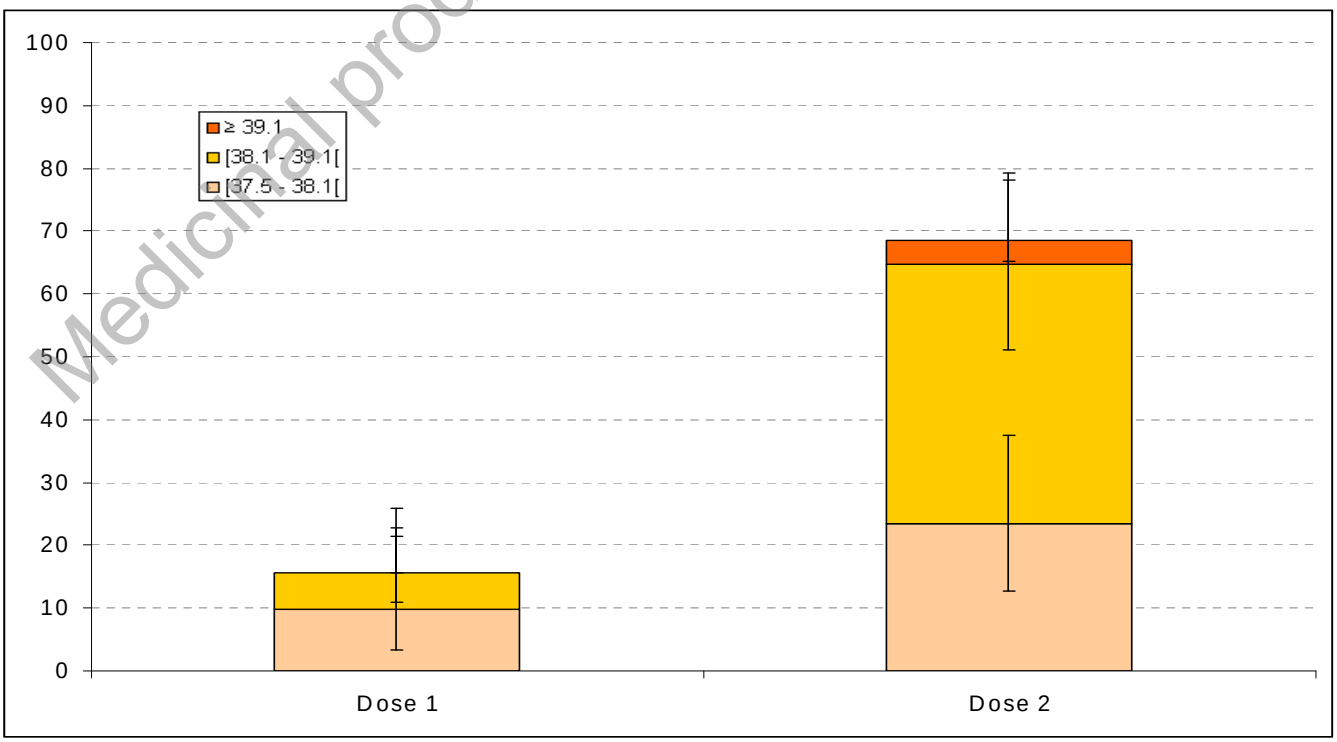
The figure also demonstrates that rates for general symptoms after the first full adult dose in the third additional cohort of 53 subjects resembled those observed after the first half adult dose in the total 104 subjects for which data are now available. Therefore the rate of fever after the second half adult dose stands out as a problematic finding.



In the next figure the MAH again compares symptom reporting rates between the initial and second cohorts after the first half adult dose with those after the second half adult dose in the initial cohort. While rates of reporting for each general symptom were higher in the second cohort there was still a very marked difference in the rate of reporting any fever between the first and second doses.



A further breakdown of the fevers reported shows that a substantial proportion of the post-dose 2 reports concerned Grade 2 fevers, which are in the range associated with triggering of febrile convulsions in this at-risk age group.

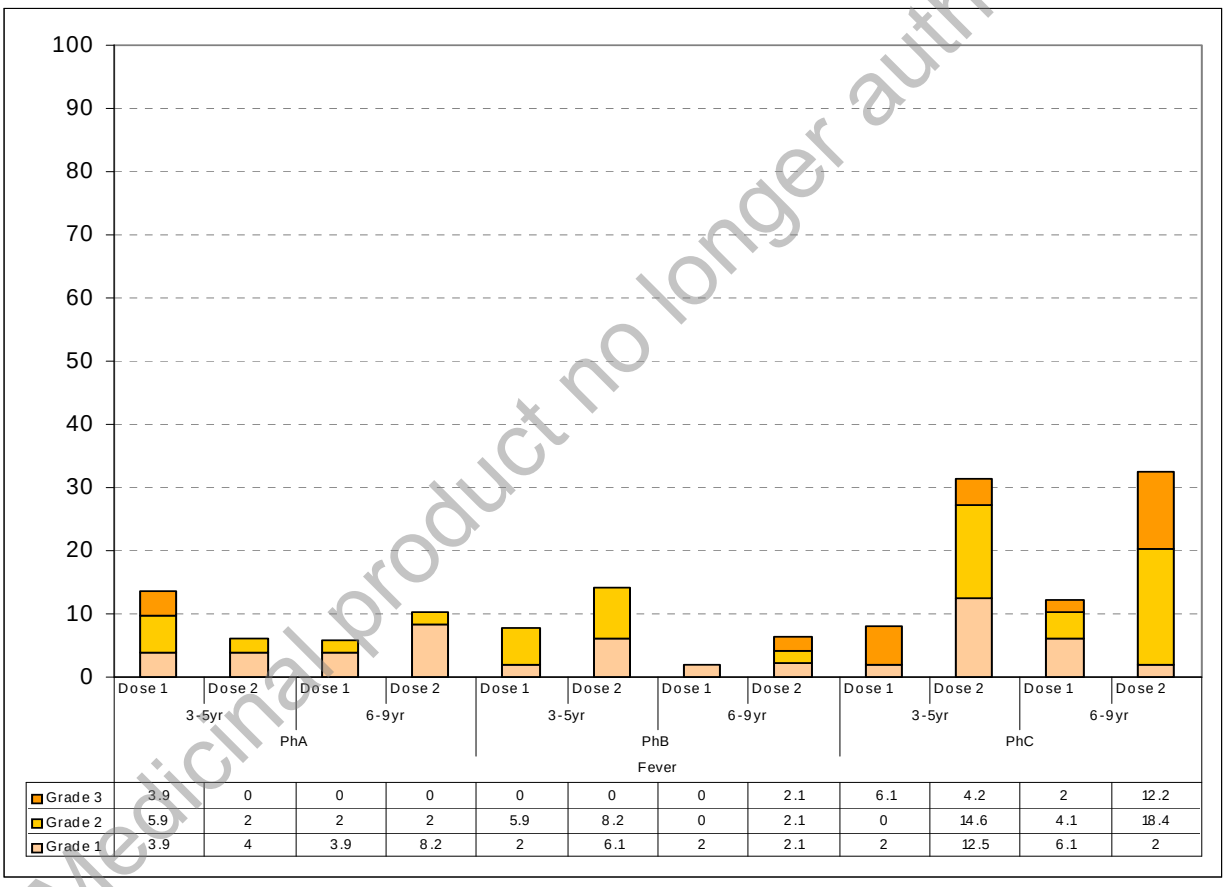


The MAH points out that the post-dose 2 safety data observed with Pandemrix H1N1 in children aged 6-35 months were not expected based on the data observed with administration of two half adult doses of H5N1 AS03-adjuvanted vaccine in children aged 3-5 years.

The figure below usefully summarises these data for Part A (two half adult doses) and Part C (two full adult doses) of the study of H5N1/AS03 in children aged 3-5 years and 6-9 years. It will be observed that the post-dose 2 fever rates even after two adult doses of H5N1/AS03 were lower than reported after the second half adult dose of Pandemrix H1N1 in study H1N1-009 in younger children, although in both cases the proportion with higher fevers increased. Also, that after two half adult doses of H5N1/AS03 there was no increment in the rate of any fever in the children aged 3-5 years and only a modest increment in children aged 6-9 years.

This figure also demonstrates that rates of any fever after the first half adult dose or first full adult dose of H5N1/AS03 in children aged 3-5 or 6-9 years were slightly lower than observed after the first half adult dose of Pandemrix H1N1 in children aged 6-35 months. This could reflect a difference between age groups or could represent a difference between H1N1 and H5N1 strains or both.

Rates of fever reported with H5N1/AS03 in the previously reported study D-PAN-H5N1 009



Grade 3	3.9	0	0	0	0	0	0	2.1	6.1	4.2	2	12.2
Grade 2	5.9	2	2	2	5.9	8.2	0	2.1	0	14.6	4.1	18.4
Grade 1	3.9	4	3.9	8.2	2	6.1	2	2.1	2	12.5	6.1	2

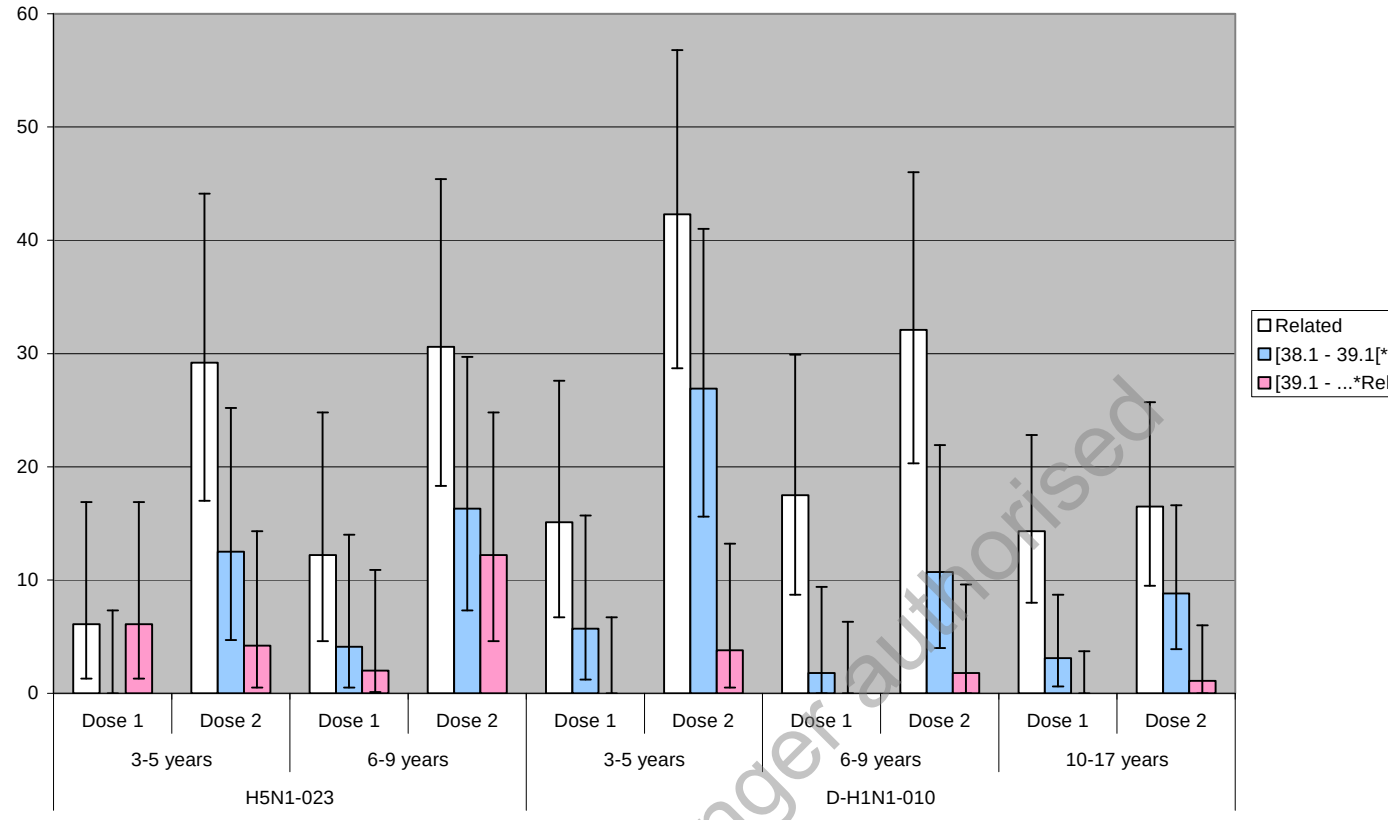
The table below compares the rates of adverse reactions (i.e. data are based only on symptoms considered vaccine-related by investigators) after two half adult doses of H5N1/AS03 in children aged 3-5 years and after each half adult dose of Pandemrix H1N1 in children aged 6-35 months. This table demonstrates the clear differences between the two studies in the most closely comparable subgroups according to dose and age.

The table also demonstrates that the rates of Grade 2 fever were very much higher after the second dose of Pandemrix H1N1 compared to the first dose or to two doses of half dose H5N1/AS03 in older children but the per-dose rates of Grade 3 fever were comparable between the H5N1 and H1N1-containing vaccines.

	HALF DOSE H5N1/AS03	HALF DOSE H1N1/AS03		
ADVERSE REACTIONS PER DOSE	3-5 YEARS	6-35 MONTHS		
	OVERALL	OVERALL	POST-D1	POST-D2
INDURATION	9.9%			
PAIN	48.5%	36.3%	31.4%	41.2%
REDNESS	10.9%	24.5%	19.6%	29.4%
SWELLING	11.9%	19.6%	15.7%	23.5%
FEVER (>38°C)*	2.0%	21.6%	5.9%	37.3%
FEVER (>39°C)				
- PER-DOSE FREQUENCY	2.0%	1.0%	0.0%	2.0%
- PER-SUBJECT FREQUENCY	3.9%	2.0%		
DROWSINESS	7.9%	21.6%	7.8%	35.3%
IRRITABILITY	7.9%	29.4%	21.6%	37.3%
LOSS OF APPETITE	6.9%	24.5%	9.8%	39.2%
SHIVERING	1.0%			

Preliminary safety data from study H1N1-010 (children aged from 3-17 years)

Finally, the MAH has no safety data as yet regarding administration of half adult doses to children aged 3 years upwards as recommended in the SPC. However, the MAH has preliminary safety data after the first and second adult doses administered to children aged from 3-17 years in study H1N1-010. The data for fevers are summarised in the figure below, which 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 second dose decrease with increasing age.



The table on the next page provides the solicited general symptom rates considered related to vaccination and by age strata from study H1N1-010.

There is a 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.

Table 2 Incidence of solicited general symptoms related to vaccination, 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

Post-Marketing experience

MAH data - spontaneous reports

As of 23rd November 2009, the MAH had received 54 spontaneous reports corresponding to one event coding to a MedDRA PT containing the word "fever" in subjects ≤ 12 years old for which Pandemrix was a suspected drug. As of 20th November 2009, an estimated 206,900 children had received at least one dose of Pandemrix in post-marketing use.

Because mass vaccination campaigns are in progress, it was deemed important to include all available data. Therefore, unverified cases and cases in which data entry is in progress (n=8; 15%) were included in this analysis.

The 54 reports describe 26 (49%) females, 27 (51%) males and one subject of unspecified gender. The median age was 8 years (range, 11 months – 11 years). Sixteen (30%) of the reports were serious and 38 (70%) were non-serious.

Two reports of febrile convulsions were received but three additional reports included the terms fever and convulsion. The five cases are summarised by the assessor as follows:

A febrile convulsion was reported in a 5-year-old male from Norway who had had a previous febrile convulsion and had asthma. Sometime in October 2009, the subject developed an upper respiratory tract infection, which was reported as "ongoing" after the febrile convulsion had resolved but the timing of the onset of this event in relation to the vaccination or the seizure was not elucidated. On 26 October 2009, the subject received the 1st dose of Pandemrix H1N1. Two hours after he developed a fever (39.9°C) and one hour later he experienced a febrile convulsion that lasted 15 minutes. On 27 October 2009, the fever had resolved.

A second report from Norway concerned febrile convulsion, cyanosis, musculoskeletal stiffness, foaming at the mouth, pyrexia and crying in a 14-month-old male. The parents stated he had chronic otitis since the age of 4 months and recurrent fevers < 38°C. Three weeks before vaccination, the child had an episode of fever and otitis.

He received unspecified antibiotics until 21 October 2009 and had "high fever" from 22 - 24 October 2009. On 26 October 2009 he received the 1st dose of Pandemrix H1N1. Eight hours later, he had fever (39.4 - 39.9°C), which was treated with ibuprofen. Two hours later (i.e. 10 hours after vaccination) he had a febrile convulsion with stiffness, froth from mouth and unresponsiveness for 15 minutes. There was also facial cyanosis (gray colour) and abnormal crying. The events resolved spontaneously before the ambulance arrived but he was still hospitalised.

A third report from Norway included convulsion, pyrexia, restlessness and injection site swelling in a 9-year-old female. Concurrent medical conditions included epilepsy, panhypopituitarism and psychomotor retardation. On 28 October 2009 she subject received the 1st dose of Pandemrix H1N1. Two hours later, she experienced "one convulsion followed by a series of seizures." She slept for several hours and the next morning she experienced 4 seizures in 10 minutes. The seizures were treated with diazepam. The mother reported that the seizures were different from usual. On 29 October 2009, the subject experienced restlessness, fever (38°C) and injection site swelling.

A report from the UK concerned convulsion, pyrexia, lethargy, and somnolence in a male child of unspecified age. The medical history was not reported but concurrent medications included fluticasone, salbutamol, montelukast and prednisolone. On 05 November 2009, the patient received Pandemrix H1N1. The next day, she experienced convulsion, fever, lethargy and drowsiness on waking. No additional details were provided.

A report from Sweden concerned convulsion, loss of consciousness, dyspnoea, lethargy and pyrexia in a 6-year-old female. There was no history of febrile convulsions. On 4 November 2009 she received

Pandemrix H1N1. Two days later she reportedly fell in a doorway and seemed to have breathing difficulties. A teacher found the girl in a "fainted state," but observed neither convulsions nor urinary incontinence. An ambulance was called and during the transport to the hospital, the girl was indolent but had normal respiration and circulation. Upon admission to the hospital, she was noted to be febrile (38.8°C). Neurological status was normal. No treatment was given. On 07 November 2009, she had recovered and was discharged.

Assuming that all 54 reports of fever are valid and that 206,700 children were vaccinated, the reporting rate for fever in children is 1 report per 3828 children vaccinated, or 0.03%. This is rare, by CIOMS IV criteria.

Assuming that the number of reported febrile convulsions could be as few as two or as many as five, and that 206,700 children were vaccinated, the reporting rate for febrile convulsions in children is between 1 report per 41,340 and 1 report per 103,350 children vaccinated. These are very rare, by CIOMS IV criteria.

The MAH's disproportionality analysis considers SAEs, all spontaneous reports and all post-marketing surveillance in age groups. The results of the most recent weekly analysis show that neither pyrexia nor febrile convulsions have been reported disproportionately often after immunisation with Pandemrix compared to all other GSK vaccines.

Disproportionality analysis

Event	Number of cases	EB05	EB95	EBGM
Pyrexia	285	1.287	1.563	1.42
Febrile convulsion	2	0.367	1.614	0.816

The MAH discusses that the ACIP has reported in 2009 that in a study of 791 healthy children aged 1-15 years post-vaccination fever following administration of a single dose of unadjuvanted, trivalent influenza vaccine was noted among 12% of those aged 1-5 years, 5% among those aged 6-10 years and 5% among those aged 11-15 years.

The MAH considers that spontaneous reports of fever do not indicate an increased incidence with Pandemrix compared to unadjuvanted seasonal influenza vaccine. However, because of the known limitations of passive reporting, relatively frequent events, like fever, are better studied in randomised, controlled trials. In contrast, spontaneous reporting is often useful for yielding information about less frequent events, such as febrile seizures.

Other sources of relevant safety information

The following data from post authorisation spontaneous reporting in Sweden and the Netherlands became available during the procedure and were considered supportive for this variation:

Swedish data

Vaccination with Pandemrix H1N1 started in on Sweden 12th October 2009 in risk groups at all ages ≥6 months, pregnant women and health care personnel. As of 25th November 3,798,000 doses had been distributed and more than 3 million people (i.e. one third of the Swedish population) had been vaccinated. Children aged from 6 months to 12 years receive two half adult doses of Pandemrix. A total of 1000 ADRs reports had been received by the MPA from Health Care Professionals and around 1300 reports from consumers.

An overview on the adverse events reported in Sweden can be found here:
http://www.lakemedelsverket.se/english/All-news/NYHETER---2009/Summary-of-Adverse-Drug-Reaction-reports-in-Sweden-with-Pandemrix-received-through-November-20/

The MPA has further published recommendations on the website regarding vaccination in young children < 3 years including use of antipyretic treatment in case of high fever.

Data from The Netherlands

Around 350,000-400,000 children received a first half adult dose of Pandemrix during the week commencing November 23 in The Netherlands. The second doses will be given in the week commencing 14 December. An overview on adverse reactions experiences in The Netherlands can be found here: http://www.lareb.nl/kennis/signalen.asp

Discussion on safety

Clinical data

The data from study H1N1- 009 show that the reactogenicity of the second half adult dose is greater than the first within the initial cohort and also when comparing the total 104 who have received a first half adult dose with the 51 who have received a second half adult dose. The patterns of reporting by age stratum indicate that local and general reactogenicity is higher after the second half adult dose for most individual symptoms and in all age strata.

The major concern is the rate of fever after the second half adult dose in children aged 6-35 months, which would not be predicted from the prior experience with H5N1/AS03 vaccine in older children aged 3-5 years. Nevertheless, it is clear that fever may also occur after the first half adult dose and febrile convulsions have been reported in association.

As the CHMP considered that these data should be added to the SPC along with a warning regarding fever rates, the PI was updated to reflect this. In addition, and not proposed by the MAH, section 4.8 was updated to clarify that febrile convulsion has been reported specifically in association with Pandemrix H1N1 (the current wording indicates convulsion only with seasonal vaccine experience).

The additional data from H1N1-010 also show higher rates of fever after the second full adult dose in children aged from 3 years upwards but with decreasing rates with increasing age. It would be expected that rates after a second half adult dose in this age group would be lower. Nevertheless, the warning in section 4.4 could prudently avoid a strict upper age cut-off, especially in light of the additional data reported.

Post marketing experience

With regard to the spontaneous reporting of ADRs in this age group thus far it can only be stated that fever has certainly prompted ADR reports from health care professionals and consumers.

There seem to be at least four febrile convulsions known to the MAH that are very likely due to vaccination with a half adult dose of Pandemrix H1N1 and it is clear that this can occur even after the first dose. Children < 3 years are in the highest risk group for febrile convulsions although feverish illnesses are very common in this age group and relatively few are reported to result in convulsions. Febrile convulsions have therefore been included in the adverse events section under the sub-section on experience with Pandemrix (H1N1) vaccine.

There are no data known so far regarding any possible effect of prophylactic or early post-dose paracetamol on immune responses to influenza vaccines. Therefore it is considered appropriate for the SPC and PL to suggest that antipyretic medication is given at the first sign of increasing temperature to over 38 degrees Celsius. Taking into account the available data in 3-6 year-olds, the CHMP recommended that this warning should not just apply to those aged < 3 years.

1.3 Conclusions and Benefit / Risk Assessment

In variation II/025 the MAH provided an abridged study report describing safety and immunogenicity data following vaccination with one half of the adult dose of Pandemrix (i.e. 1.9 µg HA +$AS03_B$) in 51 children aged 6-35 months. The safety and HI immune response data were reported according to the three pre-defined age strata with 17 subjects per stratum. These data raised no particular concerns and have already been summarised in the SPC. The CHMP did not feel able to recommend the option of a single half adult dose in this age group based only on the HI data available.

This variation is based on further information sent from the MAH to the Rapporteur between November 20th and December 2nd, including the data filed in the variation received 27th November 2009.

The HI data after each half adult dose demonstrate a marked immune response to the second dose in terms of increments in GMTs in each of the three age strata. The limited post-dose 1 NA data from CDC support a conclusion that there is a good response to a first half adult dose but likely leave room for a marked increment in NA also to occur after a second dose. The available data are insufficient to indicate whether a single half adult dose in this age group would be sufficient but this hypothesis cannot be ruled out.

The available data clearly indicate increased reactogenicity with the second half adult dose of Pandemrix H1N1 in children aged 6-35 months but the major concern is the increase in rate of fever, including Grade 2/3 fever, with the second dose. The post-dose 2 findings were unexpected based on the observations made in 3-5 year-old children who received H5N1/AS03 vaccine in the previously reported study. Post-marketing data seem to confirm that fevers are very common after the second dose. Fever also seems to occur commonly or very commonly after the first dose and febrile convulsion has been reported even after the first dose. However, the MAH's assessment suggests that the rate of febrile convulsion may not be unusually high.

Children aged 6-35 months mounted a good immune response to the first half adult dose based on HI and NA data available. It is not known at this time whether the increment in HI antibody observed after the second half adult dose will confer added protection. However, the new safety data post dose 2 throw some doubt on the benefit-risk relationship for a second dose.

At this time the CHMP proposes that SPC section 4.2 should reflect the data, with appropriate cross references, to leave the selection of one or two half adult doses in this age group open.
The option to administer a second dose should take into consideration the safety and immunogenicity information provided in the SPC sections 4.4, 4.8 and 5.1.

1.4 Changes to the Product Information

The detailed changes can be found in the final approved highlighted SPC/Annex II/ /PL attached to this report.
Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH:

- Annex II was updated to reflect the status of the specific obligation to submit safety and immunogenicity data from Study D-Pan H1N1-009.
- Section 4.2 of the SPC was amended to reflect that preliminary immunogenicity data in a limited number of children aged 6-35 months show that there is a further immune response to a second dose of 0.25 ml administered after an interval of three weeks. It was further added that the use of a second dose should take into consideration the information provided in the relevant SPC sections.
- SPC Section 4.4 was further revised to point out that not only fever is increased after the second dose, but to indicate an increase in the rates of injection site reactions and general symptoms. Furthermore, a recommendation to use measures to lower fever, such as antipyretic

medication after each vaccination are recommended in young children (e.g. up to approximately 6 years of age).

- The wording in section 4.8 was revised to provide more clarity, and the adverse reaction "febrile convulsions" was moved to the sub-section on post marketing experience with Pandemrix (H1N1) due to the available data from spontaneous reporting.
- In addition, post-dose 2 HI data and post-dose 1 NA have been added to section 5.1.

The PL was updated accordingly