Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemrix

pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/2009 (h1n1)v like strain (x-179a)

Procedure No.: EMEA/H/C/000832/II/0048

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
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Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000832/II/0048

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

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics and Annex II Update of section 5.1 of the SmPC to include neutralizing immune response data for post dose 1 and post dose 2 in the studies Flu D-Pan H1N1-009, FLU D-Pan-H1N1-010 and FLU D-Pan-H1N1-023 covering individuals 6 months to 17 years of age, as well as persistence data (HI and neutralizing response) at Month 6 from study D-Pan-H1N1-023. The MAH also took the opportunity to update Annex II in line with CHMP recommendations.
Rapporteur: Co-Rapporteur:	Ian Hudson Barbara van Zwieten-Boot
Product presentations affected:	See Annex A to the Opinion
Dossier modules:	1,2 and 5
Product Information affected:	Summary of Product Characteristics and Annex II

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2. Steps taken for the assessment

Step	Step date
Submission date:	3 December 2010
Start of procedure:	19 December 2010
Rapporteur's preliminary assessment report circulated on:	13 December 2010
CHMP opinion:	17 February 2011

3. Scientific discussion

3.1. Introduction

Pandemrix is an adjuvanted vaccine against pandemic influenza caused by A H1N1v 2009 virus. It is supplied in two separate vials as a suspension (antigen) and emulsion (adjuvant) to mix for injection. The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

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

Pandemrix was granted Marketing Authorisation (MA) 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 (SmPC) 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 onset of the H1N1v pandemic and the declaration of WHO Phase 6 in June 2009, the MAH applied for a variation (PU/0017) to change the pandemic vaccine strain composition from A/VietNam/1194/2004 H5N1-like strain (NIBRG-14) to A/California/7/2009 H1N1 strain (NYMC X-179A). The recommendation for the approval of the Pandemic Update PU/0017 was adopted by the CHMP on 24 September 2009. The MA under exceptional circumstances for the current H1N1v vaccine was granted by the European Commission on 29 September 2009.

Upon review of the MAH application, on 24 June 2010 the CHMP recommended to change the status of the MA outside the scope of Art. 14(8) of Regulation (EC) 726/2004 (switch from MA granted under "exceptional circumstances" into a full MA (SW/041)).

Following CHMP request originated from 3 clinical Follow up Measures (FUMs), with this variation procedure (II/48) the MAH provided safety and immunogenicity (SNA response) data for post dose 1 and post dose 2 obtained from the pediatric studies Flu D-Pan H1N1-009, FLU D-Pan-H1N1-010 and FLU D-Pan-H1N1-023 covering individuals 6 months to 17 years of age. The MAH also submitted antibody persistence data (HI and neutralizing response) at Month 6 (M6) obtained from study D-Pan-H1N1-023. The scope of this variation is to include the available new information in section 5.1 of the SmPC.

3.2. Clinical aspects

Rationale for the proposed change

The MAH committed to the following FUMs:

Clinical	Submission of clinical study report Month 7 for study **D-Pan H1N1-010**	early November 2010
Clinical	Submission of clinical study report Month 7 for study **D-Pan H1N1-023**	early November 2010

The Company also committed to submit the Neutralizing Immune response data at Month 7 from studies D-Pan-H1N1-010 & -023 in early November 2010.

On 12 October 2010 the MAH requested a one-month extension in order to be able to submit the neutralising antibody (SNA) data along with the month 7 (M7) data. This was agreed by CHMP.

On December 1 2010 the Company provided the M7 reports for D-Pan H1N1-010 and 023 as well as the SNA data for D21 and D42 in D-Pan-H1N1-009 in an unplanned Month 7 annex report.

The three studies (D-Pan H1N1-009, -010 and -023) provided immunogenicity and safety data following primary vaccination with either a full adult dose (0.5 mL) or a half adult dose (0.25 mL) of Pandemrix administered as a two-dose vaccination schedule in children and adolescents aged from 6 months to 17 years old. The MAH provided SNA data from all three studies and also M6 HI and SNA data from study 023.

The MAH proposed to update section 5.1 of the SmPC accordingly.

Analysis of data submitted

Please see previous CHMP assessment report for details of the design of the three studies and the results reported up to D84. The same lots of HA and AS03 were used in these three studies in Spain and Germany.

It was intended that each study would include a booster dose at M6. However, when the D42 results were analysed the added value of the booster dose was considered to be limited and therefore the protocols were amended to drop this dose.

Blood samples have been/will be drawn at D0, D21, D42 in each study and then at M6 in study D-Pan-H1N1-023, at M12 in D-Pan-H1N1-010 and at M11-12 in D-Pan-H1N1-009.

Haemagglutination Inhibition testing was performed as previously described. The samples taken at M6 in study D-Pan-H1N1-023 from which data are now reported were tested for HI antibody at a different time and assay variability was not evaluated between the two testing runs. Due to potential assay variability, interpretation of the HI responses up to D42 vs. M6 should be done with caution.

The SNA assays were planned to be performed using the A/California/7/2009 strain. However, the assays were performed using the A/Netherlands/602/9 strain, which is antigenically similar to the A/California-like vaccine strain. Currently reported are the SNA data up to D42 in D-Pan-H1N1-009 and -010 and up to M6 in D-Pan-H1N1-023. CMI testing is planned.

- Study D-Pan-H1N1-009 – Spain

This is an open, randomised, multicentre study in two parallel groups to assess the safety and immunogenicity data of Pandemrix when administered on D0 and D21 to healthy children aged 6 to 35 months.

A total of 157 subjects aged 19.5 ± 9.5 months old (mean ± SD) at the time of the first vaccine dose were enrolled. Subjects were randomised (1:2) as follows:

- Group A: 53 received two full adult doses;
- Group B: 104 received two half adult doses.

Immunogenicity

The new immunogenicity data reported are confined to SNA up to D42. The SNA subset included 102 subjects from the ATP-I cohort at D42 (33 in Group A; 69 in Group B). The synoptic report states that SNA was to be determined for each age stratum and overall, in a randomised subset of approximately 60% of subjects with a [2:1:1] ratio among the three age strata.

As shown in the table below the D0 SNA seropositivity rate across the age strata was 13.3% in Group A and 6.2% in Group B and the GMTs were low (5.40 and 5.35, respectively).

At D21 the seropositivity rates had increased to 96.7% and 88.7% in Groups A and B, respectively, with GMTs at 51.23 and 37.88. At D42 all subjects were seropositive and the Geometric meantitre (GMT) was numerically lower in the half adult dose group.

Review by age strata showed a general trend to lower GMTs as age increased. However, all children with data had SNA titres of at least 1:80 at D42 and the majority had titres of at least 1:320.

Table 6 **H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Day 42 in study D-Pan-H1N1-009 (ATP cohort for immunogenicity, neutralizing antibody subset)**

				>= 8 1/DIL				GMT			Vaccine response rate				
						95% CI			95% CI						95% CI
Study vaccine	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	N	n	%	LL	UL
3.75 µg HA+ AS03A	6-11 months	PRE	14	1	7.1	0.2	33.9	5.32	2.88	9.83	-	-	-	-	-
		PI(D21)	15	14	93.3	68.1	99.8	41.67	18.32	94.76	14	8	57.1	28.9	82.3
		PII(D42)	15	15	100	78.2	100	2052.25	953.94	4415.11	14	14	100	76.8	100
	12-23 months	PRE	8	1	12.5	0.3	52.7	4.36	3.55	5.35	-	-	-	-	-
		PI(D21)	7	7	100	59.0	100	48.56	21.15	111.48	7	5	71.4	29.0	96.3
		PII(D42)	9	9	100	66.4	100	1754.69	809.54	3803.31	8	8	100	63.1	100
	24-35 months	PRE	8	2	25.0	3.2	65.1	6.88	2.37	20.00	-	-	-	-	-
		PI(D21)	8	8	100	63.1	100	79.06	17.47	357.72	8	5	62.5	24.5	91.5
		PII(D42)	8	8	100	63.1	100	1826.43	773.86	4310.64	7	7	100	59.0	100
	Overall	PRE	30	4	13.3	3.8	30.7	5.40	3.76	7.77	-	-	-	-	-
		PI(D21)	30	29	96.7	82.8	99.9	51.23	29.85	87.90	29	18	62.1	42.3	79.3
		PII(D42)	32	32	100	89.1	100	1907.39	1250.94	2908.34	29	29	100	88.1	100
1.9 µg HA+ AS03B	6-11 months	PRE	31	3	9.7	2.0	25.8	6.96	3.68	13.14	-	-	-	-	-
		PI(D21)	30	28	93.3	77.9	99.2	51.01	27.52	94.55	28	16	57.1	37.2	75.5
		PII(D42)	30	30	100	88.4	100	1629.26	1053.34	2520.07	28	27	96.4	81.7	99.9
	12-23 months	PRE	16	0	0.0	0.0	20.6	4.00	4.00	4.00	-	-	-	-	-
		PI(D21)	15	13	86.7	59.5	98.3	27.55	15.48	49.05	14	8	57.1	28.9	82.3
		PII(D42)	16	16	100	79.4	100	1458.42	867.77	2451.09	16	16	100	79.4	100
	24-35 months	PRE	18	1	5.6	0.1	27.3	4.41	3.59	5.41	-	-	-	-	-
		PI(D21)	17	14	82.4	56.6	96.2	29.66	16.20	54.31	17	10	58.8	32.9	81.6
		PII(D42)	17	17	100	80.5	100	1294.84	809.39	2071.45	17	17	100	80.5	100
	Overall	PRE	65	4	6.2	1.7	15.0	5.35	3.94	7.26	-	-	-	-	-
		PI(D21)	62	55	88.7	78.1	95.3	37.88	26.46	54.22	59	34	57.6	44.1	70.4
		PII(D42)	63	63	100	94.3	100	1488.85	1144.23	1937.25	61	60	98.4	91.2	100

GMT = geometric mean antibody titre calculated on all subjects; N (for seropositivity rates and GMTs) = number of subjects with available results; n/% (for seropositivity rates and GMTs) = number/percentage of subjects with titre within the specified range; N (for Vaccine Response) = Number of subjects with pre- and post-vaccination results available; n/% (for Vaccine Response) = Number/percentage of responders;

Vaccine response rate (VRR) is defined as the percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre. 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Safety

Up to Day 84, the percentages reporting at least one unsolicited Adverse Event (AE) were 88.7% in Group A and 94.2% in Group B. Many of the unsolicited AEs mapped to the SOC Infections and infestations and were actually Upper Respiratory Tract Infections (URTIs) (45.3% and 56.7% in respective groups). Percentages reporting Grade 3 unsolicited AEs up to Day 84 were 15.1% and 17.3%, in respective groups and AEs considered to be related to vaccination by the investigator were reported in 15.1% 11.5%. No Adverse Events of Special Interest (AESIs) or potential Immune-Mediated Diseases (pIMDs) were reported during the study through Month 7 and there were no

withdrawals due to (S)AEs. None of the 9 SAEs reported by 6 subjects were considered to be related to study vaccination.

- Study D-Pan-H1N1-010 (Spain)

This is an ongoing non-randomised, open-label Phase III study conducted in 5 centres in Spain to evaluate the safety and immunogenicity of Pandemrix in children aged 3 to 17 years. There were 210 children enrolled with a mean age at D0 of 9.2 ± 4.47 years (mean and SD).

The new immunogenicity data reported are confined to SNA up to D42. The SNA subset included 107 subjects randomly selected from the ATP-I cohort at D42 to obtain approximately equal numbers in each age stratum.

As shown below, the D0 SNA seropositivity rate was 10.1% overall with a range of 3.1% to 16.2% but with no age-associated trend. The D0 GMT values were low.

At D21 only one subject (aged 3-5 years) was still seronegative and all subjects were seropositive at D42. The GMTs showed a trend to decrease with increasing age. While all except one child had a titre of at least 1:80 at D42 the proportions with titres of at least 1:320 were 93, 84 and 62% in the three strata by increasing age.

Table 8 **H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Day 42 in study D-Pan-H1N1-010 (ATP cohort for immunogenicity, neutralizing antibody subset)**

				>= 8 1/DIL				GMT			Vaccine Response rate				
						95% CI			95% CI					95% CI	
Study vaccine	Age stratum	Timing	N	n	%	LL	UL	value	LL	UL	N	n	%	LL	UL
3.75 µg HA+ AS03$_A$	3-5 years	PRE	32	1	3.1	0.1	16.2	4.1	3.9	4.4	-	-	-	-	-
		PI(21)	32	31	96.9	83.8	99.9	60.2	42.4	85.5	32	26	81.3	63.6	92.8
		PII(D42)	29	29	100	88.1	100	1277.4	995.1	1822.9	29	29	100	88.1	100
	6-9 years	PRE	37	6	16.2	6.2	32.0	6.1	4.2	8.8	-	-	-	-	-
		PI(21)	37	37	100	90.5	100	149.0	80.7	275.0	37	32	86.5	71.2	95.5
		PII(D42)	37	37	100	90.5	100	751.0	491.0	1148.6	37	37	100	90.5	100
	10-17 years	PRE	30	3	10.0	2.1	26.5	5.3	3.6	7.9	-	-	-	-	-
		PI(21)	30	30	100	88.4	100	113.0	71.5	178.8	30	26	86.7	69.3	96.2
		PII(D42)	29	29	100	88.1	100	553.4	388.4	788.4	29	29	100	88.1	100
	Overall	PRE	99	10	10.1	5.0	17.8	5.2	4.3	6.2	-	-	-	-	-
		PI(21)	99	98	99.0	94.5	100	102.2	76.4	136.8	99	84	84.8	76.2	91.3
		PII(D42)	95	95	100	96.2	100	804.6	640.6	1010.5	95	95	100	96.2	100

GMT = geometric mean antibody titre calculated on all subjects
For seropositivity rates and GMTs:
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
Vaccine response rate is defined as the percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre.
For Vaccine Response rates:
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of responders
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at day 0; PI(21) = Post vaccination at Day 21; PII(D42) = Post vaccination at Day 42

Appendix Table 4 Distribution of titre of neutralizing antibodies against Flu A/Neth/602/09 H1N1 Ab in study D-Pan-H1N1-010 (ATP cohort for immunogenicity at Day 42, neutralizing antibody subset)

			<32 1/DIL		>=32 1/DIL		>=56 1/DIL		>=80 1/DIL		>=160 1/DIL		>=320 1/DIL	
Sub-group	Timing	N	n	%	n	%	n	%	n	%	n	%	n	%
3-5Y	PRE	32	32	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PI(21)	32	6	18.8	26	81.3	15	46.9	12	37.5	4	12.5	1	3.1
	PII(D42)	29	0	0.0	29	100	29	100	29	100	29	100	27	93.1
6-9Y	PRE	37	33	89.2	4	10.8	4	10.8	3	8.1	1	2.7	1	2.7
	PI(21)	37	4	10.8	33	89.2	25	67.6	22	59.5	11	29.7	5	13.5
	PII(D42)	37	0	0.0	37	100	36	97.3	36	97.3	33	89.2	31	83.8
10-17Y	PRE	30	28	93.3	2	6.7	1	3.3	1	3.3	1	3.3	1	3.3
	PI(21)	30	4	13.3	26	86.7	21	70.0	19	63.3	8	26.7	6	20.0
	PII(D42)	29	0	0.0	29	100	29	100	29	100	29	100	18	62.1
Overall	PRE	99	93	93.9	6	6.1	5	5.1	4	4.0	2	2.0	2	2.0
	PI(21)	99	14	14.1	85	85.9	61	61.6	53	53.5	23	23.2	12	12.1
	PII(D42)	95	0	0.0	95	100	94	98.9	94	98.9	91	95.8	76	80.0

Overall = Subjects aged between and including 3 years to 17 years; S- = Subjects who are having Seronegative status before vaccination; S+ = Subjects who are having Seropositive status before vaccination ;
N = number of subjects with available results; n/% = number/percentage of subjects with titre within the specified range
PRE = Pre-vaccination at day 0; PI(21) = Post vaccination at Day 21; PII(D42) = Post vaccination at Day 42

Across all ages the incidence of unsolicited AEs up to Day 84 was 49.5% but ranged from 70% in those aged 3-5 years to 46% and 41% in the two older cohorts.

The most frequently reported unsolicited AEs were URTI (13.3%) and cough (5.7%). Again the highest incidences occurred in the youngest age group (20.8% and 9.4%, respectively). Grade 3 AEs were reported in 15%, 7% and 7% per group by ascending age while AEs that were considered related to vaccination by the investigator were reported in 4%, 7% and 6%, respectively.

No deaths and no pIMDs were reported up to Month 7. One subject reported one SAE during the additional study period, which was considered not related to study vaccination. None of the (S)AEs led to study withdrawal through Month 7.

- Study D-Pan-H1N1-023 (Germany)

This ongoing non-randomised, open-label study was initiated in 8 centres in Germany in children aged 3 to 17 years. All subjects were enrolled to receive two half adult doses of Pandemrix. Subjects were randomly allocated (1:1) to one of the two blood sampling schedules (stratified by age):

- Blood sampling schedule 1 (BS1) included blood sampling at D0, 21, 42 and M6
- Blood sampling schedule 2 (BS2) included blood sampling at D42, M6 and M12

There were 244 children enrolled and vaccinated with a mean age at D0 of 9.2 ± 4.09 years (mean and SD). The ATP-I at D42 included 225 subjects and the ATP-I at M6 included 206 subjects.

At M6 overall data showed that all subjects were still seropositive for HI while SPR and SCR exceeded 90% and the GMFR was 27. The GMTs showed a trend to be higher with increasing age.

Table 12 **HI antibody response against vaccine-homologous A/California/7/2009 (H1N1)v-like at Month 6 in study D-Pan-H1N1-023 (ATP cohort for antibody persistence at Month 6)**

				≥10 1/DIL			GMT			SPR			SCR			SCF		
					95% CI			95% CI			95% CI			95% CI			95% CI	
Study group	Age stratum	Pre-vacc status	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
BS1	3-5 years	S-	26	**100**	86.8	100	**145.7**	123.5	172.0	**100**	86.8	100	**100**	86.8	100	**29.15**	24.70	34.40
		S+	1	**100**	2.5	100	**57.0**	-	-	**100**	2.5	100	**100**	2.5	100	**5.70**	-	-
		Total	27	**100**	87.2	100	**140.8**	118.2	167.6	**100**	87.2	100	**100**	87.2	100	**27.44**	22.42	33.57
	6-9 years	S-	27	**100**	87.2	100	**154.0**	125.4	189.1	**100**	87.2	100	**100**	87.2	100	**30.80**	25.07	37.82
		S+	1	**100**	2.5	100	**160.0**	-	-	**100**	2.5	100	**100**	2.5	100	**8.00**	-	-
		Total	28	**100**	87.7	100	**154.2**	126.5	187.9	**100**	87.7	100	**100**	87.7	100	**29.35**	23.53	36.61
	10-17 years	S-	36	**100**	90.3	100	**199.7**	150.3	265.4	**100**	90.3	100	**100**	90.3	100	**39.94**	30.06	53.08
		S+	17	**100**	80.5	100	**425.7**	282.6	641.2	**100**	80.5	100	**82.4**	56.6	96.2	**9.64**	5.67	16.41
		Total	53	**100**	93.3	100	**254.6**	199.0	325.7	**100**	93.3	100	**94.3**	84.3	98.8	**25.32**	18.60	34.47
	Overall 3-17 years	S-	89	**100**	95.9	100	**168.3**	146.6	193.2	**100**	95.9	100	**100**	95.9	100	**33.67**	29.33	38.65
		S+	19	**100**	82.4	100	**363.7**	235.4	562.1	**100**	82.4	100	**84.2**	60.4	96.6	**9.29**	5.78	14.91
		Total	108	**100**	96.6	100	**192.8**	166.8	222.8	**100**	96.6	100	**97.2**	92.1	99.4	**26.84**	22.73	31.69
BS2	3-5 years	Total	23	**100**	85.2	100	**129.4**	94.6	176.9	**87.0**	66.4	97.2	-	-	-	-	-	-
	6-9 years	Total	27	**100**	87.2	100	**148.2**	119.0	184.4	**100**	87.2	100	-	-	-	-	-	-
	10-17 years	Total	47	**100**	92.5	100	**243.6**	185.9	319.3	**100**	92.5	100	-	-	-	-	-	-
	Overall 3-17 years	Total	97	**100**	96.3	100	**182.6**	154.4	215.9	**96.9**	91.2	99.4	-	-	-	-	-	-

GMT = geometric mean antibody titre calculated on all subjects

SCR = Seroconversion rate defined as: For initially seronegative subjects, antibody titer ≥ 40 after vaccination; For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer;

SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]); SPR = percentage of vaccinees with serum H1N1 HI antibody titer ≥1:40; seroprotection = A/California/7/2009(H1N1) antibody titre >= 40 1/DIL

S- = seronegative subjects (antibody titre < 10 1/DIL) prior to vaccination; S+ = seropositive subjects (antibody titre >= 10 1/DIL) prior to vaccination

N = Number of subjects with pre-vaccination results available; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit;

The analysis of SNA data up to D42 and at M6 was based on the ATP-I cohort. It was planned to assess SNA in one third of the study population that was randomly selected to obtain approximately equal numbers from each of the three age strata.

SNA seropositivity at D0 was detected in 19-33% per age stratum and was lowest in the 3-5 years stratum. Overall 18.2% of subjects seropositive before vaccination had titres ≥ 1:160.

The overall seropositivity rate at D0 (26.7%) increased up to 90.7% at D21 (BS1) and 100% at D42 (BS1 and BS2). Similarly across all ages the GMT rose 8.6-fold at D21 and then 8.1-fold at D42 with vaccine response rates of 62.8% at D21 and 100% at D42.

At D21 the GMTs showed a trend to increase with age (27.7, 65.9 and 109.4) with vaccine response rates of 50%, 71.4% and 69.2%. However at D42 there was no appreciable difference between GMTs by age stratum and all subjects met the criteria for a vaccine response.

As shown in the second table below at M6 the vaccine response rate was 95.5% overall while the GMTs were 193.3 and 157.7 for BS1 and BS2 respectively. Vaccine response rates by age stratum were in the range 92-100% while the GMTs did not show a consistent age-associated trend.

Table 10 **H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Day 42 in study D-Pan-H1N1-023 (ATP cohort for immunogenicity at Day 42, neutralizing antibody subset)**

					>= 8 1/DIL				GMT			Vaccine Response rate				
							95% CI			95% CI					95% CI	
Study vaccine	Group	Age stratum	Timing	N	n	%	LL	UL	value	LL	UL	N	n	%	LL	UL
1.9 µg HA+ AS03B	BS1	3-5 years	PRE	16	3	18.8	4.0	45.6	4.9	3.9	6.1	-	-	-	-	-
			PI(21)	16	13	81.3	54.4	96.0	27.7	13.0	58.8	16	8	50.0	24.7	75.3
			PII(D42)	15	15	100	78.2	100	433.2	295.2	635.6	15	15	100	78.2	100
		6-9 years	PRE	15	5	33.3	11.8	61.6	7.1	3.9	12.7	-	-	-	-	-
			PI(21)	14	13	92.9	66.1	99.8	65.9	24.6	176.4	14	10	71.4	41.9	91.6
			PII(D42)	15	15	100	78.2	100	473.7	301.5	744.1	15	15	100	78.2	100
		10-17 years	PRE	14	4	28.6	8.4	58.1	8.0	3.0	21.3	-	-	-	-	-
			PI(21)	13	13	100	75.3	100	109.4	34.5	346.7	13	9	69.2	38.6	90.9
			PII(D42)	14	14	100	76.8	100	438.4	191.3	1004.8	14	14	100	76.8	100
		Overall	PRE	45	12	26.7	14.6	41.9	6.5	4.6	9.1	-	-	-	-	-
			PI(21)	43	39	90.7	77.9	97.4	55.6	32.7	94.7	43	27	62.8	46.7	77.0
			PII(D42)	44	44	100	92.0	100	448.3	330.9	607.4	44	44	100	92.0	100
	BS2	3-5y	PII(D42)	12	12	100	73.5	100	533.4	298.4	953.7	-	-	-	-	-
		6-9y	PII(D42)	13	13	100	75.3	100	260.1	141.9	476.6	-	-	-	-	-
		10-17y	PII(D42)	15	15	100	78.2	100	199.5	112.7	353.2	-	-	-	-	-
		Total	PII(D42)	40	40	100	91.2	100	292.1	208.9	408.4	-	-	-	-	-

BS = blood sampling schedule
GMT = geometric mean antibody titre calculated on all subjects
For seropositivity rates and GMTs:
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
Vaccine response rate is defined as the percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre.
For Vaccine Response rates:
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of responders
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at day 0; PI(21) = Post vaccination at Day 21; PII(D42) = Post vaccination at Day 42

Table 13 **H1N1 Neutralizing antibody response against A/Netherlands/602/9 up to Month 6 in study D-Pan-H1N1-023 (ATP cohort for antibody persistence at Month 6)**

					>= 8 1/DIL			GMT			Vaccine Response rate		
						95% CI			95% CI			95% CI	
Study vaccine	Group	Age stratum	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL
1.9 µg HA+ AS03B	BS1	3-5 years	PRE	16	**18.8**	4.0	45.6	**4.9**	3.9	6.1	-	-	-
			PI(21)	16	**81.3**	54.4	96.0	**27.7**	13.0	58.8	**50.0**	24.7	75.3
			PII(D42)	15	**100**	78.2	100	**433.2**	295.2	635.6	**100**	78.2	100
			PII(M6)	16	**100**	79.4	100	**158.9**	110.4	228.8	**100**	79.4	100
		6-9 years	PRE	15	**33.3**	11.8	61.6	**7.1**	3.9	12.7	-	-	-
			PI(21)	14	**92.9**	66.1	99.8	**65.9**	24.6	176.4	**71.4**	41.9	91.6
			PII(D42)	15	**100**	78.2	100	**473.7**	301.5	744.1	**100**	78.2	100
			PII(M6)	15	**100**	78.2	100	**203.3**	133.7	309.3	**93.3**	68.1	99.8
		10-17 years	PRE	13	**23.1**	5.0	53.8	**7.9**	2.7	22.8	-	-	-
			PI(21)	12	**100**	73.5	100	**97.6**	28.3	336.4	**66.7**	34.9	90.1
			PII(D42)	13	**100**	75.3	100	**377.6**	164.3	868.1	**100**	75.3	100
			PII(M6)	13	**100**	75.3	100	**232.1**	81.8	658.4	**92.3**	64.0	99.8
		Overall	PRE	44	**25.0**	13.2	40.3	**6.4**	4.5	9.1	-	-	-
			PI(21)	42	**90.5**	77.4	97.3	**53.0**	31.0	90.6	**61.9**	45.6	76.4
			PII(D42)	43	**100**	91.8	100	**428.7**	318.5	577.1	**100**	91.8	100
			PII(M6)	44	**100**	92.0	100	**193.3**	138.4	270.0	**95.5**	84.5	99.4
	BS2	3-5y	PII(D42)	12	**100**	73.5	100	**533.4**	298.4	953.7	-	-	-
			PII(M6)	12	**100**	73.5	100	**156.6**	89.8	273.3	-	-	-
		6-9y	PII(D42)	11	**100**	71.5	100	**264.8**	134.3	522.3	-	-	-
			PII(M6)	12	**100**	73.5	100	**166.0**	88.7	310.6	-	-	-
		10-17y	PII(D42)	12	**100**	73.5	100	**173.5**	93.4	322.3	-	-	-
			PII(M6)	12	**100**	73.5	100	**150.9**	62.7	363.1	-	-	-
		Total	PII(D42)	35	**100**	90.0	100	**291.3**	203.0	417.9	-	-	-
			PII(M6)	36	**100**	90.3	100	**157.7**	109.7	226.7	-	-	-

BS = blood sampling schedule
GMT = geometric mean antibody titre calculated on all subjects
For seropositivity rates and GMTs:
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range

All subjects who were seropositive before vaccination had titres ≥ 1:40 at D21 and titres ≥ 1:80 at D42. By M6 81.8% still had titres ≥ 1:80.

Among those who were seronegative before vaccination, 50% had titres ≥ 1:32 at D21 while all had titres ≥ 1:40 at D42. By M6 97.0% still had titres ≥ 1:40. In the BS2 group, 97.1% had titres ≥ 1:56 at D42 but by M6 the rate had dropped to 80.6%.

Across all ages, the per-subject incidence of unsolicited AEs up to D84 was 49.2% but ranged from 69% in subjects aged 3-5 years to 39% and 45% in the older strata.

The most frequently reported unsolicited AEs were URTIs (6.6%), cough (6.1%) and nasopharyngitis (6.1%). AEs that were considered to be related to vaccination by the investigator were reported in 14.8%, 3.1% and 3.4% by ascending age strata and Grade 3 AEs were reported in 4.9%, 1.5% and 4.2%.

No deaths and no AESIs/pIMDs were reported up to Month 7. During this time period, 7 SAEs were reported for 6 subjects but all were considered not related to study vaccination. None of the SAEs led to study withdrawal through Month 7.

Three non-serious AEs led to premature withdrawal from the study through Month 7. These cases concerned urticaria (parents and investigator decision), pain (parents decision) and tonsillitis (investigators decision).

Changes to the Product Information (additions in red)

Section 5.1

Children aged 10-17 years

(…)

The Day 180 seroprotection rate in the children who had received two half (0.25 ml) doses was 100%.

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like[1]				
	Half dose			Full dose	
	Post dose 1	Post dose 2	Month 6	Post dose 1	Post dose 2
	N=13	N=14	N=13	N=30	N=29
Vaccine Response Rate[2]	69.2%	100%	92.3%	86.7%	100%
	[38.6;90.9]	[76.8;100]	[64.0;99.8]	[69.3;96.2]	[88.1;100]

[1]antigenically similar to A/California/7/2009 (H1N1)v-like

[2]percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre

Children aged 3 to 9 years

(…)

The Day 180 seroprotection rate in the children who had received two half (0.25 ml) doses was 100% in both age groups.

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like[1]									
	3-5 years					6-9 years				
	Half adult dose			Adult dose		Half adult dose			Adult dose	
	Post dose 1 N=16	Post dose 2 N=15	Month 6 N=16	Post dose 1 N=32	Post dose 2 N=29	Post dose 1 N=14	Post dose 2 N=15	Month 6 N=15	Post dose 1 N=37	Post dose 2 N=37
Vaccine Response Rate[2]	50.0% [24.7; 75.3]	100% [78.2; 100]	100% [79.4; 100]	81.3% [63.6; 92.8]	100% [88.1; 100]	71.4% [41.9; 91.6]	100% [78.2; 100]	93.3% [68.1; 99.8]	86.7% [69.3; 96.2]	100% [88.1; 100]

[1]antigenically similar to A/California/7/2009 (H1N1)v-like

[2]percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre

Children aged 6-35 months

(…)

The neutralising antibody responses were as follows:

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like[1]							
	6-11 months				12-23 months			
	Half dose		Adult dose		Half dose		Adult dose	
	Post dose 1 N=28	Post dose 2 N=28	Post dose 1 N=14	Post dose 2 N=14	Post dose 1 N=14	Post dose 2 N=16	Post dose 1 N=7	Post dose 2 N=8
Vaccine Response Rate[2]	57.1% [37.2; 75.5]	96.4% [81.7; 99.9]	57.1% [28.9; 82.3]	100% 76.8; 100]	57.1% [28.9; 82.3]	100% [79.4; 100]	71.4% [29.0; 96.3]	100% [63.1; 100]

[1]antigenically similar to A/California/7/2009 (H1N1)v-like

[2]percentage of vaccinees who, if initially seronegative reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre

Serum neutralising antibody	Immune response to A/Netherlands/602/9 (H1N1)v-like[1]			
	24-35 months			
	Half dose		Adult dose	
	Post dose 1 N=17	Post dose 2 N=17	Post dose 1 N=8	Post dose 2 N=7
Vaccine Response Rate[2]	58.8% [32.9;81.6]	100% [80.5;100]	62.5% [24.5;91.5]	100% [59.0;100]

[1]antigenically similar to A/California/7/2009 (H1N1)v-like

[2]percentage of vaccinees who, if initially seronegative, reach an antibody titre ≥32 1/DIL after vaccination or, if initially seropositive, reach an antibody titre ≥ 4-fold the pre-vaccination antibody titre

(…)

Conclusions and Benefit / Risk Assessment

As previously noted the MAH has encountered difficulties in developing an in-house SNA but has reported SNA data from subsets of adults after contracting out testing to other laboratories.

The additional SNA data that are now reported from children in three studies up to D42 concern randomised subsets and limited numbers, but the data are spread across the age strata. In general these data suggest quite low pre-vaccination SNA seropositivity rates and very good responses across the age range 6 months to 17 years to half doses of Pandemrix.

The data up to 6 months from study D-Pan-H1N1-023 show good levels of persistent seropositivity based on HI and SNA and regardless of the baseline SNA seropositivity.

These new data, together with the additional safety data, raise no new concerns and the CHMP deemed appropriate that the data should be reflected in the SmPC.

The benefit/risk balance for Pandemrix remains unchanged.

4. Conclusion

On 17 February 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Annex II.