European Medicines Agency

London, 19 Novmeber 2009
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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/0024

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 results from a study in children aged from 6-35 months (D-PAN-H1N1-008, called "H1N1-008" in this report).

In support of this variation the MAH has submitted a synoptic report of day 21 (D21) safety and immunogenicity data (HI only) from study H1N1-009.

This variation has been submitted to fulfil the specific obligation SOB 056 for which the MAH committed to provide the post-dose 1 HI immunogenicity data (uncleaned) from this study to CHMP.

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

1.2 Clinical aspects

FLU D-PAN H1N1-009

This is an on-going 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 data provided in the abridged report of 23 October 2009 have a data lock point at 19 October 2009.

The MAH provided an abridged study report that covers the post-dose 1 immunogenicity results (i.e. at D21) after a single dose of 1.9 µg/$AS03_B$ (i.e. half the adult dose of HA and of AS03 in 0.25 ml volume) together with data on reactogenicity, AEs and SAEs for the first 51 children enrolled.

The analyses reported thus far were performed on uncleaned data and the primary analysis was done on the total vaccinated cohort for each age stratum and overall. The analysis of immunogenicity was provided as a descriptive analysis of the humoral immune response in children 6 to 35 months of age and also within each age stratum.

Study design and objectives

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.

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.
  Only the data from this phase are currently reported.
  The 7-day post-dose 1 reactogenicity was assessed after Step 1 by a GSK internal Safety Review Committee, who provided a recommendation to proceed with the next recruitment phase. Therefore, step 2 of the study is currently ongoing.

- Step 2: Open-label, randomised enrolment of 102 subjects in a 1:1 randomisation ratio between vaccine group 1.9 µg/$AS03_B$ (completion of enrolment) and vaccine group 3.75 µg/$AS03_A$

- Step 3: Open enrolment of 51 subjects into vaccine group 3.75 µg/$AS03_A$.

Dosing with the full adult dose will still go ahead and the study protocol remains unchanged at present since the data are limited to only the first 51 subjects. Any change to the protocol would be subject to a variation of the paediatric investigation plan (PIP) agreed for Pandemrix.

Results

Demography

As was planned, the study enrolled 51 subjects into Step 1, including 17 in each age stratum, all of whom completed to the post-dose 1 time point. Within each stratum the age range covered that intended by the protocol.

The mean age across all strata was 18.9 months for the total vaccinated subjects. The overall male-female distribution was 60.8% versus 39.2% with the imbalance coming from the 12-23 month and 24-35 month groups and 48/51 were Caucasian.

Study Group B		1.9 µg H1N1/ $AS03_B$							
Age category		All ages, 6-35 months N = 51		6-11 months N = 17		12-23 months N = 17		24-35 months N = 17	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	18.9	-	8.8	-	17.6	-	30.3	-
	SD	9.35	-	1.39	-	2.91	-	3.74	-
	Median	19.0	-	9.0	-	19.0	-	32.0	-
	Minimum	7	-	7	-	12	-	24	-
	Maximum	35	-	11	-	21	-	35	-
Gender	Female	20	39.2	8	47.1	6	35.3	6	35.3
	Male	31	60.8	9	52.9	11	64.7	11	64.7

Immunogenicity data

The table below summarises the immunogenicity data overall and by age strata.

- At Day 0 only three subjects (all in the 6-11 month stratum) were seropositive and two of these three were seroprotected. It may be that there was some residual maternal antibody in these subjects.
- At Day 21, the overall seropositivity rate increased to 100% with an observed GMT of 340. The GMT was numerically lower in the cohort aged 24-35 months.
- At Day 21 the SCR was 100% in the 12-23 and 24-35 month old groups and 94% in the youngest age stratum (6-11 months). The SPR was 100% in all three age strata. The SCF ranged between 44.4 and 76.9.

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	
	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
Overall																
PRE	51	5.9	1.2	16.2	5.97	4.74	7.51	**3.9**	0.5	13.5	-	-	-	-	-	-
PI(D21)	50	100	92.9	100	**340.64**	278.73	416.31	**100**	92.9	100	**98.0**	89.4	99.9	**56.9**	44.7	72.4
6-11 months Age stratum																
PRE	17	17.6	3.8	43.4	8.50	4.19	17.24	**11.8**	1.5	36.4	-	-	-	-	-	-
PI(D21)	17	100	80.5	100	**376.88**	238.23	596.23	**100**	80.5	100	**94.1**	71.3	99.9	**44.4**	24.1	81.5
12-23 months Age stratum																
PRE	17	0.0	0.0	19.5	5.00	5.00	5.00	**0.0**	0.0	19.5	-	-	-	-	-	-
PI(D21)	17	100	80.5	100	**384.46**	278.61	530.51	**100**	80.5	100	**100**	80.5	100	**76.9**	55.7	106.1
24-35 months Age stratum																
PRE	17	0.0	0.0	19.5	5.00	5.00	5.00	**0.0**	0.0	19.5	-	-	-	-	-	-
PI(D21)	16	100	79.4	100	**269.04**	203.70	355.34	**100**	79.4	100	**100**	79.4	100	**53.8**	40.7	71.1

Whereas there were only three children seropositive at baseline in this study, all in the age stratum 6-11 months, the assessor obtained an additional breakdown of responses for these three vs. the other 14 in the same stratum to see whether baseline serostatus interfered with immune responses. Since the data are still blinded the MAH is currently unable to confirm the exact ages of the three children who were seropositive at baseline (i.e. the younger they are the more likely it is that the baseline serostatus may reflect maternal antibody).

The MAH provided four additional tables as shown below. The GMT at D0 and D21 was higher for the three seropositive at D0. The minimum GMT for these three seropositive children increased from 10 to 57, demonstrating that all three must have had an increment in HI antibody in response to vaccination. At D21 two of the three met the definition of seroconversion, the child who was not seroprotected at D0 achieved the required titre and the SCF was much lower for these three compared to the others.

Seropositivity rates and GMTs for HI antibody for children aged 6 months to 11 months by serostatus at baseline (Total vaccinated cohort)

			>= 10 1/DIL				GMT				
					95% CI			95% CI			
Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
seroneg	PRE	14	0	0.0	0.0	23.2	5.00	5.00	5.00	<10.00	<10.00
	PI(D21)	14	0	0.0	0.0	23.2	353.34	259.56	481.01	160.00	905.00
seropos	PRE	3	3	100	29.2	100	100.79	0.70	14525.99	10.00	320.00
	PI(D21)	3	3	100	29.2	100	509.24	2.87	90432.26	57.00	3620.00

SCR for HI antibody for children aged 6 months to 11 months by serostatus at baseline (Total vaccinated cohort)

				SCR		
					95% CI	
Sub-group	**Timing**	**N**	**n**	**%**	**LL**	**UL**
seroneg	PI(D21)	14	14	100	76.8	100
seropos	PI(D21)	3	2	66.7	9.4	99.2

SCF for HI antibody for children aged 6 months to 11 months by serostatus at baseline (Total vaccinated cohort)

			SCF		
				95% CI	
Sub-group	**Timing**	**N**	**Value**	**LL**	**UL**
seroneg	PI(D21)	14	70.67	51.91	96.20
seropos	PI(D21)	3	5.05	0.58	44.15

SPR for HI antibody for children aged 6 months to 11 months by serostatus at baseline (Total vaccinated cohort)

				SPR		
					95% CI	
Sub-group	**Timing**	**N**	**n**	**%**	**LL**	**UL**
seroneg	PRE	14	0	0.0	0.0	23.2
	PI(D21)	14	14	100	76.8	100
seropos	PRE	3	2	66.7	9.4	99.2
	PI(D21)	3	3	100	29.2	100

Clinical safety

The safety analysis was performed on the total vaccinated cohort of 51 subjects, for which all parents/guardians returned the symptom records.

As shown below, for total and general symptoms the reporting rates were comparable between the 6-11 and 12-23 month age strata but were lower in the oldest stratum of 24-35 months. In contrast the rates of local symptoms did not show a trend according to age. Only one symptom was of Grade 3 and this was irritability that occurred in a child in the youngest age stratum and lasted for one day.

Pain at the injection site was the most frequently reported solicited local symptom with a mean duration of 2.2 days. Redness and swelling were reported less frequently and with mean durations of 1.9 days and 2.6 days, respectively. Pain was most frequently reported in the 24-35 month age group. The assessor considers that this may simply reflect the superior ability of older children to voice complaints of pain to their parents/guardians. In contrast, almost all cases of redness and swelling occurred in the 12-23 month age group. The only case of swelling in the oldest age stratum persisted for 6 days.

The most frequently reported solicited general symptom was irritability (mean duration 1.8 days), followed by loss of appetite (2.1 days), drowsiness (1.3 days) and fever above 37.5°C (1.4 days). The majority of these symptoms were considered to be related to vaccination. Solicited and unsolicited general symptoms most often occurred in the youngest age stratum and least often in the oldest stratum. No child had a fever above 39°C and no child in the 24-35 months stratum had a documented fever. It should be noted then that prophylactic antipyretic medication was not taken in this study and that 12 children received an antipyretic at some time during the 20 days after the dose.

Fifty-one unsolicited AEs were reported in 33 subjects and the most frequently reported was upper respiratory tract infection (25%). Two unsolicited AEs were considered to be related to vaccination (diarrhoea and rash), each reported in one subject. Details of the rash were not provided but it was not of Grade 3.

The MAH provided additional information on the three cases of rash reported as unsolicited AEs. These occurred in children aged 18 (M), 20 (M) and 29 (F) months with onset at D17, D1 and D0, respectively. Two were of Grade 1 and the other has not been graded. Only one rash resulted in a medically-attended visit (see table below) and was considered vaccine-related by the investigator. However, it seems that the child has not been withdrawn from the study (at least not at the time of the cut-off for this report). Rash is already included in the SPC.

Five unsolicited AEs were Grade 3, including one report of each of pyrexia, gastroenteritis, laryngitis, otitis media and upper respiratory tract infection, but none was considered by the investigator to be related to vaccination. Nineteen subjects had unsolicited AEs resulting in a medically-attended visit, as shown in the table on the next page.

Unsolicited AEs reported Days 0-20 post-vaccination period (Total vaccinated cohort)

Number of subjects with at least one unsolicited symptom reported	33
Number of unsolicited symptoms classified by MedDRA Preferred Term	49
Number of unsolicited symptoms reported	51

Unsolicited AEs with medically attended visit Days 0-22 post-vaccination period

Number of subjects with at least one unsolicited symptom reported	20
Number of unsolicited symptoms classified by MedDRA Preferred Term*	27
Number of unsolicited symptoms reported	27

No AESI or pIMD were reported up to Day 21

The statistical analysis of selected serum biochemistry safety parameters was not available at the time of finalisation of the abridged study report. Based on a review of the available serum biochemistry data the MAH reports that no safety signal has been detected

Up to D21 there have been no SAEs, no withdrawals due to AEs and no deaths.

Conclusions and Benefit / Risk Assessment

The abridged study report describes the preliminary safety and immunogenicity results 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 have been reported according to the three pre-defined age strata with 17 subjects per stratum.

Based on the HI data three subjects, all in the 6-11 month age stratum, were seropositive at baseline (two of the three were seroprotected). The most likely (but not the only possible) explanation for their baseline serostatus is the persistence of maternal antibody. Details of the immune responses in this age group for the three seropositive subjects and the 14 seronegative subjects showed that each of these three subjects had a measurable HI response based on the shift in minimum GMT observed and all three were seroprotected at D21. Therefore, if some children in this age group still have some maternal antibody that reacts with H1N1v in HI assays they still show measurable responses to vaccination.

The CHMP highlighted that there are currently no established CHMP criteria for the interpretation of immune responses to influenza vaccines in children. It is not likely that HI titres alone can wholly explain the degree of protection observed and it is not proven that a direct extrapolation of criteria from adults to children is possible. Despite these uncertainties, all the 50 children with Day 21 HI data were "seroprotected", the seroconversion rates were at least 94% and the seroconversion factors were at least 44. The GMT was numerically but not significantly lower in the oldest age stratum but this had no detectable effect on meeting the three criteria (SPR, SCR and SCF). The reverse cumulative distributions by age cohort will be provided and compared when the MAH reports the D42 data. However, it is clear from the GMTs that the majority of children must have achieved HI titres considerably in excess of 1:40.

Thus the D21 HI data suggest that a single administration of half the adult dose may be sufficient for healthy children in the age group 6-35 months. In contrast, and as observed in older children and adults, the data with the corresponding H5N1 vaccine clearly showed that two half or full adult doses (according to age) were needed to achieve the sort of HI responses reported with a single half adult dose of H1N1v vaccine in study H1N1-009. In this regard the assessor notes that in a published study with half the adult dose of an adjuvanted seasonal influenza vaccine (Fluad) in children aged 6-35 months the seroprotection rate to the H1N1 seasonal strain after one dose was from 40-65% in various age sub-groups. There are no such data in this age group with the experimental AS03-adjuvanted seasonal influenza vaccine that might help put the results into perspective.

Despite these encouraging HI data the CHMP considers that it would be highly desirable to have the neutralising antibody data available before making a decision on the suitability of a single half-adult dose in this age group. It may be 2-3 months before such data can be generated, by which time it is very likely that the current pandemic wave will be over. Therefore if a decision to allow a single dose now based on HI data is not made then it will likely be too late to affect current practice.

Nevertheless, taking into account the few data available (N=51) and the lack of confirmation of the findings with NA data the Rapporteur is unable to recommend at this time an amendment to the dose recommendations for children aged from 6-35 months. As a result, the current recommendation for 2 x half adult doses administered at least 3 weeks apart should remain.

The safety profile of a single half adult dose of Pandemrix H1N1 appears to be generally comparable with that reported with Pandemrix H5N1 in older children (aged 3-9 years) although redness and swelling appeared to be very common in children aged 12-23 months. General symptoms were most often reported in those aged < 12 months but only one (irritability lasting one day) was of Grade 3. In addition, in a population that was not apparently given prophylactic antipyretic medication the per subject rates of any fever were < 20%, only three had a fever above 38°C and none had a fever above 39°C. Therefore the tolerability of a single half-adult dose appears to be quite acceptable.

Safety data on a second half adult dose are not yet available. Based on the H5N1 data the second dose was not notably more reactogenic than the first dose in children aged 3-5 years. Therefore the decision to allow a single half-dose in children aged 6-35 months would not be driven by any known concerns over the safety of a second dose.

Submission of the further data from this study is included in the Specific Obligations and will be dealt with in sequential assessment reports.

Finally, the CHMP considers that the plan to administer a full adult dose at D0 and D21 in this study could be difficult to justify based on current evidence. While this would mean a modification of the commitments made under the PIP the CHMP recommends that the MAH should give urgent consideration to the possibility of dropping the full adult dose administrations in this study.

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.

SPC section 4.2 -Posology and method of administration
This section was amended to highlight that the dose recommendations are based on limited data in children aged 6 months to 9 years and that no data is available in children aged less than 6 months and from 10-17 years. Furthermore, the posology sub-sections on children aged from 6 months to 3 years and on children aged 3-9 years has been merged. The combined section states now that “the available data suggest that administration of 0.25 ml of vaccine (i.e. half of the adult dose) at an elected date and a second dose administered at least three weeks later may be sufficient. There are very limited safety and immunogenicity data available on the administration of a half dose of Pandemrix (i.e. 1.875 µg HA and half the amount of AS03 adjuvant in 0.25 ml)”.

SPC section 4.4 -Special warnings and precautions for use
This section was revised to reflect as in section 4.2 that no or very limited or limted safety and immunogenicity data are available in studies with Pandemrix manufactured with H1N1 or H5N1 antigen.

SPC section 4.8 - Undesirable effects
A section was added to describe the safety data especially in Children aged 6-35 months from study H1N1-009

SPC section 5.1 Pharmacodynamic properties
This section was further revised in line with statements included in sections 4.2 and 4.2 and to include stratified data from study H1N1-009 by age group and serostatus in the proposed table.

The PL was updated accordingly.