Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemrix

Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)

Procedure No.: EMEA/H/C/000832/II/0052

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

22 September 2011
EMA/CHMP/756004/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/832/II/52

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 To update section 5.1 of the SmPC with clinical data generated in the paediatric studies D-Pan-H1N1-009, D-Pan-H1N1-010 and D-Pan-H1N1-023 at the Month 12 timepoint.
Rapporteur:	Ian Hudson
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1,2 and 5
Product Information affected:	Summary of Product Characteristics

2. Steps taken for the assessment

Step	Step date
Submission date:	23 June 2011
Start of procedure:	24 July 2011

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Step	Step date
Rapporteur's preliminary assessment report circulated on:	25 July 2011
CHMP opinion:	22 September 2011

3. Scientific discussion

3.1. Introduction

Pandemrix is an adjuvanted vaccine against influenza caused by the 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.

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) as a "mock-up vaccine" in the EU in May 2008. 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 mock-up vaccine strain composition from A/VietNam/1194/2004 H5N1-like strain (NIBRG-14) to the pandemic 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)).

During the 2009-2010 influenza pandemic, Pandemrix was the predominant pandemic vaccine used within the EU, with more than 30 million doses administered.

This variation aims to update the SmPC with new haemagglutination inhibition (HI) and serum neutralising antibody (SNA) data up to Month 12 from Studies D-Pan-H1N1-009, D-Pan-H1N1-010 and D-Pan-H1N1-023, which provided safety and immunogenicity data following primary vaccination with either a full adult dose (0.5 ml) or a half adult dose (0.25 ml) of Pandemrix when administered as a two-dose vaccination schedule in children and adolescents aged from 6 months to 17 years old.

Reactogenicity data up to post dose 2, HI and SNA antibody responses up to D42 or Month 6 (latter for study 023 only) were assessed in variations between November 2009 and December 2010 (II-24, II-28, II-32, II-33, II-42, II-43 and II-48) and are currently reflected in the Pandemrix SmPC.

The variation can be classified as follows:

Variation(s) requested		Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

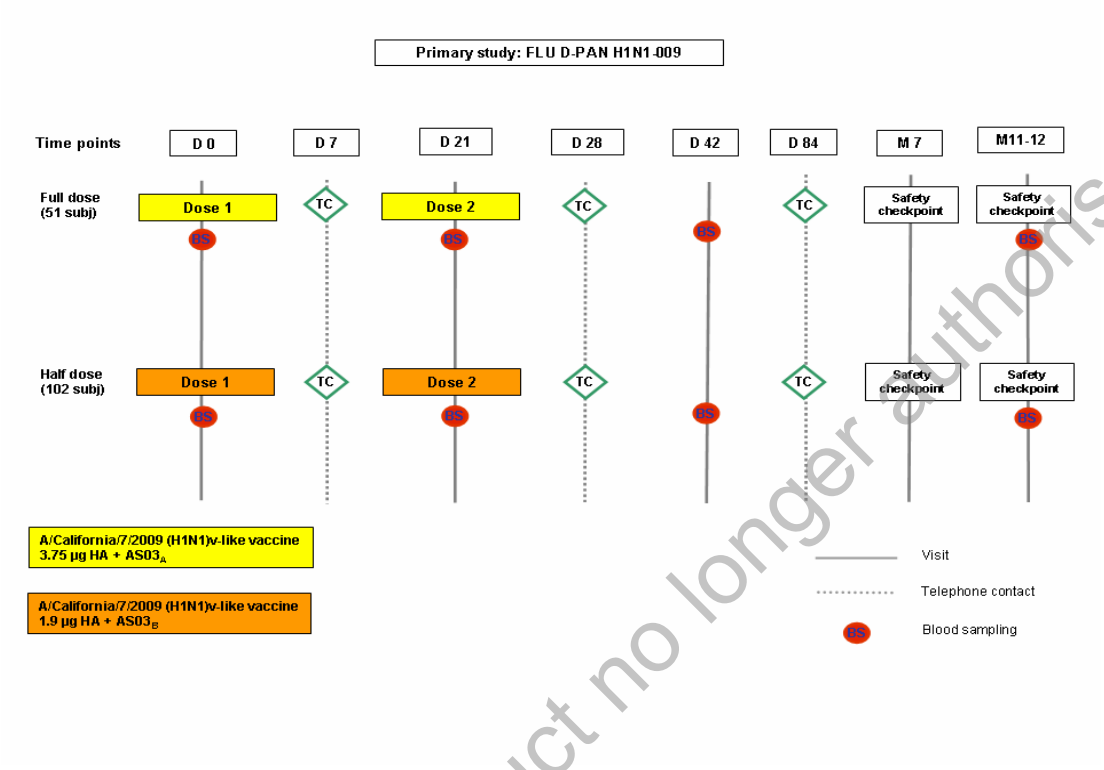
To update section 5.1 of the SmPC with clinical data generated in the paediatric studies D-Pan-H1N1-009, D-Pan-H1N1-010 and D-Pan-H1N1-023 at the Month 12 timepoint.

3.2. Clinical aspects

3.2.1 Study Design

D-Pan H1N1-009 (Children aged from 6 to 35 months)

This study was conducted in Spain. Children aged from 6-35 months received two adult doses or two half adult doses of Pandemrix administered 21 days apart as shown in the figure.



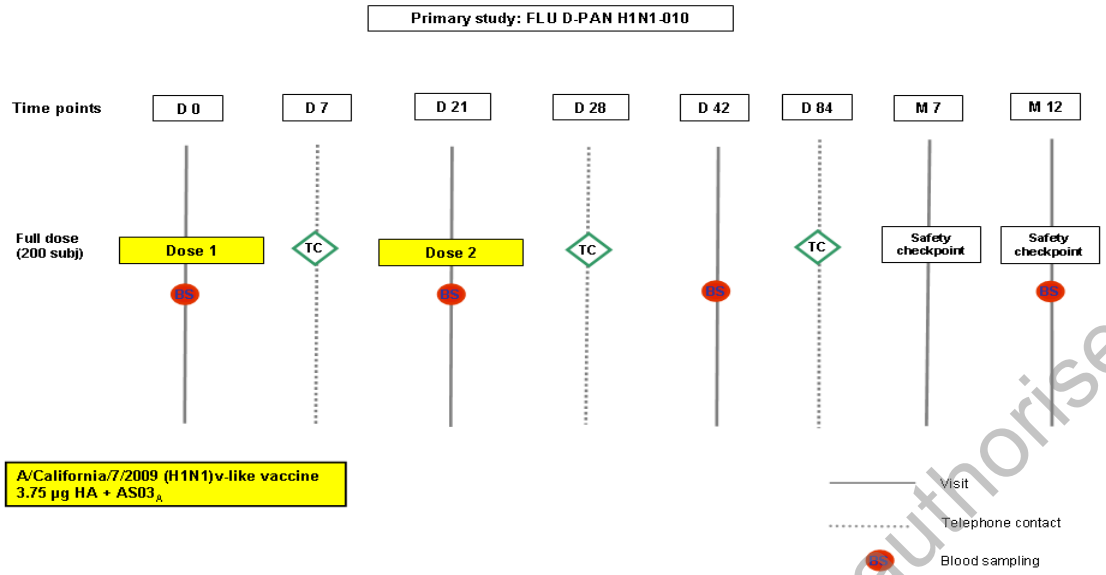
The study enrolled 157 subjects who were allocated to adult dose (3,75 microgram antigen + full dose of adjuvant ("$ASO3_A$"), Group A) or half adult dose (1.9 microgram antigen + half dose of adjuvant ("$ASO3_B$"), Group B) vaccinations. Subjects were stratified by age 6 to 11 months, 12 to 23 months and 24 to 35 months with a ratio 1:1:1. Enrolment in the full dose group was closed before completion because of an observed increased incidence of fever after the 2nd dose. Blood samples were to be drawn prior to vaccination (Day 0) and at Day 21, Day 42 and Month 11/12.

The month 12 (M12) results pertain to the following secondary objectives:

- To further evaluate immunogenicity of two doses of full or half dose Pandemrix in terms of the vaccine homologous HI titres at Month 11-12 in all subjects and per age strata.
- To describe the SNA titres at Month 11-12 in a subset of the subjects' samples.
- To describe medically attended events (MAEs), Adverse events of special interest (AESIs), potential immune-mediated diseases (pIMDs) and serious adverse events (SAEs) during the whole study period.

D-Pan-H1N1-010 (full adult dose vaccine in children aged 3-17 years)

The study was conducted in Spain. Two doses of Pandemrix were administered 21 days apart to subjects aged 3 to 17 years. The study enrolled 210 subjects who were stratified by age strata (3 to 5 years, 6 to 9 years and 10-17 years) with a ratio 1:1:2. Blood samples were to be drawn prior vaccination (Day 0) and at Day 21, Day 42 and Month 12.



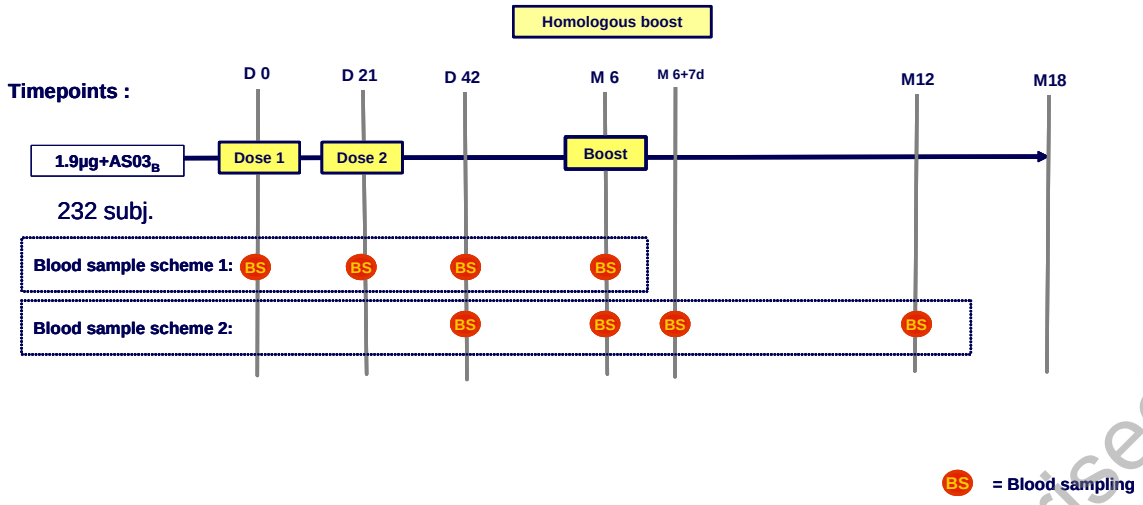
The M12 results pertain to the following secondary objectives:

- To further evaluate immunogenicity of two doses of Pandemrix in terms of the vaccine homologous HI antibody response at Month 12 in all subjects and per age strata.
- To describe the SNA response at Month 12 in a subset of subjects' samples.
- To describe MAEs, AESIs, pIMDs and SAEs during the whole study period.

D-Pan-H1N1-023 (half adult dose vaccine in children aged 3-17 years)

This study was conducted in Germany to evaluate the safety and immunogenicity of a prime-boost schedule of Pandemrix (half-dose) adjuvanted with $AS03_B$ in subjects aged 3 to 17 years. All subjects received two initial half doses of Pandemrix according to a 0, 21-day schedule. The booster dose planned at Month 6 was not given on the investigator's decision.

A total of 232 subjects were randomised (1:1) to one of the two blood sampling schedules and stratified by age (3 to 5 years, 6 to 9 years and 10 to 17 years with the ratio 1:1:2). Blood samples were to be taken at Day 0, Day 21, Day 42 and Month 6 for children allocated to the blood sampling schedule 1 (BS1) and at Day 42, Month 6, Month 6+7 days and Month 12 for children allocated to BS2. Blood samples at Month 6+7 days were not taken since no booster dose was administered.



The M12 results pertain to the following secondary objectives:

- To assess the vaccine homologous HI antibody response in terms of geometric mean titres (GMTs), seroconversion rates (SCRs), seroprotection rates (SPRs) and seroconversion factor (SCF) six months after the booster administration.
  HI antibody titres were tested at Month 12 in the BS2 group, but since the booster dose was not administered, the SCRs and SCF could not be assessed as per protocol.
- To further describe the humoral immune responses in terms of the three age strata.
- To describe the SNA titres in a subset of one third of subjects.
- To describe MAEs, AESIs, pIMDs and SAEs during the whole study period.

In view of neutralising antibody (SNA) testing the homologous neutralising activity was measured against the virus strain A/Netherlands/602/9, which is antigenically similar to the strain A/California/7/2009. A seropositive subject (in terms of SNA) is considered a subject whose reciprocal antibody titre is greater than or equal to the cut-off value of 1:8. The GMT and Vaccine Response Rate (VRR) were calculated. VRR is defined as the incidence rate of vaccinees that have either a pre-vaccination titre <1:8 and a post-vaccination titre ≥1:32 or a pre-vaccination titre ≥1:8 and at least a 4-fold increase in post-vaccination titre.

The number of subjects enrolled and vaccinated (total vaccinated cohort, TVC) and the number of subjects in the According-to-protocol (ATP) cohort for persistence at Month 12 in the three studies are shown in the table below.

TVC and ATP cohort for persistence at Month 12 (D-Pan-H1N1-009, -010 and -023

	D-Pan-H1N1-009 Group A (3.75 µg HA full dose ASO3$_A$)	**D-Pan-H1N1-009 Group B (1.9 µg HA half a dose ASO3$_B$)**	**D-Pan-H1N1-009 Total**
TVC (6-35 months)	53	104	157
ATP cohort for persistence at Month 12 (6-35 months)[a]	37	83	120

a. In study D-Pan-H1N1-009: ATP cohort for antibody kinetics at Month 11-12

	D-Pan H1N1-010 (3.75 μg HA full dose $ASO3_A$)	D-Pan H1N1-023 (1.9 μg HA half a dose $ASO3_B$), overall (BS1+BS2)	D-Pan H1N1-023 (1.9 μg HA half a dose $ASO3_B$), BS2
TVC (3-17 years)	210	244	122[b]
ATP cohort for persistence at Month 12 (3-17 years)[b]	184	87[b]	87

b. In study D-pan-H1N1-023 at Month 12, blood samples were taken only in the BS2 group

There were no major differences in demographic characteristics across the three studies other than the age ranges selected by study. The majority of the subjects (at least 89%) included in the three studies were of white-Caucasian/European heritage. Each gender represented at least 40% of the subjects at any time point analysed.

In clinical study reports (CSRs) previously submitted and assessed from this study, the Day 42 samples were tested separately to the Day 0 and Day 21 samples. Bridging testing using 40 sera from Day 0 and Day 21 gave results that met the acceptance criterion in study 023 but not in 009 (for step 1 samples) and 010. For these two studies Day 0, Day 21 and Day 42 samples were therefore retested together with the Month 12 samples and the respective results were provided within this variation. Although, as expected, some variability was observed between the results of the retest and the earlier separate testing, the HI responses were comparable to those previously presented.

The available SNA data were presented as part of variation II/048. However the number of subjects tested in the 10-17 years age group in study 023 did not meet the paediatric investigation plan (PIP) requirement that at least 30% in BS1 aged 3-9 years and 10-17 years should be tested. Therefore, additional samples were tested. The additional data provided comparable results to those in prior CSRs.

The current CSR assessed within this variation provide Month 12 HI and SNA data.

3.2.2 Results: HI

D-Pan-H1N1-009 (6-35 months)

All samples from Day 0 to Month 11-12 were tested in parallel and are presented in the analysis of antibody kinetics at Month 11-12. At the last time point all children remained HI seropositive and had titres of at least 1:40. All CHMP criteria defined for adults aged 18-60 years were still exceeded with SCRs at 97.3% for full dose recipients and 97.6% for half dose recipients and SCFs ranging from 20.6 to 56.0. GMTs decreased to values close to the post-dose 1 level.

No clear trend was observed between dose groups but there was a trend towards higher values in the youngest children in both dose groups.

D-Pan-H1N1-010 (3-17 years, full adult dose)

All samples from Day 0 to Day 42 were retested with the Month 12 samples and are presented in the analysis done on the ATP cohort for persistence at Month 12 in the table on the page above.

One year after the first dose all subjects are still seropositive and all but one subject still had a titre of at least 1:40. All CHMP criteria defined for adults aged 18-60 years were still exceeded with an overall SCR of 96.1% and a SCF of 23.7. GMTs decreased to values below the post-dose 1 level (overall, 167.3 at Month 12 versus 347.3 post-dose 1). The highest GMT was observed in the oldest age group (251.0 in the 10-17 years age category vs. 123.9 and 106.3 in the 3-5 and 6-9 years age categories).

While all CHMP criteria were still exceeded irrespective of the pre-vaccination status, the overall GMT value tended to be higher in subjects seropositive at baseline.

D-Pan-H1N1-023 (3-17 years, half adult dose)

The samples at Month 12 were tested separately from previous time points. Since no blood samples were taken at Day 0 for subjects in the BS2 group, SCR and SCF at Month 12 taking Day 0 as baseline could not be calculated.

HI at Month 12 in study D-Pan-H1N1-023 (ATP cohort for persistence at Month 12)

				≥10 1/DIL			GMT			SPR		
					95% CI			95% CI			95% CI	
Study group	**Age stratum**	**Timing**	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**
BS2	**Overall 3-17 years**	PII(M12)	87	100	95.8	100	83.3	68.0	101.9	87.4	78.5	93.5
	3-5 years	PII(M12)	20	100	83.2	100	48.5	35.7	65.7	85.0	62.1	96.8
	6-9 years	PII(M12)	26	100	86.8	100	60.5	49.2	74.3	84.6	65.1	95.6
	10-17 years	PII(M12)	41	100	91.4	100	132.8	94.9	185.8	90.2	76.9	97.3

One year after the first vaccination, all subjects in the BS2 group were still seropositive. The SPR ranged from 84.6% to 90.2% across age strata and was 87.4% overall. The highest GMT was observed in the oldest age group (132.8 for 10-17 years vs. 48.5 and 60.5 in the 3-5 years and 6-9 years age groups, respectively). The overall GMT (83.3) decreased below the value observed post-dose 1 for the BS1 group (297.9).

The neutralising antibody titres were determined in subsets of the Month 11-12 samples as described above and were tested separately from samples obtained at previous time points.

3.2.3 Results: SNA

D-Pan-H1N1-009 (6-35 months)

At Month 11-12, the neutralising antibody seropositivity rate remained at 100% in both groups (full or half adult dose) and in all age strata. The vaccine response rate (VRR) was 100% in subjects receiving the full dose vaccine. For the half-dose recipients, the overall VRR was 91.8% with a trend for an increasing VRR with increasing age (from 86.4% in the 6-11 months age group to 100% in the 24-35 months age group).

The GMT decreased from 1960.6 and 1416.1 at Day 42 to 444.4 and 312.8 at Month 11-12 in the full dose and half dose groups, respectively but still remained above the post dose 1 values. The highest GMTs at Month 11-12 were noted in the 6-11 month age stratum in both vaccine groups. Titres ≥320 were still observed in 60.9% of subjects in the full dose group and 50.0% of subjects in the half dose group at Month 11-12.

D-Pan-H1N1-010 (3-17 years, full adult dose)

At Month 12 the seropositivity rate remained 100%. The overall vaccine response rate (VRR) remained high (95.2%) with a trend for higher VRR with decreasing age (from 89.3% in the 10-17 years age group to 100% in the 3-5 years age group).

At Month 12, the GMTs had decreased from 847.2 at Day 42 to 172.0 overall, and were close to (in the 6-9 and 10-17 years age strata) or even higher than (in the 3-5 years age strata) the post-dose 1 values. Titres ≥320 were observed in 20.7% of subjects, with a trend for higher percentage with decreasing age (from 7.1%. in the 10-17 years age group to 37.0% in the 3-5 years age group).

D-Pan-H1N1-023 (3-17 years, half adult dose)

At Month 12 the neutralising antibody response was tested only for subjects of group BS2, for which no data were available at Day 0 and Day 21 since no blood sample were taken. The VRR was thus not calculated.

Similarly to the observations made in D-Pan-H1N1-009 and -010, all subjects were seropositive at Month 12 but the GMTs had decreased from 289.1 at Day 42 to 139.5.

3.2.4 Clinical safety

In total, 1209 doses of H1N1/AS03 have been administered to 611 subjects in the Month 7 evaluation of safety, including 520 adult doses and 689 half adult doses.

Number of doses of H1N1/AS03 in studies D-Pan-H1N1-009, -010 and -023

Study	Age group	Schedule	Number of AS03-adjuvanted D-Pan H1N1 vaccine doses evaluated for reactogenicity	
			3.75µg HA $AS03_A$	1.9µg HA $AS03_B$
D-Pan-H1N1-009	6-35 months	0, 21 days	105	208
D-Pan-H1N1-010	3-17 yrs	0, 21 days	415	-
D-Pan-H1N1-023	3-17 yrs	0, 21 days	-	481
Total for each HA /AS03 dose			520	689
Total for AS03 adjuvanted H1N1 vaccine			1209	

In D-Pan-H1N1-009 in children aged 6-35 months, 84.9% of subjects in the full dose group and 90.4% in the half dose group experienced at least one MAE up to Month 12. Up to 100% of children aged 6-11 months and 90.0% aged 12-23 months reported at least one MAE versus 64.7% of those aged 24-35 months. In the half dose group the respective MAE incidences were 97.1%, 82.4% and 91.4% in the 3 age categories.

In D-Pan-H1N1-010 in subjects aged 3-17 years, 42.9% experienced at least one MAE up to Month 12. The incidence of MAEs was higher in those aged 3-5 years (67.9%) than in the older age categories (36.8% in 6-9 years and 33.0% in 10-17 years).

In D-Pan-H1N1-023 in subjects aged 3-17 years, 63.1% and 60.7% in BS1 and BS2 respectively experienced at least one MAE up to Month 12. The incidences of MAEs tended to be higher in those aged 3-5 years (71.0%-80.0%) compared to older subjects (61.3%-47.1% for 6-9 years and 60.0%-58.6% for 10-17 years age groups).

In D-Pan-H1N1-009 and -010, the most frequently reported MAE during the entire study period was upper respiratory tract infection (41.5% and 51.0% respectively in the full dose and half dose groups in study D-Pan-H1N1-009; 7.6% in study D-Pan-H1N1-010). The most frequently reported MAEs in study D-Pan-H1N1-023 were cough (8.2%) in group BS1 and bronchitis (9.8%) in group BS2.

No fatality was reported up to Month 12.

Up to Month 12, a total of 20 SAEs were reported for 16 subjects in the three studies. None of these SAEs was considered by the investigators as causally related to vaccination.

No AESIs or pIMDs were reported up to Month 7 in the three studies and there were no SAEs leading to premature discontinuation. There were three non-serious AEs that led to premature withdrawal from D-Pan-H1N1-023. These concerned urticaria (parents and investigator's decision), pain (parents' decision) and tonsillo-pharyngitis (investigator's decision).

Changes to the Product Information

The detailed changes can be found in the final approved highlighted SmPC attached to this report.

Overall, the CHMP agreed that the 12 month persistence data from these trials were important to be mentioned in the SmPC, also considering the previous inclusion of similar data generated in adults in the SmPC.

Further to the assessment and the scientific discussions held at the CHMP, minor editorial amendments in section 5.1 of the SmPC were requested by the CHMP and subsequently implemented by the MAH.

Conclusions and Benefit / Risk Assessment

The additional data to M12 indicate that HI and SNA titres remained substantial despite the expected decreases in GMTs. While comparisons across these studies require caution, the new data do not show or suggest a consistent benefit for full vs. half adult doses across the age range 6 months to 17 years.

As a benchmark only, the HI data showed that the CHMP criteria were still all met at M12.

The additional safety data do not suggest any new issues.

Taking together the available data on immunogenicity and safety at the 12 month timepoint from these studies, the CHMP agreed that the benefit-risk profile of Pandemrix remains positive.

4. Conclusion

On 22 September 2011 the CHMP considered the following variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics.