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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Pandemrix

(H1N1 influenza vaccine)

Procedure No: EMEA/H/C/000832

P46 102 and 103

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

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1. ASSESSMENT

Introduction

This report covers the submission of the following data from two paediatric studies in accordance with Article 46 of Regulation (EC) No. 1901/2006:

Article 46 submission of study **D-Pan-H1N1-025** (not part of any FUM): **P46 102**
Safety and immunogenicity study of GSK Biologicals' pandemic influenza candidate vaccine (GSK2340272A) in children aged 3 to 9 years

Article 46 submission of study Q**-Pan-H1N1-045** (not part of any FUM): **P46 103**
Safety and immunogenicity study of GSK Biologicals' A/California/7/2009 (H1N1)v-like vaccines GSK2340274A and GSK234074A in children 3 to less than 10 years old

The current submissions each consist of:

- A cover letter
- A short critical expert overview
- For Q-Pan H1N1-045 a statement regarding conduct of studies outside of the EU
- Study reports on D-Pan H1N1-025 and Q-Pan H1N1-045 (details of study dates and report dates are provided below)

In each case the MAH states in the cover letter that, in accordance with Article 16 (2) of Regulation No. 726/2004, the new data do not require any further regulatory action, including update of the prescribing information.

Assessment

D-Pan-H1N1-025

There are two full reports on this study that commenced 7 December 2009:

- The first is dated 7 July 2011 and covers data to M7 with a data lock 29 June 2011
- The second is dated 8 July 2011 and covers safety and effectiveness to M12 with a data lock 29 June 2011.

The study was conducted at 3 sites in the Czech Republic using full and half adult doses of D-Pan H1N1. To overcome relatively low HA yields in the production of the H1N1v antigen the Company wished to investigate the impact of applying a modified manufacturing process in which the concentration of octoxynol-10 was raised from 13-17 µg/ml to 60-103 µg/ml. However, due to the perception of a decreased pandemic threat recruitment in this study was much slower than expected and 60 of the planned 300 subjects were enrolled. Meanwhile the vaccine lot used in group C expired and so the Company decided to stop recruitment.

This was a randomised, observer-blind study in subjects aged 3 to 9 years who were to be allocated to three vaccine groups with a ratio of 1:1:1 as follows:

- Group A (AS03 group): new process vaccine containing 3.75 µg HA/AS03A on D0 and D21
- Group B (AS03/2 group): new process vaccine containing 1.9 µg HA/AS03B on D0 and D21
- Group C (H1N1 group): non-adjuvanted H1N1 containing 15 µg of HA on D0 and D21 (initial manufacturing process).

The Co- Primary Objectives were to evaluate whether the full and half dose new process adjuvanted vaccine elicited immune responses that exceeded the CHMP criteria applied to adults.

Results

There were 60 subjects enrolled of which 58 completed. The ATP-I cohort at M7 included 34 subjects (13 in the AS03 group, 9 in the AS03/2 group and 12 in the H1N1 group). The mean age of the M7 cohort was 6.9 years. The overall male-female distribution was 61.8% versus 38.2%.

The pre-vaccination seropositivity rates were 33-50%. At D21 the CHMP criteria were already met in the adjuvanted and non-adjuvanted vaccine groups. The GMTs increased further with the

administration of the second dose. At M7 all CHMP criteria were met in each group and for all age strata.

Synopsis Table 1: H1N1 HI Antibodies against Flu A/CAL/7/09 H1N1.HA Antibodies (ATP cohort for immunogenicity up to Month 7)

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
AS03: Overall																
PRE	13	46.2	19.2	74.9	14.9	6.9	32.0	46.2	19.2	74.9	-	-	-	-	-	-
PI(D21)	13	100	75.3	100	429.1	268.9	684.6	100	75.3	100	100	75.3	100	28.8	16.4	50.5
PII(D42)	13	100	75.3	100	954.6	730.0	1248.4	100	75.3	100	100	75.3	100	64.0	25.9	158.2
PII(M7)	13	100	75.3	100	155.9	104.1	233.6	100	75.3	100	92.3	64.0	99.8	10.5	6.0	18.3
AS03: 3-5 years stratum																
PRE	4	50.0	6.8	93.2	18.3	1.5	219.1	50.0	6.8	93.2	-	-	-	-	-	-
PI(D21)	4	100	39.8	100	293.4	60.2	1430.2	100	39.8	100	100	39.8	100	16.0	3.4	76.1
PII(D42)	4	100	39.8	100	987.0	347.5	2803.4	100	39.8	100	100	39.8	100	53.8	2.6	1121.7
PII(M7)	4	100	39.8	100	160.3	49.0	524.4	100	39.8	100	75.0	19.4	99.4	8.7	1.7	45.4
AS03: 6-9 years stratum																
PRE	9	44.4	13.7	78.8	13.6	5.4	34.4	44.4	13.7	78.8	-	-	-	-	-	-
PI(D21)	9	100	66.4	100	508.0	308.6	836.3	100	66.4	100	100	66.4	100	37.3	19.7	70.8
PII(D42)	9	100	66.4	100	940.6	710.3	1245.5	100	66.4	100	100	66.4	100	69.1	23.5	203.6
PII(M7)	9	100	66.4	100	154.0	91.4	259.7	100	66.4	100	100	66.4	100	11.3	5.5	23.2

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
AS03/2: Overall																
PRE	9	33.3	7.5	70.1	11.7	4.2	32.1	22.2	2.8	60.0	-	-	-	-	-	-
PI(D21)	9	100	66.4	100	285.3	137.7	591.1	100	66.4	100	88.9	51.8	99.7	24.5	10.0	59.7
PII(D42)	9	100	66.4	100	838.1	647.0	1085.5	100	66.4	100	100	66.4	100	71.9	24.4	212.1
PII(M7)	9	100	66.4	100	108.7	61.2	192.9	88.9	51.8	99.7	77.8	40.0	97.2	9.3	3.6	23.9
AS03/2: 3-5 years stratum																
PRE	1	0.0	0.0	97.5	5.0	-	-	0.0	0.0	97.5	-	-	-	-	-	-
PI(D21)	1	100	2.5	100	160.0	-	-	100	2.5	100	100	2.5	100	32.0	.	.
PII(D42)	1	100	2.5	100	1280.0	-	-	100	2.5	100	100	2.5	100	256.0	.	.
PII(M7)	1	100	2.5	100	160.0	-	-	100	2.5	100	100	2.5	100	32.0	.	.
AS03/2: 6-9 years stratum																
PRE	8	37.5	8.5	75.5	13.0	4.1	40.7	25.0	3.2	65.1	-	-	-	-	-	-
PI(D21)	8	100	63.1	100	306.7	134.5	699.4	100	63.1	100	87.5	47.3	99.7	23.7	8.4	66.5
PII(D42)	8	100	63.1	100	794.8	609.7	1036.2	100	63.1	100	100	63.1	100	61.4	18.8	200.4
PII(M7)	8	100	63.1	100	103.6	53.8	199.3	87.5	47.3	99.7	75.0	34.9	96.8	8.0	2.9	22.1
H1N1: Overall																
PRE	12	33.3	9.9	65.1	8.9	4.9	16.2	16.7	2.1	48.4	-	-	-	-	-	-
PI(D21)	12	100	73.5	100	123.2	40.5	374.9	75.0	42.8	94.5	75.0	42.8	94.5	13.8	7.2	26.5
PII(D42)	12	100	73.5	100	359.1	219.8	586.9	100	73.5	100	100	73.5	100	40.3	27.0	60.3
PII(M7)	12	100	73.5	100	84.8	53.7	134.1	91.7	61.5	99.8	83.3	51.6	97.9	9.5	5.9	15.3
H1N1: 3-5 years stratum																
PRE	3	0.0	0.0	70.8	5.0	5.0	5.0	0.0	0.0	70.8	-	-	-	-	-	-
PI(D21)	3	100	29.2	100	90.0	33.7	240.0	100	29.2	100	100	29.2	100	18.0	6.7	48.0
PII(D42)	3	100	29.2	100	359.3	218.3	591.5	100	29.2	100	100	29.2	100	71.9	43.7	118.3
PII(M7)	3	100	29.2	100	71.5	11.9	427.6	100	29.2	100	100	29.2	100	14.3	2.4	85.5
H1N1: 6-9 years stratum																
PRE	9	44.4	13.7	78.8	10.8	4.9	23.7	22.2	2.8	60.0	-	-	-	-	-	-
PI(D21)	9	100	66.4	100	136.8	28.7	652.5	66.7	29.9	92.5	66.7	29.9	92.5	12.7	5.2	31.0
PII(D42)	9	100	66.4	100	359.1	179.7	717.6	100	66.4	100	100	66.4	100	33.3	20.8	53.2
PII(M7)	9	100	66.4	100	89.8	50.3	160.5	88.9	51.8	99.7	77.8	40.0	97.2	8.3	4.7	14.7

In the ATP cohort for analysis of effectiveness, percentage of subjects with occurrence of RT-PCR confirmed H1N1 influenza was 33.3% (one subject; onset of ILI on Day 42) in the AS03 group, 14.3% (one subject; onset of ILI on Day 42) in the AS03/2 group and 20.0% (one subject; onset of ILI on Day 42) in the H1N1 group. Results from the one dose and two dose ATP cohort for analysis of effectiveness are consistent with those obtained for the ATP cohort for analysis of effectiveness.

The incidence of subjects with any symptoms (solicited and unsolicited) during the 7-day follow-up period after vaccination was 100% in the AS03 group, 95.0% in the AS03/2 group and 94.4% in the H1N1 group.

Pain at the injection site was the most frequently reported solicited adverse event for the AS03 and AS03/2 groups (overall incidence per dose of 90.0% and 75.0%, respectively). Redness and pain at the injection site were the most frequently reported solicited adverse event for the H1N1 group (overall incidence per dose 36.1% for redness and 33.3% for pain at the injection site).

In the 3-5 years age stratum, the most frequently reported solicited general symptoms (overall incidence per dose) were drowsiness (28.6%), irritability (21.4%), and loss of appetite (21.4%) in the AS03 group; irritability (30.0%) and drowsiness (20.0%) in the AS03/2 group; and drowsiness (41.7%) in the H1N1 group. Two subjects in the AS03 group experienced grade 3 fever after the first dose administration.

In the 6-9 years age stratum, the most frequently reported solicited general symptoms (overall incidence per dose) were headache (50.0%), fatigue (42.3%), and gastrointestinal symptoms (26.9%)

in the AS03 group; headache (46.7%), fatigue (40.0%) and gastrointestinal symptoms (16.7%) in the AS03/2 group; fatigue (37.5%), headache (20.8%) and gastrointestinal symptoms (8.3%) in the H1N1 group. No grade 3 fever was reported.

Up to Month 7, 13 unsolicited symptoms were reported, 6 were reported by 3 subjects from the AS03 group, 2 by 2 subjects in AS03/2 group and 5 by 4 subjects in H1N1 group. All reported events were commonly observed in children of this age. Events reported by more than one subject were rhinitis, otitis media, and nasopharyngitis. One AE (vomiting) considered as related to vaccination by the investigator and one grade 3 AE (tonsillitis) considered as unrelated were reported in the AS03 group.

Also, three SAEs (viral infection, muscle injury, adenoid vegetation) were reported for 2 subjects who received the adjuvanted vaccine. None of them were considered as related to vaccination and all resolved by the end of the reporting period. There were no AEs leading to withdrawal. One subject reported one AE of special interest (epilepsy) that was not serious and not considered as related to vaccination. No adverse events of specific interest or potential immune-mediated diseases were reported up to M7.

At D182 the mean age of subjects followed up was 6.4 years and the male-female distribution was 65.5% versus 34.5%. Six SAEs had been reported by 4 subjects but none was considered to be related to vaccination by the investigator and all subjects recovered. Three subjects experienced AEs of special interest (epilepsy, syncope and urticaria) but none was considered to be related to vaccination by the investigator. No AESIs/ pIMDs were reported during the entire study.

Unsolicited MAEs were reported by 15 subjects (75.0%), 16 subjects (80.0%) and 16 subjects (88.9%) of the AS03 group, AS03/2 group and H1N1 group, respectively. The most frequently reported unsolicited AEs with MAEs were nasopharyngitis, tonsillitis, pharyngitis, and rhinitis.

Q-Pan-H1N1-045

There are two synoptic study reports that provide data to D21 and D182.

The study was conducted in Thailand and the Philippines between 25 July 2010 and 31 January 2011 (D182 completion date). D21 was completed 23 August 2010 and the data lock was on 22 September 2010. The data lock for the D182 report was 7 April 2011.

This was a randomised, observer-blind (all groups, both epochs), parallel-group, multi-centre study of safety and immunogenicity in children aged 3 to <10 years of age. Subjects were randomised to receive one of three regimens with an aim to achieve approximately equal distribution across the two age strata (3 to <6 years; 6 to <10 years) as follows:

- Q25ASB - 69 subjects to receive one dose of 0.9 µg Q-Pan + AS03B at Day 0
- D25ASB - 69 subjects to receive one dose of 0.9 µg D-Pan + AS03B at Day 0
- Q50ASB – 53 subjects to receive one dose of 1.9 µg Q-Pan + AS03B at Day 0

Blood samples from all subjects were to be taken on Days 0, 21 and 182 for immunogenicity assessment.

The study had the following co-primary objectives:

- To assess whether Q25ASB results in an immune response to the vaccine-homologous virus at D21 that meets or exceeds the CBER and CHMP criteria applied to adults
- To assess whether D25ASB results in an immune response to the vaccine-homologous virus at D21 that meets or exceeds CBER and CHMP criteria applied to adults

The study also had the following secondary objectives:

- To demonstrate immunological equivalence between Q25ASB and D25ASB at D21 based on a GMT ratio (Q-Pan vs. D-Pan) for which the 2-sided 95% confidence limits was within 0.5 to 2.0.
- To describe the immunogenicity of Q50ASB at D21
- To describe HI data at d182
- To evaluate safety and reactogenicity up to D182

Results

Enrolment (209) slightly exceeded the target of 191 subjects to provide at least 180 evaluable subjects. All 209 subjects completed the study through the Day 182 visit. At D21, all 209 subjects were included in the ATP-I cohort. At D182, a total of 205 subjects (98.1%) were included in the ATP-I cohort.

Subject disposition at the Day 182 visit

Synopsis Table 1: Subject enrollment and disposition at Study Day 182

	Total		Q25ASB	D25ASB	Q50ASB
	n	%	n	n	n
Total cohort	209	-	76	75	58
Total vaccinated cohort	209	100	76	75	58
ATP cohort for safety at Day 182	208	99.5	76	74	58
ATP cohort for immunogenicity at Day182	205	98.1	73	74	58
Completed through Day 182	209	100	76	75	58

At D182, the ATP-I cohort consisted of approximately 45% females and 55% males overall. The mean age of subjects in the ATP-I cohort was 6.0 years overall (range 3 to 9 years). All subjects completed the Day 182 visit and therefore the demographics at baseline were the same as for D21 and as follows:

Synopsis Table 1: Key demographics (TVC)									
		Q25ASB N = 76		D25ASB N = 75		Q50ASB N = 58		Total N = 209	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	6.0	-	6.0	-	6.0	-	6.0	-
	SD	2.03	-	2.02	-	2.00	-	2.01	-
Gender	Female	30	39.5	38	50.7	27	46.6	95	45.5
	Male	46	60.5	37	49.3	31	53.4	114	54.5
Height (cm)	Mean	113.6	-	113.5	-	115.1	-	114.0	-
	SD	13.18	-	12.15	-	13.26	-	12.80	-
Weight (kg)	Mean	21.0	-	21.3	-	22.0	-	21.4	-
	SD	6.68	-	6.69	-	8.39	-	7.17	-
BMI (kg/m²)	Mean	15.9	-	16.2	-	16.1	-	16.1	-
	SD	2.59	-	2.66	-	2.95	-	2.71	-
Q25ASB = Recipients of Quebec manufactured H1N1 vaccine (0.9 µg HA) + $AS03_B$ D25ASB = Recipients of Dresden manufactured H1N1 vaccine (0.9 µg HA) + $AS03_B$ Q50ASB = Recipients of Quebec manufactured H1N1 vaccine (1.9 µg HA) + $AS03_B$									

The seropositivity rates at D0 were high, at 56.6% for the Q25ASB group, 56.0% for the D25ASB group and 41.4% for the Q50ASB group, increasing to 100% at D21.

At D21 the co-primary objectives for the study were met with SCR and SPR at 98.7% in the Q25ASB and D25ASB groups and GMFRs of 25.7 and 27.1, respectively. The CBER criteria were exceeded at D21 in both treatment groups. The adjusted GMT ratio was 0.96 (based on adjusted GMTs of 432.1 and 450.9) with 95% CIs of 0.73 and 1.26.

In subjects receiving the standard paediatric (i.e. half-adult) dose all CHMP and CBER criteria were exceeded at D21. The HI GMTs at D21 were comparable across the three groups (418.8 to 448.6).

Synopsis Table 2: Key HI A/California antibody response parameters at Day 21 (ATP-I)												
Timing	SCR			SPR			GMFR			GMT		
		95% CI			95% CI			95% CI			95% CI	
	%*	LL	UL	%**	LL	UL	value	LL	UL	value	LL	UL
Q25ASB												
Day 21	98.7	92.9	100	98.7	92.9	100	25.7	20.7	32.0	448.6	323.9	621.3
D25ASB												
Day 21	98.7	92.8	100	98.7	92.8	100	27.1	22.4	32.8	434.1	321.0	587.0
Q50ASB												
Day 21	98.3	90.8	100	98.3	90.8	100	32.2	24.7	42.0	418.8	297.6	589.1

Synopsis Table 3: Adjusted ratios of A/California antibody GMTs at Day 21(ATP-I)						
				Adjusted GMT ratio (Q25ASB / D25ASB)		
Q25ASB		D25ASB			95% CI	
N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
76	432.1	75	450.9	0.96	0.73	1.26
Adjusted GMT = geometric mean antibody titre adjusted for Age (Y), baseline titre						

At D182 the three treatment groups continued to meet the CHMP targets and the CBER guidance target for seroconversion. The D25ASB group continued to meet the CBER guidance target for seroprotection rate at D182 but this was not met by the other groups. GMTs were comparable across groups at D182.

Synopsis Table 3: Key HI A/California antibody response parameters at Day 182 (ATP-I)

Timing	SCR			SPR			GMFR			GMT		
		95% CI			95% CI			95% CI			95% CI	
	%*	LL	UL	%**	LL	UL	value	LL	UL	value	LL	UL
Q25ASB												
Day 182	63.0	50.9	74.0	75.3	63.9	84.7	6.6	5.4	8.2	117.4	84.5	163.1
D25ASB												
Day 182	71.6	59.9	81.5	85.1	75.0	92.3	8.0	6.4	10.1	128.3	95.8	171.9
Q50ASB												
Day 182	69.0	55.5	80.5	79.3	66.6	88.8	8.9	6.8	11.7	115.7	80.7	166.0

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
* Percentage of seroconverted subjects
** Percentage of seroprotected subjects (HI titer >= 40 1/DIL)
GMFR = Fold increase in serum HI GMTs post-vaccination
GMT = geometric mean antibody titer calculated on all subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

See the tables on the following pages for details of the D21 safety data:

After the vaccination injection site pain was the most common solicited local symptom reported for each of the three treatment groups and in both age strata (3 to <6 years and 6 to <10 years).

The most common solicited general symptoms reported in subjects 3 to <6 years of age were fever (6.1%, 16.1% and 20.8%, respectively) and loss of appetite (18.2%, 12.9% and 4.2%, respectively). No fever > 40.0°C was reported. Among subjects 6 to <10 years of age, the most commonly reported solicited general symptoms were headache (17.1%, 20.5% and 12.1%, respectively) and muscle aches (14.6%, 15.9% and 15.2%, respectively).

At least one unsolicited symptom was reported by 28.9% of subjects in the Q25ASB group and by 28% in the D25ASB group compared to 8.6% in the Q50ASB group.

At least one MAE through D21 was reported for 18.4%, 12% and 1.7% of subjects in the Q25ASB, D25ASB and Q50ASB groups, respectively. The most commonly reported MAE was upper respiratory tract infection, occurring in 3 (3.9%) of Q25ASB subjects, 4 (5.3%) D25ASB subjects and in one Q50ASB subject.

No SAEs, pIMDs or withdrawals due to AEs were reported from Day 0 to Day 21.

Synopsis Table 4: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (TVC)				
		Group Q25ASB		Total
Local Symptom	Type	3y - <6y N = 33	6y - <10y N = 43	N = 76
Pain, n (%)	All	16 (48.5)	25 (58.1)	41 (53.9)
	Grade 3	0	3 (7.0)	3 (3.9)
Redness, n (%)	All	0	0	0
	> 100 mm (Grade 3)	0	0	0
Swelling, n (%)	All	1 (3.0)	0	1 (1.3)
	> 100 mm (Grade 3)	0	0	0
		Group D25ASB		Total
Local Symptom	Type	3y - <6y N = 31	6y - <10y N = 44	N = 75
Pain, n (%)	All	18 (58.1)	23 (52.3)	41 (54.7)
	Grade 3	0	0	0
Redness, n (%)	All	0	1	1
	> 100 mm (Grade 3)	0	0	0
Swelling, n (%)	All	1 (3.2)	4 (9.1)	5 (6.7)
	> 100 mm (Grade 3)	0	0	0
		Group Q50ASB		Total
Local Symptom	Type	3y - <6y N = 24	6y - <10y N = 34	N = 58
Pain, n (%)	All	7 (29.2)	16 (47.1)	23 (39.7)
	Grade 3	0	0	0
Redness, n (%)	All	0	0	0
	> 100 mm (Grade 3)	0	0	0
Swelling, n (%)	All	0	1 (2.9)	1 (1.7)
	> 100 mm (Grade 3)	0	0	0

Synopsis Table 5: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period in subjects aged 3 years to <6 years (TVC)				
		Group Q25ASB	Group D25ASB	Group Q50ASB
General Symptom	Type	N = 33	N = 31	N = 24
Drowsiness, n (%)	All	5 (15.2)	3 (9.7)	1 (4.2)
	Grade 3	0	0	0
Irritability, n (%)	All	2 (6.1)	7 (22.6)	1 (4.2)
	Grade 3	0	0	0
Loss of appetite, n (%)	All	6 (18.2)	4 (12.9)	1 (4.2)
	Grade 3	1 (3.0)	1 (3.2)	0
Temperature (Axillary), n (%)	Any ≥38.0°C	2 (6.1)	5 (16.1)	5 (20.8)
	≥ 39°C (≥ Gr 3)	1 (3.0)	2 (6.5)	1 (4.2)

Synopsis Table 6: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period in subjects aged 6 years to <10 years (TVC)				
		Group Q25ASB	Group D25ASB	Group Q50ASB
General Symptom	Type	N = 41	N = 44	N = 33
Fatigue, n (%)	All	4 (9.8)	3 (6.8)	2 (6.1)
	Grade 3	1 (2.4)	0	0
Gastrointestinal, n (%)	All	2 (4.9)	1 (2.3)	0
	Grade 3	1 (2.4)	0	0
Headache, n (%)	All	7 (17.1)	9 (20.5)	4 (12.1)
	Grade 3	1 (2.4)	0	0
Joint Pain, n (%)	All	5 (12.2)	1 (2.3)	4 (12.1)
	Grade 3	1 (2.4)	0	0
Muscle Aches, n (%)	All	6 (14.6)	7 (15.9)	5 (15.2)
	Grade 3	0	0	0
Shivering, n (%)	All	4 (9.8)	2 (4.5)	0
	Grade 3	1 (2.4)	0	0
Sweating, n (%)	All	2 (4.9)	1 (2.3)	0
	Grade 3	1 (2.4)	0	0
Temperature (Axillary), n (%)	Any ≥ 38.0°C	4 (9.8)	0	0
	≥ 39°C (≥ Gr 3)	1 (2.4)	0	0

Synopsis Table 7: Percentage of subjects reporting unsolicited AEs by MedDRA Preferred Term within the 21-day (Days 0-20) post-vaccination period (TVC)						
	Q25ASB					
	3y - <6y N = 33		6y - <10y N = 43		Total N = 76	
Preferred Term	n	%	n	%	n	%
At least one symptom	12	36.4	10	23.3	22	28.9
Conjunctivitis	1	3.0	0	0.0	1	1.3
Vomiting	1	3.0	0	0.0	1	1.3
Pyrexia	1	3.0	1	2.3	2	2.6
Gastroenteritis	1	3.0	0	0.0	1	1.3
Nasopharyngitis	3	9.1	2	4.7	5	6.6
Otitis media	1	3.0	0	0.0	1	1.3
Pneumonia	1	3.0	0	0.0	1	1.3
Pneumonia viral	0	0.0	1	2.3	1	1.3
Rhinitis	1	3.0	3	7.0	4	5.3
Upper respiratory tract infection	3	9.1	2	4.7	5	6.6
Viral infection	1	3.0	0	0.0	1	1.3
Headache	1	3.0	0	0.0	1	1.3
Cough	1	3.0	1	2.3	2	2.6
Epistaxis	1	3.0	0	0.0	1	1.3
Rhinorrhoea	1	3.0	0	0.0	1	1.3
Pruritus	0	0.0	1	2.3	1	1.3

	D25ASB					
	3y - <6y N = 31		6y - <10y N = 44		Total N = 75	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
At least one symptom	13	41.9	8	18.2	21	28.0
Conjunctivitis	1	3.2	0	0.0	1	1.3
Eye pain	0	0.0	1	2.3	1	1.3
Injection site induration	0	0.0	1	2.3	1	1.3
Pyrexia	3	9.7	3	6.8	6	8.0
Gastroenteritis	1	3.2	0	0.0	1	1.3
Influenza	0	0.0	1	2.3	1	1.3
Nasopharyngitis	1	3.2	0	0.0	1	1.3
Rhinitis	2	6.5	0	0.0	2	2.7
Upper respiratory tract infection	4	12.9	1	2.3	5	6.7
Urinary tract infection	1	3.2	0	0.0	1	1.3
Varicella	1	3.2	0	0.0	1	1.3
Burns first degree	0	0.0	1	2.3	1	1.3
Excoriation	1	3.2	0	0.0	1	1.3
Cough	1	3.2	0	0.0	1	1.3
Urticaria	1	3.2	0	0.0	1	1.3

	Q50ASB					
	3y - <6y N = 24		6y - <10y N = 34		Total N = 58	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
At least one symptom	1	4.2	4	11.8	5	8.6
Toothache	0	0.0	1	2.9	1	1.7
Pyrexia	0	0.0	1	2.9	1	1.7
Nasopharyngitis	0	0.0	2	5.9	2	3.4
Upper respiratory tract infection	1	4.2	0	0.0	1	1.7
Cough	0	0.0	1	2.9	1	1.7

Up to D42 at least one unsolicited symptom was reported by 36.8% of subjects in the Q25ASB group, 37.3% of in the D25ASB group and 39.7% in the Q50ASB group (see table below). There were no AEs of grade 3 intensity reported and only 4 AEs considered by the investigator to be causally related to vaccination: 2 in Q25ASB subjects and 2 in D25ASB subjects.

Up to D182 unsolicited symptoms requiring a medically attended visit were reported by 38.2%, 38.7% and 31.0% per group. The most commonly reported MAE was upper respiratory tract infection, occurring in 7 (9.2%) of Q25ASB subjects, 8 (10.7%) of D25ASB subjects and in 5 (8.6%) of Q50ASB subjects.

Two SAEs were reported during the 182-day post-vaccination period: dengue hemorrhagic fever and Type B influenza. Both events resolved before the end of the study and both were considered by the investigator to be unrelated to study vaccine. No pIMDs were reported during the 182-day post-vaccination period.

Synopsis Table 4: Most frequently reported unsolicited AEs (≥5.0% per treatment group total) by MedDRA Preferred Term within the 42-day (Days 0-41) post-vaccination period (TVC)

	Q25ASB					
	3y - <6y N = 33		6y - <10y N = 43		Total N = 76	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
At least one symptom	16	48.5	12	27.9	28	36.8
Nasopharyngitis	5	15.2	2	4.7	7	9.2
Upper respiratory tract infection	4	12.1	2	4.7	6	7.9
Rhinitis	2	6.1	3	7.0	5	6.6
Pyrexia	3	9.1	1	2.3	4	5.3

	D25ASB					
	3y - <6y N = 31		6y - <10y N = 44		Total N = 75	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
At least one symptom	16	51.6	12	27.3	28	37.3
Pyrexia	4	12.9	5	11.4	9	12.0
Upper respiratory tract infection	4	12.9	2	4.5	6	8.0
Nasopharyngitis	3	9.7	2	4.5	5	6.7
Cough	3	9.7	1	2.3	4	5.3

	Q50ASB					
	3y - <6y N = 24		6y - <10y N = 34		Total N = 58	
Preferred Term						
At least one symptom	12	50	11	32.4	23	39.7
Pyrexia	2	8.3	4	11.8	6	10.3
Nasopharyngitis	3	12.5	2	5.9	5	8.6
Conjunctivitis	1	4.2	2	5.9	3	5.2
Cough	1	4.2	2	5.9	3	5.2
Upper respiratory tract infection	2	8.3	1	2.9	3	5.2

n/% = number/percentage of subjects reporting at least once the symptom.

2. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

D-Pan H1N1-025 provides limited information due to the small numbers enrolled. However, there were no unexpected immunogenicity and safety findings in this study

Q-Pan H1N1-045 is of particular interest since it retrospectively provides information on the likely sufficiency of single half adult doses of AS03 when combined with a quarter of the adult dose of HA and suggested that in fact a single dose of only a quarter of the HA could be used with AS03B. It is also of interest that the pre-vaccination seropositivity rates (using the MAH's rather sensitive HI) were high and actually not so very different between these and the Czech children of the same age range in study 025.

Both studies demonstrated the expected safety profile. It was notable in 045 that a quarter of the HA dose behaved similarly to half the adult HA dose, again indicating the major role of the adjuvant. The rates of all and high grade fevers were not unexpected in this age group.

The assessor concurs with the MAH that these additional data do not have implications for the Pandemrix SmPC.