

18 November 2014 EMA/711988/2014 Committee for Medicinal Products for Human Use (CHMP)

# Assessment report under Article 46

# **Pumarix**

International non-proprietary name: H5N1 influenza vaccine

Procedure No: EMEA-H-C-1212-P46-016

# Note

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



# 1. Assessment

#### Introduction

This report covers the following post-authorisation commitment undertaken by the MAH to provide:

- o Data to D182 from a paediatric study with Pumarix, which has been designated FUM 016
- Data to D365 from the same study under Article 46

The cover note to the FUM 016 documentation contains the explanations regarding the various submissions as detailed below. It was agreed between the MAH, EMA and Rapporteur that the submissions to address FUM 016 and Art 46 should be made in parallel so that a single comprehensive assessment report could be produced.

Follow-up Measure

Area	Description	Due Date
Clinical	FUM 016: The Applicant/MAH commits to provide the clinical study report	31-December-2012
	for the following study: Study Q-Pan-021 conducted in children aged 6	
	months- <18 years (2 primary doses of half adult dose - randomised,	
	observer-blind, placebo-controlled study).	. (/)

Study Q-Pan-021 is a phase 2/3, randomized, controlled, observer-blind, multi-center trial to evaluate the safety and immunogenicity of a two-dose primary vaccination series of monovalent A/Indonesia/5/2005 (H5N1) vaccine antigen adjuvanted with AS03 in children aged 6 months to < 18 years of age.

The study design for all subjects up to year one is composed of several analyses:

- Safety and immunogenicity analysis (blinded) at D42. This main analysis 21-days post-primary vaccination will be the basis of the D42 main clinical study report.
- Safety and immunogenicity analysis (blinded) at D182. This analysis will be added into a D182 annex clinical study report.
- Conclusion at study termination (unblinded) at D385. This analysis will be added into a D385
  annex clinical study report.

The study design for all consenting and eligible subjects from the placebo group after year is also composed of several analyses:

- Safety analysis (unblinded) at D42. This analysis will be the basis of the DU42 main clinical study report.
- Conclusion at study termination (unblinded) at D385. This analysis will be added into a DU385 annex clinical study report.

As a response to FUM 016, the Company is pleased to submit the Q-Pan-021 D42 main clinical study report and D182 annex clinical study report.

Please note that the Company is submitting in parallel as agreed with EMA on 14th November 2012 the Q-Pan-021 D385 annex clinical study report as an Article 46 within 6 months after the study completion for all subjects up to year one (Last Subject Last Visit).

Lastly, the DU42 main clinical study report and the DU385 annex clinical study report are planned to be submitted as an Article 46 within 6 months after the study completion for all consenting and eligible subjects in the placebo group after year one (Last Subject Last Visit), i.e. estimated date in July 2014.

The Company wishes also to highlight that it's not currently planned to file a variation regarding the Pumarix SmPC to reflect these data, but will wait for additional data from ongoing paediatric studies (H5N1-032 and H5N1-013 in the currently agreed PIP EMEA-000178-PIP01-07-M02) in order to submit a variation with a more complete set of data in children.

The submissions include:

- A cover letter
- A Clinical Overview
- The D42, D182 and D365 study reports as mentioned above.

#### Assessment

#### H5N1-021

This was a randomized, placebo-controlled, observer-blind, multi-centre study that compared the safety and immunogenicity of a two-dose primary vaccination series of monovalent A/Indonesia/5/2005 (H5N1) vaccine antigen adjuvanted with ASO3 (Pumarix) in children aged 6 months to < 18 years of age vs. saline.

The study was conducted by 17 principle investigators in 3 countries (United States [11], Canada [5] and Thailand [1]) and was initiated in March 2011.

The study objectives were as follows:

### Primary:

o To assess whether two doses of Pumarix elicited HI titres that met or exceeded the CBER requirements and CHMP criteria in terms of SPR.

#### Secondary:

- To describe at different time points the immune response to Pumarix in 3 age strata in terms of HI titres specific for vaccine-homologous virus
  - To assess whether the H5N1 SPR was ≥70% at Day 21
  - To assess whether the H5N1 SCR was ≥40% on Days 21 and 42
  - To assess whether H5N1 MGI was >2.5 on Days 21 and 42
  - To describe the seropositivity rate, GMT, SCR, SPR and MGI in terms of point estimates and 95% CI, 6 months (182 days) and 12 months (385 days) following the first dose of vaccine.
- To further describe the immunogenicity of the vaccine regimen in the 3 age strata in terms of microneutralization (MN) titers specific for the vaccine-homologous virus and for one or more drift-variant viruses.
- To describe safety in terms of solicited local and general reactogenicity events, clinical laboratory abnormalities, unsolicited AEs, medically attended adverse events (MAEs), potential immune-mediated diseases (pIMDs) and SAEs

# Randomization was to:

- 1.9 μg Q-Pan H5N1 vaccine adjuvanted with ASO3B (i.e. half adult dose Pumarix)
- Saline placebo control using a 8:3 ratio.

Centre, age strata (approximately 1:1:1 to 6 to <36 months, 3 to <9 years, and 9 to <18 years) and history of seasonal influenza vaccination (Yes/No) in the current and prior 2 seasons, including pandemic H1N1 vaccine, were to be used as the minimization factors in the randomization process.

The treatment groups were planned as follows:

- Group A: adjuvanted Q-Pan H5N1 vaccine group = ~ approximately 600 subjects (~ 200 per age stratum) received half adult Pumarix doses on Days 0 and 21.
- Group B: saline placebo group; approximately = ~ 225 subjects (~ 75 per age stratum)
   received saline placebo on Days 0 and 21.

Subjects assigned to placebo were offered Q-Pan H5N1 (as in Group A) after Day 385 and asked to be followed for an additional 385 days.

The first dose of study vaccine was administered in the deltoid region of the non-dominant arm (or left arm if dominance is not yet identified) to children aged  $\geq 12$  months or left anterolateral thigh if < 12 months. The second dose was administered in the opposite limb.

Single lots of H5N1 HA antigen and of ASO3 adjuvant were used throughout.

Blood sampling was to occur on Day 0, Day 21, Day 42, Day 182 (50% of subjects) and Day 385 (remaining 50% of subjects). No blood samples were to be collected from placebo group subjects who received Q-Pan H5N1 after Day 385.

The primary immunogenicity endpoints were:

- Vaccine virus homologous H5N1 HI antibody titres on Day 42
- o SPR on Day 42

The secondary immunogenicity endpoints were:

- o Vaccine virus homologous H5N1 HI antibody titers on Days 0, 21, 42, 182 and 385
- o Vaccine homologous H5N1 MN antibody titers on Days 0, 21, 42, 182 and 385
- H5N1 drift variant MN antibody titers on Days 0, 21, 42, 182 and 385
- SPRs and GMTs: assessed by HI on Days 0, 21, 42, 182, 385; assessed by MN on Days 0, 42, 182, 385;
- o SCR assessed by HI on Days 21, 42, 182 and 385
- o MGI assessed by HI on Days 21, 42, 182 and 385
- Vaccine response rate (VRR) assessed by MN on Days 21, 42, 182 and 385

The analysis of immunogenicity was performed on the ATP-I cohort (primary analysis). If >5% were excluded from the ATP-I analysis then a second analysis based on the TVC was to be performed.

For each treatment group, vaccine-homologous virus antibody responses in subjects who received two doses of study vaccine, as demonstrated by the SPR at Day 42 for each age stratum, were evaluated with the following hypothesis applied to each age stratum:

o Null hypothesis: SPR ≤70% vs. the alternative hypothesis: SPR >70% in group with half-volume Q-Pan H5N1 vaccine, 21 days after the second dose

Statistical tests of the primary immunogenicity endpoint were performed at an overall 0.05 type I error, apportioned so that for each age stratum the 98.3% CI was constructed to evaluate the primary objective. If the lower bound of the 98.3% CI for SPR was ≥70% for any age stratum, the study primary immunogenicity objective was met.

#### Results to D42

There were 838 subjects enrolled and vaccinated, including 607 Pumarix and 231 placebo.

Of these, 813 subjects completed up to Day 42 and 25 withdrew mostly due to loss to follow-up (12 subjects). Overall 785 subjects were included in the ATP-I cohort at Day 42 (571 Pumarix).

The mean age was 86.2 months (range 6 to 215 months), the majority were White (44.7%) or Asian (South East Asian heritage; 36.6%) and 14.6% were African American or of African heritage. Overall, 51.8% of subjects were male.

At Day 42, but not at D21, the HI immune response met the pre-defined criteria for SPR in the 3 age strata. The criteria applied to SCR and MGI were met at Day 21 and Day 42.

All of the results based on the ATP-I cohort were confirmed in the TVC.

Syn	opsis Table 1: S (A/Indone		ibodies against t Day 42 by age			strain
				SI	PR	
					98.3	% CI
Group	Sub-group	N	n	9/6	LL	UL
Q-Pan	6M-<36M	175	175	100	97.3	100
	3Y-<9Y	185	184	99.5	96.4	100
	9Y-<18Y	203	201	99.0	95.8	99.9
Saline	6M-<36M	64	0	0.0	0.0	7.2
	3Y-<9Y	71	0	0.0	0.0	6.5
	9Y-<18Y	76	1	1.3	0.0	8.6

Q-Pan = Q-Pan H5N1 1.9 µg + AS03<sub>B</sub>

Saline = Saline placebo

6M-<36M = Children aged between 6 months to <36 months

3Y-<9Y = Children aged between 3 years to <9 years

9Y-<18Y = Children aged between 9 years to <18 years

N = Number of subjects with available results

n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)

98.3% CI = 98.3% confidence interval, LL = Lower Limit, UL = Upper Limit

Synopsis Table 2: A/Indonesia/05/2005 HI antibody parameters at Days 0, 21, and 42 by age stratum (Day 42 ATP-I) GMT SCR MGI Sub-95% CI 95% CI 95% CI 95% CI Group group **Fiming** Value LL UL LL UL LL UL Value LL UL PRE 5.3 5.5 0.5 Q-Pan 5.1 0.0 3.0 PI(D21) 38.7 7.3 33.9 58.7 57.5 64 9 64 442 51.1 66.0 499 84 PII(D42) 777.1 705.6 855.9 100 97.9 100 100 97.9 100 148.5 134.5 164.1 3Y-<9Y 3.9 PRE 5.6 5.3 5.9 1.1 0.1 44.6 50.9 51.0 9.1 PI(D21) 65.7 8.0 7.0 39.2 59.8 52.3 66.9 58.5 97.0 PII(D42) 543.8 484.9 609.8 99.5 97.0 100 99.5 96.9 85.3 110.1 100 9Y-<18Y 5.7 5.4 0.5 PRE 0.0 2.7 6.1 PI(D21) 35.3 31.7 39.5 52.9 45.8 59.9 515 44 4 58.5 6.2 5.5 6.9 466.2 99.0 99.9 PII(D42) 416.2 371.5 96.5 99.0 96.5 99.9 72.4 63.9 82.0 Saline 6M-<36M PRF 5.3 5.0 5.7 0.00.0 5.4 PI(D21) 52 5.0 5.4 0.0 0.0 5.4 0.0 0.0 5.4 1.0 0.9 1.0 PII(D42) 5.1 4.9 5.3 0.0 0.0 5.6 0.0 0.0 5.6 1.0 0.9 1.0 3Y-<9Y 5.6 5.1 5.1 PRF 6.0 0.0 0.0 PI(D21) 5.4 5.0 5.7 1.4 0.0 0.0 0.0 1.0 0.9 PIÌ(D42) 5.4 5.0 5.7 0.0 0.0 5.1 0.0 5.1 1.0 0.9 1.0 0.0 9Y-<18Y PRE 5.4 5.1 5.8 0.0 0.0 4.7 0.9 PI(D21) 5.4 5.1 5.7 0.0 0.0 4.7 0.0 0.0 4.7 1.0 1.1 PII(D42) 5.8 5.3 6.3 7.1 7.1 1.0 12 0.0 1.3 0.0 11 1.3

Q-Pan = Q-Pan H5N1 1.9 µg + AS03<sub>B</sub>

Saline = Saline placebo

6M-<36M = Children aged between 6 months to <36 months

3Y-<9Y = Children aged between 3 years to <9 years

9Y-<18Y = Children aged between 9 years to <18 years

GMT = geometric mean antibody titer calculated on all subjects

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

At D0 just under 10% of subjects were seropositive but 1% or less were seroprotected. There was no important difference between age strata for HI on D0 but the GMTs at D42 showed an inverse relationship to age.

The supplementary tables show the results by country ( $\sim$  60 Canada, 205 Thailand and 300 US in the Pumarix group). There was no important difference between countries for the D42 HI titres (e.g. GMTs in the Pumarix group were 514, 560 and 554, respectively.

No neutralisation antibody data were included in the D42 report.

The safety analysis was performed on the TVC.

Medicinal

During the 7 days following vaccination (either dose), the percentages of subjects reporting any symptom (solicited or unsolicited) were 81.2% for Pumarix and 62.3% for placebo subjects. Rates did not appear to increase with the second vs. first doses.

Injection site pain was the most frequently reported solicited local symptom (67.2% vs. 30.1%) with Grade 3 injection site pain in 4.1% vs. 1.7%.

		Q-Pan						Saline				
					95%	CI				95%	6 CI	
Symptom	Туре	N	n	%	LL	UL	N	n	%	LL	UL	
Pain	All	603	405	67.2	63.3	70.9	229	69	30.1	24.3	36.5	
	Grade 3	603	25	4.1	2.7	6.1	229	4	1.7	0.5	4.4	
Redness	All	603	†29†				229	†29†				
(mm)	>100 Grade 3	603	†1†				229	†1†				
Swelling	All	603	41	6.8	4.9	9.1	229	1	0.4	0.0	2.4	
(mm)	>100 Grade 3	603	*1*				229	*1*				

Q-Pan = Q-Pan H5N1 1.9 µg + AS03<sub>B</sub>

Saline = Saline placebo

<u>In children aged < 6 years</u> the most commonly reported solicited general symptoms during the 7-day post-vaccination period were irritability/fussiness and drowsiness with rates of 43.5% and 34.4%, respectively, for Pumarix vs. 32.8% and 23.8%, respectively, for placebo recipients. Grade 3 irritability and drowsiness were reported by 3.4% and 3.1%, respectively, in the Pumarix group and each was reported by 1.6% of subjects in the placebo group.

The incidence of fever by dose for pooled groups was 19.2% overall including 10.6% after Dose 1 and 10.4% after Dose 2. Grade 3 fever was reported in 19 (4.6%) subjects overall including 11 (2.7%) subjects following Dose 1 and 9 (2.2%) subjects following Dose 2. A temperature of >40.0°C (Grade 4) was reported in 2 subjects overall including 1 (0.2%) subject following each dose. The table below shows figures per group:

			Q-Pan	Saline							
					95% CI					95%	. CI
Symptom	Туре	N	n.	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	294	101	34.4	28.9	40.1	122	29	23.8	16.5	32.3
	Grade 3	294	9	3.1	1.4	5.7	122	2	1.6	0.2	5.8
Irritability /	All	294	128	43.5	37.8	49.4	122	40	32.8	24.6	41.9
fussiness	Grade 3	294	10	3.4	1.6	6.2	122	2	1.6	0.2	5.8
Loss of	All	294	79	26.9	21.9	32.3	122	29	23.8	16.5	32.3
appetite	Grade 3	294	8	2.7	1.2	5.3	122	4	3.3	0.9	8.2
Temperature /	≥38.0	294	59	20.1	15.6	25.1	122	21	17.2	11.0	25.1
(Axillary) (°C)	≥39.0 Grade 3	294	14	4.8	2.6	7.9	122	5	4.1	1.3	9.3
	>40.0 Grade 4	294	*2*				122	*2*			

Saline = Saline placebo

In children aged  $\geq$  6 years the most commonly reported solicited general symptoms during the 7-day post-vaccination period were muscle aches, headache and fatigue. The incidence rates were 39.8%, 32.4% and 28.8%, respectively, for Pumarix and 15.9%, 16.8% and 17.8%, respectively, for placebo recipients. Grade 3 muscle aches, headache, and fatigue were reported at rates of 2.3%, 2.6% and

1.3%, respectively, in the Pumarix group vs. 0.9%, 2.8% and 1.9%, respectively, in the placebo group.

For the pooled group the incidence of fever was 5.3% overall including 2.9% of subjects each following Dose 1 and Dose 2. Grade 3 fever was reported in 6 (1.4%) subjects overall including 3 (0.7%) subjects following each dose. The table below shows figures per group:

		•	(	Q-Pan					Saline		
					95%	6 CI				95%	6 CI
Symptom	Туре	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	All	309	89	28.8	23.8	34.2	107	19	17.8	11.0	26.3
	Grade 3	309	4	1.3	0.4	3.3	107	2	1.9	0.2	6.6
Gastrointestinal	All	309	42	13.6	10.0	17.9	107	17	15.9	9.5	24.2
	Grade 3	309	4	1.3	0.4	3.3	107	2	1.9	0.2	6.6
Headache	All	309	100	32.4	27.2	37.9	107	18	16.8	10.3	25.3
	Grade 3	309	8	2.6	1.1	5.0	107	3	2.8	0.6	8.0
Joint pain at	All	309	50	16.2	12.3	20.8	107	9	8.4	3.9	15.4
other location	Grade 3	309	†2†				107	†2†			
Muscle aches	All	309	123	39.8	34.3	45.5	107	17	15.9	9.5	24.2
	Grade 3	309	7	2.3	0.9	4.6	107	1	0.9	0.0	5.1
Shivering	All	309	25	8.1	5.3	11.7	107	7	6.5	2.7	13.0
	Grade 3	309	2	0.6	0.1	2.3	107	1	0.9	0.0	5.1
Sweating	All	309	25	8.1	5.3	11.7	107	4	3.7	1.0	9.3
	Grade 3	309	†2†				107	†2†			
Temperature /	≥38.0	309	19	6.1	3.7	9.4	107	3	2.8	0.6	8.0
(Axillary) (°C)	≥39.0	309	5	1.6	0.5	3.7	107	1	0.9	0.0	5.1
	Grade 3										
	>40.0	309	0	0.0	0.0	1.2	107	0	0.0	0.0	3.4
	Grade 4										

Overall, 244 (40.2%) Pumarix and 98 (42.4%) placebo recipients reported at least one unsolicited AE up to Day 42 (Days 0-41). The most commonly reported events were cough, nasopharyngitis, rhinorrhoea, pyrexia, upper respiratory tract infection and diarrhoea.

Medicinal Plans

		Q-	Pan			Sa	aline	
Preferred term	n	%	LL	UL	n	%	LL	UL
At least one symptom	244	40.2	36.3	44.2	98	42.4	36	49.1
Cough	36	5.9	4.2	8.1	17	7.4	4.3	11.5
Nasopharyngitis	29	4.8	3.2	6.8	18	7.8	4.7	12
Rhinorrhoea	27	4.4	3	6.4	13	5.6	3	9.4
Pyrexia	24	4	2.5	5.8	11	4.8	2.4	8.4
Upper respiratory tract infection	23	3.8	2.4	5.6	7	3	1.2	6.1
Diarrhoea	15	2.5	1.4	4	14	6.1	3.4	10
Vomiting	17	2.8	1.6	4.4	9	3.9	1.8	7.3
Oropharyngeal pain	17	2.8	1.6	4.4	7	3	1.2	6.1
Headache	9	1.5	0.7	2.8	9	3.9	1.8	7.3
Nasal congestion	9	1.5	0.7	2.8	6	2.6	1	5.6
Ear infection	10	1.6	0.8	3	4	1.7	0.5	4.4
Teething	10	1.6	0.8	3	2	0.9	0.1	3.1
Rash	6	1	0.4	2.1	5	2.2	0.7	5
Dizziness	7	1.2	0.5	2.4	3	1.3	0.3	3.7
Ear pain	5	0.8	0.3	1.9	3	1.3	0.3	3.7
Pharyngitis streptococcal	4	0.7	0.2	1.7	3	1.3	0.3	3.7
Nausea	4	0.7	0.2	1.7	2	0.9	0.1	3.1
Otitis media	4	0.7	0.2	1.7	2	0.9	0.1	3.1
Pain in extremity	4	0.7	0.2	1.7	2	0.9	0.1	3.1

Q-Pan = Q-Pan H5N1 1.9 µg + AS03<sub>8</sub>

Saline = Saline placebo

At least one MAE was reported by 87 (14.3%) in the Pumarix group and 34 (14.7%) in the placebo group up to Day 42. The most commonly reported MAEs were ear infection, upper respiratory tract infection and cough.

		Q-	Pan			Sa	line	
Preferred term	n	%	LL	UL	n	%	LL	UL
At least one symptom	87	14.3	11.6	17.4	34	14.7	10.4	20
Ear pain	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Diarrhoea	4	0.7	0.2	1.7	2	0.9	0.1	3.1
Vomiting	2	0.3	0.0	1.2	2	0.9	0.1	3.1
Pyrexia	5	0.8	0.3	1.9	2	0.9	0.1	3.1
Bronchiolitis	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Bronchitis	2	0.3	0.0	1.2	3	1.3	0.3	3.7
Conjunctivitis infective	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Ear infection	. 7	1.2	0.5	2.4	3	1.3	0.3	3.7
Gastroenteritis	*3*				*3*			
Gastroenteritis viral	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Impetigo	2	0.3	0.0	1.2	2	0.9	0.1	3.1
Nasopharyngitis	4	0.7	0.2	1.7	3	1.3	0.3	3.7
Otitis media	3	0.5	0.1	1.4	2	0.9	0.1	3.1
Otitis media acute	*3*				*3*			
Pharyngitis	3	0.5	0.1	1.4	1	0.4	0.0	2.4
Pharyngitis streptococcal	4	0.7	0.2	1.7	3	1.3	0.3	3.7
Sinusitis	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Upper respiratory tract infection	8	1.3	0.6	2.6	1	0.4	0.0	2.4
Viral infection	2	0.3	0.0	1.2	1	0.4	0.0	2.4
Cough	6	1.0	0.4	2.1	3	1.3	0.3	3.7
Oropharyngeal pain	4	0.7	0.2	1.7	1	0.4	0.0	2.4
Rhinorrhoea	3	0.5	0.1	1.4	2	0.9	0.1	3.1

# Up to D42:

- No pIMDs were reported
- Two SAEs were reported but neither was fatal or considered related to the study vaccine. There was a case of febrile convulsion in a child aged 30 months but it occurred on Day 11 post-dose.

- o No subject prematurely discontinued due to an AE or SAE
- No subject reported a pregnancy

Haematological and biochemical abnormalities that were deemed by the investigators to qualify as AEs included increased blood bilirubin (2 subjects, 1 in each treatment group). Unblinded data also showed reports of raised eosinophil count (2 subjects) and decreased neutrophil count, increased transaminases and decreased WBC count (1 subject each).

#### Results to D182

A synoptic study report was provided. At D182 576 subjects from the Pumarix group (95%) and 222 from the placebo group (96%) either attended for follow-up or were contacted by telephone (n=380). In accordance with the initial protocol sera were obtained from 308 and 108 subjects in respective groups with very comparable numbers by age stratum.

The HI results at D182 showed that all Pumarix subjects remained seropositive although the GMT had dropped to 64. The GMTs continued to show an inverse relationship to age, with values of 91, 57 for 3 to <9 years and 50 for 9-17 years.. There was no natural acquisition of anti-H5N1 antibody apaprent in the placebo group in the intervening 6 month period (i.e. no change in seropositivity rate or GMT).

The SPR was 84% for Pumarix and 0 for placebo, the SCRs were 83% and 0 and the MGI for the Pumarix group was 11.9. There was an inverse relationship with age as shown in the tables below. There were no appreciable differences by country.

Table 16 Seroprotection rates (SPR) for HI antibodies against H5N1 strain at Day 0 and Day 182 by age stratum (Day 182 ATP cohort for immunogenicity)

				1		SF	'R		
							95	% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	
Flu A/Ind/05/05 (H5N1).HA Ab	Q-Pan	6M-<36M	PRE	107	0	0.0	0.0	3.4	
			PII(D182)	84	80	95.2	88.3	98.7	
		3Y-<9Y	PRE	101	0	0.0	0.0	3.6	
			PII(D182)	89	75	84.3	75.0	91.1	
		9Y-<18Y	PRE	100	0	0.0	0.0	3.6	
			PII(D182)	87	63	72.4	61.8	81.5	
	Saline		PRE	36	0	0.0	0.0	9.7	
			PII(D182)	29	0	0.0	0.0	11.9	
		3Y-<9Y	PRE	37	0	0.0	0.0	9.5	
			PII(D182)	34	0	0.0	0.0	10.3	
		9Y-<18Y	PRE	35	0	0.0	0.0	10.0	
			PII(D182)	31	0	0.0	0.0	11.2	

Table 17 Seroconversion rate (SCR) for HI antibodies against H5N1 strain at Day 182 by age stratum (Day 182 ATP cohort for immunogenicity)

					(	SCR	
						9	5% CI
Strain	Group	Sub-group	N	n	%	LL	UL
Flu A/Ind/05/05 (H5N1).HA Ab	Q-Pan	6M-<36M	84	80	95.2	88.3	98.7
		3Y-<9Y	89	75	84.3	75.0	91.1
		9Y-<18Y	87	61	70.1	59.4	79.5
	Saline	6M-<36M	29	0	0.0	0.0	11.9
		3Y-<9Y	34	0	0.0	0.0	10.3
		9Y-<18Y	31	0	0.0	0.0	11.2

Table 18 Mean geometric increase (MGI) for HI antibodies against H5N1 strain at Day 182 by age stratum (Day 182 ATP cohort for immunogenicity)

					MGI	
						95% CI
Strain	Group	Sub-group	N	Value	LL	UL
Flu A/Ind/05/05 (H5N1).HA Ab (1/DIL)	Q-Pan	6M-<36M	84	17.8	15.3	20.8
		3Y-<9Y	89	11.0	9.7	12.4
		9Y-<18Y	87	8.8	7.5	10.4
	Saline	6M-<36M	29	1.0	0.9	1.0
		3Y-<9Y	34	1.1	1.0	1.2
		9Y-<18Y	31	1.0	0.9	1.2

There are no data reported on neutralising antibody titres.

By D182 6 Pumarix and 1 placebo subject had reported SAEs. These have no been unblinded by treatment group but review of these events does not suggest any relationship to vaccine.

Jedicinal product reasons as After the cut-off date the synopsis mentions that a case of Type 1 diabetes was reported and the case

#### Results to D385

A synoptic study report was provided for the unblinded D385 data. The D385ATP-I comprised 372 subjects – 268 Pumarix and 104 placebo – with slightly lower numbers from the lowest age cohort vs. the older cohorts (108, 126 and 138).

Almost all in the Pumarix group were still seropositive (98%) vs. 6% in the placebo group and GMTs were 33 vs. 5.

In the Pumarix group 53% were seroprotected, 50% met the SCR criterion and the MGI was 6. The tables below show these results by age cohort and demonstrate that the age-related apttern of GMTs was maintained. There were no important differences by country.

Table 23 Seropositivity rates and GMTs for HI antibodies against H5N1 strain at Day 0 and Day 385 by age stratum (Day 385 ATP cohort for immunogenicity)

						≥ 10	1/DI	L		GMT			
							95%	6 CI		95%	6 CI		
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/Ind/05/05 (H5N1).HA Ab	Q-Pan	6M-<36M	PRE	77	6	7.8	2.9	16.2	5.4	5.1	5.8	<10.0	28.0
			PII(D385)	63	63	100	94.3	100	65.6	55.9	76.9	14.0	320.0
		3Y-<9Y	PRE	89	15	16.9	9.8	26.3	6.0	5.5	6.6	<10.0	40.0
			PII(D385)	85	85	100	95.8	100	32.8	28.1	38.4	10.0	160.0
		9Y-<18Y	PRE	101	16	15.8	9.3	24.4	5.9	5.4	6.5	<10.0	40.0
			PII(D385)	95	90	94.7	88.1	98.3	21.6	18,6	25.1	<10.0	226.0
	Saline	6M-<36M	PRE	31	4	12.9	3.6	29.8	5.5	5.0	6.1	<10.0	14.0
			PII(D385)	26	1	3.8	0.1	19.6	5.1	4.9	5.4	<10.0	10.0
		3Y-<9Y	PRE	36	7	19.4	8.2	36.0	5.9	5.2	6.6	<10.0	20.0
			PII(D385)	34	3	8.8	1.9	23.7	5.4	4.9	5.8	<10.0	14.0
		9Y-<18Y	PRE	37	4	10.8	3.0	25.4	5.5	5.0	6.0	<10.0	14.0
			PII(D385)	36	2	5.6	0.7	18.7	5.3	4.8	5.9	<10.0	28.0

Table 24 Seroprotection rates (SPR) for HI antibodies against H5N1 strain at Day 0 and Day 385 by age stratum (Day 385 ATP cohort for immunogenicity)

							SPR	
							95	% CI
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/Ind/05/05 (H5N1).HA Ab	Q-Pan	6M-<36M	PRE	77	0	0.0	0.0	4.7
			PII(D385)	63	54	85.7	74.6	93.3
		3Y-<9Y	PRE	89	2	2.2	0.3	7.9
			PII(D385)	85	47	55.3	44.1	66.1
		9Y-<18Y	PRE	101	1	1.0	0.0	5.4
			PII(D385)	95	27	28.4	19.6	38.6
~0.	Saline	6M-<36M	PRE	31	0	0.0	0.0	11.2
* * * * * * * * * * * * * * * * * * * *			PII(D385)	26	0	0.0	0.0	13.2
		3Y-<9Y	PRE	36	0	0.0	0.0	9.7
			PII(D385)	34	0	0.0	0.0	10.3
		9Y-<18Y	PRE	37	0	0.0	0.0	9.5
			PII(D385)	36	0	0.0	0.0	9.7

Table 25 Seroconversion rates (SCR) for HI antibodies against H5N1 strain at Day 385 by age stratum (Day 385 ATP cohort for immunogenicity)

			SCR				
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
Flu A/Ind/05/05 (H5N1).HA Ab	Q-Pan	6M-<36M	63	53	84.1	72.7	92.1
		3Y-<9Y	84	45	53.6	42.4	64.5
		9Y-<18Y	95	23	24.2	16.0	34.1
	Saline	6M-<36M	26	0	0.0	0.0	13.2
		3Y-<9Y	34	0	0.0	0.0	10.3
		9Y-<18Y	36	0	0.0	0.0	9.7

Table 26 Mean geometric increase (MGI) for HI antibodies against H5N1 strain at Day 385 by age stratum (Day 385 ATP cohort for immunogenicity)

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
Flu A/Ind/05/05 (H5N1).HA Ab (1/DIL)	Q-Pan	6M-<36M	63	12.1	10.3	14.2
		3Y-<9Y	84	5.5	4.7	6.6
		9Y-<18Y	95	3.6	3.1	4.3
	Saline	6M-<36M	26	1.0	0.9	1.1
		3Y-<9Y	34	0.9	0.8	1.0
		9Y-<18Y	36	1.0	0.8	1.1

From Day 0 to the Day 385 contacts, at least one MAE was reported for 189 (31.1%) and 77 (33.3%) in the Pumarix and placebo group, respectively.

SAEs were reported for 8 subjects (1.3%) and 4 subjects (1.7%) per group. No fatal SAEs were reported. None of the SAEs was considered related to Pumarix.

One pIMD was reported in the Pumarix group but this concerned alopecia assessed as not related to study vaccine by the investigator.

Two subjects reported a pregnancy resulting in one spontaneous abortion and one healthy live birth.

Haematological and biochemical abnormalities that were deemed by the investigators to qualify as MAEs through the Day 385 contact included:

- increased AST in 2 Pumarix and one placebo group subject
- increased ALT in 2 Pumarix subjects
- increased blood bilirubin, increased red blood cell count, increased haemoglobin, increased haematocrit (each reported in 1 subject in the Q-Pan group)
- decreased haematocrit and a haemoglobin abnormality (each reported in 1 subject in the placebo group).

# 2. Rapporteur's overall conclusion and further action if required

The study demonstrates that two half adult doses of Pumarix are highly immunogenic from the age of 6 months up to 17 years in healthy subjects. A single dose was not adequately immunogenic and therefore the data do support a 2-dose regimen.

The data raise the possibility that even lower doses of antigen and/or adjuvant could be used, especially in the youngest age groups, and/or that a different ratio of antigen/adjuvant could be used. However, the neutralising antibody data are currently awaited from both studies.

The data to D385 indicate that seropositivity rates remained high despite and the falls in seroprotection rates were very much as expected from other datasets.

The inclusion of a placebo group is unusual in this age group but it allows for a clear assessment of the safety of Pumarix. This has already been described to be a reasonably reactogenic vaccine and there are no new concerns raised by the data.

There are no very urgent implications for the Pumarix SmPC based on these data since no usage of H5N1 adjuvanted vaccine is ongoing. It is agreed that a single variation may be filed when the complete data from the ongoing paediatric studies become available.

$\boxtimes$	PAC fulfilled (all commitments fulfilled) - No further action required
	PAC not fulfilled (not all commitments fulfilled) and further action required: