EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/65558/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pandemic Influenza Vaccine H5N1 Baxter

International non-proprietary name: pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)

Procedure No.: EMEA/H/C/001200/II/0015

Note

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

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Table of contents

List of abbreviations

AE	Adverse event
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
EMA	European Medicines Agency
EP (or Ph. Eur.)	European Pharmacopeia
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GM	Geometric mean
GMT	Geometric mean titre
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
PAC	Post authorisation commitment
PI	Product Information
SAE	Serious adverse event
SAR	Serious adverse reaction
SPC	Summary of Product Characteristics
SRH	Single radial hemolysis
TBS	Tris-buffered saline
Vero cells	A continuous cell line originally derived from the kidney of the African green monkey Cercopithecus aethiops.
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Baxter AG submitted to the European Medicines Agency on 9 April 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**Common name:**	**Presentations:**
Pandemic influenza vaccine H5N1 Baxter	pandemic influenza vaccine (whole virion, Vero cell derived, inactivated)	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for paediatric population in the active immunization against A/H5N1 subtype of influenza virus. Consequently, the MAH proposed the update of sections 4.2 and 5.1 of the SmPC.

In addition, the MAH proposed to update the safety information in section 4.8 of the SmPC.

The Package Leaflet and Labelling were proposed to be updated in accordance.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/67/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/67/2011 was completed.

The PDCO issued an opinion on compliance for the PIP P/67/2011 (EMA/PDCO/808557/2012).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur	**Jan Mueller-Berghaus**	**Co-Rapporteur:**	**Andrea Laslop**

Submission date:	9 April 2013
Start of procedure:	26 April 2013
Rapporteur's preliminary assessment report circulated on:	13 June 2013
Co-Rapporteur's preliminary assessment report circulated on:	17 June 2013
Joint Rapporteur's updated assessment report circulated on:	16 July 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 July 2013
MAH's responses submitted to the CHMP on:	21 August 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	23 September 2013
PRAC RMP advice and assessment overview adopted by PRAC	10 October 2013
CHMP opinion:	24 October 2013

2. Scientific discussion

2.1. Introduction

The widespread occurrence of highly pathogenic avian virus H5N1 infections in birds and the several H5N1 outbreaks in humans have raised concerns of a potential pandemic since H5 represents a new haemagglutinin subtype to which the human population have very little or no immunity. Vaccines represent the main prophylactic measure against pandemic influenza.

Pandemic Influenza Vaccine H5N1 Baxter has initially been licensed as a mock up pandemic vaccine in 29 European countries under the trade name Celvapan. However, due to the emergence of the H1N1 pandemic and following a duplication of licenses by informed consent, Celvapan was varied into the pandemic A/H1N1 influenza vaccine after approval by the EU Commission on 06 October 2009. The duplicate H5N1 dossier was maintained under the name of Pandemic Influenza Vaccine H5N1 Baxter.

As of August 2012 Pandemic Influenza Vaccine H5N1 Baxter is approved in a total of 32 countries worldwide. Additionally, authorisation for Singapore is pending approval. As it is a mock up vaccine, Pandemic Influenza Vaccine H5N1 Baxter can only be marketed following a strain change during an actual pandemic. Therefore, exposure to the product is limited to clinical trials. Pandemic Influenza vaccine H5N1 Baxter is composed of non-adjuvanted, purified, inactivated whole virions formulation of A/Vietnam/1203/2004 7.5µg HA, a clade 1 strain of human influenza type A, subtype H5N1, isolated in Vietnam as isolate n. 1203 in 2004. Since there is no data for Pandemic Influenza vaccine H5N1 Baxter in subjects under 18 years of age, the administration of the vaccine in case of a pandemic shall follow national recommendations. However, during the approval of the product the Company was asked to obtain at least limited data in children and adolescents since in a pandemic children may be very vulnerable to infection and so would constitute a special target group for vaccination.

Following the submission of study 810706 in accordance with Article 46 of Regulation (EC) 1901/2006, agreed by the CHMP 26 March 2013, the MAH applied now to include in the PI the paediatrics data from subjects 6 months to 17 years of age. Within this variation application Baxter also fulfils PAC P46-020, including the update of the PI with the paediatric data of study 810706.

No separate Paediatric investigation plan (PIP) is available for the Pandemic Influenza vaccine H5N1 Baxter since the proposed H5N1 paediatric study was agreed to be included within the PIP for the prepandemic influenza Vepacel (EU/1/12/752/001-002). Positive compliance verification on the agreed paediatric study 810706 was conceded in January 2013 by the PDCO. Vepacel has the same active substance (A/Vietnam/1203/2004) and was licensed in Europe on 17 February 2012 for pre-pandemic from the age of 18 years onwards. Vepacel is also undergoing a variation for extension of indication to the paediatric population in parallel.

In this assessment report only the main results of study 810706 are summarised, as the study has been assessed already in January 2013 (please refer to P46-020). During the current procedure it was concluded that safety and immunogenicity data generated in the paediatric population are acceptable to support the use in children and thus should be included in the PI of Pandemic Influenza Vaccine H5N1 Baxter.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

A Phase I/II Study to Assess the Safety and Immunogenicity of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in Healthy Infants, Children and Adolescents Aged 6 Months to 17 Years.

Methods

This phase1/2 clinical study was designed to determine the safety and immunogenicity of the H5N1 influenza vaccine (A/Vietnam/1203/2004) in healthy male and female infants, children and adolescents from 6 months to 17 years. All subjects received a two dose regimen (7.5 µg or 3.75 µg HA per dose) of H5N1 influenza vaccine 21 days apart. A subset received additionally a booster vaccination of H5N1 influenza vaccine (A/Indonesia/05/2005) 12 months after the primary vaccination (at the same dose used for primary vaccination). The study duration for each subject was at least 201 days, or approximately 381 days for the subset of subjects receiving a booster vaccination.

Subjects were stratified by age as follows:

Stratum A: approximately 300 children and adolescents aged 9 to 17 years. Subjects in Stratum A were vaccinated with the 7.5 µg H5N1 HA antigen dose. A subset of at least 75 subjects received a booster vaccination.

Stratum B: approximately 300 children aged 3 to 8 years. Subjects in Stratum B were randomized 1:1 to receive either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. A subset of at least 150 subjects (75 in each dose group) received a booster vaccination.

Stratum C: approximately 70 infants and young children aged 6 to 35 months. Subjects in Stratum C were randomized 1:1 to receive either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. All subjects received a booster vaccination.

Children and adolescents aged 9 to 17 years were considered to be closest to adults in terms of immune status at baseline and safety responses, and therefore received the 7.5 µg dose only. Both the 7.5 µg and 3.75 µg doses were instead investigated in children aged 3 to 8 years. Based on potential concerns that half the adult dose may not be sufficiently immunogenic in the youngest subset, both the 7.5 µg and 3.75 µg doses were also investigated in children aged 6 to 35 months.

All subjects received the primary vaccination as two injections of either 7.5 µg or 3.75 µg µg HA antigen strain A/Vietnam/1203/2004 at a 21-day interval via intramuscular injection in the deltoid muscle of the upper arm or in the anterolateral muscle of the thigh depending on the age of the subject. On Day 360 a subset, comprising of at least 75 subjects from Stratum A, and at least 150 subjects from Stratum B (75 subjects in each dose group) and 70 subjects from Stratum C (35 subjects in each dose group) received a heterologous booster vaccination, strain A/Indonesia/05/2005) at the same dose used for primary vaccination.

Objectives

- To assess the safety and tolerability of a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the primary immune response to a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the immunogenicity of two different doses of a non-adjuvanted H5N1 influenza vaccine in healthy infants and children aged 6 months to 8 years;
- To assess persistence of H5N1 influenza antibodies 360 days after the first vaccination with a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the immune response to a heterologous booster vaccination with a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years.

Outcomes/endpoints

Primary endpoints

Immunogenicity

- Rate of subjects with antibody response to the vaccine strain associated with protection 21 days after the second vaccination defined as titre measured by Microneutralization (MN) test ≥ 1:20.

Safety

- Frequency and severity of systemic reactions until 7 days after the first vaccination.

Healthy children were eligible for enrolment if they were 6 months to 17 years of age, with their parent(s) / legal representative providing signed consent form and able to understand the protocol requirements and to fill in the diary card. As recommended in Guideline EMEA/CHMP/VWP/263499/2006, the study was to enrol approximately 300 children and adolescents (9 to 17 years of age, Stratum A) and 300 children (3 to 8 years of age, Stratum B). Additionally, approximately 70 infants and young children (6 to 35 months of age, Stratum C) were to be enrolled in this study. Assuming an approximate dropout rate of 10%, it was expected that 270 subjects in Strata A and B (and 63 subjects in Stratum C) would have evaluable immunogenicity results after two vaccinations.

Blinding (masking)

This was a partially blinded study, i.e. single blinded for children aged 3 to 8 years (Stratum B) and infants and young children aged 6 to 35 months (Stratum C) only. For this reason, measures to maintain blinding and unblinding are not applicable for this study.

Assays and interpretation of results

The immunogenicity parameters for the interpretation of the HI and SRH assays results that the MAH has adhered to are described in the Table below, based on current recommendations.

Table 1. Criteria for antibody response (as indicated in adults and elderly for seasonal Influenza vaccines)

	CBER		CHMP	
	< 65 years	≥ 65 years	18-60 years	> 60 years
Seroconversion rate	LL of 95% CI ≥ 40%	LL of 95% CI ≥ 30%	> 40%	> 30%
Seroprotection rate	LL of 95% CI ≥ 70%	LL of 95% CI ≥ 60%	> 70%	> 60%
Mean Geometric Increase (Seroconversion factor)	No standard defined		> 2.5	> 2.0

CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; CI= Confidence Interval; LL = Lower limit

It has been demonstrated that the MN assay is more sensitive and/or specific than the HI assay for detection of functional/protective antibodies against avian influenza strains. Thus immunogenicity evaluation was focused on the MN assay (any MN result < 1:10 (undetectable) was expressed as 1:3.9 and considered negative), supported by antibody response determined by SRH.

The SRH method was based on the passive haemolysis of erythrocytes (sheep or turkey), sensitized with influenza virus particles, by antibodies directed against the viral haemagglutinin in the presence of a complement.

Results

Participant flow

	Stratum A (9 to 17 years)			Stratum B (3 to 8 years)				Stratum C (6-35 months)			
	7.5µg	Not assigned	**total**	3.75µg	7.5µg	Not assigned	**total**	3.75µg	7.5µg	Not assigned	**total**
Enrolled	300	5	**305**	150	153[n]	3	**306**	36	36	1	**73**
1st Vaccination	300	0	**300**	150	153	0	**303**	36	36	0	**72**
2nd Vaccination	296	0	**296**	150	153	0	**303**	36	36	0	**72**
Booster	191	0	**191**	73	77	0	**291**	33	28	0	**61**
Reason for withdrawal											
Screen failure	0	2	**2**	1	1	0	**2**	0	1	1	**2**
Lost to follow up	5	0	**5**	0	4	0	**4**	0	1	0	**1**
Physician decision	0	0	**0**	1	1	0	**2**	0	1	0	**1**
Discount. By subject	15	3	**18**	12	10	2	**24**	2	5	0	**7**
Other	2	0	**2**	7	5	1	**13**	1	1	0	**2**

Baseline data

Demographic data

Both genders were relatively evenly represented in all three strata, and most subjects (>90%) in Strata A and C were considered "white;" in Stratum B 73.6% of subjects were white, and 22.9% were Asian in the 3.75 µg group and 76.2% of subjects were white and 23.1% were Asian in the 7.5 µg group.

Baseline Antibody Titres

For purposes of analysis, any MN result < 1:10 (undetectable) is expressed as 1:3.9 and considered negative; SRH areas ≤ 4 mm^2 are considered negative; and any HI result < 1:10 (undetectable) is expressed as 1:5 and considered negative.

Seroprotection pre-vaccination (Table 2)

In stratum A (9 to 17 years), 27.2% of subjects had antibody titres associated with protection (≥ 1:20) against the primary vaccination strain (A/Vietnam/1203/2004) at baseline as measured by MN.

Among younger subjects, in strata B and C, baseline titre levels were low (≤1.4% as measured by MN). Comparable results were obtained for the PP dataset.

Baseline seropositivity rates as measured by SRH were mostly consistent with those determined by MN, although baseline SRH antibody titre levels associated with protection were observed in 15.6% of Stratum A subjects, which was a lower rate compared to MN assay results.

Table 2. Baseline rates of subjects with antibody responses against A/Vietnam Strain associated with protection and geometric antibody titres (GMTs); Day 1;

Age		MN (≥1:20)		SRH (≥25mm²)		HI	
		3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
9-17 years	**Protection %**	**-**	**27.2**	**-**	**15.6**	**-**	**0.0**
	GM	-	11.8	-	7.6	-	5.0
3-8 years	**Protection %**	**1.4**	**0.0**	**4.9**	**3.5**	**0.0**	**0.0**
	GM	5.2	4.8	6.3	6.3	5.0	5.0
6-36 months	**Protection %**	**0.0**	**0.0**	**2.8**	**0.0**	**0.0**	**0.0**
	GM	4.0	4.0	6.4	6.4	5.0	5.0

Source: Study report, Table 18; Table 19, Table 26, Table 31and Table 32
The **Intent-to-Treat (ITT)** dataset contains all randomized and vaccinated subjects with available data for the respective analysis.

Table 3. Reverse Cumulative Distribution Measured by MN and SRH (A/Vietnam) on Day 1

age	MN >=1:5		SRH >=4	
	3,75µg	7,5µg	3,75µg	7,5µg
9-17 years	-	**75.7 %**	-	**46.9 %**
3-8 years	25.2 %	**20.5 %**	**53.8 %**	**58.2%**
6-36 months	2.8 %	**3.0 %**	**63.9%**	**66.7 %**

Source: Table 22, 30 of the study report

Numbers analysed

A total of 675 subjects (300 Stratum A, 303 Stratum B and 72 Stratum C) were available for the safety dataset, 656 subjects (296 Stratum A, 291 Stratum B and 69 Stratum C) for the intent-to-treat (ITT) dataset and 591 subjects (270 Stratum A, 259 Stratum B and 62 Stratum C) for the per-protocol (PP) dataset.

Outcomes and estimation

Priming

Primary immunogenicity endpoint

1. Antibody response 21 days after the second vaccination (MN); ITT dataset

Two vaccinations 21 days apart with the Vero cell-derived H5N1 vaccine containing 7.5 µg HA antigen of the clade 1 A/Vietnam/1203/2004 strain induced an antibody response associated with protection (MN titre ≥ 1:20) in 85.4% of older subjects (Stratum A: aged 9 to 17 years), as measured by the MN assay. Among subjects aged 3 to 8 years (Stratum B), 72.9% of those receiving the 7.5µg dose showed a response associated with protection, compared to 57.1% of those receiving the 3.75 µg dose. For subjects aged 6 to 35 months (Stratum C), 68.8% of subjects who received the 7.5 µg dose

had titres associated with protection 21 days after the second dose, compared to 54.3 % of those receiving the 3.75 µg dose.

Similar results were obtained for the PP dataset.

Table 4. Antibody response 21 days after the first and second vaccination (Vietnam Strain) ITT

Age group			MN (≥1:20)		SRH (≥25mm²)		HI	
			3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
9-17 years	Day 0	Protection %	-	27.2	-	15.6	-	0.0
		GM	-	11.8	-	7.6	-	5.0
	Day 21	**Protection %**	-	52.6	-	63.8	-	3.4
		GMT	-	19.1	-	25.0	-	5.8
	Day 43	**Protection %**	**-**	**85.4**	**-**	**75.1**	**-**	**5.5**
		GMT (fold increase*)	**-**	**36.1 (3.1)**	**-**	**35.3 (4.7)**	**-**	**6.3 (1.3)**
3-8 years	Day 0	Protection %	1.4	0.0	4.9	3.5	0.0	0.0
		GM	5.2	4.8	6.3	6.3	5.0	5.0
	Day 21	**Protection %**	8.6	17.7	47.1	46.1	2.8	1.4
		GMT	8.9	10.1	18.5	18.2	5.6	5.3
	Day 43	**Protection %**	**57.1**	**72.9**	**64.2**	**75.4**	**5.8**	**5.7**
		GMT (fold increase*)	**23.8 (4.6)**	**30.3 (6.3)**	**27.7 (4.3)**	**37.2 (5.9)**	**6.3 (1.3)**	**6.3 (1.3)**
6-36 months	Day 0	Protection %	0.0	0.0	2.8	0.0	0.0	0.0
		GM	4.0	4.0	6.4	6.4	5.0	5.0
	Day 21	**Protection %**	0.0	3.0	25.7	13.8	0.0	0.0
		GMT	6.1	5.7	11.0	9.5	5.0	5.0
	Day 43	**Protection %**	**54.3**	**68.8**	**55.9**	**63.0**	**2.9**	**7.1**
		GMT (fold increase*)	**25.2 (6.3)**	**27.5 (6.8)**	**25.5 (4.0)**	**31.3 (4.6)**	**5.7 (1.1)**	**6.7 (1.3)**

*seroconversion factor

Secondary immunogenicity endpoints

2. Rate of subjects with antibody response associated with protection 21 days after the first vaccination defined as titre measured by MN test ≥ 1:20.

An antibody response associated with protection as determined by MN after the first vaccination was shown in 52.6% of subjects in Stratum A (9 to 17 years old), receiving the 7.5 µg vaccine dose (Table 5 above). Protection rates were lower among younger subjects (≤17.1% in Stratum B [3 to 8 year olds], and ≤3.0% in Stratum C [6 to 35 month olds]), with more subjects showing protection after receiving the 7.5 µg dose as compared with the 3.75 µg dose.

3. Rate of subjects with antibody response associated with protection 21 days after the first and second vaccination defined as Hemagglutination Inhibition Antibody (HIA) titre ≥ 1:40 or Single Radial Hemolysis (SRH) area ≥ 25 mm2.

Antibody response associated with seroprotection according to SRH was consistent with the MN assay results. Among subjects aged 9 to 17 years, 63.8% had antibody levels (SRH assay) associated with seroprotection after the first vaccination and 75.1% after the second vaccination (Table 4).

In Stratum B, among subjects receiving the 7.5 µg dose, 46.1% showed antibody levels associated with protection after the first vaccination, compared to 75.4% after the second vaccination. The differences between the seroprotection rates of the two doses were not statistically significant.

Among Stratum C subjects (aged 6 to 35 months) who received the 7.5 µg dose, 13.8% and 63.0% of subjects showed antibody levels associated with protection, after the first and second vaccinations, respectively. The differences between the seroprotection rate of the two doses were not statistically significant (25.7% and 55.9 % for the toddles receiving the 3.75µg dose).

The rate of antibody response associated with protection was also determined by HI against Vero cell-derived and MDCK-derived A/Vietnam strains. Results were much lower and highly inconsistent with those determined by MN and SRH.

4. Antibody response 21 days after the first and second vaccination as measured by MN, HI and SRH assay.

Antibody responses 21 days after the first and the second vaccination are displayed in Table 4. Results as measured by SRH assay were consistent to the MN results; GMTs according to the HI assay were much lower and highly inconsistent with those determined by MN and SRH.

5. Fold increase of antibody response 21 days after the first and second vaccination as compared to baseline as measured by MN, HI and SRH assay.

The fold increase in antibody titre for Strata A, B and C (respectively), for the 7.5 µg dose group, was 1.6, 2.1, and 1.4 at Day 22 and 3.1, 6.3 and 6.8 at Day 43 as determined by MN assay. In the 3.75 µg dose group, in Strata B and C, the fold increases were 1.7 and 1.6 at Day 22 and 4.6 and 6.3 at Day 43. Results as determined by the SRH assay were similar to those of the MN assay; fold increases as determined by the HI assay were, again, much lower and highly inconsistent with those determined by MN and SRH.

6. Rate of subjects with seroconversion (defined as a minimum four fold titre increase as compared to baseline [for MN and HI assay] or as either a ≥ 25 mm² haemolysis area after the vaccination in case of a negative pre-vaccination sample [≥4 mm2] or a ≥ 50% increase in haemolysis area if the pre-vaccination sample is > 4 mm² [for SRH assay]) 21 days after the first and second vaccination as measured by MN, HI and SRH assay:

Table 5. Rate of subjects with seroconversion (%)

Age group			MN (≥1:20)		SRH (≥25mm²)		HI	
			3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
Seroconversion rates %								
9-17 years	Day 22		-	9.1	-	48.4	-	3.4
	Day 43		-	**31.8**	-	**63.5**	-	**5.5**
3-8 years	Day 22		12.9	16.4	44.2	43.3	2.8	1.4
	Day 43		**53.4**	**72.2**	**63.5**	**78.3**	**5.8**	**5.7**
6-36 months	Day 22		8.6	9.1	25.7	13.8	0.0	0.0
	Day 43		**60.0**	**65.6**	**64.7**	**77.8**	**2.9**	**7.1**

(Source: Study report Table 21, 29 and 34;
MN: (efined as a ⩾ 4 fold increase after vaccination
SRH: defined as either a ⩾ 25 mm² hemolysis area after vaccination if baseline sample is negative [⩽ 4mm²] or a ⩾ 50% increase in hemolysis area if the baseline sample is >4 mm²
HI: defined as a ⩾ 4 fold increase after vaccination)

When measured by MN assay seroconversion was observed in 9.1%, 16.4%, and 9.1% in Strata A, B and C (respectively), at 21 days after the first vaccination for the 7.5 µg dose study group; and 12.9% and 8.6% in Strata B and C (respectively), among those in the 3.75 µg dose group.

A substantial increase in seroconversion rate as measured by MN was observed after the second vaccination: 31.8%, 72.2%, and 65.6% in Strata A, B and C (respectively), for the 7.5 µg dose study group; and in 53.4% and 60.0% in Strata B and C (respectively), among those in the 3.75 µg dose group.

Results as determined by SRH assay (see Table 5) were somewhat higher but generally support the MN assay results; the seroconversion rate in the oldest subjects (Stratum A) was significantly higher compared to the MN assay after the second vaccination (63.5%), which could be due to the higher baseline MN antibody levels observed in this age group.

Seroconversion rates according to the HI assay were, again, much lower and highly inconsistent with those determined by MN and SRH.

Table 6. Summary of priming (post dose-2, 7.5µg dose, seronegative and seropositive subjects at baseline- ITT)

Post dose-2 7,5µg	9-17 years		3-8 years		6-36 months	
	MN	SRH	MN	SRH	MN	SRH
Seroconversion rate %	**31.8** **(no requirement)**	**63.5**	**72.2**	**78.3**	**65.6**	**77.8**
Seroconversion factor (GM increase)	**3.1**	**4.7**	**6.3**	**5.9**	**6.8**	**4.6**
Seroprotection rate %	**85.4**	**75.1**	**64.2**	**75.4**	**55.9** **(no requirement)**	**63.0** **(required is ≥70%)**

Persistence and Booster

Genetic characterization of HA sequences of the majority of H5N1 viruses has demonstrated two distinct phylogenetic clades with non-overlapping case distributions. Clade 1 viruses circulated in Cambodia, Thailand, and Vietnam and were responsible for human infections in those countries during 2004 and 2005 (e.g. A/Vietnam/1203/2004). Clade 2 viruses circulated in birds in China and Indonesia (during 2004-2005) and subsequently (during 2005-2006) spread westward to the Middle East, Europe, and Africa. Six different subclades of clade 2 have been recognized and three of these (subclades 1, 2 and 3) have been responsible for most of the human cases in Indonesia, China, and outside of Asia (e.g. A/Indonesia/05/2005).

7. Rate of subjects with antibody response associated with protection 360 days after the first vaccination and 21 days after the booster vaccination (heterologous H5N1) as measured by MN, HI and SRH assay.

Results as determined by the SRH assay showed a similar trend compared to those of the MN assay; seroconversion rates according to the HI assay were much lower and highly inconsistent with those determined by MN and SRH (see Table below).

Table 7. Rate of subjects with seroprotection after one year (before and after booster)

Age group			MN (≥1:20)		SRH (≥25mm²)		HI (≥1:40)	
			3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
Serumneutralisation rate (%)								
9-17 years	Pre boost	A/Vietnam	-	**31.1**	-	**31.2**	-	**0.0**
		A/Indonesia	-	**15.4**	-	**21.4**	-	**0.0**
	Post boost	A/Vietnam	-	**94.1**	-	**81.8**	-	**9.8**
		A/Indonesia	-	**93.1**	-	**86.4**	-	**6.9**
3-8 years	Pre boost	A/Vietnam	13.5	**16.5**	11.4	**9.3**	0.0	**0.0**
		A/Indonesia	5.7	**12.5**	7.4	**4.2**	0.0	**0.0**
	Post boost	A/Vietnam	91.7	**94.7**	77.5	**86.3**	9.0	**15.0**
		A/Indonesia	91.4	**97.2**	83.1	**84.9**	9.0	**11.7**
6-36 months	Pre boost	A/Vietnam	19.4	**28.0**	6.7	**0.0**	0.0	**0.0**
		A/Indonesia	10.3	**5.3**	6.9	**8.7**	21.1	**35.7**
	Post boost	A/Vietnam	93.8	**100.0**	87.1	**96.0**	0.0	**0.0**
		A/Indonesia	100.0	**100.0**	74.2	**96.9**	21.1	**35.7**

(Source: Table 18, 26 and 31 in study report)

8. Antibody response 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay.

Table 8. Antibody responses after one year (before (Day 361) and after booster (Day 382)) and fold increase compared to Day 361; ITT

Age group			MN (≥1:20)		SRH (≥25mm²)		HI (≥1:40)	
			3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
GMTs (fold increase* compared to Day 361)								
9-17 years	Pre boost	A/Vietnam	-	**15.6**	-	**12.3**	-	**5.0**
		A/Indonesia	-	**11.0**	-	**12.0**	-	**5.0**
	Post boost	A/Vietnam	-	**68.5** (4.4)	-	**41.1** (3.5)	-	**7.9** (1.6)
		A/Indonesia	-	**86.1** (7.8)	-	**42.8** (3.6)	-	**6.9** (1.4)
3-8 years	Pre boost	A/Vietnam	9.8	**11.2**	8.8	**8.9**	5.0	**5.0**
		A/Indonesia	8.0	**8.6**	7.3	**7.0**	5.0	**5.0**
	Post boost	A/Vietnam	64.5 (6.5)	**77.1** (6.9)	35.8 (4.2)	**43.7** (4.8)	8.1 (1.7)	**9.5** (1.8)
		A/Indonesia	95.1 (11.9)	**121.4** (14.2)	40.6 (5.7)	**40.8** (5.8)	7.8 (1.7)	**8.0** (1.5)
6-36 months	Pre boost	A/Vietnam	9.4	**9.9**	8.2	**7.3**	5.0	**5.0**
		A/Indonesia	7.8	**6.0**	8.5	**8.7**	5.0	**5.0**
	Post boost	A/Vietnam	87.0 (9.2)	**124.7** (13.5)	40.0 (4.9)	**55.6** (7.6)	12.9 (4.0)	**29.7** (6.0)
		A/Indonesia	125.0 (16.0)	**179.7** (30.2)	40.2 (4.8)	**52.6** (5.9)	12.2 (3.7)	**26.9** (5.7)

(Source: Table 19, 27 and 32 in study report)
*seroconversion factor

The SRH assay showed a similar trend compared to those of the MN assay. HI assay results were highly inconsistent with the MN and SRH assay results.

9. Fold increase of antibody response 21 days after the booster vaccination as compared to before the booster vaccination as measured by MN, HI and SRH assay.

See Table 8

10. Rate of subjects with seroconversion 21 days after the booster vaccination as measured by MN, HI and SRH assay:

Table 9. Rate of subjects with seroconversion compared to Day 361 (%)

Age group			MN (≥1:20)		SRH (≥25mm²)		HI	
			3,75µg	7,5µg	3,75µg	7,5µg	3,75µg	7,5µg
Seroconversion rates %								
9-17 years	A/Vietnam		-	**47.9**	-	**60.7**	-	9.4
	A/Indonesia		-	**74.5**	-	**76.3**	-	6.9
3-8 years	A/Vietnam		70.8	**74.7**	70.6	**81.7**	10.0	13.5
	A/Indonesia		80.0	**90.3**	86.8	**85.9**	10.0	9.6
6-36 months	A/Vietnam		86.7	**95.8**	82.8	**100.0**	30.8	33.3
	A/Indonesia		100.0	**100.0**	72.4	**100.0**	30.8	33.3

(Source: Table 21, 29 and 34 of the study report)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was overall well conducted. The dropout rate (13.5%) was low for such long study duration. The number of subjects to be enrolled in Stratum C has been reduced (from initially 300 to at least 70 subjects) in response to difficulties in enrolment due to the concomitant H1N1 pandemic (Amendment 4, version 2011 Mar 09). It is agreed that the inclusion of a higher number of children was difficult to arrange at a later stage, therefore this modification was deemed acceptable. Additionally, in order to reduce the burden on study participants, the number of subjects receiving the 12-months booster has been reduced (Amendment 3, version 2010 Dec21), which is acceptable. This is in line with the "Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier" (EMEA/CHMP/VWP/263499/2006), which allows for some degree of extrapolation if it is not possible to generate data from all age and risk categories. Both amendments were also accepted by the PDCO.

Efficacy data (immunogenicity) and additional analyses

In the current applicable guidance for influenza vaccines it is highly recommended to evaluate immunological responses based on haemagglutination inhibition (HI) and /or serum radial haemolysis (SRH, only measuring IgG antibodies). The MAH interpretation of the HI and SRH results followed the immunogenicity requirements defined by the Note for Guidance on Harmonization for Influenza vaccines (CPMP/BWP/214/96). Despite the uncertainties whether the CHMP serological criteria are equally valid for pandemic vaccines as for seasonal influenza vaccines and for the evaluation of immunogenicity in adults as in the paediatric population, for the time being the mentioned CHMP immunogenicity criteria remain a useful benchmark and the approach pursued in this dossier is acceptable. Cell mediated immunity (CMI) could have been explored. However, it is recognised that in paediatric trials the amount of blood needed for such analysis represent a limitation for measurement of CMI and clinically validated assays exist.

Regarding the HI assays low responsiveness was observed throughout all analyses most probably due to a low sensitivity of the assay. This finding is consistent with other H5N1 vaccines.

With regards to the MN assay, similar parameters to HI and SRH were defined by the MAH using a cut-off of ≥1:20. The MN assay is based on the ability of neutralizing antibodies to prevent the attachment of virus to cells as well as intracellular penetration and propagation. Such assays are commonly used to detect protective antibodies in human reconvalescent sera or sera from vaccinees. At present, however, a neutralising antibody titre associated with protection against a potential pandemic strain has not been clinically validated yet. The MAH conducted studies in mice to show that the cut-off titre of 1:20 is appropriately defined for the MN assay and that the neutralising antibody response as measured in cell culture corresponds to a functional immune response in vivo. Standard SRH assays were conducted to confirm the results obtained with the MN assay. Validation reports for both the SRH and the MN assay were already provided during the initial MAA for the product.

Priming

Following administration of Pandemic Influenza Vaccine H5N1 Baxter, seroconversion and seroneutralization rates are slightly lower in comparison with those obtained in children (3-17 years) vaccinated with Celvapan (H1N1). This is expected due to the low immunogenicity of H5N1 and other purely avian strains vs. H1N1 pandemic virus. However, after priming with 7.5µg of the candidate vaccine most of the CHMP criteria are fulfilled and the results are comparable with those achieved in adults and elderly (H5N1). Of note, after the first dose the rate of infants and toddlers with neutralizing antibody titres ≥ 20 (MN) were lower than those of adults and elderly once (17.1 % and 3.0 % vs. 44.4 % and 51.9 %, respectively). This is probably explained by lower rates of subjects with pre-existing antibody titres and emphasizes the need of two doses especially for naïve subjects.

Surprisingly, according to baseline data a proportion of study subjects was not immunologically naïve to H5N1, and some subjects even had titres in the seroprotective range against H5N1 (up to 27.2% for stratum A in the MN assay). Thus during the procedure the MAH was asked to present all MN and SRH results for study 810706 according to baseline seronegativity (i.e. separately for subjects with baseline MN titre <1:3.9 and baseline SRH titre <1:5 and subjects with baseline MN titre >1:3.9 and baseline SRH titre >1:5). The analysis of the immune response in children seronegative at baseline show that all three age cohorts develop adequate seroconversion rates and GM fold increases 21 days after the second vaccination. The observed seroprotection rates are lower than those in subjects seropositive at baseline. In conclusion, the immune response in children immunologically naïve or seronegative at baseline is considered to be comparable with the immune response observed in the overall adult population previously studied (trials 810705, 810601).

With the lower dose of 3.75 µg, seroprotection was missed in age strata B and C with both assays. Furthermore, point estimates of antibody titres, fold increase and percent seroconversion/seroprotection, were substantially lower than for the full dose, showing a clear dose effect and the need for the full dose in order to achieve a serological response in the three paediatric age groups, which would be comparable to the response seen in healthy adult vaccinees.

The surprisingly high rates (by MN and SRH) of children 9-17 years with high seroneutralising antibodies (≥1:20), which have been noted, might be due to the fact that older children have been vaccinated with seasonal influenza vaccines (or exposed to circulating seasonal strains) and thus an antibody response against N1 is at least partially responsible for the pre-existing immunity towards H5N1 viruses. It is unlikely that these children have already a specific immunity against H5N1.

Persistence and booster

For all age groups, a moderate decline in antibody titres occurred during a time period of one year. The MN- or SRH-based analyses (Pre-boost) using the A/Indonesia strain revealed that a proportion of subjects after priming with the A/Vietnam strain gained cross-neutralizing antibodies.

Booster vaccination with a heterologous vaccine strain (A/Indonesia/2005, clade2) showed a clear increase in antibody titres for all age groups. The criterion set for seroprotection (i.e. at least 70% of adults with a protective titre) has been achieved in all age groups (using MN and SRH assay). The fact that the response profile and magnitude following the heterologous booster (A/Indonesia) has been similar to the homologous booster indicates that the vaccine can produce a good cross-clade memory response.

As a conclusion, booster outcomes achieved in the different age strata are comparable to each other and to effects observed in healthy adults.

2.4.3. Conclusions on the clinical efficacy

The immunogenicity results presented for Pandemic Influenza Vaccine H5N1 Baxter are acceptable and indicate that good levels of protection should be achieved in vaccinees from 6 months of age onwards using a two 7.5 ug HA dose vaccination schedule 21 days apart. Antibody levels seem to modestly decrease over time, as expected. Following up with a booster 12 months after a 2-dose primary vaccination induces a strong antibody response against both strains used for the booster or primary vaccinations. This demonstrates the vaccine's ability to induce a cross-reactive memory response after a two dose priming that can be effectively boosted up to one year after initial priming in infants, children and adolescents aged 6 months to 17 years.

2.5. Clinical safety

2.5.1. Introduction

Overall for Pandemic Influenza Vaccine H5N1 Baxter safety data are available in adults from four completed clinical studies (phase 1/2 study 810501, phase 3 study 810601, phase 1/2 study 810701, and phase 2 study 810703) and one partially completed study (phase 3 study 810705). In these studies, 4535 subjects were exposed to at least one vaccine dose of the Vero cell-derived H5N1 influenza vaccine. The safety results of all five clinical studies are highly consistent. The most frequently reported systemic reaction after vaccination was headache (which occurred in 10.8% of adults and 8.5% of elderly after the first vaccination, according to the pooled safety data on the relevant vaccine formulation). Other commonly reported systemic reactions were fatigue, malaise, chills, myalgia, hyperhidrosis, nasopharyngitis, arthralgia, pyrexia and pharyngolaryngeal pain. Systemic reactions were mostly mild. Of interest, fever occurred only at a low rate (with the highest point estimate across all studies being 4.8% in the 7.5 µg non-adjuvanted group in study 810501), and was mostly mild in severity. Injection site pain was the most frequently reported local reaction: it was very common in subjects aged < 60 years after both the first (11.4%) and the second vaccination (10.2%), but was reported less often by elderly subjects (5.0% and 2.8% after first and second vaccination respectively). Other local reactions that were commonly reported were injection site haemorrhage, injection site induration and swelling. In general, in adults the frequency of local as well as systemic adverse events was lower after the second than after the first vaccination.

Serious adverse reactions (SARs) occurred in adults only at a low rate, and no common pattern or apparent safety signal emerged from these SAEs that were assessed to be (possibly) related to vaccination.

Study 810706

Safety was assessed in terms of adverse events (AEs) that occurred within 7 or 21 days after vaccination, regardless of the presumed relationship between the event and the study product. AEs were grouped by system organ class. Each event was divided into defined severity grades (mild, moderate and severe). All AEs were described on the electronic case report forms (eCRFs) using standard medical terminology and graded by the investigator for severity and relatedness to the study product based on the criteria specified in the study protocol.

Patient exposure

The H5N1 influenza vaccine was administered in a 2-dose primary vaccination scheme at a 21-day interval, followed by a heterologous booster 360 days after the first vaccination. Healthy infants, children and adolescents aged 6 months to 17 years (N=675) were administered the first vaccination with the H5N1 vaccine containing the strain A/Vietnam/1203/2004 at a dose of 7.5 µg (N=300: Stratum A, N=153: Stratum B, and N=36: Stratum C) or 3.75 µg (N=150: Stratum B, and N=36: Stratum C), and 657 received a second vaccination at the same HA dose 21 days after the first (7.5 µg: N=296: Stratum A, N=148: Stratum B, and N=34: Stratum C; 3.75 µg: N=143: Stratum B, and N=36: Stratum C). The booster vaccination, containing the strain A/Indonesia/05/2005, was administered to 402 subjects 360 days after the first vaccination (7.5 µg: N=191: Stratum A, N=77: Stratum B, and N=28: Stratum C; 3.75 µg: N=73: Stratum B, and N=33: Stratum C).

Adverse events

Most of the subjects did not report any systemic or local reactions after vaccination (Table below). The highest rate of reporting was after the first vaccination compared to the second and booster vaccination. No real dose dependency was seen between the 7.5 µg and 3.75 µg dose groups in regards to frequency of adverse events in the age group 3 to 8 years. In Stratum B (6 months to 35 months) a slightly higher rate of systemic reactions was observed in the higher dose group compared to the lower dose group.

Table 10. Number of subjects with systemic and injection site reactions within 21 days after vaccination

		Stratum A (9-17 years)	Stratum B (3-8 years)		Stratum C (6-35 months)	
Parameter	Vaccination	7.5 µg % (95% CI)	7.5 µg % (95% CI)	3.75 µg % (95% CI)	7.5 µg % (95% CI)	3.75 µg % (95% CI)
Systemic Reactions	1st vacc.	30.3 (25.2 ; 35.9)	18.3 (12.5; 25.4)	23.3 (16.8 ; 30.9)	41.7 (25.5 ; 59.2)	33.3 (18.6 ; 51.0)
	2nd vacc.	18.9 (14.6 ; 23.9)	10.7 (6.3 ; 16.9)	12.7 (7.7; 19.3)	32.4 (17.4 ; 50.5)	30.6 (16.3 ; 48.1)
	booster vacc.	21.5 (15.9 ; 28.0)	10.3 (4.5 ; 19.2)	15.3 (7.9 ; 25.7)	17.9 (6.1 ; 36.9)	15.2 (5.1 ; 31.9)
Injection Site Reactions	1st vacc.	32.0 (26.8 ; 37.6)	26.8 (20.0 ; 34.5)	24.0 (17.4 ; 31.6)	19.4 (8.2 ; 36.0)	19.4 (8.2 ; 36.0)
	2nd vacc.	25.7 (20.8 ; 31.0)	22.8 (16.3 ; 30.4)	14.8 (9.4 ; 21.7)	14.7 (5.0 ; 31.1)	16.7 (6.4 ; 32.8)
	booster vacc.	30.4 (23.9 ; 37.4)	37.2 (26.5 ; 48.9)	30.6 (20.2 ; 42.5)	14.3 (4.0 ; 32.7)	18.2 (7.0 ; 35.5)

Within 7 days after the first vaccination, systemic reaction rates (excluding fever) in the 7.5 µg and 3.75 µg dose groups respectively were: 30.0 % in Stratum A, 15.7 % and 20.7 % in Stratum B, and 33.3 % and 30.6 % in Stratum C. Symptoms lasted a few days and all subjects recovered. Only few

systemic reactions were reported in the period from 7 to 21 days after the first vaccination as shown by the slight increase in systemic reaction rates observed within 21 days after first vaccination (Table above).The majority of reactions were mild to moderate in severity.

Within 21 days after the second vaccination, systemic reaction rates (excluding fever) were 18.6% of subjects in Stratum A, 9.4% and 12.0% in Stratum B, and 29.4% and 27.8% in Stratum C in the 7.5 µg and 3.75 µg dose groups respectively. Severe systemic reactions occurring after the first and second vaccinations were: fatigue and nausea (1 subject), arthralgia and myalgia (1 subject), vomiting, myalgia and headache (1 subject), nasopharyngitis (1 subject) and myalgia (1 subject), fatigue (1 subject) in Stratum A and cough (1 subject) in Stratum C. The most commonly-reported specifically queried symptoms after the first and second vaccinations were headache, malaise, fatigue and muscle pain in Strata A and B, and irritability, nonsalable or excessive crying, disturbed sleep, loss of appetite and drowsiness in Stratum C.

Systemic reaction rates (excluding fever) within 21 days of the booster vaccination with the A/Indonesia/05/2005 strain were: 21.5% in Stratum A, 10.3% and 13.9% in Stratum B, and 17.9% and 6.1% in Stratum C in the 7.5 µg and 3.75 µg dose groups respectively. The majority of reactions were mild to moderate in severity. Severe systemic reactions occurring after the booster vaccination were headache (1 subject) and fatigue (1 subject) in Stratum A. The most commonly-reported specifically queried symptoms after the booster vaccination were headache, malaise, fatigue and muscle pain in Strata A and B, and irritability, loss of appetite and drowsiness in Stratum C.

Fever

Fever occurred at low rates after each vaccination, with generally lower rates after the second and booster vaccination as compared to the first vaccination. Fever rates within 7 days after the first, second and booster vaccination ranged from 1.0% to 2.7% in Stratum A, from 1.4% to 6.4% in Stratum B, and from 10.7% to 19.4% in Stratum C. The majority of fever cases were ≤ 38.4° C (only five subjects had body temperatures of ≥39.5° C, with a highest reported body temperature of 40.0° C).

Table 11. Number of subjects in % with fever within 7 days after vaccination

Stratum	Dosis	<38.0	38.0-38.4	38.5-38.9	39.0-39.4	39.5-39.9	40.0-40.4	40.5-40.9	**Total n**
Vaccination 1									
A	7,5µg	98.3	0.7	0.7	0.3	0.0	0.0	0.0	**300**
B	3,75µg	94.0	3.3	2.0	0.7	0.0	0.0	0.0	**150**
	7,5µg	95.4	2.0	1.3	0.0	0.7	0.7	0.0	**153**
C	3,75µg	83.3	11.1	0.0	0.0	5.6	0.0	0.0	**36**
	7,5µg	80.6	11.1	5.6	2.8	0.0	0.0	0.0	**36**
Vaccination 2									
A	7,5µg	97.3	2.0	0.3	0.3	0.0	0.0	0.0	**296**
B	3,75µg	95.8	1.4	1.4	1.4	0.0	0.0	0.0	**142**
	7,5µg	96.6	2.0	0.0	1.3	0.0	0.0	0.0	**149**

C	3,75µg	88.9	8.3	0.0	2.8	0.0	0.0	0.0	**36**
	7,5µg	88.2	8.8	2.9	0.0	0.0	0.0	0.0	**34**
Booster									
A	7,5µg	99.0	0.5	0.0	0.0	0.0	0.0	0.0	**191**
B	3,75µg	98.6	0.0	0.0	1.4	0.0	0.0	0.0	**72**
	7,5µg	93.6	2.6	2.6	0.0	1.3	0.0	0.0	**78**
C	3,75µg	87.9	9.1	3.0	0.0	0.0	0.0	0.0	**33**
	7,5µg	89.3	7.1	3.6	0.0	0.0	0.0	0.0	**28**

Non-serious reactions

The symptoms are displayed in the following 3 tables after the first vaccination, after the second vaccination and after booster vaccination respectively.

First vaccination

After the first vaccination Injection site pain was mostly reported in all age Strata. In Stratum A Injection site pain and Headache were reported with a high incidence. With a lower incidence Injection site pain, Headache and Fatigue were reported in Stratum B compared to Stratum A. The younger age group reported disturbed sleep and Irritability with the highest incidence.

Second vaccination

With a lower frequency but with still the highest incidences Injection site pain, Headache and Fatigue were reported in Stratum A and B after the second vaccination compared to the first vaccination. Almost with the same frequency Injection site pain, Irritability and Disturbed sleep were reported in Stratum C after the second vaccination compared to the first vaccination.

Booster vaccination

Injection site pain was reported with a higher frequency after the booster vaccination compared to the second vaccination in Stratum A and B. All other reported events were documented with a lower frequency compared to vaccination 1 and 2 in all age Strata.

Less severe reactions were reported after the booster vaccination compared to first and second vaccination, although less children were vaccinated with the booster vaccine (see Table below).

Table 12. Reactions after booster vaccination

Subject No	Stratum	Dose group	1st vaccination	2nd vaccination	Booster vaccination
120034	A	7.5 µg	Fatigue, nausea		
130045	A	7.5 µg			Headache
140011	A	7.5 µg	Nasopharyngitis		Fatigue
150007	A	7.5 µg		Inj. site erythema	
160058	A	7.5 µg	Inj. site induration		
170006	A	7.5 µg	Inj. site induration		
170012	A	7.5 µg	Inj. site swelling		
180013	A	7.5 µg	Myalgia	Fatigue	
180016	A	7.5 µg	Arthralgia		
190003	A	7.5 µg		Inj. site erythema	
520020	A	7.5 µg	Vomiting, myalgia and headache		
150026	B	7.5 µg	Inj. site induration, inj. site swelling and inj. site erythema	Inj. site swelling and inj. site erythema	
140052	C	3.75 µg		Cough	
170014	C	7.5 µg		Inj. site swelling and inj. site erythema	

Serious adverse event / deaths / other significant events

There were no deaths and no vaccine-related SAEs reported during the study.

In total 8 SAEs were reported, which were not associated to the study vaccine (Hennoch-Schonlein purpurea, acute appendicitis, stomach pain, ankle fracture, stomatitis, visual field defect, abdominal injury and conjunctivitis viral).

The majority (~70%) of subjects did not experience any systemic or injection site reactions after vaccination and no real dose effect was seen in Stratum B and C who received either 7.5 µg or 3.75 µg HA per vaccination.

Laboratory findings

Alanine amino transferase (ALT) levels were determined prior to the first vaccination (Day 1), prior to the second vaccination (Day 22) and 21 days after the second vaccination (Day 43) in the first approximately 100 subjects in Stratum A (children and adolescents aged 9 to 17 years) and Stratum B (children aged 3 to 8 years). Only 1 subject showed an abnormal result with a toxicity grade of 1 on Day 43.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

None.

Post marketing experience

Not applicable.

2.5.2. Discussion on clinical safety

In summary these are the key elements gathered from the safety follow-up period following H5N1 administration:

- There were no deaths and no vaccine-related SAEs reported during the study;
- In total 8 SAEs were reported, which were not associated to the study vaccine (Hennoch-Schonlein purpurea, acute appendicitis, stomach pain, ankle fracture, stomatitis, visual field defect, abdominal injury and conjunctivitis viral);
- The majority (~ 70%) of subjects did not experience any systemic or injection site reactions after vaccination and no real dose effect was seen in Stratum B and C who received either 7.5 µg or 3.75 µg HA per vaccination;
- Injection site reaction rates within 21 days after vaccination were ≤30.4% in Stratum A, ≤ 37.2% and ≤30.6% in Stratum B and ≤19.4% and ≤19.4% in Stratum C, in the 7.5 μg and 3.75 μg dose group, respectively. The most commonly reported specifically queried symptom after each vaccination was injection site pain in all three strata;
- Systemic reaction rates within 21 days after the first, second and booster vaccination were ≤ 30.3% in Stratum A, ≤16.3% and ≤21.3% in Stratum B and ≤36.1% and ≤30.6% in Stratum C, in the 7.5 μg and 3.75 μg dose group, respectively. The most commonly reported specifically queried symptoms of systemic reactions after each vaccination were headache, malaise, fatigue and muscle pain in Strata A and B. In Stratum C, irritability, inconsolable or excessive crying, disturbed sleep, loss of appetite and drowsiness were the most commonly reported symptoms after the first and second vaccination and irritability, loss of appetite and drowsiness were most commonly reported after the booster vaccination;
- Fever occurred at low rates after each vaccination, with generally lower rates after the second and booster vaccination as compared to the first vaccination. Fever rates within 7 days after the first, second and booster vaccination ranged from 1.0% to 2.7% in Stratum A, from 1.4% to 6.4% in Stratum B, and from 10.7% to 19.4% in Stratum C. The majority of fever cases were ≤ 38.4° C (only five subjects had body temperatures of ≥39.5° C, with a highest reported body temperature of 40.0° C).
- Adverse reactions were predominantly mild or moderate in severity. Severe reactions (although non-serious) were experienced by a total of 14 subjects; all subjects recovered from these symptoms without sequelae.

In the event of a pandemic, vaccination is universally regarded as the most important public health intervention for preventing infection or reducing disease severity, which applies for both adults (including elderly) and children. Moreover, particularly children may be vulnerable to infection and so constitute a special group for vaccination.

Pandemic influenza vaccine H5N1 was demonstrated to be safe and well-tolerated in this study. The safety and reactogenicity profile of H5N1 seen was as expected, based on previous experience with

this vaccine in adults and elderly once. The rank order of frequency of each solicited systemic reaction observed in this study differed slightly in the younger population: pyrexia was numerically more frequent in children than in adults and elderly once. Systemic reactions observed in the study were numerically in same frequency reported in children as in adults and elderly, e.g. pain. 8 unrelated SAEs were reported within the study and 14 subjects reported severe systemic or local reactions after vaccination. Concerning abnormal laboratory results 1 subject showed an abnormal result.

All reported adverse reactions have now been adequately reflected in the Product Information.

2.5.3. Conclusions on clinical safety

In conclusion, Pandemic Influenza Baxter H5N1 showed a good tolerability and safety profile in children and adolescent in study 810706. The availability of protective vaccines against strains with potential pandemic such as H5N1 is expected to have a fundamental impact on public health. The demonstrated benefits exceed the risks associated with the use of the vaccine both for adults and children.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged for this medicinal product and should follow a half-yearly cycle until otherwise agreed by the CHMP.

The next data lock point will be 28 February 2014.

The annex II section related to the PSUR refers to the EURD list which remains unchanged.

As soon as a pandemic is declared in the framework of Decision 2119/98/EC, the MAH will initiate Pandemic Pharmacovigilance practices.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The MAH has submitted a updated version of the RMP (v1.0 dated August 19th 2013) and has adequately answered all issues that were raised during the procedure.

All issues regarding the RMP are resolved.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Important Identified Risks	*None*
Important Potential Risks	Hypersensitivity reactions, including anaphylaxis
	AESIs (including neuritis, convulsion, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's (facial) palsy, and demyelinating disorders)
	Low efficacy/laboratory confirmed vaccination failure
	Administration of ineffective vaccine against current circulating virus
	Interactions with other vaccines

	Medication error due to administration of vaccines from different manufacturers for the first and second immunizations of an individual
	Graft versus host disease
	Transplant rejection
	Immune thrombocytopenia
Missing Information	Limited information on safety in pregnant or lactating women
	Limited information on serum calcium levels after vaccine administration in the paediatric population
	Limited information on the use of the vaccine in the pediatric population aged six to 35 months

Pharmacovigilance plans

Study/Activity type, title, and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Pregnancy registry, category 3	To collect efficacy and safety information on the use of the vaccines in the population of pregnant/lactating females during the course of an active pandemic	Limited information on safety in pregnant or lactating women	Planned	To be determined
Prospective cohort study, category 3	To collect clinical safety and effectiveness data during the course of an active pandemic	• Low efficacy / laboratory confirmed vaccination failure • Administration of ineffective vaccine against current circulating virus	Planned	To be determined

Risk minimisation measures

Safety Concern	Routine Risk Minimization Activities	Additional Risk Minimization Activities
Hypersensitivity reactions, including anaphylaxis	Discussed in SmPC Sections 4.3 and 4.4.	None proposed
AESIs (including neuritis, convulsion, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's (facial) palsy, and demyelinating disorders)	Encephalomyelitis, neuritis, Guillain-Barré syndrome, and convulsion are listed in Section 4.8 as Undesirable Effects in SmPC.	None proposed

Safety Concern	Routine Risk Minimization Activities	Additional Risk Minimization Activities
Low efficacy/laboratory confirmed vaccination failure	Discussed in SmPC Section 4.4.	None proposed
Administration of ineffective vaccine against current circulating virus	Discussed in SmPC Section 4.4.	None proposed
Interactions with other vaccines	Discussed in SmPC Section 4.5.	None proposed
Medication error due to administration of vaccines from different manufacturers for the first and second immunizations of an individual	Discussed in SmPC Section 4.5.	None proposed
Graft versus host disease	None	None proposed
Transplant rejection	None	None proposed
Immune thrombocytopenia	None	None proposed
Limited information on safety in pregnant or lactating women	Discussed in SmPC Section 4.6.	None proposed
Limited information on serum calcium levels after vaccine administration in the pediatric population	Discussed in SmPC Section 5.3.	None proposed
Limited information on the use of the vaccine in the pediatric population aged six to 35 months	Discussed in SmPC Section 4.8.	None proposed

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.2, 4.8 and 5.1 of the SmPC have been updated (see below: new text is underlined; delete text is strikethrough). The Labelling and Package Leaflet has been updated accordingly.

- **Section 4.1 Therapeutic indications**

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

~~*PANDEMIC INFLUENZA VACCINE H5N1 BAXTER has been evaluated in infants, children and adolescents from 6 months to 17 years and in adults 18-59 years of age and in older people 60 years of age and above.*~~

- **Section 4.2 Posology and method of administration**

Posology

Adults and ~~older people~~ children from 6 months onwards:

One dose of 0.5 ml at an elected date.

~~*Infants, children, and adolescents from 6 months to 17 years:*~~

~~*One dose of 0.5 ml at an elected date.*~~

A second dose of vaccine should be given after an interval of at least 3 weeks.

For the changes in sections 4.8 and 5.1 and all other changes please refer to the attached PI.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and core SmPC for pandemic vaccines, which were reviewed by QRD and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Pandemic Influenza Vaccine H5N1 Baxter is a vaccine to protect against influenza caused by the H5N1 subtype of the influenza A virus in an officially declared pandemic. Vaccination is considered to be the most effective option to limit the spread or severity of a pandemic. Since avian influenza H5N1 is viewed as a possible candidate for a pandemic, an effective vaccine against this highly pathogenic virus is needed also in children.

Study 810706 shows that a two-dose vaccination with 7.5 µg A/Vietnam/1203/2004 vaccine administered 21 days apart induces a substantial antibody response in healthy subjects from 6 months to 17 years old. Specifically, 85.4% of subjects aged 9 to 17 years (Stratum A) reached antibody titres associated with protection (MN titre ≥ 1:20) at 21 days after the second vaccination, as well as 72.9% of subjects aged 3 to 8 years (Stratum B) and 68.6% of subjects aged 6 to 35 months (Stratum C). Good immunogenicity results were also confirmed by SRH assay, in line with the results of the healthy adult population.

A booster vaccination with a cross-clade influenza H5N1 strain (A/Indonesia/05/2005) administered 12 months after a 2-dose primary vaccination also induces a strong antibody response against both the strains used either for the booster or primary vaccinations. This demonstrates the vaccine's ability to induce a cross-reactive memory response after a two dose priming that can be effectively boosted up to one year after initial priming in infants, children and adolescents aged 6 months to 17 years.

Uncertainty in the knowledge about the beneficial effects

Lower, but still acceptable, immune responses are measured in the younger age group vs. the older ones. The reason for this is not fully understood, however it is believed that it might reflect a greater exposure of older subjects to seasonal influenza viruses or vaccines (possibly N1 antigens) and it might also be linked to the immune system being under development in the youngest. Study 810706 did not include immunocompromised and chronically ill paediatric subjects, however the immunogenicity of the vaccine in these subjects is not expected to differ substantially from immunocompromised and chronically ill adults subjects, which were previously studied.

Risks

Unfavourable effects

In study 810706, a total of 675 subjects received the first vaccination on Day 1 with either 7.5 µg or 3.75 µg HA antigen strain A/Vietnam/1203/2004. Of these subjects, 657 received the second vaccination of HA antigen strain A/H5N1/Vietnam/1203/2004 on Day 21 at the same dose as Day 1. Of those subjects who received two primary vaccinations, 402 received the booster vaccination of HA

antigen strain A/Indonesia/05/2005 on Day 361 with the same dose as used in the primary vaccination. Key results are summarised as follows:

- Within 7 days after the first vaccination, systemic reaction rates (excluding fever) in the 7.5 µg and 3.75 µg dose groups respectively were: 30.0% in Stratum A, 15.7% and 20.7% in Stratum B, and 33.3% and 30.6% in Stratum C, of which most were mild or moderate, except for 5 subjects in Stratum A, who reported severe systemic reactions. Symptoms lasted a few days and all subjects recovered.
- In general, the rates of systemic reactions (excluding fever) after the first and second vaccination were acceptable and comparable to the rates previously observed in the adult population. The frequency differed only slightly between the 7 days and the 21 days window after the first vaccination. In two subjects severe systemic reactions (severe fatigue, severe cough) occurred after the second vaccination. Both subjects recovered. The rates of systemic reactions after the booster vaccination were lower than after the first and second vaccination. Only two subjects experienced severe systemic reactions which both lasted less than 24 hours.
- The majority of injection site reactions were mild in severity. Injection site pain was the most frequently reported injection site reaction in all age groups. There were four subjects for whom severe local reactions were reported after the first and second vaccination, respectively. All subjects recovered from these symptoms. The rates of injection site reactions were higher in all age groups when compared to the adult population. No severe injection site reactions were reported after the booster vaccination. The most frequently reported local reaction in all age groups was injection site pain.
- The most commonly reported specifically queried symptoms for the first and second vaccinations were headache, malaise, fatigue and muscle pain in Strata A and B, and irritability, inconsolable or excessive crying, disturbed sleep disorder, loss of appetite and drowsiness for Stratum C. Similar results were shown after booster vaccination, but with lower frequency. The nature of the most frequently reported specifically queried symptoms is not unusual. The frequency is overall slightly higher when compared to the adult and elderly population.
- Fever occurred at low rates after each vaccination, with generally lower rates after the second and booster vaccination as compared to the first vaccination. Fever rates ranged from 1.0% to 2.7% in Stratum A, from 1.4% to 6.4% in Stratum B and from 10.7% to 19.4% in Stratum C. The majority of fever cases were $\leq 38.4^{\circ}$ C. There was only one subject (Stratum B, 7.5µg dose group) with fever >40°C (occurring 6 days after vaccination, duration 3 days) related to the first vaccination and there were no subjects with fever >39.4°C related to the second vaccination. Furthermore, there were no subjects with fever >39.9°C related to the booster vaccination.
- No AEs related to the primary vaccinations occurred between 21 days after the second vaccination and 360 days after the first vaccination except one subject. There were no deaths or serious adverse events related to vaccination during the entire study period. Adverse reactions were predominantly mild to moderate in severity.
- No safety concerns arose from the laboratory results.

Uncertainty in the knowledge about the unfavourable effects

No safety signals have been identified in the age group from 6 months to 17 years. The number of patients is not sufficient to detect rare events, but this is expected as rare events can only be detected

in post-marketing settings due to the very large size otherwise needed to power clinical trials. Study 810706 did not include immunocompromised and chronically ill paediatric subjects, however the safety profile is not expected to differ substantially from healthy children.

Benefit-Risk Balance

This application concerns the potential use in children of the vaccine in a declared pandemic only, i.e. an emergency situation. Albeit limited, the number of children, particularly of toddlers (6 to 36 months) studied for this application is in line with the "Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier" (EMEA/CHMP/VWP/263499/2006). Additionally, the data generated with Celvapan (H1N1), which was used during the last pandemic, may be considered as supportive as these vaccines are similarly manufactured. Celvapan is approved for all age groups, the only exception are children below the age of 6 months.

A prime-boost vaccination strategy of a two dose primary vaccination with an A/Vietnam/1203/2004 strain vaccine followed by a heterologous H5N1 influenza booster vaccination was shown to be well tolerated in a paediatric population at the age of 6 months to 17 years. This vaccination schedule was shown to induce a broad humoral immune response in all age groups, similar to those in adults or elderly. Additionally, the candidate vaccine demonstrated its ability to induce a long-lasting cross-clade immunological memory that can be effectively boosted up to one year followed by a two dose primary schedule. Cellular immunity and efficacy has not been tested for comprehensible reasons (avian influenza strains are highly pathogenic, not circulating and CMI in children would require a large amount of blood to be drawn).

Moreover, the submitted data indicate that the vaccine was shown to be safe and well tolerated in a paediatric population from the age of 6 months to 17 years. The Vero cell line culture technology used for production of this influenza vaccine provides a theoretically added safety for individuals with egg allergies.

After vaccination with this inactivated H5N1 influenza vaccine it is anticipated that the majority of subjects receiving this vaccine will be protected against avian influenza caused by the strain contained in the vaccine and are expected to benefit from some level of protection against avian influenza caused by closely related strains.

In conclusion, the benefit risk balance of Pandemic Influenza Vaccine H5N1 Baxter is considered to be positive in the paediatric population in all investigated age groups and the extension of indication is deemed approvable.

4. Recommendations

The application for extension of indication to the paediatric population is approvable since all remaining concerns have been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.1.6 a	Change(s) to therapeutic indication(s) - Addition of a new	II

Variation(s) accepted		Type
	therapeutic indication or modification of an approved one	

Extension of Indication to include new population (paediatric) for Pandemic Influenza Vaccine H5N1 Baxter.

As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC were updated in order to include the new efficacy and safety information. The Package Leaflet and Labelling are updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template version 9 and with the SmPC guideline and Core SmPC for pandemic vaccines.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to conduct post-authorisation measures**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/67/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, in the Package Leaflet.