EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/59623/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vepacel

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

Procedure No.: EMEA/H/C/002089/II/0007

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

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 Innovations GmbH submitted to the European Medicines Agency on 4 April 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**Common name:**	**Presentations:**
Vepacel	A/H5N1 prepandemic influenza vaccine (whole virion, vero-cell-derived, inactivated)	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.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 the treatment of children and adolescent from the age of 6 months onwards. Consequently, the MAH proposed the update of sections 4.2, 4.8 and 5.1 of the SmPC.

The Package Leaflet was 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, including the additional monitoring status.

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

Information on paediatric requirements

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

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

The PDCO issued an opinion on compliance for the PIP P/67/2011.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniel Brasseur **Co-Rapporteur: Andrea Laslop**

Submission date:	4 April 2013
Start of procedure:	26 April 2013
Rapporteur's preliminary assessment report circulated on:	19 June 2013
Co-Rapporteur's preliminary assessment report circulated on:	17 June 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:	24 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

Vepacel, a Vero cell-derived prepandemic influenza vaccine, is a H5N1 (A/Vietnam/1203/2004) monovalent unadjuvanted inactivated whole virion vaccine that is available as a suspension for injection in multi-dose vials or syringes. Vepacel contains 7.5 µg/dose of Haemagglutinin. It was licensed on 17/02/2012 for the active immunisation against H5N1 subtype of influenza A virus in adults from 18 years onwards.

The immunogenicity of Vepacel in adults has been investigated in seven completed MAH clinical studies (Phase 1/2 study 810501, Parts A and B; Phase 3 study 810601, Parts A, B, C and D; Phase 1/2 study 810701, Parts A and B; Phase 2 study 810703, Parts A and B; Phase 3 study 810705, Parts A, B, C, D and E; Phase 1/2 study 810802, Parts A and B; and Phase 1/2 study 810706), and in one completed study not MAH-sponsored (Phase 1 Study NIAID).

Studies 810501, 810601, 810701, 810703 and 810705 Parts A to D were already provided by the MAH on 03 August 2010. Study 810705 addendum to Parts A and C as well as Part E, and study 810802 Part A were provided on 27 June 2011.

With this procedure, the MAH proposes to extend the indication to include healthy children from 6 months to 17 years of age based on data from study 810706. This is a study in children that was ongoing during the initial marketing authorization procedure, and whose finished study report has been submitted in December 2012 in order to fulfil a post-authorization commitment.

The PDCO adopted an opinion confirming the compliance of all studies to the agreed paediatric investigation plan as set out in the latest PDCO Decision (P/67/2011) of 11 March 2011.

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 trial parts that were 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

The Phase 1/2 study 810706 is a partially blinded, prospective, multicentre clinical study to assess the immunologic response and safety of the H5N1 pandemic influenza vaccine (A/Vietnam/1203/2004) (Vepacel) in a total of at least 670 male and female healthy infants, children and adolescents from 6 months to 17 years of age.

Assays used for the evaluation of immunogenicity in the study are:

Microneutralization (MN) Test

A classical cytopathic effect (CPE) based MN assay was performed. Serum samples are serially diluted with cell culture medium in two-fold steps. The serum dilutions are mixed at a ratio of 1:1 with a virus stock suspension adjusted to a virus titre of approximately 2,000 $TCID_{50}$/mL (i.e. the final virus titre will be 1,000 $TCID_{50}$/mL or 100 $TCID_{50}$ per well), incubated for 1 hour at room temperature and transferred to a microtitre plate containing a monolayer of cells permissive for influenza virus infection. The plates are incubated for 5-6 days at 36 ± 2 °C in a CO2-incubator. The cultures are inspected under a light microscope for the presence of a cytopathic effect (CPE) caused by H5N1 in the cell layer. The neutralizing titre is calculated by the number of virus negative wells and the serum dilution according to the method of Spearman. For purposes of analysis, any MN result < 1:10 (undetectable) is expressed as 1:3.9 and is considered negative.

Single Radial Haemolysis (SRH) Test

SRH was carried out according to published methods (Schild et al., 1975). The SRH method is based on the passive haemolysis of erythrocytes, sensitized with influenza virus particles, by antibodies directed against the viral haemagglutinin in the presence of a complement.

Prior to the test, complement present in the sera is inactivated through incubation for 30 minutes at 56°C. A 10% suspension of erythrocytes derived from sheep or turkey are primed with influenza antigen diluted to 2000 HAU/mL. The primed erythrocytes are washed, mixed with guinea pig complement and added to a suspension of molten 1.5% agarose in PBS comprising a two-to-one mix of standard and low-melting-point agarose. This preparation is spread onto PVC plates and allowed to gel before a series of 2.56 mm holes are made with a calibrated punch. Test and control sera are added to the wells and the plates are incubated for 16 hours at 4°C to allow diffusion of the antiserum into the gel. The plates are subsequently incubated for 90 minutes at 37°C to allow antibody-dependent complement-mediated haemolysis to occur. The diameters of haemolysis halos are then measured and the anti-influenza titre of the test sera expressed as the area of the region of haemolysis in square millimetres.

Haemagglutination Inhibition (HI) Test

HI titres were determined by HI tests against H5N1 antigens. Antibody titrations were done in duplicate; pre- and post-vaccination sera were titrated simultaneously. The titre assigned to each sample was the geometric mean of two independent determinations. For purposes of analyses, any HIA results < 1:10 (undetectable) were expressed as 1:5 and were considered negative.

Interpretation of results

The interpretation of the HI and SRH results was linked to the immunogenicity requirements defined by the Note for Guidance on Harmonisation for Influenza vaccines (CPMP/BWP/214/96), see table below:

Table 2: Parameters of the Note for Guidance (CPMP/BWP/214/96)

Defined from D0 to D21 and D0 to D42	Age	
	18 to 60 years	> 60 years
Seroconversion*or significant increase† rate of titer	>40%	>30%
Mean Geometric fold increase‡	>2.5	>2.0
Seroprotection rate (HI titer ≥1:40, SRH area ≥25mm^2)	>70%	>60%

* Proportion of subjects with a pre-vaccination HI titer <1:10 to a post-vaccination HI titer ≥1:40
Proportion of subjects with a baseline hemolysis area of ≤4 mm² and an area of ≥25 mm² post vaccination

† Proportion of subjects with HI titres ≥1:10 before vaccination and ≥4-fold increase of the titer.
Proportion of subjects with a ≥ 50% increase in hemolysis area if the pre-vaccination area is >4 mm²

‡ Geometric mean of individual ratios (post-/pre-vaccination titres: D21/D0 or D42/D0)

With regards to the MN assay similar parameters were used by the MAH for the calculation of seroneutralisation rates using a cut-off of ≥1:20. Further as proposed in guideline EMEA/CHMP/VWP/263499/2006 the proportions of achieving at least a fourfold increase in the neutralising antibody titre (criterion for seroconversion) and GMTs were reported along with reverse cumulative distribution curves.

To allow the use of the immunogenicity criteria it should be demonstrated that the influenza vaccine is antigenically similar to the egg-cultured vaccine, as requested in the Note for Guidance on influenza vaccines (CPMP/BWP/214/96). The MAH elaborated in detail on this issue during the initial MAA for the mock up vaccine Pandemic Influenza Vaccine H5N1 Baxter (formerly named Celvapan- H5N1), and provided data on the characterization of egg-derived and Vero cell-derived influenza virus vaccine strains of previous influenza seasons. In summary, no significant differences in their infectivity, antigenicity and immunogenicity in mice were demonstrated. Moreover the egg-derived seed virus remains genetically stable during five passages in Vero cells. Hence it was concluded that the production system has no influence on the antigenicity of the vaccine.

Further experiments carried out during the initial MAA for Celvapan (H5N1) for validation and interpretation purposes of SRH, HI and MN data are also relevant for the current application and are quickly summarised below.

Concerning the HI assay, the evaluation of human sera by HI assays revealed a high variability in the test results, although varying designs of the assay were applied (e.g. use of horse or turkey erythrocytes as well as utilising antigen from different type of strains or from different sources). Similar findings were reported for some other H5N1 vaccines. To counteract for the high variability and low sensitivity of the HI assay the MAH provided immunogenicity data based on the SRH assay, following the EMEA Scientific Advice (EMEA/CHMP/SAWP/310862/2007) given for the mock up vaccine.

Concerning the MN assay, at present it is not known which neutralising antibody titre confers protection against a potential pandemic strain. Several studies have indicated that a cut-off of 1:20 is appropriate whereas others have used a cut-off of 1:40. Moreover there is a high variability in test results depending on the laboratory and the specific neutralisation assay employed and because no international reference material is available for standardisation. In the context of the dossier for the mock up H5N1 vaccine, the MAH performed passive immune transfer studies in mice to evaluate whether the chosen cut-off titre of 1:20 was appropriately defined. A MN titre of 1:5 (mouse immune sera) or 1:7 (guinea pig immune sera), respectively, was demonstrated to correlate with 50% protection against a lethal challenge. In addition two independent passive immune transfer experiments in mice using pooled human immune sera from vaccinees enrolled in study 810601 were conducted. These data suggest 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. With regard to assay validation, the validation data were found to be satisfactory.

The performance of the SRH assay was found to be satisfactorily validated.

In conclusion, only the MN and SRH assay results were considered relevant to the evaluation of the immunogenicity of the Pandemic Influenza Vaccine H5N1 Baxter. In analogy, because of the lacking reliability of HI assay results, only the MN and SRH assay results were reported for Vepacel (which is has the same active substance as Pandemic Influenza Vaccine H5N1 Baxter) both for the initial marketing authorisation and for the current application.

Study participants

Subjects were stratified into three strata: children and adolescents aged 9 to 17 years (Stratum A), children aged 3 to 8 years (Stratum B) and infants and young children aged 6 to 35 months (Stratum C).

Subjects were recruited into five study cohorts:

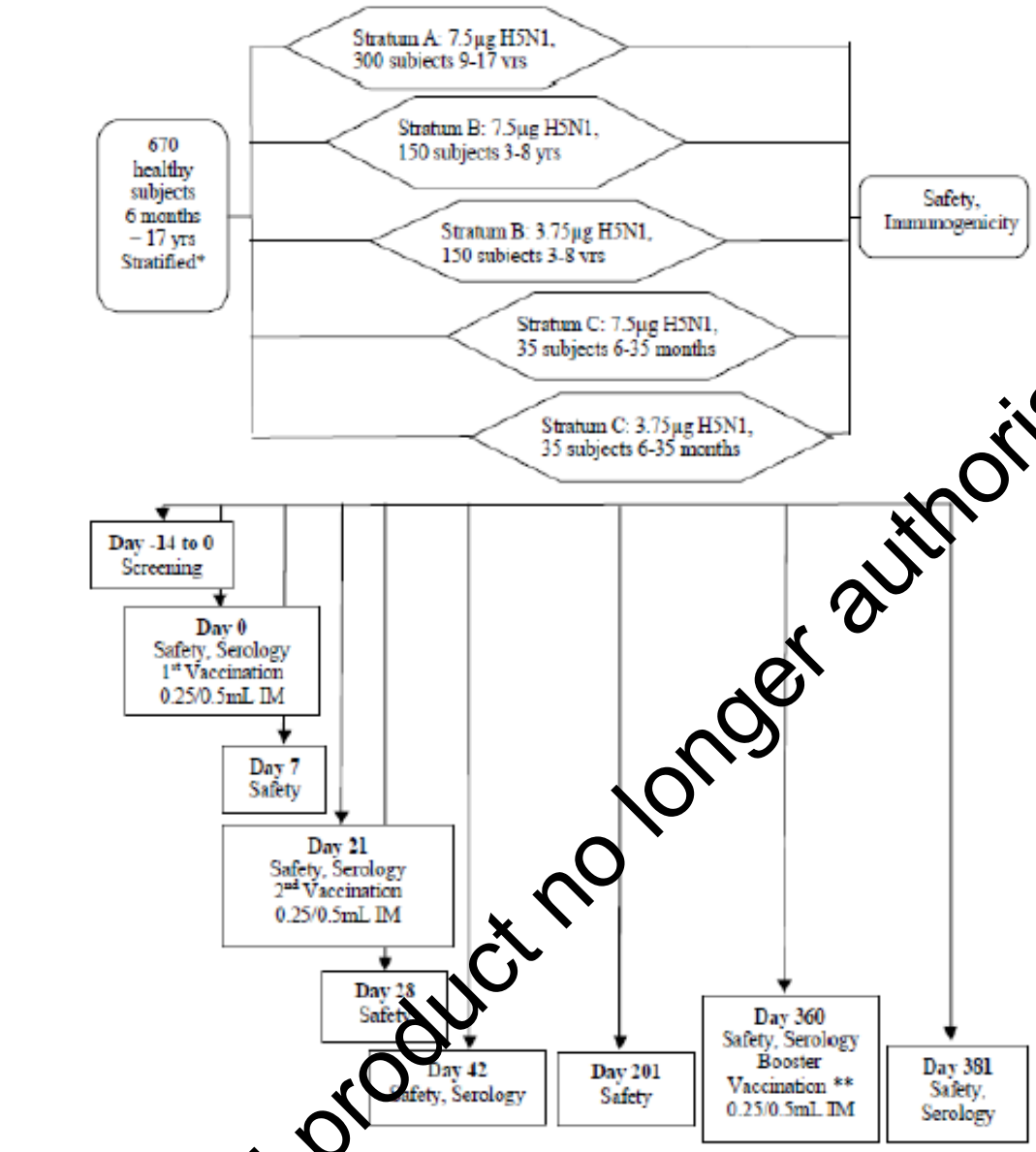
Cohort 1: Cohort 1 consisted of the first approximately 30 subjects from Stratum A, of which all received the 7.5 µg HA antigen dose. Safety data obtained at Day 7 after the first vaccination was reviewed by a Data Monitoring Committee (DMC) and a recommendation obtained (i) to administer the second vaccination to Cohort 1 and (ii) to proceed to Cohort 2.

Cohort 2: Cohort 2 consisted of the remaining approximately 270 subjects from Stratum A. When safety data through Day 7 after the first vaccination for approximately 120 subjects in this Cohort were available, these were reviewed by a DMC (as described above for Cohort 1) and a recommendation obtained to proceed to Cohort 3. The DMC review also included all safety data after the first and second vaccination for subjects in Cohort 1 available at that point in time.

Cohort 3: Cohort 3 consisted of the first approximately 30 subjects from Stratum B randomized 1:1 to either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. Safety data through Day 7 after the first vaccination was reviewed by a DMC (as described above for Cohort 1) and a recommendation obtained to proceed to Cohort 4. The DMC review also included all safety data after the first and second vaccination for subjects in Stratum A available at that point in time.

Cohort 4: Cohort 4 consisted of the remaining approximately 270 subjects from Stratum B and the first approximately 30 subjects from Stratum C, both randomized 1:1 to either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. When safety data through Day 7 after the first vaccination for the approximately 30 subjects in Stratum C were available, these were reviewed by a DMC (as described above for Cohort 1) and a recommendation obtained to proceed to Cohort 5. The DMC review also included all safety data after the first and second vaccination for subjects in Stratum A and Stratum B available at that point in time.

Cohort 5: Cohort 5 consisted of the remaining approximately 40 subjects from Stratum C randomized 1:1 to either the 7.5 µg or 3.75 µg H5N1 HA antigen dose.



* Enrollment will be performed step-wise.
** A booster vaccination must be administered to a subset of subjects in Strata A and B and all subjects in Stratum C. One clinical study report will be prepared for all data generated in Strata A and B (Part A) and Stratum C (Part B).

Treatments

All subjects received the primary vaccination as two injections of either 7.5 µg or 3.75 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.

Children and adolescents aged 9 to 17 years (Stratum A) were vaccinated with the 7.5 µg H5N1 HA antigen dose. Children aged 3 to 8 years (Stratum B) and infants and young children aged 6 to 35 months (Stratum C) were randomized 1:1 to receive either the 7.5 µg or 3.75 µg H5N1 HA antigen dose.

On Day 360 a subset of at least 375 subjects, 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.

Identity of Investigational Product(s)

The investigational product was provided in multi dose vials (i.e. 10 doses of 0.5 mL). A single 0.5 mL dose contained 7.5 µg HA antigen of the H5N1 influenza strain A/Vietnam/1203/2004 (or A/Indonesia/05/2005 for the booster vaccination for the subject subset). The investigational product was administered at either a dose of 0.5 mL (i.e. 7.5 µg HA antigen; Strata A, B and C) or 0.25 mL (i.e. 3.75 µg HA antigen: Strata B and C). The vaccine was free of preservatives, therefore each vial was to be used within one vaccination session or within 3 hours (following first opening), whichever was less.

Objectives

The objectives of this study were:

- 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 an unadjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years.

Outcomes/endpoints

Primary Immunogenicity Endpoints

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

Secondary Immunogenicity Endpoints

- Rate of subjects with antibody response associated with protection 21 days after the first and second vaccination defined as HIA titre ≥ 1:40 or SRH area ≥ 25 mm^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;
- Antibody response 21 days after the first and second vaccination as measured by MN, HI and SRH assay;
- 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;
- 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 mm^2 haemolysis area after

the vaccination in case of a negative pre-vaccination sample [≤ 4 mm^2] or a ≥ 50% increase in haemolysis area if the pre-vaccination sample is > 4 mm^2 [for SRH assay]) 21 days after the first and second vaccination as measured by MN, HI and SRH assay;

- Rate of subjects with antibody response associated with protection 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;
- Antibody response 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;
- 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;
- Rate of subjects with seroconversion 21 days after the booster vaccination as measured by MN, HI and SRH assay.

Sample size

As recommended in the guideline EMEA/PDCO Standard paediatric investigation plan for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic (EMEA/405779/2009), 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 the 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. With a sample size of 270 subjects, the two-sided 95% CI of the proportion of subjects with antibody response associated with protection in Stratum A and B, expressed in percentages, does not extend more than 5.6% (13.8% with 63 subjects in Stratum C) from the sample proportion assuming that the estimated proportion was 70%.

The sample size of 300 subjects in Strata A and B provides a 95.1% chance (50.5% chance with 70 subjects in Stratum C) to detect at least one AE that occurs at a frequency of 1:100.

Randomisation

For Stratum B (3 to 8 years) and Stratum C (6 to 35 months), subjects were centrally randomized at an equal number to receive either the 7.5 µg or 3.75 µg HA dose of the H5N1 influenza vaccine. Randomization was performed via an interactive voice response system (IVRS). Randomization was carried out in blocks with a block size > 2 using the random number generator algorithm of Wichmann and Hill 1982 as modified by McLeod.

No randomization was required prior to administration of the booster vaccination, since the booster vaccination was to be administered at the same dose used for primary vaccination.

All subjects in Stratum A (9 to 17 years) received the 7.5 µg HA dose of the H5N1 influenza vaccine, so no randomization was required.

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.

Statistical methods

Primary Immunogenicity Endpoints

The rates of subjects with antibody response to the vaccine strain associated with protection 21 days after the second vaccination defined as titre measured by MN test ≥ 1:20 and their two-sided 95% CIs were calculated separately for each age stratum and treatment. The analysis was performed on the per protocol (PP) and intent to treat (ITT) datasets.

Secondary Immunogenicity Endpoints

For the following secondary immunogenicity endpoints point estimates and two-sided 95% CIs were calculated.

- Rate of subjects with antibody response associated with protection 21 and 360 days after the first, and 21 days after the second and booster vaccination defined as HIA titre ≥1:40 or SRH area ≥25 mm^2;
- Rate of subjects with antibody response associated with protection 21 and 360 days after the first and booster vaccination defined as MN titre ≥1:20;
- Antibody response 21 and 360 days after the first, and 21 days after the second and booster vaccination as measured by MN, HI and SRH assay;
- Fold increase of antibody response 21 after the first, second and booster vaccination as compared to baseline as measured by MN, HI and SRH assay;
- 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 mm^2 haemolysis area after the vaccination in case of a negative pre-vaccination sample [≤4 mm^2] or a ≥50% increase in haemolysis area if the pre-vaccination sample is > 4 mm^2 [for SRH assay]) 21 days after the first, second and booster vaccination as measured by MN, HI and SRH assay;

The analysis was carried out separately for each age stratum and treatment. For the log-transformed MN antibody titres in Stratum B and C a longitudinal analysis was performed within a repeated mixed model ANCOVA framework, accounting for the fixed effect of vaccine doses, study days, age, interaction of vaccine doses and study days, baseline titre as a covariate and for the random subject effect. Least-square vaccine group means and 95% CIs were computed and then back transformed by exponentiation into geometric means.

Analysis Datasets

The ITT dataset was to contain all randomized and vaccinated subjects with available data for the respective analysis. Subjects were analysed as treated.

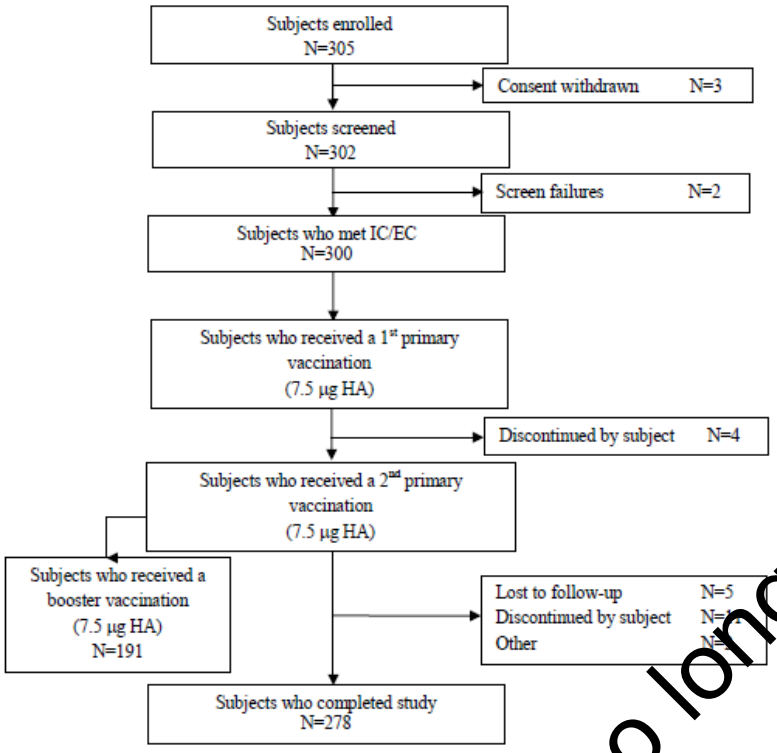
The PP dataset was to contain all randomized and vaccinated subjects, who fulfilled the exclusion/inclusion criteria, had no major protocol violations and for whom data for the respective analysis was available.

The safety analysis dataset contained all vaccinated subjects who had received the study vaccine at least once. Subjects were analysed as treated.

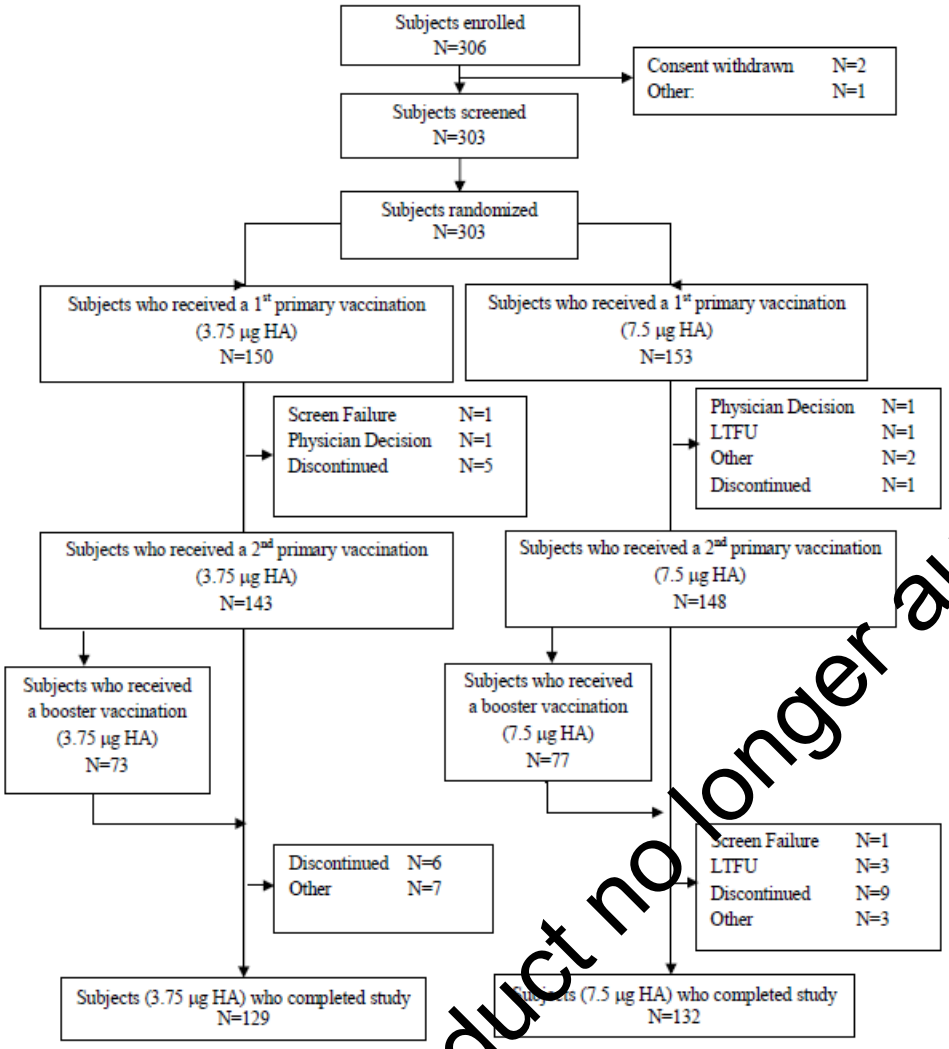
Results

Participant flow

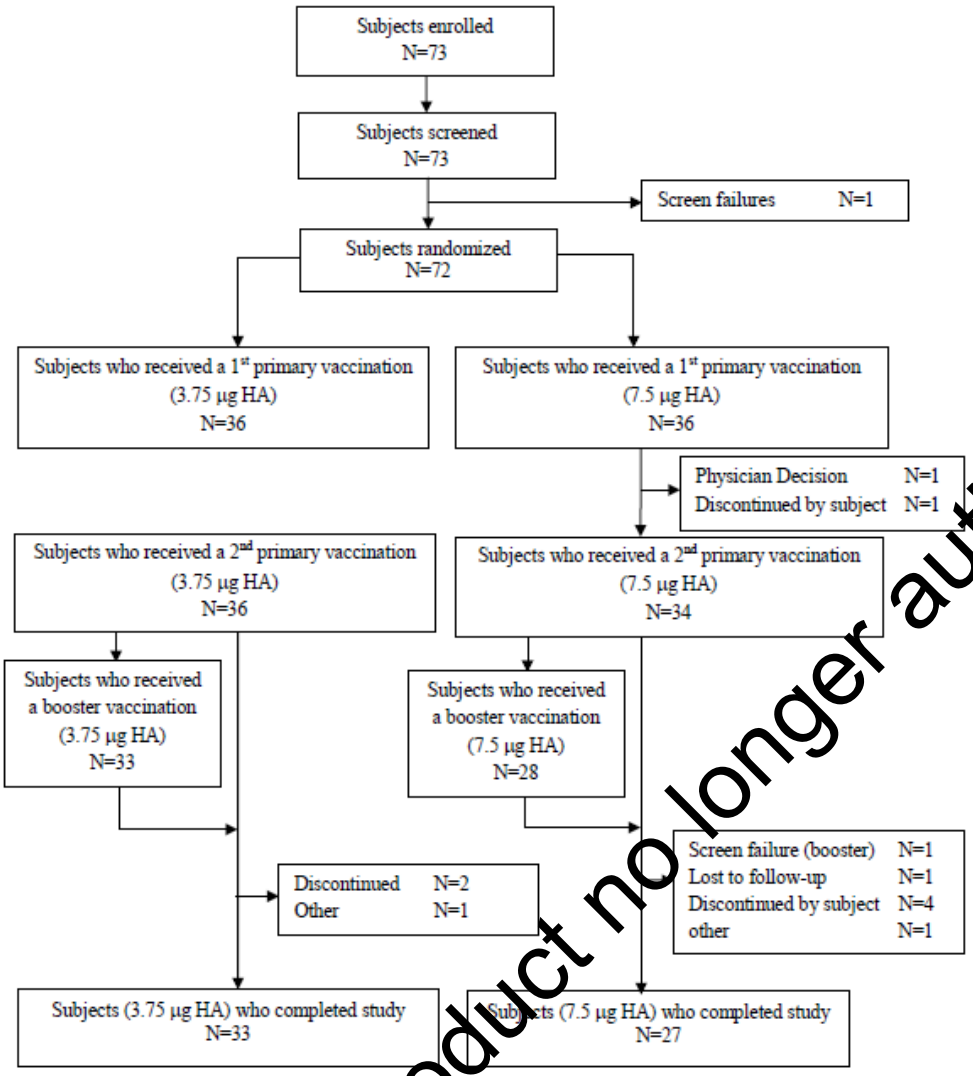
Stratum A (children and adolescents aged 9 to 17 years)[ix]



Stratum B (children aged 3 to 8 years) [x;ix]



Stratum C (infants and young children aged 6 to 35 months)[ix]



Recruitment

First subject in: 21 December 2009; Study Completion Last subject out: 24 May 2012.

Duration: 2 years and 5 months.

Conduct of the study

Changes in the Conduct of the Study or Planned Analyses

Four protocol amendments were implemented since the original version (e.g. changes in exclusion criteria, numbers enrolled etc.) and were considered acceptable by the CHMP upon assessment.

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.

Demographic and Baseline Characteristics - Categorical Data
(Study 810706: Intent-to-Treat Analysis Set)

Stratum=A (9 to 17 Years)

Parameter	Category	7.5 µg N=29 n (%)
Gender	Male	139 (47.0%)
	Female	157 (53.0%)
Race	White	278 (93.9%)
	Asian	13 (4.4%)
	American Indian or Alaska Native	2 (0.7%)
	Multiple	3 (1.0%)

Demographic and Baseline Characteristics - Categorical Data
(Study 810706: Intent-to-Treat Analysis Set)

Stratum=B (3 to 8 Years)

Parameter	Category	3.75 µg N=144 n (%)	7.5 µg N=147 n (%)
Gender	Male	80 (55.6%)	74 (50.3%)
	Female	64 (44.4%)	73 (49.7%)
Race	White	106 (73.6%)	112 (76.2%)
	Black or African American	2 (1.4%)	0 (0.0%)
	Asian	33 (22.9%)	34 (23.1%)
	Multiple	3 (2.1%)	1 (0.7%)

Demographic and Baseline Characteristics - Categorical Data
(Study 810706: Intent-to-Treat Analysis Set)

Stratum=C (6 to 35 Months)

Parameter	Category	3.75 µg N=36 n (%)	7.5 µg N=33 n (%)
Gender	Male	19 (52.8%)	17 (51.5%)
	Female	17 (47.2%)	16 (48.5%)
Race	White	33 (91.7%)	33 (100.0%)
	Multiple	3 (8.3%)	0 (0.0%)

Baseline Antibody Titres

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 stratum B (3-8 years) and stratum C (6 -35 months) antibody titres ≥ 1:20 as measured by MN were present in 1.4% and 0.0% of subjects, respectively. Comparable results were obtained for the PP dataset. Baseline SRH antibody titre levels associated with protection were observed in 15.6% of Stratum A subjects, 4.9% of stratum B subjects and 2.8% of stratum C subjects.

Numbers analysed

Planned

At least 670 male and female adolescents, children and infants (300 in Strata A [9 to 17 years] and B [3 to 8 years] and 70 in Stratum C [6 to 35 months]), who meet all inclusion criteria and none of the exclusion criteria were invited to participate in the study.

Analysed

Safety dataset: 675 subjects (300 Stratum A, 303 Stratum B and 72 Stratum C).
Intend-to-treat (ITT) dataset: 656 subjects (296 Stratum A, 291 Stratum B and 69 Stratum C).
Per-protocol (PP) dataset: 591subjects (270 Stratum A, 259 Stratum B and 62 Stratum C).

Outcomes and estimation

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.

MN Assay

Because no CHMP immunogenicity criteria for children are available, those for adults were used to evaluate the immunogenicity outcomes.

Criteria in analogy to the CHMP criteria for adults for the MN-Assay / CHMP criteria for adults for the SRH-Assay			
MN-Assay		**SRH-Assay**	
Seroprotection (≥ 1:20)*	> 70%	Seroprotection (> 25 mm²)	> 70%
Seroconversion	> 40%	Seroconversion	> 40%
Fold Increase	> 2.5	Fold Increase	> 2.5
* The cut-off of ≥1:20 was established by passive immune transfer studies using sera from clinical trials with Pandemic Influenza Vaccine H5N1.			

Results fulfilling the CHMP criteria are highlighted in **bold**.

MN-Assay Seroprotection (% with titre ≥1:20), **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
1	75/276	27.2	22.0-32.8	0/146	0.0	0.0 – 2.5	0/33	0.0	0.0 -10.6
22	144/274	52.6	46.8 – 58.6	25/146	17.1	11.4 – 24.2	1/33	3.0	0.1 – 15.8
43	234/274	**85.4**	80.7 – 89.4	105/144	**72.9**	64.9 – 80.0	22/32	68.8	50.0 – 83.9
after booster with 7.5 µg non-adjuvanted, strain A/Indonesia at D 361									
361	61/196	31.1	24.7 – 38.1	13/79	16.5	9.1 – 26.5	7/25	28.0	12.1 – 49.4
382	177/188	**94.1**	98.8 – 97.0	71/75	**94.7**	86.9 – 98.5	27/27	**100.0**	87.2 – 100.0
A/Indonesia									
361	29/188	15.4	10.6 – 21.4	9/72	12.5	5.9 – 22.4	1/19	5.3	0.1 – 26.0
382	175/188	**93.1**	88.5 – 96.3	70/72	**97.2**	90.3 – 99.7	19/19	**100.0**	82.4 – 100.0
MN-Assay Seroconversion, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
22	25/274	9.1	6.0 – 13.2	24/146	16.4	10.8 – 23.5	3/33	9.1	1.9 – 24.3
43	87/274	31.8	26.3 – 37.6	104/144	**72.2**	64.2 – 79.4	21/32	**65.6**	46.8 – 81.4
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D 361 (a compared to D 1 / b compared to D 361)									
Day	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
382 a	101/188	**53.7**	46.3 – 61.0	68/75	**90.7**	81.7 – 96.2	27/27	**100.0**	87.2 – 100.0
382 b	90/188	**47.9**	40.5 – 55.3	56/75	**74.7**	63.3 – 84.0	23/24	**95.8**	78.9 – 99.9

A/Indonesia (compared to D 361)									
382	140/188	**74.5**	67.6 – 80.5	65/72	**90.3**	81.0 – 96.0	19/19	**100.0**	82.4 – 100.0
MN-Assay Fold Increase, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	N	FI	95%CI	N	FI	95%CI	N	FI	95%CI
22	274	1.6	1.5 – 1.7	146	2.1	1.9 – 2.4	33	1.4	1.1 – 1.8
43	274	**3.1**	2.8 – 3.4	144	**6.3**	5.5 – 7.3	32	[illegible]	5.1 – 9.2
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D 361 (a compared to D 1 / b compared to D 361)									
Day	N	FI	95%CI	N	FI	95%CI	N	FI	95%CI
382 a	188	**5.2**	4.4 – 6.2	75	**15.2**	12.1 – 19.1	27	**30.9**	21.6 – 44.3
382 b	188	**4.4**	3.9 – 4.9	75	**6.9**	5.7 – 8.3	24	**13.5**	10.0 – 18.2
A/Indonesia (compared to D 361)									
382	188	**7.8**	6.8 – 9.0	72	**14.2**	11.3 – 17.8	19	**30.2**	20.7 – 43.8
MN-Assay Geometric Mean Titer, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	N	GMT	95%CI	N	GMT	95%CI	N	GMT	95%CI
1	276	11.8	10.8-12.8	146	4.8	4.5 – 5.1	33	4.0	3.8 -4.2
22	274	19.1	17.7 – 20.6	146	10.1	9.0 – 11.4	33	5.7	4.6 – 7.0
43	274	36.1	33.4 – 39.0	144	30.3	26.6 – 34.4	32	27.5	20.4 – 37.0
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D361									
361	196	15.6	14.4 – 17.0	79	11.2	9.7 – 12.9	25	9.9	7.0 – 14.1
382	188	68.5	59.8 –	75	77.1	63.3 – 93.7	27	124.7	88.1 –

			78.4						176.6
A/Indonesia									
361	188	11.0	10.1 – 12.1	72	8.6	7.4 – 9.9	19	6.0	4.4 – 8.0
382	188	86.1	73.2 – 101.3	72	121.4	95.7 – 154.0	19	179.7	128.0 – 252.4

In conclusion, 7 of 9 CHMP criteria could be fulfilled with the MN assay for the primary vaccination up to day 43 in the tree age strata. Seroprotection was narrowly missed for stratum C and seroconversion was missed for Stratum A. After the booster dose at day 361, all CHMP criteria were met for both strains, A/Vietnam and A/Indonesia in all three age strata. The low value for seroconversion in stratum A could be the consequence of the high seroprotection rate at baseline.

SRH Assay

SRH-Assay Seroprotection (≥25mm²), **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
1	45/288	15.6	11.6-20.3	5/141	3.5	1.2 – 8.1	0/30	0.0	0.0 - 11.6
22	178/279	63.8	57.9 – 69.4	65/141	46.1	37.7 – 54.7	4/29	13.8	3.9 – 31.7
43	214/285	**75.1**	69.6 – 80.0	104/138	**75.4**	67.3 – 82.3	17/27	63.0	42.4 – 80.6
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D 361									
361	59/189	31.2	24.7 – 38.3	7/75	9.3	3.8 – 18.3	0/24	0.0	0.0 – 14.2
382	144/176	**81.8**	75.3 – 87.2	63/73	**86.3**	76.2 – 93.2	24/25	**96.0**	79.6 – 99.9
A/Indonesia									
1	36/174	20.7	14.9 – 27.5	5/72	6.9	2.3 – 15.5	0/25	0.0	0.0 – 13.7
361	37/173	21.4	15.5 – 28.3	3/71	4.2	0.9 – 11.9	2/23	8.7	1.1 – 28.0
382	152/176	**86.4**	80.4 – 91.1	62/73	**84.9**	74.6 – 92.2	24/25	**96.0**	79.6 – 99.9
SRH-Assay Seroconversion, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									

	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	n/N	%	95%CI	n/N	%	95%CI	n/N	%	95%CI
22	135/279	**48.4**	42.4 – 54.4	61/141	**43.3**	35.0 – 51.9	4/29	13.8	3.9 – 31.7
43	181/285	**63.5**	57.6 – 69.1	108/138	**78.3**	70.4 – 84.8	21/27	**77.8**	57.7 – 91.4
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia (a compared to D 1 / b compared to D 361)									
382a	121/174	**69.5**	62.1 – 76.3	64/72	**88.9**	79.3 – 95.1	24/25	**96.0**	79.6 – 99.9
382b	105/173	**60.7**	53.0 – 68.0	58/71	**81.7**	70.7 – 89.9	23/23	**100.0**	85.2 – 100.0
A/Indonesia (a compared to D 1 / b compared to D 361)									
382a	125/174	**71.8**	64.5 – 78.4	60/72	**83.3**	72.7 – 91.1	25/25	**100.0**	86.3 – 100.0
382b	132/173	**76.3**	69.3 – 82.4	61/71	**85.9**	75.6 – 93.0	23/23	**100.0**	85.2 – 100.0
SRH-Assay Fold Increase, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	N	FI	95%CI	N	FI	95%CI	N	FI	95%CI
22	279	**3.3**	2.8 – 3.8	141	**2.9**	2.4 – 3.5	29	1.4	1.0 – 2.0
43	285	**4.7**	4.1 – 5.3	138	**5.9**	5.0 – 6.9	27	**4.6**	3.1 – 6.9
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D 361) (a compared to D 1 / b compared to D 361)									
382a	174	**5.4**	4.6 – 6.4	72	**6.8**	5.7 – 8.3	25	**8.5**	6.4 – 11.2
382b	173	**3.5**	3.3 – 4.1	71	**4.8**	4.0 – 5.8	23	**7.6**	6.1 – 9.4
A/Indonesia (a compared to D 1 / b compared to D 361)									
382a	174	**4.2**	3.6 – 4.9	72	**7.4**	6.1 – 8.9	25	**10.9**	8.5 - 13.9
382	173	**3.6**	3.1 –	71	**5.8**	4.8 – 6.9	23	**5.9**	4.5 – 7.8

b			4.0						
SRH-Assay Geometric Mean Titer, **7.5** µg non-adjuvanted, strain A/Vietnam (Study 810706 – ITT)									
	Stratum A (9-17y)			Stratum B (3-8y)			Stratum C (6-35 mo)		
A/Vietnam									
Day	N	GMT	95%CI	N	GMT	95%CI	N	GMT	95%CI
1	288	7.6	6.8 - 8.5	141	6.3	5.7 – 6.9	30	6.6	5.6 – 7.8
22	279	25.0	21.7 – 28.9	141	18.2	14.9 – 22.4	29	9.5	6.8 – 13.1
43	285	35.3	31.4 – 39.7	138	37.2	32.2 – 43.0	27	31.3	22.6 – 43.4
after booster with **7.5** µg non-adjuvanted, strain A/Indonesia at D 361									
361	189	12.3	10.5 – 14.5	75	8.9	7.5 – 10.6	24	7.3	6.1 – 8.6
382	176	41.1	36.6 – 46.1	73	43.7	37.9 – 51.4	25	55.6	47.4 – 65.2
A/Indonesia									
1	174	10.2	8.9 – 11.8	72	5.7	4.9 – 6.7	25	4.8	4.1 – 5.6
361	173	12.0	10.5 – 13.6	71	7.0	6.0 – 8.1	23	8.7	6.6 – 11.5
382	176	42.8	39.6 – 46.3	73	40.8	35.5 – 47.0	25	52.6	45.1 – 61.4

In summary, 8 of 9 CHMP criteria could be fulfilled with the SRH assay for the primary vaccination up to day 43 in the three age strata. Seroprotection was missed for stratum C. After the booster dose at day 361, all CHMP criteria were met for both strains, A/Vietnam and A/Indonesia in all three age strata.

Results for the 3.75 µg dose

MN Assay

Four of 6 CHMP criteria could be fulfilled with the MN assay for the primary vaccination up to day 43 with the lower dose in the two age strata. Seroprotection was missed for both age strata. After the booster dose at day 361, all CHMP criteria were met for both strains, A/Vietnam and A/Indonesia in both strata.

SRH Assay

Four of 6 CHMP criteria could be fulfilled with the SRH assay for the primary vaccination up to day 43 with the lower dose in the two age strata. Seroprotection was missed for both age strata, as with the MN assay. After the booster dose at day 361, again all CHMP criteria were met for both strains,

A/Vietnam and A/Indonesia in both strata. Nevertheless, the point estimates are markedly lower for the 3.75 µg dose than for the higher dose, which is already licensed in adults and elderly.

Antibody Response after Two-Dose Primary Vaccination

Rate of subjects with antibody response associated with protection (MN titre ≥1:20) at 21 days after the second vaccination as measured by MN assay

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) against the A/Vietnam/1203/2004 strain in 85.4% of subjects aged 9 to 17 years (Stratum A) at 21 days after the second vaccination. Among subjects aged 3 to 8 years (Stratum B), 72.9% of those receiving the 7.5 µg dose achieved an MN titre ≥ 1:20 at 21 days after the second vaccination, 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 MN antibody titres ≥ 1:20 21 days after the second dose, compared to 54.3% of those receiving the 3.75 µg dose (Table 1). Similar results were obtained for the PP dataset.

Table 1. Rate of Subjects with Antibody Response Associated with Protection (≥1:20) Measured by MN (Study 810706: Intent-to-Treat Analysis Set)

Stratum	Strain	Day	3.75 µg n/N (%) 95% CI[a]	7.5 µg n/N (%) 95% CI[a]
A (9 to 17 Years)	Vietnam	Day 1	NA	75/276 (27.2%) 22.0% to 32.8%
		Day 22	NA	144/274 (52.6%) 46.5% to 58.6%
		Day 43	NA	234/274 (85.4%) 80.7% to 89.4%
		Day 361	NA	61/196 (31.1%) 24.7% to 38.1%
		Day 382	NA	177/188 (94.1%) 89.8% to 97.0%
	Indonesia	Day 361	NA	29/188 (15.4%) 10.6% to 21.4%
		Day 382	NA	175/188 (93.1%) 88.5% to 96.3%
B (3 to 8 Years)	Vietnam	Day 1	2/139 (1.4%) 0.2% to 5.1%	0/146 (0.0%) 0.0% to 2.5%
		Day 22	12/139 (8.6%) 4.5% to 14.6%	25/146 (17.1%) 11.4% to 24.2%

Stratum	Strain	Day	3.75 µg n/N (%) 95% CI[a]	7.5 µg n/N (%) 95% CI[a]
		Day 43	76/133 (57.1%) 48.3% to 65.7%	105/144 (72.9%) 64.9% to 80.0%
		Day 361	10/74 (13.5%) 6.7% to 23.5%	13/79 (16.5%) 9.1% to 26.5%
		Day 382	66/72 (91.7%) 82.7% to 96.9%	71/75 (94.7%) 86.9% to 98.5%
	Indonesia	Day 361	4/70 (5.7%) 1.6% to 14.0%	9/72 (12.5%) 5.9% to 22.4%
		Day 382	64/70 (91.4%) 82.3% to 96.8%	70/72 (97.2%) 90.3% to 99.7%
C (6 to 35 Months)	Vietnam	Day 1	0/36 (0.0%) 0.0% to 9.7%	0/33 (0.0%) 0.0% to 10.6%
		Day 22	0/35 (0.0%) 0.0% to 10.0%	1/33 (3.0%) 0.1% to 15.8%
		Day 43	19/35 (54.3%) 36.6% to 71.2%	22/32 (68.8%) 50.0% to 83.9%
		Day 361	6/31 (19.4%) 7.5% to 37.5%	7/25 (28.0%) 12.1% to 49.4%
		Day 382	30/32 (93.8%) 79.2% to 99.2%	27/27 (100.0%) 87.2% to 100.0%
	Indonesia	Day 361	3/29 (10.3%) 2.2% to 27.4%	1/19 (5.3%) 0.1% to 26.0%
		Day 382	29/29 (100.0%) 88.1% to 100.0%	19/19 (100.0%) 82.4% to 100.0%

[a] Clopper-Pearson exact CI.
[generated by 810706_csra_effic.sas]
Source: CSR 810706 Table 18

Of note, 27.2% of the patients in the 9 to 17 years group are not naïve by MN assay, which is unexpected for a vaccine against H5N1. This is in contrast to the 3 to 8 year group, where practically all patients were naïve but one.

Rate of subjects with antibody response associated with protection (MN titre ≥1:20) at 21 days after the first vaccination as measured by MN assay

At 21 days after the first vaccination, 52.6% of subjects in Stratum A (9 to 17 years old), receiving the 7.5 µg vaccine dose, achieved an MN titre ≥ 1:20. Protection rates (MN titre ≥ 1:20) at 21 days after the first vaccination were lower among younger subjects (≤17.1% in Stratum B [3 to 8 year olds], and ≤3.9% 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.

Rate of subjects with antibody response associated with protection 21 days after the first and second vaccination defined as HIA titre ≥ 1:40 or SRH area ≥ 25 mm^2

Antibody response associated with seroprotection according to SRH was consistent with the MN assay results. Among subjects aged 9 to 17 years (Stratum A), 63.8% had antibody levels associated with seroprotection (SRH area ≥ 25 mm2) 21 days after the first vaccination, and 75.1% after the second vaccination. 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;

among those receiving the 3.75 µg dose, 47.1 % and 64.2% showed antibody levels associated with seroprotection after the first and second vaccinations, respectively. 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, compared to 25.7 % and 55.9% of subjects who received the 3.75 µg dose, after the first and second vaccinations, respectively.

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.

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

When measured by MN assay, in Stratum A (9 to 17 years of age), the GMT increased from 11.8 at baseline to 19.1 at Day 22, and to 36.1 at Day 43. In Stratum B (3 to 8 years of age), among those receiving the 7.5 µg and 3.75 µg doses, respectively, the GMT increased from 4.8 and 5.2 at baseline to 10.1 and 8.9 at Day 22, and to 30.3 and 23.8 at Day 43. In Stratum C (6 to 35 months of age), baseline GMT for the 7.5 µg and 3.75 µg dose groups were both 4.0, which rose to 5.7 and 6.1, respectively, by Day 22 and to 27.5 and 25.2,respectively by Day 43. Results as measured by SRH assay were consistent to the MN results; GMTs as measured by the HI assay were much lower and highly inconsistent with those determined by MN and SRH.

Fold increase of antibody response 21 days after the first and second vaccinations compared to baseline as measured by MN assay is displayed in Table 2:

Table 2. Fold increase of Antibody Response as Compared to Baseline as Measured by MN (Study 810706: Intent-to-Treat Analysis Set)

Stratum	Strain	Day	3.75 µg N GM 95% CI	7.5 µg N GM 95% CI
A (9 to 17 Years)	Vietnam	Day 22[a]	NA	274 1.6 1.5 to 1.7
		Day 43[a]	NA	274 3.1 2.8 to 3.4
		Day 382[a]	NA	188 5.2 4.4 to 6.2
		Day 382[b]	NA	188 4.4 3.9 to 4.9
	Indonesia	Day 382[b]	NA	8.8 8.8 to 9.0
B (3 to 8 Years)	Vietnam	Day 22[a]	139 1.7 1.5 to 1.9	146 2.1 1.9 to 2.4
		Day 43[a]	133 4. 3.9 to	144 6.3 5.5 to 7.3
		Day 382[a]	11.0 to 14.3	75 15.2 12.1 to 19.1
		Day 382[b]	72 6.5 5.2 to 8.2	75 6.9 5.7 to 8.3
	Indonesia	Day 382	70 11.9 9.1 to 15.7	72 14.2 11.3 to 17.8
C (6 to 35 Months)	Vietnam	Day 22[a]	35 1.6 1.3 to 1.9	33 1.4 1.1 to 1.8
		Day 43[a]	35 6.3 4.3 to 9.1	32 6.8 5.1 to 9.2
		Day 382[a]	32 21.7 15.4 to 30.7	27 30.9 21.6 to 44.3
		Day 382[b]	30 9.2 7.3 to 11.7	24 13.5 10.0 to 18.2
	Indonesia	Day 382[b]	29 16.0 12.0 to 21.4	19 30.2 20.7 to 43.8

[a] as compared to Day 1.
[b] as compared to Day 361.
[generated by s10706_csra_effic.sas]
Source CSR 810706 Table 20

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 comparable 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.

Rate of subjects with seroconversion 21 days after the first and second vaccination as measured by MN, HI and SRH assay

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.

Table 3. Rate of Subjects with Seroconversion Measured by MN (Study 810706: Intent-to-Treat Analysis Set)

Stratum	Strain	Day	3.75 µg n/N (%) 95% CI[b]	7.5 µg n/N (%) 95% CI[b]
A (9 to 17 Years)	Vietnam	Day 22[c]	NA	25/274 (9.1%) 6.0% to 13.2%
		Day 43[c]	NA	87/274 (31.8%) 26.3% to 37.6%
		Day 382[c]	NA	101/188 (53.7%) 46.3% to 61.0%
		Day 382[d]	NA	90/188 (47.9%) 40.5% to 55.3%
	Indonesia	Day 382[d]	NA	140/188 (74.5%) 67.6% to 80.5%
B (3 to 8 Years)	Vietnam	Day 22[c]	18/139 (12.9%) 7.9% to 19.7%	24/146 (16.4%) 10.8% to 23.5%
		Day 43[c]	71/133 (53.4%) 44.5% to 62.1%	104/144 (72.2%) 64.2% to 79.4%
		Day 382[c]	60/72 (83.3%) 72.7% to 91.1%	68/75 (90.7%) 81.7% to 96.2%
		Day 382[d]	51/72 (70.8%) 58.9% to 81.0%	56/75 (74.7%) 63.3% to 84.0%
	Indonesia	Day 382[d]	56/70 (80.0%) 68.7% to 88.6%	65/72 (90.3%) 81.0% to 96.0%

C (6 to 35 Months)	Vietnam	Day 22[c]	3/35 (8.6%) 1.8% to 23.1%	3/33 (9.1%) 1.9% to 24.3%
		Day 43[c]	21/35 (60.0%) 42.1% to 76.1%	21/32 (65.6%) 46.8% to 81.4%
		Day 382[c]	31/32 (96.9%) 83.8% to 99.9%	27/27 (100.0%) 87.2% to 100.0%
		Day 382[d]	26/30 (86.7%) 69.3% to 96.2%	23/24 (95.8%) 78.9% to 99.9%
	Indonesia	Day 382[d]	29/29 (100.0%) 88.1% to 100.0%	19/19 (100.0%) 82.4% to 100.0%

[a] defined as a ≥ 4 fold increase after vaccination.
[b] Clopper-Pearson exact CI.
[c] as compared to Day 1.
[d] as comapred to Day 361.
[generated by 810706_csra_effic.sas]

Results as determined by SRH assay were somewhat higher but generally consistent with 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 much lower and highly inconsistent with those determined by MN and SRH.

Antibody Response after the Booster Vaccination

The number of subjects with antibody response associated with protection 360 days after the first vaccinations and 21 days after the heterologous H5N1 booster vaccination were analysed. When determined by MN assay, rates of subjects with an MN titre ≥ 1:20 at Day 361 (pre-booster) in Strata A, B and C (7.5 μg dose group) were 31.1%, 16.5% and 28.0% (when measured against the primary vaccine strain, A/Vietnam/1203/2004). These rates increased by 21 days post-booster (Day 382) after the heterologous booster vaccination to 94.1%, 94.7%, and 100.0% (against the A/Vietnam/1203/2004 strain), respectively. In the 3.75 µg dose group, in Strata B and C, prior to the booster vaccination, the rates were 13.5% and 19.4% against the A/Vietnam/1203/2004 strain, compared to after the booster vaccination, when rates were 91.7% and 93.8%.

Against the A/Indonesia/05/2005 strain, 15.4%, 12.5% and 5.3% of subjects in Strata A, B and C (7.5 μg dose), and 5.7% and 10.3% of subjects in Stratum B and C (3.75 μg dose) showed MN titres ≥ 1:20 pre-booster (Day 361). After the booster, seroprotection rates against the A/Indonesia/05/2005 strain increased substantially to 93.1%, 97.2% and 100.0% in Strata A, B and C with the 7.5 µg dose, and 91.4% and 100.0% in Strata B and C with the 3.75 µg dose.

Results as determined by the SRH assay showed a similar trend compared to those of the MN assay. HI assay results were much lower and highly inconsistent with those determined by MN and SRH.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This variation for the extension of the indication is based on data from one clinical study involving a total of 656 vaccinated subjects (ITT). Healthy children and adolescents were recruited into three different age strata, stratum A (9-17 years), stratum B (3-8 years) and stratum C (6-35 months). All subjects in stratum A received two 7.5 µg doses of H5N1 vaccine strain A/Vietnam 21 days apart, while

subjects in stratum B and C were randomized to either a 3.75 µg or a 7.5 µg dose. The study was partially blinded for strata B and C and well designed to evaluate immunogenicity and persistence of antibodies after a two dose priming schedule. The effects of a heterologous booster immunisation with the same dose as the primary vaccination (7.5 and 3.75 µg, strain A/Indonesia) 12 months after the initial vaccination and cross-reactivity of elicited antibodies were explored as well in a subset of subjects.

Efficacy data and additional analyses

All three serological criteria specified for the evaluation of the initial vaccination were met with the 7.5 µg dose after the second vaccination in stratum B, while in stratum C seroprotection was narrowly missed and in stratum A seroconversion was missed when evaluated by the MN assay. This could be due to the high baseline seropositivity in stratum A (see below). SRH assay results also met all three criteria in stratum A and B, but missed seroprotection in stratum C. These data are in line with and comparable to serological results achieved in healthy adults from 18 - 60 years of age in studies 810501, 810601 and 810705. Overall the antibody response was lower in the younger compared to the older age groups

According to baseline data, a substantial proportion of study subjects was not immunologically naïve to H5N1, and some subjects even had titres in the seroprotective range against H5N1. In the 9-17 years age group, 27.2% had neutralizing antibody titres (MN titre ≥ 1:20) before vaccination, versus 0.7% in the 3-8 years age group and 0.0% in subjects aged 6- 35 months. Detectable levels of neutralizing antibodies (MN titre ≥ 1:7.7) at baseline were observed in 75.7% of subjects aged 9-17 years, compared with 22.8 % in the 3-8 years age group and 2.9% in the 6-35 month olds. An age distribution of those subjects aged 9-17 years with MN titres ≥ 1:20 and MN titres ≥ 1:7.7 is provided in the table below.

Table 1
Proportion of Subjects with MN Titre ≥ 1:20 and MN Titre ≥ 1:7.7 at Baseline in 9 to 17 Years Age Group (Study 810706: Intent-to-Treat Analysis Set)

Age at Screening (Years)	MN titre ≥ 1:20 at baseline	MN titre ≥ 1:7.7 at baseline
9	4/30 (13.3%)	16/30 (53.3%)
10	9/41 (22.0%)	26/41 (63.4%)
11	10/32 (31.3%)	27/32 (84.4%)
12	13/32 (40.6%)	25/32 (78.1%)
13	10/32 (31.3%)	26/32 (81.3%)
14	7/34 (20.6%)	26/34 (76.5%)
15	8/28 (28.6%)	23/28 (82.1%)
16	10/35 (28.6%)	29/35 (82.9%)
17	4/12 (33.3%)	11/12 (91.7%)
Total	75/276 (27.2%)	209/276 (75.7%)

The MAH was asked to clarify this aspect during the procedure. The high rate of subjects with H5N1-neutralizing antibodies at baseline in the 9-17 years age group might be explained by the fact that the study was undertaken after the first wave of the 2009 H1N1 pandemic. The H1N1pdm09 virus has been shown to induce a recall response that boosts pre-existing heterosubtypic antibody responses

directed against the HA stalk (Pica et al., 2012), including antibodies which cross-neutralize H5N1 (Li et al., 2012; Qiu et al., 2012; Wrammert et al., 2011). A number of seroepidemiological studies reported high rates of H1N1pdm09 infection in the pediatric population (Broberg et al., 2011; Hoschler et al., 2012; von Kries et al., 2011) and substantially higher seasonal influenza seroprevalence in older compared to younger children (Bodewes et al., 2011; Sauerbrei et al., 2009), thus increasing the potential of the H1N1pdm09 virus to boost heterosubtypic neutralizing antibodies. The high baseline H5N1 MN titres in the older age group but not the younger age groups might reflect the greater exposure of these subjects to seasonal influenza viruses.

Therefore in analogy to study 810705 assessed in the initial dossier, all MN and SRH results for study 810706 were asked to be presented 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). 21 days after the second vaccination, seronegative children in all three age cohorts show seroconversion rates and GM fold increases for the 7.5 µg dose well above the predefined adults CHMP criteria for both the MN and SRH assay. Seroprotection rates for the higher dose are in the range of or slightly below the CHMP criteria in all three age cohorts. Results are lower with the 3.75 µg dose and seroprotection was missed in age strata B and C with both assays, indicating the need for the higher dose in order to induce an adequate immune response in the two younger age cohorts. Conversely, seroprotection rates are higher for seropositive subjects in all 3 cohorts, while seroconversion and GM fold increases are lower than in the corresponding seronegative cohorts, as expected. In conclusion, the immune response in immunologically naïve children is considered to be comparable with the immune response in the overall study population (trials 810705, 810601).

Antibody persistence at the 12 months blood draw was detected, albeit modest. Following booster vaccination with the heterologous strain A/Indonesia at the same dose as the primary vaccination (7.5 or 3.75 µg), all CHMP criteria could be fulfilled 21 days post-vaccination in all three age groups with either assay and either antigen (A/Vietnam and A/Indonesia). These results underline the excellent boosterability and cross-reactivity of Vepacel as already seen in all other investigated populations (i.e. healthy adult, elderly, chronically ill and immunocompromised subjects – trial 810705 part E).

2.4.3. Conclusions on the clinical efficacy

Study 810706 shows that a two dose vaccination with the 7.5 µg A/Vietnam/1203/2004 vaccine administered 21 days apart induces a substantial antibody response in subjects from 6 months to 17 years of age. Immunogenicity results were comparable across assays, MN and SRH, and in line with the results of the healthy adult population in trials 810501, 810601 and 810705, previously assessed. 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 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.

The antibody response was slightly lower in the younger compared to the older age groups, as expected based on the different immune status at baseline among age groups, but overall it can be concluded that the immunogenicity of Vepacel in healthy children and adolescents from 6 months to 17 years is sufficiently substantiated and shown to be comparable to the immunogenicity of Vepacel in healthy adults.

2.5. Clinical safety

2.5.1. Introduction

Overall for Vepacel safety data in adults are available 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, 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 by the investigator (mild, moderate and severe).

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). An overview of the number of subjects who were administered the H5N1 influenza vaccine according to age stratum (9 – 17 years: Stratum A; 3 – 8 years: Stratum B, and 6 – 35 months: Stratum C) is provided in the following table:

Study Completion/Withdrawal Information (Study Groups According to First Actual Treatment) (Study 810706)

Stratum=A (9 to 17 Years)

	7.5 µg	Not assigned	Total
Enrolled	300	5	305
1st Vaccination	300	0	300
2nd Vaccination	296	0	296
Booster Vaccination	191	0	191
Completed	278	0	278
Reason for Withdrawal:			
Screen Failure	0	2	2
Lost to Follow-Up	5	0	5
Physician Decision	0	0	0
Discontinuation by Subject	15	3	18
Other	2	0	2

Adverse events

Systemic Reactions within 7 Days after the First Vaccination (primary endpoint)

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 (children and adolescents aged 9 to 17 years), 15.7% and 20.7% in Stratum B (children aged 3 to 8 years), and 33.3% and 30.6% in Stratum C (infants and young children aged 6 to 35 months). The majority of systemic reactions experienced by the subject after the first vaccination were mild or moderate with 5 subjects from Stratum A experiencing severe systemic reactions. One subject experienced severe fatigue and severe nausea lasting 2 days from which the subject recovered. Another subject experienced severe nasopharyngitis lasting 7 days. A third subject experienced severe myalgia lasting 3 days. A fourth subject experienced severe arthralgia lasting 4 days and severe myalgia lasting less than 24 hours. A fifth subject experienced severe vomiting, severe myalgia and severe headache, all lasting less than 24 hours. All subjects recovered from these symptoms.

Comparable results were obtained when fever was included in the systemic reaction rates 7 days after the first vaccination.

Number of Subjects Systemic Reactions (excluding fever) Within 7 Days After the 1st Vaccination by Severity
(Study 810706: Safety Analysis Set)

		Severity of Systemic Reactions (excluding fever)				
Stratum	Treatment	No Reaction n (%)[a]	Mild[b] n (%)[a]	Moderate[b] n (%)[a]	Severe[b] n (%)[a]	Total n[a]
A (9 to 17 Years)	7.5 µg	210 (70.0%)	64 (21.3%)	21 (7.0%)	5 (1.7%)	300
B (3 to 8 Years)	3.75 µg	119 (79.3%)	27 (18.0%)	4 (2.7%)	0 (0.0%)	150
	7.5 µg	129 (84.3%)	22 (14.4%)	2 (1.3%)	0 (0.0%)	153
C (6 to 35 Months)	3.75 µg	25 (69.4%)	8 (22.2%)	3 (8.3%)	0 (0.0%)	36
	7.5 µg	24 (66.7%)	10 (27.8%)	2 (5.6%)	0 (0.0%)	36

[a] Number of Subjects.
[b] When a single subject experiences multiple AEs, this AE is shown only once at its most serious severity.
[generated by 810706_csra_ae.sas]

Most subjects did not experience any systemic reactions within 7 days after the first vaccination. Stratum B and C received either 3.75µg or 7.5µg. No distinct differences in rates of systemic reactions between the two dose groups were observed. Five subjects experienced severe systemic reactions, of which all recovered.

Overall no safety concerns arise from these results.

Systemic Reactions within 21 Days after the First and Second Vaccinations

The majority of subjects experienced no systemic reactions within 21 days after either vaccination.

Within 21 days after the first vaccination, rates of subjects with systemic reactions (excluding fever) in the 7.5 µg and 3.75 µg dose group respectively were: 30.3% in Stratum A, 16.3% and 21.3% in Stratum B, and 36.1% and 30.6% in Stratum C. Therefore very few systemic reactions occurred between 7 and 21 days after the first vaccination. The majority of systemic reactions (excluding fever) after the first vaccination were mild or moderate. Severe systemic reactions were reported in 5 subjects (all from Stratum A, all within 7 days after vaccination).

Lower systemic reaction rates were observed after the second vaccination as compared to after the first; : 18.6% in Stratum A (7.5µg), 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 group respectively. Systemic reactions after the second vaccination were mostly mild. Two subjects experienced severe systemic reactions after the second vaccination. In Stratum A, one subject experienced severe fatigue on the day of vaccination lasting 5 days. In Stratum C, one subject experienced a severe cough one day after vaccination lasting less than 24 hours. Both subjects recovered from these symptoms.

Specifically Queried Systemic Symptoms of AEs after the First and Second Vaccinations

Certain symptoms of systemic reactions (shivering, nausea, vomiting, sweating, headache, malaise, fatigue, muscle pain, and joint pain for Strata A and B, and shivering, nausea, vomiting, sweating, irritability, inconsolable or excessive crying, disturbed sleep, loss of appetite and drowsiness for Stratum C), were specifically queried in the subject diary.

In the older two age strata, headache, malaise, fatigue and muscle pain were the most frequently experienced symptoms after the first and second vaccination. In Stratum A the rate of subjects that experienced these symptoms after the first and second vaccinations respectively were: headache: 18.7% and 10.1%; malaise: 6.7% and 2.0%; fatigue: 9.0% and 5.1%; and muscle pain: 6.3% and 1.4%. In Stratum B the rate of subjects that experienced these symptoms after the first and second vaccination respectively were: headache: ≤ 6.7% and ≤ 4.9%; malaise: ≤ 4.7% and ≤ 3.4%; fatigue: ≤

5.9%; and ≤ 6.7% and muscle pain: ≤ 3.9% and ≤ 2.8%). In Stratum C, irritability, inconsolable or excessive crying, disturbed sleep, loss of appetite and drowsiness were the most commonly reported symptoms: irritability: ≤ 19.4% and ≤11.8%; inconsolable or excessive crying: ≤ 8.3% and ≤2.9%; disturbed sleep: ≤ 16.7% and ≤ 5.9%; loss of appetite: ≤ 8.3% and ≤ 8.8% and drowsiness: ≤ 2.8% and ≤ 11.8% (after the first and second vaccinations respectively). In Strata B and C, these percentages reflect both dose groups (3.75µg and 7.5µg).

Fever, Malaise, Shivering and Irritability after the First and Second Vaccinations

Fever related to the first vaccination occurred at the following rates: 1.7% in Stratum A (7.5 µg), 4.6% and 6.0% in Stratum B, and 19.4% and 16.7% in Stratum C, in the 7.5 µg and 3.75 µg dose group respectively. Rates of fever related to vaccination 7 days after the second vaccination in the 7.5 µg and 3.75 µg dose group respectively were: 2.7% in Stratum A, 3.4% and 4.2% in Stratum B and 11.8% and 11.1% in Stratum C. After the first vaccination, 1 subject (Stratum B, 7.5 µg) had a body temperature of 40.0ºC; this subject also experienced nasopharyngitis and pyrexia 6 days after the first vaccination that were of 6 days and 3 days duration respectively. Both symptoms were assessed as unrelated to the vaccination by the investigator and/or Baxter. No subject experienced a body temperature above 39.4 ºC after the second vaccination.

Malaise related to the first vaccination was reported in 22 subjects (7.3%) in Stratum A and 5 subjects (3.3%) and 7 subjects (4.7%) in Stratum B for the 7.5 µg and 3.75 µg dose groups respectively. Rates of malaise after the second vaccination were similar to those observed after the first vaccination across both age Strata A and B. Malaise was reported mainly as mild, except for 2 subjects in Stratum A after the first vaccination, and 5 subjects in Stratum A and 2 subjects in Stratum B (one from each dose group) after the second vaccination who reported moderate malaise.

Shivering related to the first vaccination was reported in 3 (1.0%) subjects in Stratum A and 0 (0.0%) and 2 (1.3%) subjects in Stratum B (7.5 µg and 3.75 µg dose group, respectively), all of which were mild. Shivering related to the second vaccination was reported in 4 (1.4%) subjects in Stratum A and 0 (0.0%) and 1 (0.7%) subject in Stratum B (7.5 µg and 3.75 µg dose group, respectively). All cases of shivering were mild except for 1 subject in Stratum A, who experienced moderate shivering after the second vaccination.

After the first vaccination, irritability judged as related to vaccination was reported in 16 (22.2%) infants and young children in each dose group in Stratum C. After the second vaccination, irritability was reported in 5 (14.7%) and 4 (11.1%) subjects in the 7.5 µg and 3.75 g dose groups respectively (Table 11). Irritability was reported as mild to moderate.

Injection Site Reactions Occurring within 21 Days after the First and Second Vaccination

The majority of subjects experienced no injection site reactions within 21 days after either vaccination.

After the first vaccination, rates of subjects with injection site reactions were: 32.0% in Stratum A, 26.8% and 24.0% in Stratum B and 19.4% and 19.4% in Stratum C in the 7.5 µg and 3.75 µg dose group respectively. Within 21 days after the second vaccination, rates of subjects with injection site reactions were lower: 25.7% in Stratum A, 22.8% and 14.8% in Stratum B and 14.7% and 16.7% in Stratum C, in the 7.5 µg and 3.75 µg dose group respectively.

The majority of injection site reactions were mild. Four subjects reported severe injection site reactions after the first vaccination:

- site induration on the day of the vaccination which lasted for 4 days;
- severe injection site induration on the day of the vaccination which lasted less than 24 hours;
- severe injection site swelling on the day of the vaccination which lasted less than 24 hours;

- severe injection site erythema, severe injection site induration and severe injection site swelling on the day of vaccination which lasted 4 days for each event).

All subjects recovered from these symptoms.

Four subjects reported severe injection site reactions after the second vaccination (2 cases of severe injection site erythema on the day of vaccination lasting 2 days and 3 days respectively; one case of severe erythema and severe swelling at the injection site on the day of vaccination lasting 2 days; one case of severe erythema, severe induration and severe swelling at the injection site on the day of vaccination lasting 3 days). All subjects recovered from these symptoms.

The most frequently reported local symptom in all strata after either vaccination was injection site pain. Rates following the first vaccination were 28.3% in Stratum A, 25.5% and 21.3% in Stratum B and 13.9% and 13.9% in Stratum C with dose levels of 7.5 µg and 3.75 µg respectively. After the second vaccination, injection site pain rates were lower for all dose groups across all strata.

Adverse Events between Day 43 and Day 202/361

There were no systemic reactions reported between Day 43 and Day 202 (for subjects not receiving a booster vaccination) or between Day 43 and Day 361 (for subjects randomised to receive a booster vaccination – pre-booster), with the exception of 1 subject in Stratum B (7.5 µg dose group) who experienced a systemic reaction (hand, foot and mouth disease) of unknown severity (severity was not recorded).

Systemic Reactions within 21 Days after the Booster Vaccination

The majority of subjects experienced no systemic reactions following the booster vaccination.

After the booster vaccination, rates of subjects with systemic reactions (excluding fever) in the 7.5 µg and 3.75 µg dose group respectively were: 21.5% in Stratum A, 10.3% and 13.9% in Stratum B, and 17.9% and 6.1% in Stratum C.

The majority of systemic reactions (excluding fever) experienced by the subject after the booster vaccination were mild or moderate, with 2 subjects from Stratum A experiencing severe systemic reactions related to vaccination. One subject experienced severe headache 2 days after the booster vaccination and another subject experienced fatigue on the day of the booster vaccination, both lasted less than 24 hours.

Specifically Queried Symptoms of AEs after the Booster Vaccination

In the older two age strata, headache, malaise, fatigue and muscle pain were the most frequently experienced queried symptoms after the booster vaccination for Stratum A and B respectively, headache: 10.5% and ≤ 6.9%; malaise: 6.3% and ≤ 2.6%; fatigue: 8.4%; and ≤ 6.9% and muscle pain: 6.8% and ≤2.8%. In Stratum C, irritability, loss of appetite and drowsiness were most commonly reported after the booster vaccination: irritability: ≤ 3.6%; loss of appetite: ≤ 3.6% and drowsiness: ≤ 7.1%.

Fever, Malaise, Shivering and Irritability after the Booster Vaccination

Fever related to the booster vaccination occurred at the following rates: 1.0% in Stratum A, 6.4% and 1.4% in Stratum B and 10.7% and 12.1% in Stratum C in the 7.5 µg and 3.75 µg dose group respectively. Apart from 1 subject in Stratum B (7.5 µg dose group) experiencing maximum temperatures of 39.5ºC, and 1 subject in Stratum B (3.75 µg dose group) with a maximum temperature of 39.4ºC, fever did not exceed 38.9 ºC after the booster vaccination for any age strata.

Malaise related to the booster vaccination was reported in 15 subjects (7.9%) in Stratum A and 2 subjects (2.6%) and 2 subjects (2.8%) in Stratum B for the 7.5 µg and 3.75 µg dose groups

respectively which is comparable to the rate after the first and second vaccination. These were mild for all subjects except for 3 subjects in Stratum A and 1 subject in Stratum B (3.75 µg dose group) who showed moderate malaise.

Shivering related to the booster vaccination occurred in 5 (2.6%) subjects in Stratum A; 3 mild cases and 2 moderate cases. After the booster vaccination, irritability judged as related to vaccination was reported in 1 (3.6%) subject and 1 (3.0%) subject in the 7.5 µg and 3.75 µg dose groups respectively (Stratum C), both of which were mild.

Injection Site Reactions Occurring within 21 Days after the Booster Vaccination

The majority of subjects experienced no local reactions within 21 days after the booster vaccination.

After the booster vaccination, rates of subjects with injection site reactions in the 7.5 µg and 3.75 µg dose group respectively were: 30.4% in Stratum A, 37.2% and 30.6% in Stratum B and 14.3% and 18.2% in Stratum C. The majority of subjects experienced mild injection site reactions with no severe cases reported.

The most frequently reported local symptom in all strata after the booster vaccination was injection site pain. Rates following the booster vaccination with a dose level of 7.5 µg and 3.75 µg respectively were 29.3% in Stratum A, 32.1% and 26.4% in Stratum B and 7.1% and 12.1% in Stratum C.

The rates of injection site reactions within 21 days after the booster vaccination are comparable to the rates reported after the first and second vaccination with the exception of stratum B. There were higher rates of local reactions after the booster vaccination than after the first and second vaccination.

Serious adverse event/deaths/other significant events

No deaths or SAEs related to vaccination were reported throughout the study.

Eight subjects experienced SAEs, all of which were assessed by the investigator as unrelated to vaccination. One subject in Stratum A experienced moderate mesenteric lymphadenitis after the booster vaccination. The remaining 7 subjects experienced SAEs between Day 43 and Day 202 or 361. These included: 3 subjects in Stratum A with 3 SAEs: 1 subject experienced severe Henoch-Schönlein Purpura, which was assessed by the investigator and Baxter as unlikely related to vaccination, 1 subject sustained a moderate ankle fracture and 1 subject experienced loss of peripheral vision. In addition, 3 subjects in the 3.75 µg dose group in Stratum B experienced 3 SAEs: 1 subject experienced moderate stomach pain, 1 subject was reported to have severe stomatitis and 1 subject sustained moderate blunt abdominal trauma. One subject in the 7.5 µg dose group in Stratum B experienced mild acute viral conjunctivitis.

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).

One subject showed an abnormal result (51) with a toxicity grade of 1 on Day 43.

2.5.2. Discussion on clinical safety

During study 810706, 675 subjects (300 in Stratum A, 303 in Stratum B and 72 in Stratum C) 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 (296 Stratum A, 291 Stratum B and 70 Stratum C) 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 (191 Stratum A, 150 Stratum B and 61 Stratum C) 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.

To be in accordance 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 context" (EMEA/CHMP/VWP/263499/2006) it was planned to include 300 subjects in each age stratum. However, for stratum C the number of subjects was reduced from originally planned 300 to approximately 70 subjects due to recruitment problems as the timing of the clinical trial coincided with the H1N1 pandemic. Reduction of sample size in stratum C was accepted by the PDCO during the request of modification of an agreed PIP. Furthermore, the waiver for the 2 to less than 6 months old subset was agreed by the PDCO.

When compared to the benign safety profile already established in the adult population, (including chronically ill, immunocompromised and elderly subjects) where a total of 4612 subjects were exposed to at least one injection of the 7.5 µg vaccine and 3700 subjects are included in the long term safety database, the rates of systemic adverse reactions excluding fever were comparable whereas the rates of injection site reactions were somewhat higher in healthy infants, children and adolescents. Fever rates were higher than in the adult population. However, this is not unusual (higher fever rates in the paediatric population than in adults also seen for other vaccines, e.g. TBE vaccines, Twinrix) and most cases of fever were limited to <38.5°. The rates of fever and injection site reactions are considered acceptable.

Overall, the nature of reported adverse events is not unusual for influenza vaccines and is comparable to that of licensed inactivated seasonal influenza vaccines. Furthermore, the frequency of adverse events does not raise any concerns.

The type and incidence of adverse reactions to vaccinations in children has been reflected in the Product Information.

2.5.3. Conclusions on clinical safety

Safety results after the primary and cross-clade booster vaccinations in paediatric subjects aged 6 months to 17 years were as expected highly consistent with the safety results in adults and elderly (clinical studies 810501, 810601, 810701, 810703, 810705 and 810802) and did not raise any concern.

2.5.4. PSUR cycle

In light of the data submitted and assessed for the paediatric population, the PSUR cycle remains unchanged. The PSUR cycle for the medicinal product 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 related to the PSUR refers to the EURD list, which remains unchanged.

As soon as a pandemic is duly recognised by the WHO or the Union, the MAH will initiate Pandemic Pharmacovigilance practices as detailed in Annex II of the PI.

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	Limited information on safety in pregnant or lactating women	Planned	To be determined

	females during the course of an active pandemic			
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
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

The MAH proposed the update of section 4.1 of the SmPC. The reference to immunocompromised and chronically ill subjects has been deleted from the indication for simplification, as the data are reflected in section 5.1, to which the indication is referring.

As a consequence of this new indication, sections 4.2, 4.8 and 5.1 of the SmPC have been updated (new text is underlined and deleted text is marked as strikethrough). The Package Leaflet has been updated accordingly.

- **Section 4.1 Therapeutic indications**

Active immunisation against H5N1 subtype of influenza A virus.

This indication is based on immunogenicity data from ~~healthy~~ subjects from the age of 6 months onwards ~~as well as adult immunocompromised and chronically ill subjects~~ following administration of two doses of vaccine prepared with H5N1 subtype strains (see section 5.1).

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

Posology

Adults and children from 6 months onwards ~~from the age of 18 years~~:

One dose of 0.5 ml at an elected date.

~~Paediatric population:~~

~~The safety and efficacy of Vepacel in subjects under 18 years of age have not yet been established.~~

~~No data are available for Vepacel in this age group.~~

- **Section 4.8 Undesirable effects**

Infants, Children, and Adolescents

Children and adolescents aged 3 to 17 years:

In a clinical trial 300 adolescents aged 9 to 17 years and 153 children aged 3 to 8 years were administered the H5N1 vaccine. The incidence and nature of symptoms after the first and second vaccination were similar to those observed in the healthy adults and older people.

Infants and children aged 6 to 35 months:

In a clinical trial the H5N1 vaccine was administered to 36 infants and children aged 6 to 35 months.

The observed adverse reactions from a pediatric clinical trial with the H5N1 vaccine are listed below.

(...)

Adverse Reactions (Infants, Children and Adolescents)				
System Organ Class (SOC)	*Preferred MedDRA Term*	*Frequency*		
		6 – 35 months	*3 – 8 years*	*9 – 17 years*
INFECTIONS AND INFESTATIONS	*Nasopharyngitis*	*Common*	*Common*	*Common*
METABOLISM AND NUTRITION DISORDERS	*Decreased appetite*	*Common*	*Uncommon*	*Uncommon*
PSYCHIATRIC DISORDERS	*Insomnia* *Sleep disorder*	*-* *Common*	*-* *-*	*Uncommon* *-*

Adverse Reactions (Infants, Children and Adolescents)				
System Organ Class (SOC)	Preferred MedDRA Term	Frequency		
		6 – 35 months	3 – 8 years	9 – 17 years
NERVOUS SYSTEM DISORDERS	Dizziness	-	-	Uncommon
	Headache	-	Common	Very Common
	Crying	Common	-	-
	Somnolence	Very Common	-	-
	Hypoaesthesia	-	-	Uncommon
EYE DISORDERs	Eye irritation	-	Uncommon	-
EAR AND LABYRINTH DISORDERS	Vertigo	-	-	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough	-	Uncommon	Uncommon
	Oropharyngeal pain	-	Common	Common
	Rhinorrhoea	-	Uncommon	Uncommon
GASTROINTESTINAL DISORDERS	Abdominal pain	-	-	Common
	Nausea	Common	Common	Common
	Vomiting	Common	Common	Common
	Diarrhoea	Common	Uncommon	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Hyperhidrosis	Common	Uncommon	Common
	Pruritus	-	-	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	-	Common	Common
	Myalgia	-	Common	Common
	Pain in extremity	-	-	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site pain	Very common	Very common	Very common
	Injection site induration	Common	Common	Common
	Injection site erythema	Common	Common	Common
	Injection site swelling	Common	Common	Common
	Injection site hemorrhage	Common	Common	Uncommon -
	Injection site pruritus	-	Uncommon	Uncommon
	Axillary pain	-	Uncommon	Uncommon
	Fatigue	-	Common	Common
	Pyrexia	Very Common	Common	Uncommon
	Chills	-	-	Common
	Irritability	Very Common	-	-
	Malaise	-	Common	Common
	Feeling Cold	-	Uncommon	Uncommon

Section 5.1 Pharmacodynamic properties

~~*Paediatric population*~~

~~*No data are available on Vepacel for subjects under 18 years old.*~~

Infants, Children, and Adolescents
Immune response against A/Vietnam/1203/2004 (H5N1)

The immunogenicity of the A/Vietnam/1203/2004 strain vaccine has been evaluated in a clinical trial in children and adolescents aged 9 to 17 years (N=288), in children aged 3 to 8 years (N=146) and in infants and children aged 6 to 35 months (N=33) following a 0, 21 day schedule.

After vaccination, the rate of subjects with neutralizing antibody titers ≥ 20, seroconversion rate and seroconversion factor, as measured by MN assay, in infants, children, and adolescents aged 6 months to 17 years were as follows:

MN assay	9 – 17 years 21 Days after		3 – 8 years 21 Days after		6 – 35 months 21 Days after	
	1st Dose	2nd Dose	1st Dose	2nd Dose	1st Dose	2nd Dose
Seroneutralization rate*	52.6%	85.4%	17.1%	72.9%	3.0%	68.8%
Seroconversion rate**	9.1%	31.8%	16.4%	72.2%	9.1%	65.6%
Seroconversion factor***	1.6	3.1	2.1	6.3	1.4	6.8

* MN titer ≥ 20
** ≥ 4-fold increase in MN titer
*** geometric mean increase

Heterologous Booster Vaccinations

A heterologous booster vaccination with a 7.5 µg non-adjuvanted formulation of the A/Indonesia/05/2005 strain vaccine has been administered 12 months after a priming vaccination with two doses of the A/Vietnam/1203/2004 strain vaccine in children and adolescents aged 9 to 17 years (N=196), children aged 3 to 8 years (N=79) and infants and children aged 6 months to 35 months (N=25).

Seroneutralization rates (MN titer ≥ 20) at 21 days after a booster vaccination with the 7.5 µg dose of the A/Indonesia/05/2005 strain vaccine, tested against both the homologous and heterologous strains, were as follows:

Seroneutralization rate*	9 – 17 years		3 – 8 years		6 – 35 months	
Tested against	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia	A/Vietnam	A/Indonesia
12 Month Booster	94.1%	93.1%	94.7%	97.2%	100.0%	100.0%

* MN titer ≥ 20

~~*The European Medicines Agency has deferred the obligation to submit the results of one study with Vero Cell Derived Whole Virus H5N1 Influenza Vaccine in subjects of the paediatric population aged 6 months to 17 years in "active immunization against H5N1 subtype of influenza A virus". See section 4.2 for information on paediatric use.*~~

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

Vepacel is a vaccine to protect against influenza caused by the H5N1 subtype of the influenza A virus outside of an officially declared pandemic. Vaccination is considered to be the most effective option to limit the spread of a pandemic. Production of an H5N1 pandemic vaccine, however, can only be initiated once the exact strain is determined, i.e. after a pandemic is declared by the WHO. Vaccination of naïve individuals with an H5N1 influenza vaccine in a prepandemic setting is believed to have a significant impact on the consequences of a pandemic, i.e. it can help inducing rapid immunity and

decreasing disease severity. Since avian influenza H5N1 is considered 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 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 3 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. 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 ≤ 38.4° 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. 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

The type II variation for the extension of indication to the paediatric population is supported by data from the clinical trial 810706 in 675 healthy infants, children and adolescents (safety dataset) from 6 months to 17 years. Study 810706 is in compliance with the agreed Paediatric Investigation Plan for Vepacel.

The immunogenicity results obtained with the two assays, MN and SRH, are satisfactory and comparable across age strata and in line with those from the healthy adult population as assessed during the initial dossier for the authorization of Vepacel. In addition, the good cross-reactivity and boosterability with a heterologous strain underline the beneficial effects of Vepacel in prepandemic settings.

Vepacel was safe and well tolerated in healthy infants, children and adolescents aged 6 months to 17 years in study 810706. Most of the subjects did not experience any adverse events and most of the reported adverse events were of mild or moderate severity. The safety profile is comparable and consistent with the favourable dataset already available in the adult population (including chronically ill, immunocompromised and elderly subjects), where a total of 4612 subjects were exposed to at least one injection of the 7.5 µg of Haemagglutinin vaccine and 3700 subjects were included in the long term safety database (up to at least D180 post-vaccination).

In the age strata B and C a higher incidence of fever was observed in comparison to stratum A and to the adults. As most cases of fever were limited to <38.5° and an increase in fever reactions is commonly observed in young children also with other vaccines, this effect does not raise any specific concern.

In conclusion, the benefit risk balance of Vepacel is considered positive in the paediatric population across all three age strata investigated and the application for the extension of indication is deemed approvable.

4. Recommendations

The application for an extension of the indication to the paediatric population is approvable since the outstanding issues have all 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 accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include the paediatric population for Vepacel. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC were updated to reflect new safety and efficacy information. The Labelling and Package Leaflet are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

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

The variation proposes 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.

Additional data exclusivity / market protection

Not applicable

Paediatric data

Furthermore, 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, the Package Leaflet.