EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

Vepacel

A/H5N1 pre-pandemic influenza vaccine (whole virion, Vero cell derived, inactivated)

Procedure No. **EMEA/H/C/002089**

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxter Innovations GmbH submitted on 21 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vepacel, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 October 2010.

The applicant applied for the following indication: prophylaxis of H5N1 subtype of influenza A in either a pre-pandemic or pandemic situation in adults aged 18 years and older.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

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Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/121/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the Paediatric Investigation Plan (P/121/2010) was not yet completed as all measures were deferred until December 2012.

A waiver is applied to infants and toddlers from birth to less than 6 months for the suspension for injection for intramuscular use on the grounds that the specific medicinal product is likely to be ineffective.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance {A/h5n1 pre-pandemic influenza vaccine (whole virion, Vero cell derived, inactivated)} contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 July 2007. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

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1.2. Steps taken for the assessment of the product

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

Rapporteur: **Pieter Neels** Co-Rapporteur: **Andrea Laslop**

- The application was received by the EMA on 21 October 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 February 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 February 2011.
- During the meeting on 17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2011.
- During the CHMP meeting on 20 October 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 November 2011.
- During the meeting on 12 – 15 December 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Vepacel on 15 December 2011.

2. Scientific discussion

2.1. Introduction

Vepacel is a Pre-Pandemic monovalent Influenza Vaccine containing Vero cell-derived, inactivated whole virions of Influenza type A, subtype H5N1 (A/Vietnam/1203/2004). Vepacel contains 7.5

µg/dose of Haemagglutinin. Vepacel will be available in multidose containers, packs of 20 vials, 10 doses per vial (0.5ml/dose).

The production process of Vepacel is based on previous experience with Baxter's interpandemic and pandemic influenza process (i.e. Celvapan and Pandemic Influenza Vaccine H5N1 Baxter).

The Active Substance is the Vero cell-derived, formaldehyde- and UV-inactivated and sucrose gradient purified whole virions of influenza virus. The finished product is a suspension for injection presented in a multidose formulation with no preservative added.

For details on the composition of Vepacel please refer to Table 1.

Table 1. Composition of Prepandemic Influenza Vaccine Vepacel

	Name of Ingredients		**Content (per 0.5 mL dose)**	**Function**	**Monograph***
Active Ingredient	Vero cell-derived, formaldehyde- and UV -inactivated, sucrose gradient-purified Influenza virus		7.5 µg Haemagglutinin (HA), lower limit of confidence interval (p=95) ≥ 6µg HA	Antigen, Active Substance	Ph. Eur.
Excipients	Tween 80		0.10-0.15 % (target 0.125 % i.e. 0.63 mg/dose)	Prevention of micro-aggregation	Ph.Eur., USP
	Tris-buffered Saline	NaCl	4.0 mg	Electrolyte	Ph.Eur., USP, JP
		Tris (Trometamol)	1.2 mg	Buffer Substance	Ph.Eur., USP, JP
	Water for Injection		filled to 0.5 mL	Solvent	Ph.Eur., USP

* All certified references stated, only region specific pharmacopoeia obligatory (if available)

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2.1.1. Active Substance

The Active Substance is an aqueous solution containing Vero cell-derived, formaldehyde- and UV-inactivated, sucrose gradient-purified whole virions of influenza virus.

Manufacture

All manufacturing steps of Vepacel are performed in Baxter facilities under Good Manufacturing Practice (GMP) conditions. The involved facilities Baxter AG in Orth/Donau; Austria and Baxter BioScience s.r.o. in Jevany Bohumil, Czech Republic hold current GMP licenses (Manufacturing Authorisations).

The production process using the Vero cell technology is divided into four main stages:

- Vero Cell Propagation
- Virus Propagation and Harvesting
- Inactivation
- Purification and sterile Filtration

In the upstream processing, cells are produced and then infected with the influenza virus (i.e. H5N1).

Then the virus is harvested and inactivated by sequential formaldehyde and Ultraviolet Irradiation (UV) inactivation steps. The two separate inactivation steps were designed for two separate targets i.e. primarily protein for formaldehyde and nucleic acid as a target for UV irradiation.

The manufacturing process includes two purification steps. In Purification I, the product is concentrated and purified using ultra-centrifugation with a sucrose gradient. During Purification II, the product is homogenized and sucrose and further impurities are removed by ultrafiltration. The final stage of Active Substance manufacture is the sterile filtration of the monovalent Bulk.

Control of materials

The materials used in the production are classified in the following three categories:

- Cell Bank System
- Virus Bank System
- Raw Materials

Cell bank system

Pre-Pandemic H5N1 Influenza Vaccine Baxter is produced in Vero cells and therefore does not contain egg or chicken protein. The continuous monkey kidney cell line, Vero, (Cercopithecus aethiops) has been approved for use in vaccine production (e.g. polio, rabies and pandemic influenza).

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Virus bank system

The virus bank system, Influenza strain A/Vietnam/1203/2004 was obtained from Centers for Disease Control and Prevention (CDC), Atlanta, GA. Qualification of Virus Banks used for Production is performed according to Ph. Eur. 2308 (Influenza Vaccine (whole virion, inactivated, prepared in cell cultures).

Raw Materials

Except for preparation of the Master Cell Bank, no animal or human serum components are used in the production of the Pre-Pandemic Influenza Vaccine. Two animal-derived components are used (Trypsin, Cytodex), which both do not contain components of bovine origin. Only qualified suppliers source these materials, which are audited by the Applicant's personnel on a regular basis.

Control of critical steps and intermediates

Critical steps in the production of the Active Substance are those associated with viral safety and sterility. All control tests on the intermediate products are carried out according to the Ph. Eur. Monograph for Vaccines for Human Use (0153) and the Monograph for the Influenza Vaccine (2308) in Ph. Eur. "Influenza Vaccine (whole virion, inactivated, prepared in cell cultures".

Process validation

Validation studies were based on the H5N1 Influenza strains A/Vietnam/1203/2004 and A/Indonesia/05/2005.

The validation of Active Substance manufacture has been carried out with the Vietnam/1203/2004 strain. For the filling of the Vietnam strain only parts of the Sterile Monovalent Bulk from Bohumil were formulated and filled for stability studies. The large scale filling was validated using the Indonesia strain.

The following production steps were covered in the course of the Process Validation:

- Master Cell Bank (retrospectively)
- Working Cell Banks (retrospectively)
- Preparation of Vero Cell Inoculum
- Fermentation, Cell Propagation from 120 L to 6,000 L
- Virus Bank System
- Virus Propagation, Harvest, and Inactivation
- Purification I
- Purification II
- Transport and Storage of sterile Monovalent Bulk

Validation data were provided for the manufacturing process, encompassing validation of the Vero Cell Bank system, the Virus Bank system, virus propagation and harvest, virus inactivation by formaldehyde and UV, virus purification and transport of the monovalent bulk. Taken together, these data demonstrate the consistency of the Active Substance manufacturing process. The development of

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the manufacturing process was appropriately documented by data on the Vero Cell Bank system, the Virus Bank system, virus propagation and harvest, virus inactivation by different concentrations/doses of and exposure times to formaldehyde and UV, virus purification by ultracentrifugation and by ultra/diafiltration, and prevention of virus aggregation (by Tween 80).

In conclusion the data generated during process validation at both facilities Orth/Austria and Bohumil/Czech Republic demonstrated a consistent manufacturing process.

Specification

Biological characterization of the active substance was carried out by determination of haemagglutination (HA) titre and of infectious titre, such as the egg infectious dose 50 (EID50/mL) or the plaque forming units (pfu/mL), as well as by determination of neuraminidase (NA) activity.

Immunological characterization was carried out by haemagglutination inhibition (HI) assay, neuraminidase inhibition (NAI) assay and Western blot analysis. Further immunological characterization was done by infection and immunization studies in mice with egg-derived and Vero-derived viruses and vaccines. Additionally, a challenge experiment was carried out in ferrets.

Physicochemical characterization was carried out by Coomassie staining of the viral proteins, separated by polyacrylamide gel electrophoresis (PAGE).

All characterization experiments described below were originally done with seasonal Influenza strains in the course of development of an Interpandemic Vero cell based whole virus Influenza vaccine.

The following product- and process-related impurities have been identified during the active substance manufacturing process and are routinely tested for during the process: Vero Cell DNA during Manufacturing of monovalent bulk; residual Vero Cell DNA in the monovalent bulk; Vero host cell protein; residuals of formaldehyde, sucrose, trypsin and benzonase.

The applicant has appropriately described the biological, immunological and physicochemical characterisation of the Active Substance, including characterisation of the HA and NA antigens. It is acknowledged that the neuraminidase activity assay is performed after inactivation of the virus because of the highly pathogenic nature of the H5N1 virus. In vivo studies demonstrated the immunogenicity (in mice) and the protective effect (in ferrets) of the Vero cell-derived influenza vaccine. Removal of impurities, including Vero cell DNA and protein, formaldehyde, sucrose, trypsin and benzonase, was sufficiently described.

The agreed specifications for the monovalent bulk include a test for Vero cell protein via ELISA, the Haemagglutinin assay and SRD test for Haemagglutinin protein, the Bradford Method for total protein, the Haemagglutination Inhibition test, H5N1 identity test using RT PCR, a safety test for preparative influenza virus on Vero cells, a test for Tween 80 concentration via photometric detection, the LAL test for bacterial endotoxine and a sterility test.

The specifications of the monovalent bulk have been sufficiently justified and are considered adequate.

The testing program for the Active Substance (monovalent bulk) as proposed by the applicant is in compliance with Ph. Eur. Monograph 2308 "Influenza Vaccine (whole virion, inactivated, prepared in cell cultures)". Specifications are sufficiently justified. The applicant has also provided information on the reference standards used in the analytical assays, including information on the HA and NA antigens/antisera. Detailed information on the bags used for the storage of the PMVH and the MVB was

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provided. For stability studies similar but smaller bags were used, which were made from identical material. As these bags have a higher surface/volume ratio, it is accepted that these bags represent worst case conditions for storage of the material with respect to interaction between content and surface.

Stability

Stability studies were performed using containers of identical material/composition as used for storage of the intermediate.

The following production stages/intermediates were included in stability studies:

- Seed Virus Bank (A/Vietnam/1203/2004)
- Purified Monovalent Virus Harvest (PMVH)
- Monovalent Bulk (MVB), the Active Substance

The applicant has provided acceptable stability results for the seed virus bank and the purified monovalent virus harvest (PMVH).

A significant decrease in total protein content was observed during storage. The Applicant was able to demonstrate that this had no influence on the antigen content as measured by SRD. During the procedure, the applicant has clarified that this was due to residual trypsin activity in the active substance which causes degradation of proteins. Importantly, the stability testing results also showed an increase over time of the Haemagglutinin antigen (at time points 18m and 24m) for both the A/Vietnam/1203/2004 strain and the A/Indonesia/05/2005 strain, as measured by the haemagglutination assay/SRD test. This increase of HA (as measured by SRD) is attributed to the enhanced formalin inactivation process used in the manufacture of (pre-) pandemic influenza vaccines which causes the cross-linking of proteins and masking of HA epitopes and which are therefore not detected by SRD assay. Some of these formalin-mediated modifications are reversible over time and allow an increased amount of HA antigen to be detected by the SRD assay. Importantly, it was demonstrated that vaccine lots with a total age range up to 92 weeks still proved efficient in clinical trial studies. Furthermore, studies in mice with 48 months old vaccine lots demonstrated the stability of the vaccine's immunogenicity and protective efficacy. Therefore, it can be concluded that the increase of HA (as measured by SRD) and the decrease in total protein do not impact the vaccine's efficiency.

In conclusion, the proposed shelf life of 24 months for the active substance was considered acceptable.

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2.1.2. Finished Medicinal Product

Pre-Pandemic H5N1 Influenza Vaccine Baxter Finished Product contains Vero cell-derived, formalin- and UV-inactivated, sucrose gradient-purified whole virions of the H5N1 influenza strain A/Vietnam/1203/2004 as active substance, and Tween 80, Tris-buffered saline and water for injection as excipients. The product is presented in a 10 mL glass vial of hydrolytic type I glass. The filling volume corresponds to a content of 10 doses with 0.5 mL. One vaccine dose of 0.5 mL contains 7.5 µg Haemagglutinin antigen in a non-adjuvanted formulation. The stopper consists of latex-free halogen-butyl rubber.

Pharmaceutical Development

The composition of the Finished Product formulation is based on extensive experience with the Applicant's Pandemic Influenza Vaccines as well as previous seasonal Influenza Vaccine, which were tested in clinical trials over several seasons. In the course of the interpandemic development, parameters as the buffer system and the detergent were varied, leading to the current formulation, which was used as a basis for the vaccine. The final composition was identical throughout the pre-clinical and clinical development except for the antigen content and adjuvantation and is also identical to the future marketed product.

The most critical aspect of formulation and filling is to maintain sterility of the finished product, as the sterile filtration is performed at the final stages of Active Substance preparation. All added buffer solutions are sterile filtered directly prior to introduction into the formulation system. Primary container components are sterilized and the vials depyrogenized before filling. The second critical aspect is the homogeneity of the product throughout the filling process. This is guaranteed by continuous stirring of the formulation vessel.

Regarding the formulation/filling, 11 out of 17 Finished Product lots showed HA contents (as measured by SRD) that were significantly higher than the target value of 15 µg/ml (ranging from 19 to 27 µg/ml). This is explained by the SRD assay which does not detect the HA epitopes that are masked due to the formalin-induced cross links. Thus, the SRD actually underestimates the HA content at the time of release.

Formulation and filling steps are performed according to established and validated procedures. The Bulk Finished Product is prepared in a closed production system that assures aseptic working conditions. The Bulk Finished Product is filled clean room Class A conditions according to EU cGMP Guide, in multi dose vials and the vials are stoppered and crimped to give the final container product.

The vaccine is contained in a multi-dose vial (10 mL tube glass vial type I). An independent container closure integrity study for the primary packaging materials was conducted to validate the integrity of the container closure system.

The vaccine is formulated to a target Haemagglutinin concentration to account for the current SRD test precision and guarantees the actual Haemagglutinin content per vial exceeds the lower limit of the specification. Overfilling of the vials ensures that the nominal amount of product doses (10 doses per vial) can be drawn from the vial. Irrespective of overfill, the product is administered based on the recommended dose (0.5 mL) and as a result the dosage administered is not impacted.

The components of the Finished Product have been adequately described and justified. No novel or unusual excipients are used and the formulation development is supported by clinical development. The manufacturing process complies with standard formulation and filling procedures used for inactivated viral vaccines.

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Adventitious agents

The vaccine is tested to be free of known adventitious agents at intermediate production steps. Importantly, since porcine trypsin has been used during the preparation of the Vero Cell Bank system and the Virus Bank system (and inactivation of porcine circovirus by gamma-irradiation has not been demonstrated), the applicant has tested the Vero cell bank system (MCB, WCB) and the Virus bank

system (Working and Production Virus bank) for the presence of porcine circovirus; the outcome was negative.

Also trypsin, which is used in the manufacturing process of the active substance, will be routinely screened for the possible presence of porcine circovirus. Control of critical steps and intermediates is sufficiently documented.

All raw materials used in production have been carefully scrutinized for TSE risk during development of the vaccine. Where possible, animal derived materials were replaced by plant-derived or synthetic materials, e.g. serum- and protein free media are used.

The only remaining component from bovine origin used was Fetal Calf Serum (FCS), which was used for propagation and storage of the Master Cell Bank (MCB), but not thereafter in the manufacturing process.

The applicant has performed a risk assessment demonstrating that the residual TSE risk for the final product caused by the fetal calf serum, which was used for propagation and storage of the Master Cell Bank, is very low and can be considered negligible.

Manufacture of the product

For the manufacture of the finished product, sterile monovalent bulks are transported from the Bohumil facility in the Czech Republic to Vienna/ Austria facilities. The Bulk Finished Product (Plain Pool) is prepared in a closed production system that has been validated to assure sterile working conditions. The calculated amounts of Tween 80 solution and Tris-Buffer are sterile filtered into the formulation tank. Due to the aseptic formulation process no preservatives are added. The formulated bulk is stored at 2 - 8 °C until filling.

The Bulk Finished Product is filled under clean room Class A conditions (EU cGMP Guide) in multi-dose vials and the vials are stoppered and crimped to give the Final Container Product. All components of the final container that come into contact with the product comply with the respective requirements in Ph. Eur. and USP concerning containers for injectables.

Visual inspection is performed under standardized viewing conditions by periodically trained staff.

The manufacturing process and process controls have been adequately documented by the applicant. Critical steps have been identified and are sufficiently controlled. In general, the manufacturing process of the Finished Product, including formulation, partitioning, and aseptic filling, was properly validated. Excipients and control of excipients were adequately described. No novel excipients are used in the formulation of the Finished Product.

Product specification

The quality control program performed on the Bulk Finished Product for Vepacel include the SRD Assay for quantification of haemagglutinin (HA), the Bradford assay to determine total protein, a PCR test for detection of residual Vero cell DNA, an ELISA test for residual benzonase as well as tests for Tween 80 concentration, sucrose, formaldehyde, ph and sterility. Quality control testing performed on Final Container Product consists of SRD Assay for quantification of haemagglutinin (HA), extractable volume, ph, bacterial endotoxin using the LAL test and sterility. All analytical methods are performed according to Ph. Eur. where applicable and are validated according to ICH guidelines.

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Specifications on the final product were set according to the current edition of Ph. Eur. Monograph for Vaccines for Human Use (0153) in conjunction with the current Monograph on cell derived Influenza vaccines (2308) and upon results of process development experience and validation of analytical procedures.

Compliance with the product specifications has been shown on over 20 conformance lots manufactured with the A/Vietnam/1203/2004. The provided data is considered acceptable.

Stability of the product

Stability studies have been performed according to ICH Guidelines Q1A and Q5C using the actual final container (10 dose vials), except for the studies performed on clinical Phase 1/2 material, which was filled in single-dose syringes of the same glass material. In addition temperature excursion studies were conducted whereby samples of the Final Vaccine were incubated at 23 - 27 °C for 3 days. These studies cover possible temperature deviations during transport and storage.

The homogeneity of the vaccine in the vial during withdrawal of the 10 doses as well as absence of antigen adsorption during use of the vaccine in two different syringes has been evaluated.

The main stability indicating parameter is the antigen content, measured by SRD-test. In addition stability indicating parameters cover identity, potency and purity as well as general quality and safety parameters. The specification used in the stability studies, is identical with the acceptance criteria defined in the release specification.

Stability results showed that the HA content of the Finished Product significantly increases over time. The root cause of this increase in HA content was identified by the Applicant. The enhanced formalin inactivation process used in the manufacture of pandemic influenza vaccines causes the cross-linking of proteins and masking of HA epitopes. Some of these formalin-mediated modifications are reversible over time and allow an increased amount of HA antigen to be detected by the SRD assay. Importantly, it was demonstrated that vaccine lots with a total age range up to 92 weeks still proved efficient in clinical trial studies.

Furthermore, studies in mice with 48 months old vaccine lots demonstrated the stability of the vaccine's immunogenicity and protective efficacy. Therefore, it can be concluded that the increase of HA as measured by SRD and the decrease in total protein do not impact the vaccine's efficiency.

In conclusion, the proposed shelf life of 24 months for Finished Product is considered acceptable.

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2.1.3. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The applicant has adequately described the manufacturing process of the active substance and finished product, the generation and control of the Vero Cell Bank system and the Virus Bank system (including the testing performed at different stages) and the control of the excipients.

The vaccine is tested to be free of known adventitious agents at intermediate production steps. Importantly, since porcine trypsin has been used during the preparation of the Vero Cell Bank system

and the Virus Bank system, the applicant has confirmed the Vero cell bank system (MCB, WCB) and the Virus bank system (Working and Production Virus bank) for absence of porcine circovirus.

Trypsin will be routinely screened for the possible presence of porcine circovirus. Control of critical steps and intermediates is sufficiently documented.

The applicant has also performed a risk assessment on TSE. He demonstrated that the residual TSE risk for the final product caused by the fetal calf serum, which was used for propagation and storage of the Master Cell Bank, is extremely low and can be considered negligible.

Validation data were provided for the manufacturing process, encompassing validation of the Vero Cell Bank system, the Virus Bank system, virus propagation and harvest, virus inactivation by formaldehyde and UV, virus purification and transport of the monovalent bulk. These data demonstrate the consistency of the Active Substance manufacturing process.

The applicant has appropriately described the biological, immunological and physicochemical characterisation of the Active Substance, including characterisation of the HA and NA antigens.

The applicant has further appropriately described the biological, immunological and physicochemical characterisation of the Active Substance, including characterisation of the HA and NA antigens. It is acknowledged that the neuraminidase activity assay is performed after inactivation of the virus because of the highly pathogenic nature of the H5N1 virus. In vivo studies demonstrated the immunogenicity in mice and the protective effect in ferrets of the Vero cell-derived influenza vaccine. Removal of impurities, including Vero cell DNA and protein, formaldehyde, sucrose, trypsin and benzonase, was sufficiently described.

Finished product

Pre-Pandemic H5N1 Influenza Vaccine Baxter Finished Product contains Vero cell-derived, formalin- and UV-inactivated, sucrose gradient-purified whole virions of the H5N1 influenza strain A/Vietnam/1203/2004 as active substance, and Tween 80, Tris-buffered saline and water for injection as excipients.

The manufacturing process and process controls have been adequately documented by the applicant. Critical steps have been identified and are sufficiently controlled. In general, the manufacturing process of the Finished Product, including formulation, partitioning, and aseptic filling, was properly validated. Excipients and control of excipients were adequately described. No novel excipients are used in the formulation of the Finished Product.

Regarding the formulation/filling, 11 out of 17 Finished Product lots showed HA contents, measured by SRD, that were significantly higher than the target value of 15 µg/ml (ranging from 19-27 µg/ml). This was explained by the SRD assay, which does not detect the HA epitopes that are masked due to the formalin-induced cross links. Thus, the SRD actually underestimates the HA content at the time of release.

Stability results showed that the HA content of the Finished Product as measured by SRD significantly increases over time. The enhanced formalin inactivation process, which causes the cross-linking of proteins and masking of HA epitopes root, was identified to be the cause of this increase in HA content. Some of these formalin-mediated modifications are reversible over time and allow an increased amount of HA antigen to be detected by the SRD assay. Importantly, it was demonstrated that vaccine lots with a total age range up to 92 weeks still proved efficient in clinical trial studies. Furthermore, studies in mice with 48 months old vaccine lots demonstrated the stability of the vaccine's immunogenicity and protective efficacy. Therefore, it can be concluded that the increase of HA and the

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decrease in total protein do not impact the vaccine's efficiency. Accordingly, the proposed shelf life of 24 months for DP is deemed acceptable.

2.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion with regards to the biological and pharmaceutical aspects of Vepacel, the CHMP considers that all issues have been resolved by the Applicant and no follow-up commitments are necessary.

2.1.5. Recommendation(s) for future quality development

There are currently no recommendations for future development issued by the CHMP.

2.2. Non-clinical aspects

2.2.1. Introduction

Nonclinical studies have been performed in vitro and in vivo to characterize and assess the immunogenicity and efficacy of Vepacel. To allow entry into clinical testing preclinical safety studies were performed including the investigation of single- and repeat dose toxicity, local tolerance and pyrogenicity. Two reproductive and developmental toxicology studies were conducted to support licensure of this vaccine.

2.2.2. Pharmacology

Protective efficacy induced by the H5N1 candidate vaccines was assessed by intranasal challenge of mice and ferrets with a lethal dose of wild-type live H5N1 virus.

The induction of H5-specific antibodies by the A/Vietnam/1203/2004 H5N1 candidate vaccine was measured in serum obtained three weeks after the primary immunization and three weeks after booster. The induction of functional antibodies was monitored by haemagglutination inhibition (HI) assay and a micro-neutralization assay. The presence of H5-specific IgG antibodies was analyzed by an Enzyme Linked Immunosorbant Assay (ELISA).

To identify potential correlates of protection, H5-specific IgG antibody titres, HI titres and neutralizing titres of the respective sera were compared to the observable level of protection. To obtain additional information on relevant correlates of protection, passive immune transfer experiments were conducted using the mouse challenge model. Passive immune transfer studies demonstrated that neutralising antibodies induced by vaccination (in mice, guinea-pigs and humans) that were transferred into naïve mice resulted in protection from lethal challenge. In these studies, vaccine-induced neutralising antibody titres of 1:5, 1:7 and 1:10 for mice, guinea-pig and human (from clinical study 810601) immune sera respectively, were shown to protect 50% of mice (PD50) from lethal challenge Similarly, passive immune transfer experiments with sera from human subjects vaccinated with Celvapan during the clinical study 820902 demonstrated that SCID mice were protected against a lethal challenge with H1N1.

To monitor the primary pharmacodynamics of the A/Vietnam/1203/2004 H5N1 candidate vaccine, in addition to mice and ferrets, guinea pigs and rats were also used.

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The intramuscular route of administration was used in ferret studies, in order to simulate the conditions of clinical administration. However, for practical reasons, the subcutaneous route was used to deliver the candidate vaccine in mice, rats and guinea pigs.

The dose used in the ferret studies was the same as the dose chosen for human use (i.e. 7.5 µg haemagglutinin), whereas for the rat study, it exceeded the human dose (i.e. 45 µg or 15 µg haemagglutinin). A range of haemagglutinin antigen doses was used (serial five-fold dilutions beginning at 3.75 µg haemagglutinin antigen per dose), in the dose-finding studies in mice and guinea pigs.

Studies in mice showed better results for cross-protection with the Vietnam strain vaccine as compared to the Indonesia strain vaccine. Cross-protection against another clade has been investigated in ferrets only for the Indonesia strain vaccine candidate and has shown to induce protection against both the homologous and the heterologous challenge.

Although cross-protection against another clade has not been studied in ferrets vaccinated with the Vietnam strain, no additional ferrets' studies are necessary, given the available cross-neutralisation data in the serology testing in humans.

2.2.3. Pharmacokinetics

In accordance with the CHMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95), pharmacokinetic studies were not conducted since they are normally not needed for a vaccine. This is acceptable and in addition there are no new adjuvants or excipients which would require the study of pharmacokinetics.

2.2.4. Toxicology

The intramuscular route of administration (i.e. clinical route) was used in all GLP studies.

The vaccines lots used for the toxicity studies were equivalent to the final vaccine formulation chosen for licensure.

Single dose and Repeatdose toxicity

The local tolerance and systemic toxic potential of Vepacel (A/Vietnam/1203/2004) was tested in two separate rat studies designed to evaluate the vaccine's safety after single and repeated dosing. Repeat dose toxicology data, including local tolerance, was also produced for the A/Indonesia/05/2005 vaccine produced.

The dose used in the single and repeat dose toxicity studies conducted with influenza strain A/Vietnam/1203/2004 exceeded the human dose (i.e. 45 µg or 36 µg haemagglutinin respectively compared to 7.5 µg, the dose chosen for human use). The dose used in the repeat dose toxicity study with A/Indonesia/05/2005 was equivalent to 80% of one human dose (i.e. 6 µg viral haemagglutinin). In the repeat dose toxicity studies, the vaccine was administered more frequently (three administrations) than the intended human use (two administrations).

Slight changes were observed in the levels of liver enzymes (< 2-fold increase) and calcium (2 - 4 % lower than control) in blood samples taken from groups of male rats which received the vaccine A/Vietnam/1203/2004. However, these effects were small and no other data to support a toxic effect were observed. These effects did not occur with the vaccine produced with influenza strain A/Indonesia/05/2005.

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In rats treated with the A/Indonesia/05/2005 vaccine, plasma bicarbonate levels were high in treated males, plasma phosphorus concentrations were slightly high for treated females and plasma creatine phosphokinase activities were slightly high in both genders. These effects were no longer detected after a 2 week recovery period. In the vaccine-treated females, a transient inflammatory response was observed at the injection sites. These effects were not observed in the study with the A/Vietnam/1203/2004 vaccine.

Genotoxicity

In accordance with the Note for Guidance CPMP/SWP/465/95, genotoxicity studies were not done. The physio-chemical characteristics of the active ingredient, inactivated viral particles, make them unsuitable for use in the standard battery of genotoxicity assays for testing pharmaceuticals. There is a considerable body of evidence on the use, and safety profile, of seasonal flu vaccines.

Carcinogenicity

In accordance with the Note for Guidance CPMP/SWP/465/95, carcinogenicity studies were not done. Influenza vaccines have a long history of use in humans that demonstrates their safety and lack of carcinogenicity.

Reproduction Toxicity

For both A/Vietnam/1203/2004 and A/Indonesia/05/2005 candidate vaccines, a reproductive and development toxicity study has been performed. The dose used was equivalent to 80% of one human dose (i.e. 6 µg viral haemagglutinin). Female rats were treated with a series of three intramuscular injections (400 ml/occasion) of either H5N1 vaccine or control on Day -42 and Day -14 before pairing and Day 7 after mating. A subgroup of animals was euthanized on Day 20 after mating (embryo-foetal phase) and others were allowed to rear their young to Day 21 of age (littering phase). Unselected offspring was euthanized on Day 21 of lactation and the selected F1 offspring was raised to sexual maturity and euthanized at six or seven weeks of age.

In the study with the A/Vietnam/1203/2004 vaccine strain, the only noteworthy finding was a marginally higher incidence of foetuses/litters with the minor abnormalities/variants of 13/14, 14/14 short ribs, incompletely ossified/unossified thoracic elements and hyoid, and undescended lobe of thymus compared to both the concurrent control and background control range.

In the study with the A/Indonesia/05/2005 vaccine strain, the only noteworthy minor visceral abnormality was variation in eye lens size in a small number of foetuses.

These minor abnormalities can be considered as biological variations.

Vaccine related effects with respect to female fertility, embryo-foetal toxicity and pre- and post-natal toxicity have not been observed with the A/Vietnam/1203/2004 or with the A/Indonesia/05/2005 candidate vaccines.

Local Tolerance

During the in-life phase of the single and repeat dose toxicity studies, inspection of the injections sites failed to reveal any vaccine-related local reactions such as redness or swelling. However, macroscopic (pale areas) and microscopic (mild inflammation) changes were evident at necropsy. These reactions are transient in nature, as they disappeared two weeks after dosing. Changes in the draining lymph nodes are observed, which is a normal physiological response to vaccination.

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Other toxicity studies

The pyrogenicity of the vaccine was investigated in a non-GLP study in rabbits (intravenous route of administration). The pyrogenicity profile of the strain A/Vietnam/1203/2004 H5N1 vaccine in rabbits was equivalent to a licensed, seasonal influenza vaccine, which has a proven safety record in humans.

2.2.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, A/H5N1 inactivated whole virion is not expected to pose a risk to the environment.

2.2.6. Conclusion on the non-clinical aspects

In general the Applicant's approach to verify the non-clinical pharmacology of the vaccine is endorsed. Overall, the pharmacology studies provided adequate evidence that the product is immunogenic in several animal models, including ferrets. The candidate vaccine induced H5-specific IgG antibodies, neutralizing- and haemagglutination inhibiting antibodies and showed protection and cross-protection against a lethal challenge with the wild-type H5N1 virus.

In summary, the toxicological results with the pre-pandemic vaccine Vepacel do not suggest any further concerns. The toxicological studies seem adequate to cover the relevant requirements for a pre-pandemic vaccine.

2.3. Clinical aspects

2.3.1. Introduction

Vepacel clinical development program is based on a strategy which was pursued with the aim of developing an effective vaccine manufactured using a production system independent of the supply of hen's eggs.

This program involves development of clade 1 strain (A/Vietnam/1203/2004) and clade 2.1 strain (A/Indonesia/05/2005) vaccines both based on a wild-type, whole virus antigen, and a whole virus clade 2.1 strain vaccine based on a reverse genetic (RG) strain of the A/Indonesia/05/2005 virus. Details on the clinical study development program with this vaccine are provided in the below tabular overview.

Some of the clinical studies included in this dossier have already been evaluated either during the initial MAA of Pandemic Influenza Vaccine H5N1 Baxter or at submission of the corresponding FUMs (i.e. clinical studies 810501, 810601, 810701, 810703).

GCP

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

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

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Tabular overview of clinical studies (with inactivated H5N1 influenza vaccine whole virion, Vero cell-derived, wild type)

Study Number Strain	Title	Participating Countries	Status
810501 A/Vietnam/1203/2004	A Phase 1/2 Dose Escalation Study of a Vero Cell-Derived, Whole Virus H5N1 Influenza Vaccine in Healthy Volunteers Aged 18 to 45 Years	Austria, Singapore	Completed. CSRs for Part A (until Day 21 after 2nd vaccination; total of 42 days), Part B (until Day 180 after first vaccination) and evaluation of cellular immunity (Part C) are available.
Continued			
810601 A/Vietnam/1203/2004 (for primary and booster vaccinations) A/Indonesia/05/2005 (for booster vaccination)	An Open-Label Phase 3 Study of a Vero Cell-Derived, Whole Virus H5N1 Influenza Vaccine to Assess the Immunogenicity and Safety and to Investigate the Need for and Timing of a Booster Vaccination	Austria, Germany	Completed Part A (until Day 21 after 2nd vaccination; total of 42 days), Part B (until Day 21 after the 6-month booster; total of 201 days), Part C (until Day 21 after the 12- to 18-month booster; total of 381-471 days) and Part D (until Day 21 after the 24-month booster) are completed. CSRs for Parts A, B, C, D, E (evaluation of cellular immunity) and F (passive immune transfer; Day 780-900) are available.
810701 A/Indonesia/05/2005	An Open-Label Phase 1/2 Study to Assess the Safety and Immunogenicity of Two Doses of a Vero Cell-Derived, Whole Virus Clade 2 H5N1 Influenza Vaccine in Healthy Volunteers Aged 21 to 45 Years	Hong Kong, Singapore	Completed CSRs for Part A (until Day 21 after 2nd vaccination; total of 42 days) and Parts A and B consolidated (until Day 180 after first vaccination) are available.
NIAID Study DMID **06-0052** A/Vietnam/1203/2004	Phase 1 clinical study with a H5N1 clade 1 A/Vietnam/1203/2004 investigational vaccine	USA	Completed. The study was not sponsored by Baxter but by the National Insitute of Allergy and Infectious Diseases (NIAID). Results have been published by Keitel et al. (*2009*).
Continued			
810703 A/Indonesia/05/2005	An Open-Label Phase 2 Study to Assess the Immunogenicity and Safety of a Booster Vaccination with a Heterologous Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in a Healthy Young Adult Population (Follow-Up to Study 810501 for subjects at the Austrian study site who had completed Day 42 in Study 810501)	Austria	Completed CSRs for Parts A (until Day 21 after the booster vaccination) and B (until Day 180 after the booster) are available.

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Study Number Strain	Title	Participating Countries	Status
810705 A/Vietnam/1203/2004	An Open-Label Phase 3 Study to Assess the Safety and Immunogenicity of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in an Adult and Elderly Population as well as in Specified Risk Groups	Austria, Belgium, Finland, Germany, Latvia, Lithuania, Netherlands	Completed Parts A, B, C (until Day 21 after 2nd vaccination; total of 42 days) and D (until Day 180 after the 2nd vaccination; total of 201 days) and Part E (21 days after booster vaccination) and Part F (cellular immunity) are completed and CSRs are available.
810706 A/Vietnam/1203/2004 (for primary vaccination) A/Indonesia/05/2005 (for booster vaccination)	A Phase 1/2 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	Finland, Spain, Singapore and Australia	Ongoing
810802 A/Vietnam/1203/2004 (for primary vaccination) A/Indonesia/05/2005 (for booster vaccination)	An Open-Label Phase 1/2 Study to Assess the Immunogenicity and Safety of a Single Prime-Boost Vaccination Schedule with a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in Healthy Volunteers Aged 18 to 59 Years	Austria, Finland	Completed CSRs for Parts A (until Day 21 after the booster vaccination) and B (until Day 180 after the booster) are available.

2.3.2. Pharmacokinetics

Vepacel is a prophylactic vaccine designed to induce a specific immune response against clades of H5N1 virus following intramuscular injection. Pharmacokinetic parameters such as absorption, distribution, elimination, production of active metabolites, plasma concentration-effect relationships, dose-time dependencies and interactions are generally not pertinent to vaccines. The kinetic properties of vaccines do not provide information useful in establishing adequate dosing recommendations and therefore clinical pharmacokinetic studies are generally not carried out.

Pharmacokinetic interaction studies

No interaction studies with other vaccines or medicinal products have been performed for Vepacel.

The administration of other vaccines at the same time as Vepacel should be performed only in accordance with official recommendations. If other injectable vaccines are to be given at the same time, administration should be into separate sites and, preferably, into separate limbs (see SmPC, Section 4.2).

A protective immune response may be diminished in persons undergoing immunosuppressive therapy or persons with an impaired immune system (see SmPC, Section 4.5). In such cases, antibody concentrations should be determined in order to assess the response and the need for sequential doses. Study 810705 included immune compromised subjects; immunogenicity results for this population are provided in the Clinical efficacy of Special population section.

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2.3.3. Pharmacodynamics

Mechanism of action

The pharmacodynamics of the vaccine relates to its effect on the immune system, in terms of efficacy in inducing protection against the H5N1 virus. The immunological response to Vepacel is covered in the clinical efficacy section.

Primary and Secondary pharmacology

No specific pharmacodynamic clinical studies have been performed, as the protective efficacy of pandemic influenza vaccines cannot be established in clinical trials (CHMP/VWP/263499/2006). Three studies (810501, 810601 and 810705) were designed to evaluate the humoral and cellular immune response using four different antigen dose levels altogether (see Clinical Efficacy section). Standard technologies for measurement of antibodies induced by influenza infection or immunization were used, i.e. measurement of haemagglutination inhibition (HI) neutralizing (MN) and single radial haemolysis (SRH) antibodies. The use of a functional antibody measurement such as neutralizing titre was preferred when attempting to establish a serological correlate of protection. However no studies have been carried out to establish a correlate between neutralizing antibody and protection from influenza illness (clinical correlate of protection).

To allow entry into clinical testing and to evaluate the primary pharmacodynamics of Vepacel (including cross neutralization and protective efficacy), several nonclinical studies were performed in relevant animal models (see Section 2.3 Nonclinical Aspects). Secondary nonclinical pharmacodynamic studies (safety pharmacology) were not conducted, since toxicology studies with this vaccine formulation indicated no safety concerns, confirming the generally good safety profile shown with influenza vaccines in extensive use in humans.

Although all immunogenicity endpoints were assessed using HI, SRH and MN assays in the clinical studies presented in this application, due to the high variability of the data obtained with different HI assay conditions, to the discrepancy between HI and MN data and the highly consistent results produced using the MN and SRH tests, the immunogenicity evaluation has mainly focused on determination of functional neutralizing antibody (MN) responses which were further confirmed by the SRH results.

In addition, due to increasing reports that T-cell responses are important and may be better correlates of vaccine protection than functional antibody responses) especially in the elderly, the Applicant included in clinical studies 810501 Part C, 810601 Part E and 810705 Part F additional immunogenicity assays focused on cellular immune response.

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2.4. Clinical efficacy

2.4.1. Dose response studies

The first clinical phase 1/2 study (810501) was initiated on 12 June 2006 (in Austria and Singapore) with the clade 1 strain vaccine. Study 810501 was designed as a randomized, partially blinded, dose-escalating, six-arm phase 1/2 clinical study. All subjects received two intramuscular injections of the whole virion, Vero cell-derived influenza vaccine containing 3.75µg, 7.5µg, 15µg or 30µg H5N1 (A/Vietnam/1203/20004) HA antigen in an adjuvanted formulation with aluminium hydroxide, or 7.5µg

or 15µg H5N1 HA antigen in a non-adjuvanted formulation on Day 0 and Day 21. The study was conducted in healthy volunteers aged 18 to 45 years.

Based on the MN and SRH data with the homologous vaccine strain (A/Vietnam), the highest immune responses were achieved following two immunisations with the non-adjuvanted vaccine formulations. Moreover after the first vaccination significantly higher seroprotection rates by SRH assay and seroneutralisation rates (percentage of subjects with MN titre ≥ 1:20) by MN assay were observed in the non-adjuvanted vaccine groups compared to the adjuvanted vaccine groups indicating no adjuvanting effect but rather an inhibitory effect of aluminium across all antigen concentrations.

With both the SRH and the MN assay all three CHMP criteria were fulfilled following two immunisations with the non-adjuvanted 7.5µg vaccine formulation, with a seroprotection rate of 78.6% by SRH assay and seroneutralisation rate of 76.2% by MN assay, seroconversion rates of 69.0% and 73.8% and a GM fold increase of 5.3 and 6.3, respectively.

Moreover cross-neutralisation experiments indicate a high responsiveness for the original prototype A/Hong Kong strain (76.2%) and a reasonable cross-neutralising response for the further evolved strain A/Indonesia (45.2%). The neutralising antibody responses against all three virus strains persist over 6 months with low to moderate decline rates (A/Vietnam: 54.8%; A/Indonesia: 33.3%; A/Hong Kong: 71.4%). Thus, the choice of the non-adjuvanted 7.5µg formulation is justified.

2.4.2. Main studies

Study 810601 (for title see tabular overview)

Methods

Study 810601 was designed as a randomized, open-label, non-controlled Phase 3 clinical study in 550 male and female subjects, stratified in equal numbers to two age cohorts of 18 to 59 years (Stratum A) and 60 years and older (Stratum B) to assess the safety and immune response to Vepacel (A/Vietnam/1203/2004) vaccine, as well as the need for, and timing of, a booster vaccination in an adult and elderly population.

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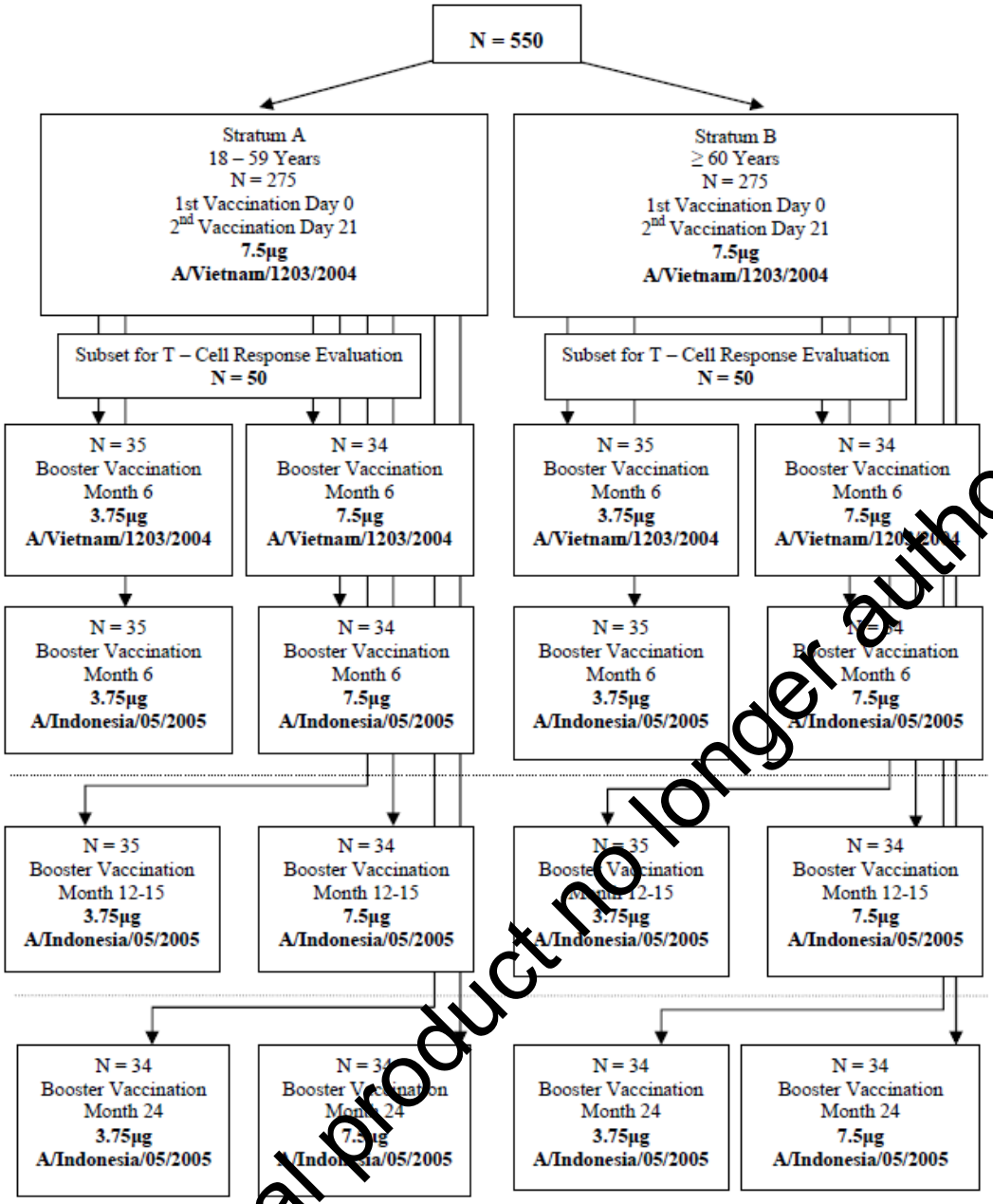

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Study Participants

Only subjects who meet all the inclusion and none of the exclusion criteria and provided written informed consent were invited to participate in the study.

Subjects were well distributed by age in Stratum A. In Stratum B, the majority of subjects were between 60 and 70 years of age. Subjects were evenly distributed by gender. Height and weight were normally distributed.

The majority of subjects returned to each visit within the allotted interval of 21 ± 3 days after vaccination. Adherence to visit schedule was similar between age strata.

Treatments

Baxter's candidate H5N1 influenza vaccine for intramuscular injection is a monovalent non-adjuvanted inactivated virus vaccine containing Vero cell-derived, formaldehyde and UV-inactivated, sucrose gradient purified whole H5N1 influenza virions. The vaccine contains no preservative.

During Part A of the study, each subject received two vaccinations 21 days apart by intramuscular injection in the opposite upper arm (musculus deltoideus) from which blood was drawn.

The investigational product is provided in multidose vials. For the first and second vaccinations, all subjects were administered the following dosage:

- 7.5µg of H5N1 HA antigen strain A/Vietnam/1203/2004 per 0.5 mL

Half of the subjects will be randomized to receive a 6-month booster vaccination with one of the following dosages:

- 3.75µg HA antigen, strain A/Vietnam/1203/2004 per 0.25 mL
- 7.5µg HA antigen, strain A/Vietnam/1203/2004 per 0.5 mL
- 3.75µg HA antigen, strain A/Indonesia/05/2005 per 0.25 mL
- 7.5µg HA antigen, strain A/Indonesia/05/2005 per 0.5 mL

The remaining half of the subjects, who did not receive a 6-month booster, will receive a 12 to 15- or 24-month booster vaccination with one of the following dosages:

- 3.75µg HA antigen, strain A/Indonesia/05/2005 per 0.25 mL.
- 7.5µg HA antigen, strain A/Indonesia/05/2005 per 0.5 mL

Objectives

- To assess the immune response of an H5N1 influenza vaccine in an adult and elderly population.
- To assess the safety and tolerability of an H5N1 influenza vaccine in an adult and elderly population.
- To assess the need of and the timing of a booster vaccination.

For a subset of subjects further objectives of the study are:

- To evaluate the cell mediated immune response induced by an H5N1 influenza vaccine after the first, second and booster vaccination.

Endpoints

Primary Immunogenicity Endpoint

- Number of subjects with antibody response to the vaccine strain (A/Vietnam/1203/2004) associated with protection 21 days after the second vaccination defined as titre measured by microneutralization (MN) test ≥20.

Secondary Immunogenicity Endpoints

- Number of subjects with antibody response associated with protection 21 days after the first vaccination measured by MN assay

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- Number of subjects with HIA titre ≥40 measured 21 days after the first and second vaccinations
- Antibody titre 21 days after the first and second vaccinations as measured by MN and HI assays
- Fold increase of antibody response as compared to baseline 21 days after the first and second vaccinations as measured by MN and HI assays
- Number of subjects with seroconversion (defined as a minimum four fold titre increase) 21 days after the first and second vaccinations as measured by MN and HI assays
- Number of subjects with antibody response associated with protection 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by MN assay
- Number of subjects with HIA titre ≥40 measured 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination
- Antibody titre 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by MN and HI assays
- Fold increase of antibody response 21 days after a booster vaccination as compared to before the booster vaccination at 180, 360-450 and 720 days after the first vaccination as measured by MN and HI assays
- Number of subjects with seroconversion (defined as a minimum four fold titre increase) 21 days after a booster vaccination as measured by MN and HI assays
- Number of subjects with antibody response associated with protection 21 days after the first and second vaccinations defined as Single Radial Haemolysis (SRH) area ≥25 mm^2
- Antibody titre 21 days after the first and second vaccinations measured by SRH assay
- Fold increase of antibody response as compared to baseline 21 days after the first and second vaccinations measured by SRH assay
- Number of subjects with seroconversion (defined 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) measured by SRH assay 21 days after the first and second vaccinations
- Number of subjects with antibody response associated with protection 180, 360 and 720 days after the first vaccination and 21 days after a booster vaccination defined as SRH area ≥25 mm^2
- Antibody titre 180, 360-450 and 720 days after the first vaccination and 21 days after a booster vaccination as measured by SRH assay
- Fold increase of antibody response 21 days after a booster vaccination as compared to booster vaccination at 180, 360-450 and 720 days after the first vaccination as measured by SRH assay
- Number of subjects with seroconversion (defined as either a ≥25 mm^2 haemolysis area after the booster vaccination in case of a negative prevaccination sample [</=4 mm^2) or a ≥50% increase in haemolysis area if the pre-vaccination sample is >4 mm^2) measured by SRH assay 21 days after the booster vaccination

For the subset of subjects included in the evaluation of cellular immunity:

- T-cell response after each vaccination as determined by the frequency of cytokine producing T-cells induced by homologous and heterologous influenza antigens

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- Increase in frequency of cytokine producing T-cells induced by homologous and heterologous influenza antigens after each vaccination as compared to baseline

Sample size

The sample size of 550 subjects was based on the following calculations: 275 subjects aged between 18 to 59 years of age and 275 subjects 60 years of age and older will be enrolled into the study. Assuming an approximate drop out rate of 10%, it is expected that at least 250 of the 275 subjects in each age group will have evaluable immunogenicity results after vaccination. With this sample size, the two-sided 95% confidence interval of the rate of subjects with antibody response associated with protection does not extend more than 6.4% from the observed rate assuming the observed rate lies in the region of 60%. If the rate of subjects with antibody response associated with protection is approximately 70% the above interval will extend no more than 6.1% from the observed rate.

The sample size of 275 in each age stratum to receive the test vaccine provides a 93.7% chance to detect at least one AE that occurs at a frequency of 1% and a 74.8% chance to detect at least one event that occurs at a frequency of 0.5%.

Furthermore, with 275 subjects the two-sided 95% confidence interval of the probability of occurrence of AE(s) will extend □6% from the observed proportion when the expected AE rate is approximately 25%.

Randomisation

Half of the subjects in each age stratum will be randomly selected to receive a 6-month booster vaccination. These subjects will be randomized 1:1:1:1 to receive the non-adjuvanted H5N1 influenza vaccine containing one of the following:

- 3.75µg HA antigen strain A/Vietnam/1203/2004
- 7.5µg HA antigen strain A/Vietnam/1203/2004
- 3.75µg HA antigen strain A/Indonesia/05/2005
- 7.5µg HA antigen strain A/Indonesia/05/2005

The remaining subjects will be randomized into two equal groups, one receiving a 12 to 15- month and the other a 24-month booster vaccination. At both the 12 to 15-month and the 24-month booster, subjects will be randomized 1:1 to receive a booster with the non-adjuvanted H5N1 vaccine containing either 3.75µg or 7.5µg HA antigen of the A/Indonesia/05/2005 strain.

Blinding

This is an open-label study.

Statistical methods

Analysis of Primary Endpoint (Immunogenicity)

The rates of subjects with antibody response associated with protection 21 days after the second vaccination and their 95% confidence intervals are calculated separately for both age strata.

All subjects with available antibody response fulfilling the eligibility criteria are included in the analysis.

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Analysis of Secondary Endpoints (Immunogenicity)

Point estimates and 95% confidence intervals are calculated for all secondary immunogenicity endpoints. The analysis is carried out separately for both age strata. In order to assess the effect of the strain (A/Vietnam/1203/2004, A/Indonesia/05/2005) and of different doses (3.75µg HA antigen, 7.5µg HA antigen) for the 6-month booster and of different doses (3.75 µg HA antigen, 7.5 µg HA antigen) for the 12 to 15-month and the 24-month booster of the vaccine of the vaccine on the antibody response, measured by MN, SRH and HI assays, antibody response will be analyzed by analysis of covariance. The model will include doses, the strain and the interaction term between dose and strain as influencing factors and baseline values as covariates. Antibody response values will be log transformed prior to the analysis. Antibody responses will be analyzed separately for each assay. If an interaction of strain and dose is detected, an analysis of subgroups will be performed.

For the subset of subjects included in the evaluation of the T-cell mediated response minimum, maximum, 25% and 75% quantiles, median and the respective 95% confidence interval will be calculated for all parameters reflecting T-cell response before and after each vaccination. In addition, parameters reflecting T-cell response will be investigated by non-parametric procedures. Wilcoxon Signed Rank test will be used for analysis of paired baseline and post-vaccination values.

All subjects with available data are included in the analysis.

Results

Baseline data

Seropositive antibody titres against the H5N1 vaccine strain (A/Vietnam/1203/2004) at baseline were shown in 4.1% and 16.9% of subjects for MN, and 4.5% and 5.3% for SRH in Stratum A and B, respectively. This is in agreement with data previously reported that a percentage of the population particularly, the elderly will have antibodies cross-reactive to H5N1 (Treanor et al., 2006) or other potential pandemic viruses (Stephenson et al., 2003; Epstein SL, 2006) without having been exposed to this virus. This situation of pre-existing titres occurs frequently with studies with trivalent seasonal influenza vaccines and is accepted as long as the vaccine fulfils one of the two other serological criteria for licensure i.e. seroprotection or GM fold increase, should pre-existing antibody titres result in a lower seroconversion level.

Numbers analysed

The primary immunogenicity endpoint was analyzed for the intent to treat (ITT) and per protocol (PP) datasets. Secondary immunogenicity endpoints were analyzed for the ITT dataset only.

Intent to treat dataset

Immunogenicity analyses were performed on the ITT dataset for the first (ITT 1) and second (ITT 2) vaccinations. Subjects are included in the ITT datasets if they:

- received the 1st/2nd vaccination;
- have available serology data at Day 21 after the 1st/2nd vaccination.

The ITT 1 dataset comprises 542 subjects (270 in Stratum A and 272 in Stratum B), and ITT 2 consists of 535 subjects (265 in Stratum A and 270 in Stratum B). Subjects excluded from the ITT datasets are listed in the dossier, Module 5 Section 16.2.3.

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Per protocol dataset

The primary endpoint was also analyzed for the per protocol dataset. Subjects are included in the per protocol analysis if they:

- fulfil inclusion/exclusion criteria;
- have no major protocol violations;
- received both vaccinations;
- have available serology data at Day 21 after the 1st/2nd vaccination.

Ten (10) subjects who were included in the ITT 2 dataset were excluded from the PP dataset. For the analysis of the primary immunogenicity endpoint (MN titre after the second vaccination) 525 subjects (257 in Stratum A and 268 in Stratum B) were included in the PP dataset.

Outcomes

Study part A: day (D) 21 after the second vaccination

Following two vaccinations all three CHMP criteria (as specified in the guideline CPMP/BWP/214/96) were fulfilled by MN assay in the age group of adults, and 2 out of 3 criteria were met in the elderly. Specifically, the adults group achieved a seroneutralisation (or seroprotection SP) rate of 72.5%, a seroconversion (SC) rate of 60.8% and a 4.7 fold GM increase; in the elderly a SP rate of 74.1%, a SC rate of 26.7% and a 2.8 fold increase was obtained.

The results of the MN assay were generally consistent with the SRH assay. Following two vaccinations 2 out of 3 CHMP criteria were fulfilled in the adults and all three 3 requirements were met in the elderly. In the adults group a SP rate of 63.3%, a SC rate of 60.2% and a 4.6 fold GM increase were achieved. In the elderly a SP rate of 67.7%, a SC rate of 62.4% and a 4.6 fold increase was obtained.

Study Part B: through D21 after 6 months booster

Antibody persistence

The data on antibody persistence reveal a decline in seroneutralisation/seroprotection rates of 35% to 40% for both age groups using either the MN or the SRH assay. The decline in the neutralizing antibody responses is however less pronounced than the decline in antibody responses determined by SRH assay. Whereas a substantial number of vaccinees have neutralizing antibody titres (of at least of 1:10) up to 180 days post vaccination, for only approximately 50% of adults and elderly subjects antibodies ≥4mm2 are detectable in the SRH assay.

Data post-booster

Half of the subjects were randomized into 4 groups to receive different dosages (see the above section on Treatments). The SP results by MN assay are summarised in the two tables below.

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Number of Subjects with Microneutralization Antibody Titer ≥1:20 (for Subjects Randomized to the 6 Month Booster) – Stratum=A (18–59 Years) (Study 810601, ITT Dataset)

Strain	Day	Booster							
		A/Vietnam				A/Indonesia			
		3.75 µg		7.5 µg		3.75 µg		7.5 µg	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
A/Vietnam	0	1/30 (3.3%)	0.1%; 17.2%	0/29 (0.0%)	0.0%; 11.9%	2/30 (6.7%)	0.8%; 22.1%	0/30 (0.0%)	0.0%; 11.6%
	21	17/30 (56.7%)	37.4%; 74.5%	19/29 (65.5%)	45.7%; 82.1%	15/30 (50.0%)	31.3%; 68.7%	17/30 (56.7%)	37.4%; 74.5%
	42	24/30 (80.0%)	61.4%; 92.3%	23/29 (79.3%)	60.3%; 92.0%	22/30 (73.3%)	54.1%; 87.7%	25/30 (83.3%)	65.3%; 94.4%
	180	12/30 (40.0%)	22.7%; 59.4%	8/29 (27.6%)	12.7%; 47.2%	13/30 (43.3%)	25.5%; 62.6%	11/30 (36.7%)	19.9%; 56.1%
	201	20/29 (69.0%)	49.2%; 84.7%	25/29 (86.2%)	68.3%; 96.1%	21/29 (72.4%)	52.8%; 87.3%	25/29 (86.2%)	68.3%; 96.1%
	360-450	10/24 (41.7%)	22.1%; 63.4%	17/28 (60.7%)	40.6%; 78.5%	14/29 (48.3%)	29.4%; 67.5%	15/29 (51.7%)	32.5%; 70.6%
A/Indonesia	0	1/30 (3.3%)	0.1%; 17.2%	0/29 (0.0%)	0.0%; 11.9%	0/30 (0.0%)	0.0%; 11.6%	0/30 (0.0%)	0.0%; 11.6%
	21	8/30 (26.7%)	12.3%; 45.9%	7/29 (24.1%)	10.3%; 43.5%	8/30 (26.7%)	12.3%; 45.9%	9/30 (30.0%)	14.7%; 49.4%
	42	14/30 (46.7%)	28.3%; 65.7%	7/29 (24.1%)	10.3%; 43.5%	14/30 (46.7%)	28.3%; 65.7%	12/30 (40.0%)	22.7%; 59.4%
	180	4/30 (13.3%)	3.8%; 30.7%	2/29 (6.9%)	0.8%; 22.8%	9/30 (30.0%)	14.7%; 49.4%	7/30 (23.3%)	9.9%; 42.3%
	201	14/29 (48.3%)	29.4%; 67.5%	19/29 (65.5%)	45.7%; 82.1%	21/29 (72.4%)	52.8%; 87.3%	27/29 (93.1%)	77.2%; 99.2%
	360-450	3/24 (12.5%)	2.7%; 32.4%	4/28 (14.3%)	4.0%; 32.7%	10/29 (34.5%)	17.9%; 54.3%	12/29 (41.4%)	23.5%; 61.1%

Number of Subjects with MN Antibody Titer ≥1:20 (for Subjects Randomized to the 6-Month Booster) – Stratum=B (≥60 Years) (Study 810601, ITT Dataset)

Strain	Day	Booster							
		A/Vietnam				A/Indonesia			
		3.75 µg		7.5 µg		3.75 µg		7.5 µg	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
A/Vietnam	0	4/31 (12.9%)	3.6%; 29.8%	5/32 (15.6%)	5.3%; 32.8%	8/32 (25.0%)	11.5%; 43.4%	3/32 (9.4%)	2.0%; 25.0%
	21	17/31 (54.8%)	36.0%; 72.7%	17/32 (53.1%)	34.7%; 70.9%	19/32 (59.4%)	40.6%; 76.3%	20/32 (62.5%)	43.7%; 78.9%
	42	24/31 (77.4%)	58.9%; 90.4%	22/32 (68.8%)	50.0%; 83.9%	23/32 (71.9%)	53.3%; 86.3%	24/32 (75.0%)	56.6%; 88.5%
	180	15/30 (50.0%)	31.3%; 68.7%	11/30 (36.7%)	19.9%; 56.1%	14/32 (43.8%)	26.4%; 62.3%	14/32 (43.8%)	26.4%; 62.3%
	201	20/31 (64.5%)	45.4%; 80.8%	21/32 (65.6%)	46.8%; 81.4%	19/32 (59.4%)	40.6%; 76.3%	21/32 (65.6%)	46.8%; 81.4%
	360-450	14/30 (46.7%)	28.3%; 65.7%	16/31 (51.6%)	33.1%; 69.8%	13/30 (43.3%)	25.5%; 62.6%	18/31 (58.1%)	39.1%; 75.5%
A/Indonesia	0	2/30 (6.7%)	0.8%; 22.1%	1/32 (3.1%)	0.1%; 16.2%	3/32 (9.4%)	2.0%; 25.0%	5/32 (15.6%)	5.3%; 32.8%
	21	8/31 (25.8%)	11.9%; 44.6%	11/32 (34.4%)	18.6%; 53.2%	14/32 (43.8%)	26.4%; 62.3%	17/32 (53.1%)	34.7%; 70.9%
	42	15/31 (48.4%)	30.2%; 66.9%	15/32 (46.9%)	29.1%; 65.3%	20/32 (62.5%)	43.7%; 78.9%	23/32 (71.9%)	53.3%; 86.3%
	180	11/30 (36.7%)	19.9%; 56.1%	7/30 (23.3%)	9.9%; 42.3%	11/32 (34.4%)	18.6%; 53.2%	9/32 (28.1%)	13.7%; 46.7%
	201	17/31 (54.8%)	36.0%; 72.7%	17/32 (53.1%)	34.7%; 70.9%	24/32 (75.0%)	56.6%; 88.5%	23/32 (71.9%)	53.3%; 86.3%
	360-450	8/30 (26.7%)	12.3%; 45.9%	12/31 (38.7%)	21.8%; 57.8%	11/30 (36.7%)	19.9%; 56.1%	18/31 (58.1%)	39.1%; 75.5%

Based on these data it can be concluded that a homologous or heterologous booster immunisation has no added value as regards higher seroconversion rates but might elicit stronger cross-reactive antibody responses. Generally the antibody responses following the homologous and heterologous booster are however less pronounced compared to study 810703 indicating a moderate anamnestic response. In summary the responses are comparable to what is expected for seasonal revaccination.

Study Part C: through D21 after 12-15 months booster

The antibody response by MN assay measured 21 days after the 12 to 15 month booster against strains A/Vietnam and A/Indonesia is shown in the following table:

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Number of Subjects with Antibody Titer ≥1:20 (for Subjects Randomized to the 12- to 15-Month Booster) Measured by Microneutralization (Study 810601, ITT Dataset)

Strain	Day	Stratum							
		A (18–59 years)				B (≥60 years)			
		3.75 µg A/Indonesia		7.5 µg A/Indonesia		3.75 µg A/Indonesia		7.5 µg A/Indonesia	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
A/Vie.	0	1/29 (3.4%)	0.1%; 17.8%	2/29 (6.9%)	0.8%; 22.8%	6/31 (19.4%)	7.5%; 37.5%	4/31 (12.9%)	3.6%; 29.8%
	21	13/29 (44.8%)	26.4%; 64.3%	11/29 (37.9%)	20.7%; 57.7%	19/31 (61.3%)	42.2%; 78.2%	15/31 (48.4%)	30.2%; 66.9%
	42	22/29 (75.9%)	56.5%; 89.7%	18/29 (62.1%)	42.3%; 79.3%	21/31 (67.7%)	48.6%; 83.3%	23/31 (74.2%)	55.4%; 88.1%
	180	10/29 (34.5%)	17.9%; 54.3%	7/29 (24.1%)	10.3%; 43.5%	16/31 (51.6%)	33.1%; 69.8%	11/31 (35.5%)	19.2%; 54.6%
	360-450	9/29 (31.0%)	15.3%; 50.8%	9/29 (31.0%)	15.3%; 50.8%	15/31 (48.4%)	30.2%; 66.9%	12/31 (38.7%)	21.8%; 57.8%
	381-471	21/28 (75.0%)	55.1%; 89.3%	28/29 (96.6%)	82.2%; 99.9%	26/31 (83.9%)	66.3%; 94.5%	26/31 (83.9%)	66.3%; 94.5%
A/Ind.	0	1/29 (3.4%)	0.1%; 17.8%	2/29 (6.9%)	0.8%; 22.8%	7/31 (22.6%)	9.6%; 41.1%	3/31 (9.7%)	2.0%; 25.8%
	21	5/29 (17.2%)	5.8%; 35.8%	5/28 (17.9%)	6.1%; 36.9%	14/31 (45.2%)	27.3%; 64.0%	10/31 (32.3%)	16.7%; 51.[illegible]
	42	10/29 (34.5%)	17.9%; 54.3%	11/29 (37.9%)	20.7%; 57.7%	20/31 (64.5%)	45.4%; 80.8%	16/31 (51.6%)	33.1%; [illegible]
	180	1/29 (3.4%)	0.1%; 17.8%	4/29 (13.8%)	3.9%; 31.7%	13/31 (41.9%)	24.5%; 60.9%	4/31 (12.9%)	[illegible]
	360-450	1/29 (3.4%)	0.1%; 17.8%	5/29 (17.2%)	5.8%; 35.8%	13/31 (41.9%)	24.5%; 60.9%	5/31 (16.1%)	[illegible] 53.7%
	381-471	22/28 (78.6%)	59.0%; 91.7%	27/29 (93.1%)	77.2%; 99.2%	25/31 (80.6%)	62.5%; 92.5%	26/31 (83.9%)	[illegible] 94.5%

Collectively, the data show that booster vaccinations with either 3.75µg or 7.5µg HA antigen given 12 to 15 months after primary vaccination could elicit serological responses well exceeding the CHMP criteria for immunogenicity of seasonal influenza vaccines, with a slight dose effect observed. The heterologous booster using strain A/Indonesia/05/2005 elicited a good immune response against both strains.

Part D: through D21 after 24 months booster

The antibody response measured by MN assay against different H5N1 strains was evaluated before and after subjects received the 24 months booster (before booster: Day 720; after booster: Day 741). The immunogenicity data indicate a booster vaccination given 24 months apart at either 3.75µg or 7.5µg HA antigen could elicit an acceptable antibody response in adults (SP rate: 91.3%-100%) and elderly (SP rate: 76.7%-91.7%) subjects however with a dose effect observed. In addition the heterologous booster using strain A/Indonesia/05/2005 elicited an acceptable immune response against both strains, A/Vietnam (used for the primary immunisation) and A/Indonesia. These results are consistent with previously submitted reports on booster immunisations.

Study 810705 (for title see tabular overview)

Methods

The Phase 3 study 810705 is the first clinical trial with Baxter's Vero cell-derived inactivated H5N1 influenza vaccine including not only healthy volunteers (Cohort 1) but also specified risk groups, i.e., immune compromised individuals (Cohort 2) and chronically ill patients (Cohort 3). The study, now completed, is performed in a larger adult and elderly population than in previous studies (N=3560), with several European countries participating.

The study was designed as an open-label study with multiple cohorts (risk groups), age strata (Stratum A: adults, Stratum B: elderly subjects) and treatment groups (e.g. four treatment groups in Stratum A of Cohort 1; two treatment groups in Stratum B of Cohort 1), as detailed in table 2. All subjects received a primary immunization consisting of two vaccinations given 21 days apart. Depending on the cohort and on the treatment group, randomised subjects received either the 3.75µg or 7.5µg dose of the clade 1 (A/Vietnam/1203/2004) strain vaccine. Specific subsets in Cohort 1 (i.e. Treatment groups 1 and 4 in Stratum A and Treatment group 1 in Stratum B), Cohort 2 and Cohort 3 participated in a study extension designed to receive a 12- to 24-month booster vaccination with the clade 2 (A/Indonesia/05/2005) strain vaccine at the 7.5µg dose.

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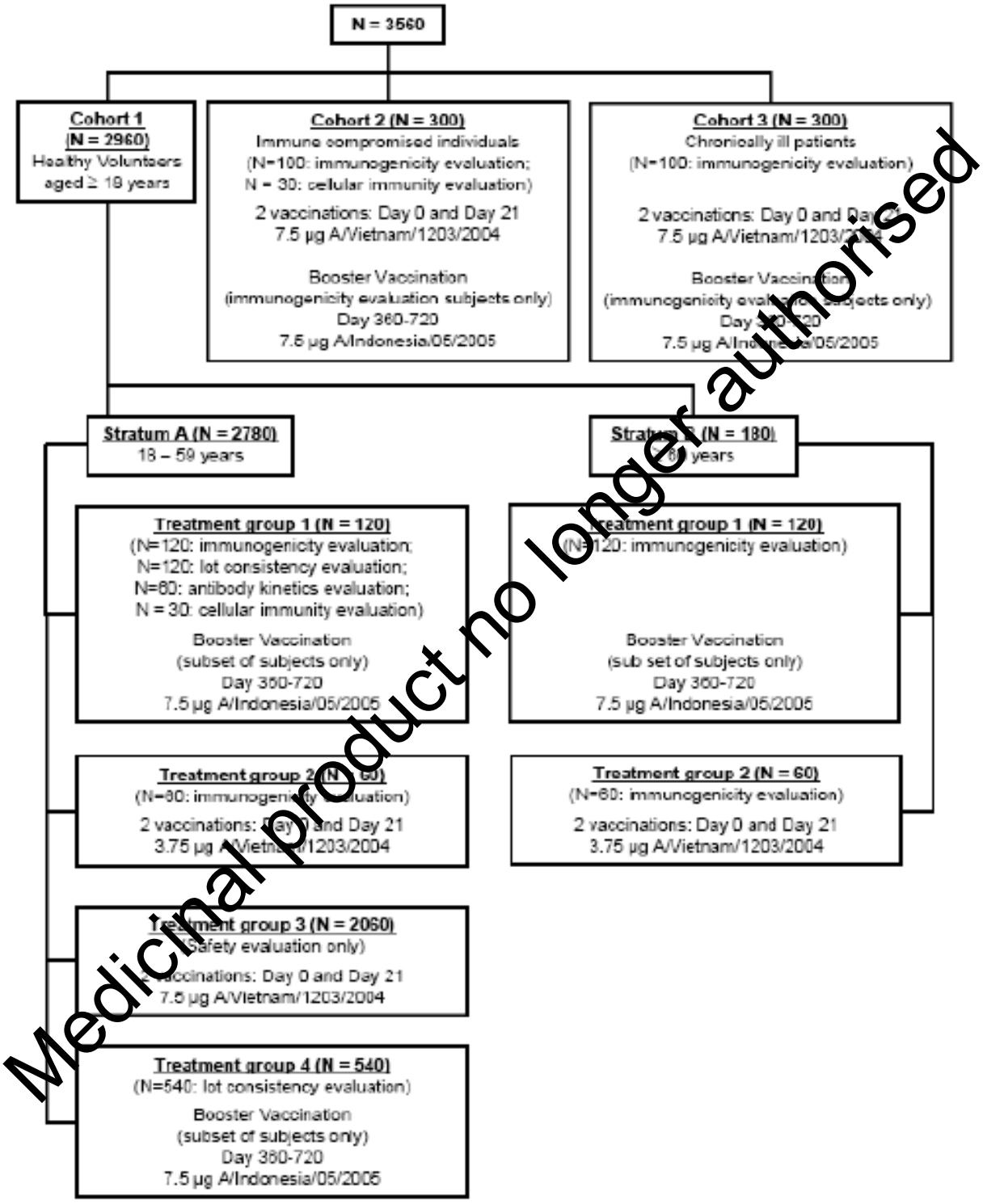
The randomisation was done with block sizes of 6, both for the randomisation to the 7.5µg vs. the 3.75µg dose, as well as the (later) randomisation to lots within the 7.5µg groups.

Table 2. Study design for Clinical Study 810705



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Results

Outcomes

Table 3. Overview of Immunogenicity in all cohorts:

	Cohort 1 (healthy)				Cohort 2 (immuno-compr.)	Cohort 3 (chronically ill)
	Stratum A (18 – 59 years)		Stratum B (≥60 years)			
	7.5 µg (n=116)	3.75 µg (n=56)	7.5 µg (n=116)	3.75 µg (n=57)	7.5 µg (n=113)	7.5 µg (n=123)
MN						
Rates of subjects with seroprotection (MN Ab titers ≥ 1:20)						
Day 42	62.4	40.7	58.0	52.5	41.5	34.2
Day 201	24.1	14.3	30.2	28.1	11.5	31.7
GMTs						
Day 42	25.7	19.5	24.4	26.3	8.1	25.9
Day 201	13.5	10.7	16.1	16.8	8.1	13.7
GM fold increase						
Day 42	3.7	2.8	2.1	1.9	2.5	3.0
Day 201	1.9	1.5	1.4	1.2	1.1	1.6
SRH						
Rates of subjects with seroprotection (SRH area ≥ 25 mm²)						
Day 42	53.0	33.9	39.5	39.0	53.4	42.3
Day 201	48.3	33.9	36.2	42.1	45.1	37.4
GMTs						
Day 42	18.0	11.1	12.3	12.4	17.9	14.2
Day 201	14.7	10.4	11.3	12.2	14.9	12.3
GM fold increase						
Day 42	1.9	1.8	1.9	1.4	1.9	2.0
Day 201	1.4	1.7	1.7	1.4	1.7	1.8

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Study Part A: Immunogenicity results through Day 42

In stratum A (adults), two CHMP criteria were met by MN assay (seroconversion, GM fold increase), while in stratum B (elderly) only GM fold increase was met and seroprotection narrowly missed. Quite high levels of antibodies were detectable already at baseline, therefore analyses according to baseline seronegativity were requested.

By SRH assay in stratum A (adults) also two CHMP criteria were met (seroconversion and GM fold increase), while in stratum B (elderly) GM fold increase and seroconversion were narrowly missed. High titres were detectable at baseline also by SRH, especially for the elderly, therefore analyses according to baseline seronegativity were requested.

PART B

Part B of the study covered immunogenicity through Day 42 for subjects in Cohorts 2 and 3 (immunocompromised and chronically ill) and is described in the section *Clinical studies in special population*.

Study Part C: lot to lot consistency

Antibody response 21 days after the first vaccination

GMTs across the three lots ranged from 17.4 to 19.1 showing a statistically significant rise over Day 0 levels.

Antibody response 21 days after the second vaccination

Statistically significant increases of GMTs were seen for all three lots after the second vaccination compared to the first one, with GMTs ranging from 26.5 to 28.6.

Study Part C: immunogenicity data from cohort 1 (healthy adults)

In this much larger group (n=640 vs. n=119 in the corresponding age stratum of treatment group 1), the results by MN assay reached the criteria for seroconversion and fold increase and narrowly miss the seroprotection criterion (see table 4 left panel MN assay).

Similar results were obtained by SRH assay (see table 4 right panel SRH assay).

Table 4. MN-ASSAY SRH-ASSAY

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Figure 14.2-25.
Reverse cumulative distribution of immune response measured by MN (A/Vietnam) assay
(Study 810705: Subjects included in the intent-to-treat dataset)

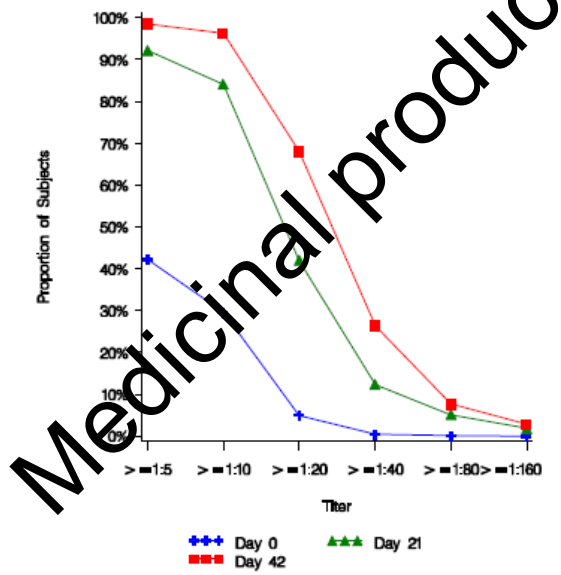
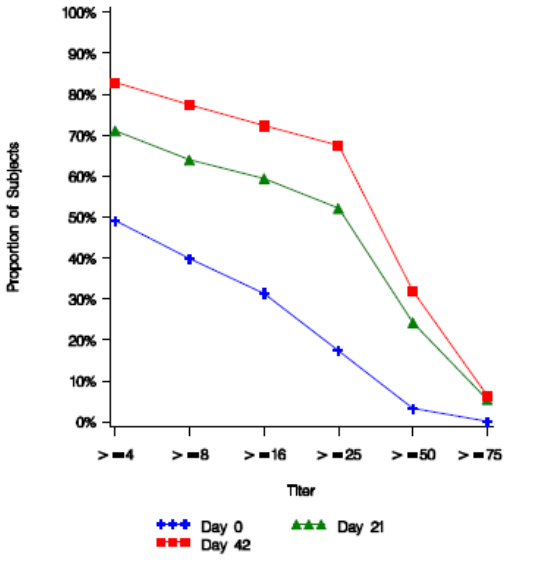


Figure 14.2-26.
Reverse cumulative distribution of immune response measured by SRH (A/Vietnam) assay
(Study 810705: Subjects included in the intent-to-treat dataset)



Study Part D: 6-Month Follow Up

Cohort 1 - healthy subjects

By MN assay antibody persistence data for the 7.5µg dose show a decline in the seroprotection rate in adults and elderly respectively to 24.1 and 30.2% by MN assay and to 48.3 and 36.2% by SRH assay. The reverse cumulative distribution by both MN and SRH indicate that the majority of subjects still have antibodies detectable at D201.

Study Part E: 21 days after booster vaccination

Cohort 1 - healthy subjects

Prior to the booster vaccination with the A/Indonesia strain (Day 360-720), a relatively low number of subjects showed MN titres associated with protection (≥1:20) to the A/Vietnam strain and even lower seroprotection rates were observed for the A/Indonesia strain.

At Day 21 after administration of the A/Indonesia strain booster vaccination, SP rates, SC and GMFI (geometric mean fold increase) by MN increased for both the A/Indonesia (booster) strain and the A/Vietnam (primary vaccination) strain in the adult and elderly population (table 5).

The SRH results were lower than the results obtained using the MN assay, but generally confirmed the MN results with regard to the boosterability of the immune response (table 6).

Table 5. Immunogenicity data of 12-24 month booster with 7.5µg dose of non-adj. A/Indonesia vaccine following 2-dose primary A/Vietnam (7.5µg non-adj. formulation) vaccination as measured by MN assay

	Healthy subjects (Cohort 1)			
	Adults (18 – 59 years)		Elderly (≥60 years)	
	A/Indonesia (n=113)	A/Vietnam (n=113)	A/Indonesia (n=91)	A/Vietnam (n=91)
				Seroprotection rates [1]
Pre-booster	6.2%	23.0%	4.4%	27.5%
21 days post-booster	82.3%	85.8%	70.3%	80.2%
				Seroconversion rates [2]
21 days post-booster	77.9%	48.7%	62.6%	25.3%
				GMFI [3]
21 days post-booster	14.9	4.5	6.7	2.6

1 MN titre ≥1:20
2 ≥ 4-fold increase in MN titre as compared to pre-booster
3 Geometric mean fold increase

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Table 6. Immunogenicity data of 12-24 month booster with 7.5µg dose of non-adj. A/Indonesia vaccine following 2-dose primary A/Vietnam (7.5µg non-adj. formulation) vaccination as measured by SRH assay

	Healthy subjects (Cohort 1)			
	Adults (18 – 59 years)		Elderly (≥60 years)	
	A/Indonesia (n=113)	A/Vietnam (n=113)	A/Indonesia (n=91)	A/Vietnam (n=91)
				Seroprotection rates [1]
Pre-booster	7.1%	34.5%	3.3%	24.2%
21 days post-booster	57.5%	69.9%	47.3%	57.1%
				Seroconversion rates [2]
21 days post-booster	54.0%	47.8%	45.1%	41.8%
				GMFI [3]
21 days post-booster	3.6	2.2	2.8	2.2

1 SRH area ≥ 25 mm2
2 either SRH area ≥ 25 mm2 if pre-booster sample is negative (≤4 mm²) or 2 fold increase in SRH area if pre-booster sample >4 mm²
3 Geometric mean fold increase

Study Part F: Cell-Mediated Immune (CMI) response

For a subset of subjects in two of the three cohorts, cohort 1 (healthy adult subjects) and cohort 2 (immune-compromised subjects), T-cell mediated immune response was evaluated.

T-cell-mediated immune response was assessed by testing peripheral blood mononuclear cells (PBMCs) in IFN-γ ELISPOT assay for reactivity against antigens of the strains used in this study for primary and booster vaccination, H5N1 A/Vietnam/1203/2004 and H5N1 A/Indonesia/05/2005 respectively, as well as against pandemic influenza antigen H1N1 A/California/07/2009, and seasonal influenza antigens H1N1 A/Brisbane/59/2007, H3N2 A/Uruguay/716/2007, and B/Brisbane/60/2008, as controls. The use of IFN-γ as a marker for T cell effector function enables the enumeration of CD8+ T-cells and of T-helper type 1 (TH1) CD4+ cells. IFN-γ producing CD8 and CD4 T-cells have been shown to contribute to the T cell response following natural infection and vaccination.

Blood samples from subjects included in the subset for evaluation of cellular immunity were taken on Day 0 (prior to first vaccination), Day 21 (prior to second vaccination), Day 42 (21 days after second vaccination), and Day 201 (6-month follow-up after second vaccination). Further assessments were carried out on Day 360-720 (prior to booster) and Day 381-741 (21 days after booster).

As expected the data on the cell mediated immune response against H5N1 and seasonal influenza strains demonstrate a significantly reduced influenza-specific T cell repertoire in immune-compromised subjects (Cohort 2) prior to vaccination compared with healthy adult subjects (Cohort 1). Influenza-specific T cell responses in immune-compromised patients at baseline were determined to be 27.7 and 44.4 (Spot-forming cells) SFCs/5x105 PBMC against A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain respectively. A level of 100 SFCs/106 PBMC has been reported in children who were protected from influenza in a recent study.

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In contrast, the frequency of influenza-specific SFCs in healthy adult subjects (Cohort 1) at baseline were 100.6 and 103.5 SFCs/5x105 PBMC against A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain respectively, twice as high as the level reported in children who were protected from influenza disease. Individuals in Cohort 1 were determined to have high baseline T cell response levels to all the influenza strains tested, particularly to the seasonal flu strains, thereby making it difficult to detect further significant increases in T-cell response levels after vaccination.

The CMI responses after vaccination in Cohort 2 demonstrate rapid recovery of the influenza-specific T cell repertoire after vaccination, with T cell response reaching 47.0 and 84.8 SFCs/5x105 at day 21 and day 42 after vaccination for A/Vietnam/1203/2004 strain and 71.6 and 121.5 SFCs/5x105 at day 21 and day 42 after vaccination for A/Indonesia/05/2005 strain. There was no decrease in the influenza-specific T cell repertoire within the 1 to 2 years period prior to the booster vaccination. The frequency of influenza-specific T cells generated after two vaccinations with H5N1 was twice as high as the level reported in children who were protected from influenza disease.

In conclusion cell-mediated immune response was induced against the homologous and heterologous H5N1 influenza strains in immune-compromised individuals of Cohort 2 but was also maintained for approximately 18 months and could be boosted, as demonstrated by a frequency of influenza-specific SFCs of 117.0 and 143.2 SFCs/5x105 PBMC for A/Vietnam/1203/2004 and A/Indonesia/05/2005 strain respectively, at 21 days after the 12 to 24 month booster vaccination. Indeed by day 360-720, at the time of the booster immunization, the GM values of the T cell responses to both H5N1 strains among immunocompromised subjects participating in the study were equivalent to those seen in the remaining healthy subjects, indicating the vaccine's ability to bring CMI response to normal levels even in immunocompromised. Some cross-reactivity was achieved against the pandemic H1N1 A/California strain and all three seasonal influenza strains (both A and B), however the seasonal strains were also reported to have relatively high baseline levels suggesting prior exposure in the form of previous influenza vaccines or natural influenza infection.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7. Summary of Efficacy for trials 810601 and 810705

Title: An Open Label Phase III Study of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine to Assess the Immunogenicity and Safety and to Investigate the Need for and Timing of a Booster Vaccination	
Study identifier	**810601**
Design	Ph 3, randomized, dose comparison, open-label, multi-center
Study Objective	• To assess the immunogenicity of an H5N1 influenza vaccine in adults and elderly; • To assess the safety and tolerability of an H5N1 influenza vaccine in adults and elderly • To assess the need for and timing of a booster dose; • To evaluate the T cell mediated immune response
Treatment and Study	First subject enrolled: 10 April 2007

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Duration	Study Part A (Day 42) Last subject completed Part A (through Day 42, 21 days after second vaccination): 02 August 2007	• 7.5 µg H5N1 HA antigen Clade 1 strain A/Vietnam/1203/2004; 2 vaccinations: Day 0 and 21 N = 561
	Study Part B (6 month booster) Last subject completed Part B (through Day 201, 21 days after 6 month booster): 10 Jan 2008	• 7.5 µg HA Clade 1 strain A/Vietnam/1203/2004 or • 3.75 µg HA Clade 1 strain A/Vietnam/1203/2004 or • 7.5 µg HA Clade 2strain A/Indonesia/05/2005 or • 3.75 µg HA Clade 2.1 strain A/Indonesia/05/2005 6-month booster: N= 225 (in appr. half of subjects, randomized 1:1:1:1)
	Study Part C (12-15 month booster) Last subject completed Part C (Day 381-471, 21 days after 12-15 month booster): 17 Sep 2008	• 7.5 µg HA Clade 2strain A/Indonesia/05/2005 or • 3.75 µg HA Clade 2.1 strain A/Indonesia/05/2005 12-15 month booster: N= 117 (in appr. 1/4 of subjects, randomized 1:1)
	Study Part D (24 month booster) Last subject completed Part D (Day 741, 21 days after 24 month booster): 11 Jul 2009	• 7.5 µg HA Clade 2strain A/Indonesia/05/2005 or • 3.75 µg HA Clade 2.1 strain A/Indonesia/05/2005 24-month booster: N = 100 (in appr. 1/4 of subjects, randomized 1:1)
	Study Part E (Cellular Immunity)	T cell mediated immunity evaluation in subset of adults and elderly subjects. N (cellular immunity subset): 40
Endpoints and definitions	Primary endpoint	<u>All subjects:</u> Number of subjects with antibody response to the vaccine strain (A/Vietnam/1203/2004) associated with protection 21 days after the second vaccination defined as titre measured by microneutralization (MN) test ≥ 20.
	Secondary Endpoints	<u>All subjects:</u> anti-HA antibodies by HI; SRH; neutralizing antibodies by MN <u>Cellular immunity subset:</u> Cell mediated immune response
Database lock	Final: 08 Feb 2010	

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**

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Analysis population and time point description	The analysis is performed on the intent-to-treat (ITT) and per protocol (PP) datasets Time points of analysis: 21 days after 1st and 2nd vaccination; pre- and 21 days post booster; 180, 360-450 and 720 days after 1st vaccination; 180-270 and 540 days after booster in 6-month booster; 270-360 after booster in 12-15 month booster group
Statistical Analysis	Antibodies against the influenza virus strain used in the vaccine will be determined by HI, MN and SRH assays. Antibody titrations of the HI assay will be done in duplicate; pre and post-vaccination sera will be titrated simultaneously. The titre assigned to each sample will be the geometric mean of two independent determinations. For purposes of analyses, any HI result ≤ 1:10 (undetectable) will be expressed as 1:5 and will be considered negative. Analysis of Primary Immunogenicity Endpoint The rates of subjects with antibody response associated with protection 21 days after the second vaccination and their 95% confidence intervals will be calculated separately for both age strata. Analysis of Secondary Immunogenicity Endpoints: Point estimates and 95% confidence intervals will be calculated for all secondary immunogenicity endpoints. The analysis will be carried out separately for both age strata. In order to assess the effect of the strain (A/Vietnam/1203/2004, A/Indonesia/05/2005) and of different doses (3.75 µg HA antigen, 7.5 µg HA antigen) for the 6-month booster and of different doses (3.75 µg HA antigen, 7.5 µg HA antigen) for the 12- to 15-month and the 24-month booster of the vaccine on the antibody response, measured by HI, MN and SRH assays, antibody response will be analyzed by analysis of covariance. The model will include doses, the strain and the interaction term between dose and strain as influencing factors and baseline values as covariates. Antibody response values will be log transformed prior to the analysis. Antibody responses will be analyzed separately for each assay. If an interaction of strain and dose is detected, an analysis of subgroups will be performed. For the subset of subjects included in the evaluation of the T-cell mediated response minimum, maximum, 25% and 75% quantiles, median and the respective 95% confidence interval will be calculated for all parameters reflecting T-cell response before and after each vaccination. In addition, parameters reflecting T-cell response will be investigated by non-parametric procedures. Wilcoxon Signed Rank test will be used for analysis of paired baseline and post-vaccination values.

Title: An Open-Label Phase III Study to Assess the Safety and Immunogenicity of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in an Adult and Elderly Population as well as in Specified Risk Groups	
Study identifier	**810705**
Design	Ph 3, randomized, dose comparison, open-label, multi-center
Study Objective	• To assess the safety and tolerability of a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population and in specified risk groups; • To assess the immune response to a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population and in specified risk groups; • To assess persistence of H5N1 influenza antibodies after vaccination with a non-adjuvanted H5N1 influenza vaccine in an adult and elderly population and in specified risk groups; • To demonstrate consistency of immune response among three different lots of a non-adjuvanted H5N1 influenza vaccine; • To evaluate the T-cell mediated immune response.
Treatment and Study	First subject enrolled: 06 Aug 2008

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Duration	Study Part A+C (healthy adults and elderly subjects) Last subject completed Parts A and C (through Day 42, 21 days after second vaccination): 30 Mar 2009	7.5 µg or 3.75 µg H5N1 HA antigen Clade 1 strain A/Vietnam/1203/2004; 2 vaccinations: Day 0 and 21 first vaccination: N (immunogenicity subset) = 561 second vaccination: N (immunogenicity subset) = 539 N (Immunogenicity subset): 886
	Study Part B (immunocompromised and chronically ill subjects) Last subject completed Part B (through Day 42, 21 days after second vaccination): 23 July 2009.	7.5 µg H5N1 HA antigen Clade 1 strain A/Vietnam/1203/2004; 2 vaccinations: Day 0 and 21 first vaccination: N (immunogenicity subset) = 561 second vaccination: N (immunogenicity subset) = 539 N (Immunogenicity subset) = 215
	Study Part D (all subjects) Last subject completed Part D (through Day 201, 180 days after second vaccination): 17 Dec 2009	N (Immunogenicity subset) = 381
	Study Part E (12-24 month booster) Last subject completed Part E (through Day 381-741, 21 days after 12-24 month booster): 01 Oct 2010	7.5 µg H5N1 HA antigen Clade 2.1 A/Indonesia/05/2005 strain 12-24 month booster N (Immunogenicity subset) = 360
	Study Part F (Cellular Immunity)	T cell mediated immunity evaluation in subset of healthy adults and immunocompromised subjects. N (cellular immunity subset): 72
Endpoints and definitions	Primary endpoints	<u>Immunogenicity subset:</u> Antibody response 21 days after the second vaccination as measured by Microneutralization (MN) assay; Number of subjects with antibody response to the vaccine strain (A/Vietnam/1203/2004) associated with protection 21 days after the second vaccination defined as titre measured by MN assay ≥1:20.
	Secondary endpoints	<u>Immunogenicity subset:</u> anti-HA antibodies by HI; SRH; neutralizing antibodies by MN <u>Cellular immunity subset:</u> Cell mediated immune response
Database lock	Final: 12 Nov 2010	

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**

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Analysis population and time point description	The analysis is performed on the intent-to-treat (ITT) and per protocol (PP) datasets. Time point of analysis: 21 days after 1st and 2nd vaccination; pre- and 21 days post booster; 180 days after 2nd vaccination
Statistical Analysis	<u>Analysis of Primary Immunogenicity Endpoint</u> The rates of subjects with antibody response associated with protection measured by MN test 21 days after the second vaccination and their 95% CIs will be calculated separately for all cohorts, age strata and dose groups. <u>Analysis of Secondary Immunogenicity Endpoints:</u> Point estimates and 95% CIs will be calculated for all secondary immunogenicity endpoints. The analysis will be carried out separately for all cohorts, age strata and dose groups.

Analysis performed across trials (pooled analyses)

A pooled immunogenicity analysis was performed for subjects in the ITT datasets of studies 810501, 810601 and 810705 who received the non-adjuvanted Vero cell-derived H5N1 influenza vaccine containing 7.5 µg of H5N1 HA antigen strain A/Vietnam/1203/2004. Separate analyses were performed for subjects 18 to 59 years of age and for subjects 60 years of age or older. The seroprotection rate results are presented in table 8 (MN assay) and in table 9 (SRH assay).

Table 8. MN-Assay Seroprotection (percent with titre ≥1:40), 7.5 µg non-adjuvanted, strain A/Vietnam (Pooled Analysis of Studies 810501, 810601 and 810705 – ITT)

Age	18-59y			≥60y		
Day	n/N	%	95%CI	n/N	%	95%CI
0	43/961	4.5	3.3 – 6.0	69/391	17.6	14.0 – 21.8
21	426/960	44.4	41.2 – 47.6	203/391	51.9	46.8 – 57.0
42	660/947	69.7	66.7 – 72.6	269/389	69.2	64.3 – 73.7

By MN assay, the pooled analysis shows that of the three CHMP criteria 2 are fulfilled both in the adult population and in the elderly population. In the adults seroprotection is narrowly missed, in the elderly seroconversion is below target.

Table 9. SRH-Assay Seroprotection, 7.5 µg non-adjuvanted, strain A/Vietnam (Pooled Analysis of Studies 810501, 810601 and 810705 – ITT)

Age	18-59y			≥60y		
Day	n/N	%	95%CI	n/N	%	95%CI
0	128/959	13.3	11.3 – 15.7	24/385	6.2	4.0 – 9.1
21	509/956	53.2	50.0 – 56.4	186/390	47.7	42.6 – 52.8
42	629/941	66.8	63.7 – 69.8	227/385	59.0	53.9 – 63.9

By SRH assay, the pooled analysis shows that 2 of the 3 CHMP criteria are fulfilled in the adult and also in the elderly population. Seroconversion and GM fold increase are met in both age groups. The seroprotection criterion is missed very narrowly in the elderly and by a wider margin in the adult.

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Clinical studies in special populations

Study 810705

In the clinical studies 810501, 810601, 810701 and 810703 immunogenicity was investigated in healthy male and female adult volunteers only, while in study 810705 immune compromised individuals and chronically ill patients were also included (cohort 2 and 3, respectively).

Part B of the study covered immunogenicity through Day 42 for subjects in Cohorts 2 and 3.

Part D of the study covered immunogenicity through Day 201 (6 month follow-up) for all subjects. The results for Cohorts 2 and 3 are described in this section.

Cohort 2– immune compromised subjects

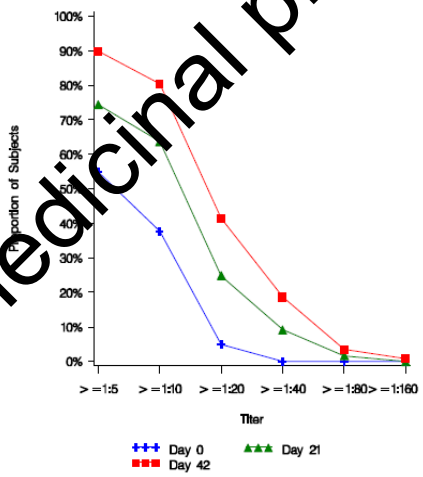
After two vaccinations, a clear trend towards a robust antibody response is observed in the MN assay, where 41.5 % of subjects achieve a titre greater than 1:20 (SP rate). This trend is more pronounced in the SRH assay, where 53.4% of subjects achieve SRH values greater than 25 mm². 32.2% and 35.6% of subjects achieved seroconversion in the MN and the SRH test respectively.

There are no established correlates of protection that would allow a more precise assessment of the clinical relevance of antibody response in immunocompromised subjects. Published data suggest that antibody response is diminished in patients with HIV/AIDS or solid organ transplant recipients. Nevertheless, clinical protection from influenza could be shown after vaccination with trivalent influenza vaccine in HIV patients, while evidence of clinical effectiveness of vaccination is currently lacking for recipients of solid organ transplants (Kunisaki et al, Lancet Infect Dis 2009).

Assessment of the clinical relevance of the antibody response in the immunocompromised cohort is difficult. Nevertheless, the available serological data demonstrate that these patients are indeed able to mount an immune response after two vaccinations with the monovalent H5N1 vaccine. This in turn suggests that a certain level of protection against infection is highly likely.

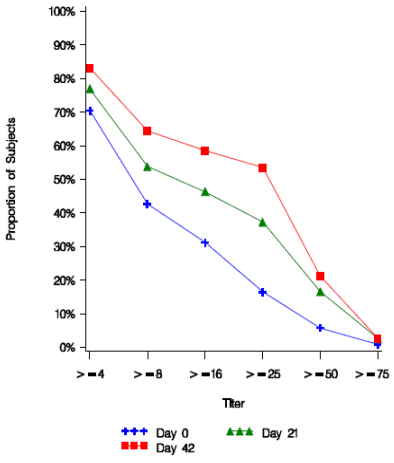
MN-ASSAY

Figure 14.2-1.
Reverse cumulative distribution of immune response measured by MN (A/Vietnam) assay (Study 810705: Subjects included in the intent-to-treat dataset, cohort 2 - immunocompromised subjects)



SRH-ASSAY

Figure 14.2-2.
Reverse cumulative distribution of immune response measured by SRH (A/Vietnam) assay (Study 810705: Subjects included in the intent-to-treat dataset, cohort 2 - immunocompromised subjects)



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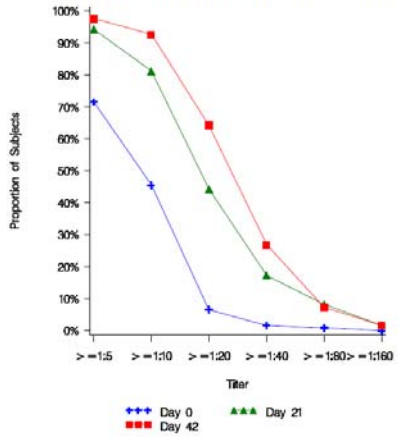
Cohort 3– chronically ill subjects

The cohort 3, chronically ill subjects, included nearly 40% elderly subjects. CHMP criteria are valid for healthy subjects, adults and elderly, thus it is not clear which CHMP criteria, if any, may be applicable to chronically ill subjects.

Based on the serological criteria established for the elderly, two of the three criteria are met by SRH assay, SC with 33.3% and fold increase with 2.0, while the rate of SP is 42.3%. By MN assay, all three criteria have been fulfilled, with a SP rate (i.e. subjects with MN titre ≥1:20) of 64.2%, a SC rate of 35% and a fold increase of 3.0. These results suggest that chronically ill subjects are able to mount an immune response to vaccination with this monovalent vaccine and that a certain amount of protection is very likely.

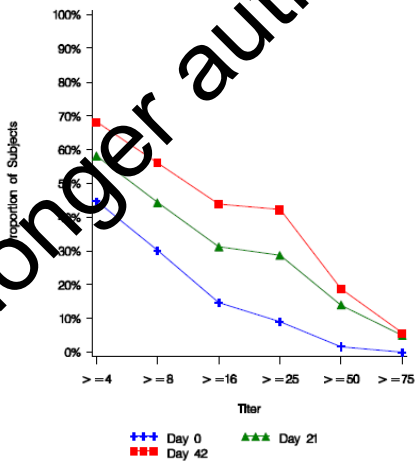
MN-ASSAY

Figure 14.2-5.
Reverse cumulative distribution of immune response measured by MN (A/Vietnam) assay
(Study 810705: Subjects included in the intent-to-treat dataset, cohort 3 - chronically ill subjects)



SRH-ASSAY

Figure 14.2-6.
Reverse cumulative distribution of immune response measured by SRH (A/Vietnam) assay
(Study 810705: Subjects included in the intent-to-treat dataset, cohort 3 - chronically ill subjects)



Study Part D: antibody persistence at 6-Month

Cohort 2 - immunocompromised subjects (7.5µg, N=113)

By MN assay, antibody titres at day 201 were nearly returned to baseline levels in the immunocompromised cohort. The SRH assay identified a higher level of antibody titres, more similar to values at day 21, i.e. three weeks after the first vaccination.

Cohort 3 – chronically ill subjects (7.5µg, N=123)

In the chronically ill cohort, the antibody titres measured by MN assay at day 201 were lower but similar to the day 21 levels. By SRH assay, a higher titre was observed with values more comparable to the day 42 levels.

Study Part E: 21 days after 12 to 24 months booster vaccination

Cohort 2 - immunocompromised subjects

On Day 360-720 (pre-booster), a low rate of subjects showed MN titres associated with protection to the A/Vietnam strain (10.4%) and A/Indonesia strain (1.5%). At Day 21 after the A/Indonesia booster vaccination, the SP rates (MN titre ≥ 1:20) were 65.7% for the A/Indonesia strain and 71.6% for the A/Vietnam strain. The GM fold increase versus baseline (pre-booster) was 7.7 for the A/Indonesia strain and 3.8 for the A/Vietnam strain. SC occurred in 61.2% and 37.3% of subjects for the A/Indonesia and A/Vietnam strains, respectively.

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The SRH results were lower than those obtained by MN assay but generally similar with regard to the boosterability of the immune response. At 21 days post-booster, SP rates (SRH area ≥25 mm2) were 41.8% and 64.2% (A/Indonesia and A/Vietnam strains, respectively). The GM fold increase in antibody response was 3.0 for the A/Indonesia strain and 1.8 for the A/Vietnam strain. SC rates were 41.8% and 43.3% for the A/Indonesia and A/Vietnam strains, respectively.

Cohort 3 – chronically ill subjects

Pre-booster (Day 360-720), a relatively low number of subjects had MN titres associated with protection against the A/Vietnam (24.7%) and the A/Indonesia strain (2.2%).

At 21 days post-booster, SP rates were 70.8% for the A/Indonesia strain and 77.5% for the A/Vietnam strain. The GM fold increase in MN titre versus baseline (pre-booster) was 8.4 for the A/Indonesia strain and 3.0 for the A/Vietnam strain. SC occurred in 65.2% and 31.5% of subjects for the A/Indonesia and A/Vietnam strains, respectively.

The SRH results were lower than the results obtained by MN assay, but generally confirmed the boosting of the immune response. At Day 21 after the booster vaccination, SP rates (SRH area ≥25 mm2) were 50.6% and 64.0% for the A/Indonesia and A/Vietnam strains, respectively. The GM fold increase in antibody response was 3.3 for the A/Indonesia strain and 2.0 for the A/Vietnam strain. SC occurred in 53.9% and 43.8% of subjects for the A/Indonesia and A/Vietnam strains, respectively.

Supportive studies

Study 810701 (Phase 1-2)

Due to the geographical spread, epidemiology and to the antigenic and genetic properties of clade 2 H5N1 viruses that showed increased case fatality rates in China and Indonesia in 2006 (62% and 82%), there was an increased interest from health organizations and national authorities to start the development of H5N1 investigational vaccine based on clade 2 viruses.

Therefore the Applicant initiated a randomized, open-label Phase 1/2 clinical study (810701) investigating the safety and immunogenicity of two different dose levels (3.75µg or 7.5µg HA antigen) of a non-adjuvanted clade 2 (A/Indonesia/05/2005) H5N1 influenza vaccine in a healthy young adult population. Subjects received two injections 21 days apart and were monitored for immunogenicity and safety until Day 180. The study was conducted in 4 centres in Hong Kong and Singapore.

Immunogenicity endpoints determined by MN, HI and SRH assay were evaluated against the H5N1 influenza strain contained in the vaccine (A/Indonesia/05/2005). In order to assess cross-reactivity of antibodies, sera were also evaluated against H5N1 influenza virus clade 1 strain A/Vietnam/1203/2004.

Results

Antibody response against the homologous clade 2 A/Indonesia/05/2005 strain

A substantial antibody response after two vaccinations with the Vero cell-derived vaccine was observed in both dose groups. Neutralizing antibody results were somewhat higher than antibody response determined by SRH, but the assays were generally consistent for all parameters.

The rate of subjects with a neutralizing (MN) antibody titre ≥20 against the vaccine strain A/Indonesia/05/2005 twenty-one (21) days after the second vaccination (primary endpoint) was 82.7% and 86.5 % in the 3.75µg and 7.5µg dose groups respectively. Antibody response associated with protection 21 days after the second vaccination for the vaccine strain, as defined by SRH area ≥25

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mm2 was determined in 71.2% and 69.2% of subjects vaccinated with the 3.75µg or 7.5µg dose, respectively. The seroprotection rate determined by SRH in the 7.5µg dose group is marginally lower than the CPMP criterion of >70% in adults, however by comparison, 86.5% of subjects had functional antibodies (MN) in this dose group. Even after the first vaccination, seroprotective titres were observed in 36.4% and 19.2% of subjects as determined by MN and 38.2% and 40.4% by SRH, in the 3.75µg and 7.5µg dose groups, respectively.

Antibody responses for the vaccine strain were similar between dose groups after the second vaccination and slightly higher in general determined with MN as compared with SRH (82.7% vs. 86.5% seroconversion; 34.5 vs. 36.0 GMT; 8.0 vs. 8.3 GM fold titre increase with MN, and 71.2% vs. 67.3% seroconversion; 20.9 vs. 22.8 GM of haemolysis area (mm2); 5.0 vs. 5.4 GM fold increase in haemolysis area with SRH in the 3.75µg and 7.5µg dose groups, respectively).

At Day 180, as expected, a decline in antibody levels was observed. However, neutralizing antibodies were shown to persist in a substantial number of subjects, with 50.0% and 55.8% of subjects in the 3.75µg and 7.5µg dose groups exhibiting a reciprocal MN titre ≥20 to the vaccine strain. The level of neutralizing antibodies (MN) at Day 180 was higher than antibody levels determined by SRH (26.9% vs. 9.6% with the 3.75µg and 7.5µg dose, respectively). GM fold increases at Day 180 as compared to baseline, and GMTs were generally higher determined by MN and similar between dose groups for both assay types.

Cross-reactivity antibody response against a clade 1 strain (A/Vietnam/1203/2004)

Cross-reactivity could be shown by MN and SRH analysis, with 25.0% vs. 21.2% subjects achieving a reciprocal MN titre ≥20, after the second vaccination in the 3.75µg and 7.5µg dose groups and SRH area ≥25 mm2 for 25.0% vs. 28.8% against the heterologous clade 1 strain (A/Vietnam/1203/2004) strain.

Cross-neutralization against the A/Vietnam/1203/2004 strain after the second vaccination was also demonstrated by seroconversion rates, GMTs and GMs of fold increase in MN titres (13.5% vs. 23.1% seroconversion; 13.3 vs. 13.6 GMT; 2.4 vs. 2.9 GM fold increase in the 3.75µg and 7.5µg dose groups, respectively). Results of SRH analysis were generally consistent with MN. At Day 180, the rate of subjects with reciprocal MN titre ≥20 against a heterologous clade 1 strain was 7.7% and 3.8% in the 3.75µg and 7.5µg dose group respectively. Seroprotective antibody response as determined by SRH was determined in 3.8% of subjects in both dose groups.

Collectively, the data show that two vaccinations given 21 days apart at either 3.75µg or 7.5µg HA antigen could elicit serological responses well exceeding the CPMP criteria for immunogenicity of seasonal influenza vaccines, as measured 21 days after the second vaccination for all MN assessments, with no dose effect observed. Crossreactivity against the Vietnam strain was demonstrated. The decline in antibody levels at Day 180 indicates that a prime-boost strategy may be beneficial with this vaccine. These results are consistent with those of previously submitted studies.

Study 810802 (Phase 1-2)

The clinical study report (CSR 810802 part A) has become available since the original submission and has been submitted with the D120 responses.

An alternative dose sparing approach is priming with only a single dose of pre-pandemic vaccine followed by a heterologous booster vaccination. Therefore, in this study (810802), such a single dose prime-boost strategy was explored by investigating the ability of a booster vaccination with either 3.75µg or 7.5µg of a non-adjuvanted A/Indonesia/05/2005 strain vaccine formulation to induce a

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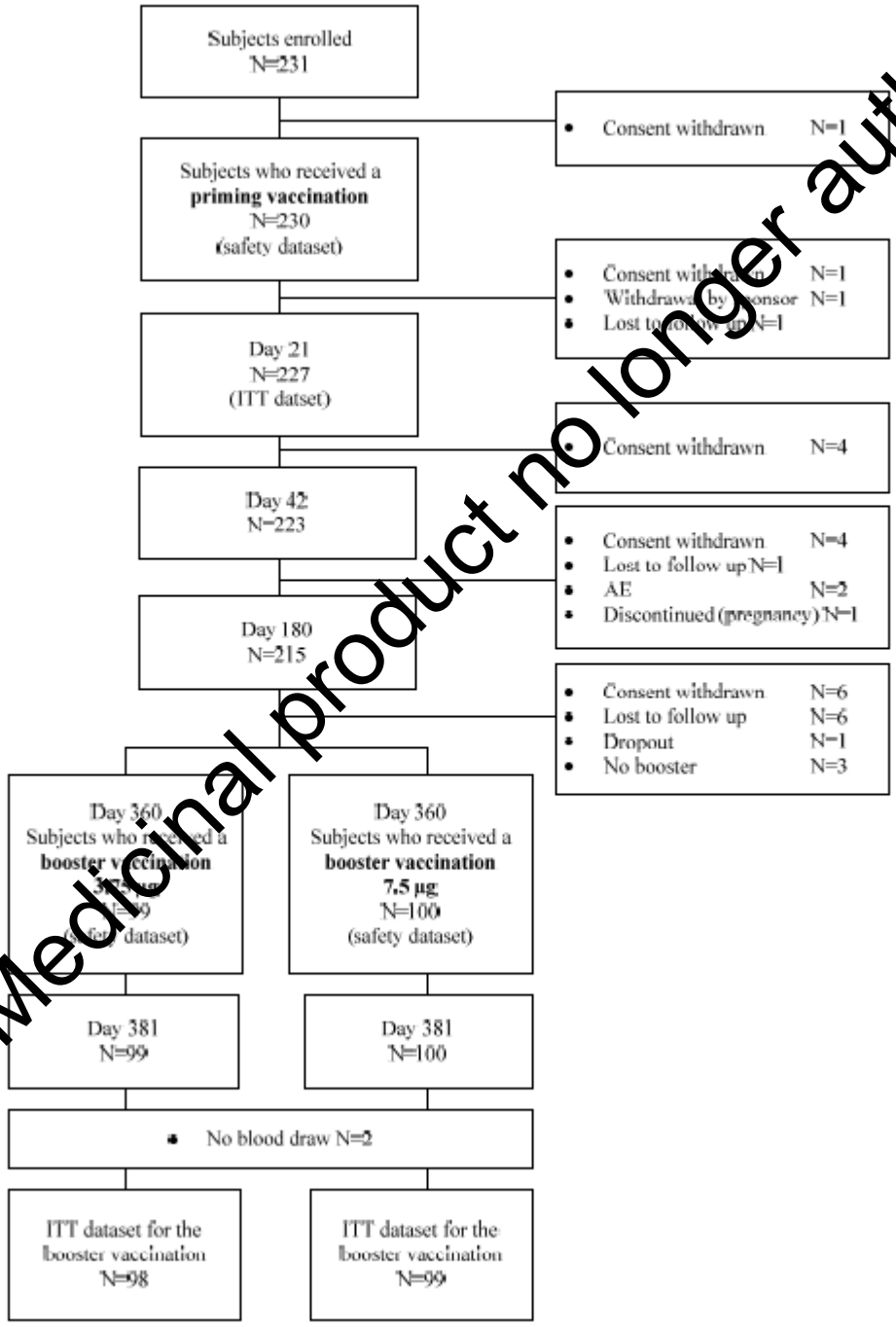
booster response after a single dose priming vaccination 12 months earlier with 7.5µg of a non-adjuvanted A/Vietnam/1203/2004 strain vaccine.

The study is conducted in two parts:

Part A: this began with the screening visit and was completed when all subjects had the Day 381 visit (i.e. Day 21 after the booster vaccination). The clinical study report (CSR) submitted covers safety and immunogenicity results. For the subject disposition see figure 10.1-1 below.

Part B: All subjects were followed until Day 180 after the booster vaccination (i.e. Day 540). Part B was completed when all subjects had the Day 540 visit.

Figure 10.1-1.
Subject Disposition for Study 810802 Part A



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A total of 230 healthy subjects received a single priming vaccination on Day 0 with the whole virion, Vero cell-derived influenza vaccine containing 7.5µg H5N1 haemagglutinin antigen strain A/Vietnam/1203/2004 in a non-adjuvanted formulation. A total of 199 subjects also received a booster vaccination with an A/Indonesia/05/2005 strain in a non-adjuvanted formulation on Day 360 (N=99, 3.75µg; N=100, 7.5µg).

	Booster Vaccination			
	Homologous Ab response (Indonesia)		Heterolgous Ab response (Vietnam)	
	3.75 µg	7.5 µg	3.75 µg	7.5 µg
Seroprotection rate > 70%				
MN	**82.7**	**92.9**	**78.6**	**85.9**
SRH	67.3	**77.8**	66.3	**79.8**
Fold increase in Ab titer > 2.5				
MN	**4.1**	**5.3**	**2.9**	**3.8**
SRH	**5.2**	**6.1**	**2.5**	**3.6**
Seroconversion rate > 40%				
MN	**43.9**	**59.6**	33.7	**43.4**
SRH	**65.3**	**76.8**	**54.1**	**69.7**

Ab – Antibody titer

A single prime-heterologous boost immunization induced a high level of protection against both the booster strain and the strain contained in the vaccine for priming as determined by MN and SRH. All CPMP efficacy criteria for seasonal influenza virus for adults (seroprotective rate > 70%, fold increase in antibody titre > 2.5 and seroconversion rate >40%), which are also applicable to pre pandemic vaccines, were achieved with the 7.5µg booster dose against both the booster and primary antigen strains, with most criteria also being met with the lower dose (3.75µg).

The results of this study elucidate the effects of receiving only one priming vaccination with Vepacel. This is a likely event in case of a pre-pandemic alert period, where not all subjects may return for the second priming vaccination due to the perceived low threat level of a pandemic being only a possibility and not a certainty.

Pooled Analysis

Combined immunogenicity data after the second vaccination (pooled data analysis of studies 810501, 810601 and 810705) demonstrate an overall functional antibody response (MN titre ≥1:20) of 69.7% in adults and 63.2% in the elderly, thus narrowly missing the CPMP criterion of >70% for seroprotection in adults but fulfilling it (>60%) in the elderly (see table 10).

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Table 10. MN and SRH antibody responses to the homologous virus strain (pooled analysis of studies 810501, 810601 and 810705 using ITT analysis sets) after the first and second vaccine doses of 7.5 µg formulation

Age group	Assay	Criteria: n/N (%) (95% CI)						
		% Seroprotection[a]			% Seroconversion[a]		GMI[a]	
		Day 0	Day 21	Day 42	Day 21	Day 42	Day 21	Day 42
Adults (18-59 yrs)	MN	4.5% (3.3; 6.0) 43/961	44.4% (41.2; 47.6) 426/960	69.7% (66.7; 72.6) 660/947	32.7% (29.7; 35.8) 314/960	56.0% (52.7; 59.2) 530/947	3.05 (2.90; 3.21)	4.49 (4.26; 4.72)
	SRH	13.3% (11.3; 15.7) 128/959	53.2% (50.0; 56.4) 509/956	66.8% (63.7; 69.8) 629/941	39.8% (36.7; 43.0) 380/954	53.7% (50.4; 56.9) 504/939	2.46 (2.29; 2.65)	3.35 (3.11; 3.61)
Elderly (>= 60 yrs)	MN	17.6% (14.0; 21.8) 69/391	51.9% (46.8; 57.0) 203/391	69.2% (64.3; 73.7) 269/389	13.3% (10.1; 17.1) 52/391	23.9% (19.8; 28.5) 93/389	1.95 (1.83; 2.08)	2.58 (2.41; 2.75)
	SRH	6.2% (4.0; 9.1) 24/385	47.7% (42.6; 52.8) 186/390	59.0% (53.9; 63.9) 227/385	41.9% (36.9; 47.0) 161/384	52.2% (47.1; 57.4) 198/52.2	2.74 (2.42; 3.09)	3.47 (3.07; 3.94)

Further data on cross-protection

A question was posed to the Applicant during the evaluation of the dossier on the extent of H5N1 strains coverage by Vepacel.

A number of investigations have been performed with respect to the induction and priming of interclade cross-reactive antibodies by the clade 1, A/Vietnam/1203/2004 and the clade 2, A/Indonesia/5/2005 vaccines in human clinical trials. These studies have demonstrated that substantial antibody responses cross-reactive for clade 0, 1, clade 2.1, clade 2.2, and clade 2.3 are induced. Following a 2-dose primary vaccination with the A/Vietnam vaccine (N=42), seroprotection rates (MN titre ≥ 1:20) of 76.2% were observed against the homologous A/Vietnam strain and 76.2% and 45.2% cross-clade against the clade 0 A/Hong Kong and the clade 2.1 A/Indonesia strain, respectively (see Table Q3-1). In addition, a heterologous A/Indonesia booster vaccination following a 2-dose primary A/Vietnam vaccination (N=12) further demonstrated the ability of the vaccine to induce a broad cross-clade response, with seroprotection rates (MN titre ≥ 1:20) of > 90% achieved against the A/Indonesia (booster) strain and cross-clade against the clade 1 A/Vietnam strain (strain used for primary vaccination) and the more divergent clade 2.2 A/turkey/Turkey and 2.3 A/Anhui strains already at 7 days after the booster (see Table Q3-2).

In conclusion, clade 1 A/Vietnam and clade 2.1 A/Indonesia vaccines induce cross-reactive functional antibodies and prime a strong immune response against representative H5N1 viruses of clades frequently causing infections of humans. In addition the Applicant has resources available to extend these studies in the future (e.g. re-test the sera of its previous H5N1 clinical studies against newly emerging representative H5N1 strain(s)).

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Table Q3–1
Antibody response against clade 0, clade 1 and clade 2.1 strains after vaccination with the 7.5 µg non-adj. A/Vietnam vaccine as measured by MN assay (study 810501 [1])

	Day	A/Vietnam/ 1203/2004 (clade 1)	A/Hong Kong/ 156/1997 (clade 0)	A/Indonesia/ 05/2005 (clade 2.1)
Seroprotection [2]	0	0.0%	4.8%	0.0%
	21	40.5%	47.6%	23.8%
	42	76.2%	76.2%	45.2%
Seroconversion [3]	21	35.7%	38.1%	19.0%
	42	69.0%	66.7%	31.0%
GMFI [4]	21	3.2	3.4	2.2
	42	5.3	5.9	3.2

1 Study 810501 is a Phase I/II dose-escalation study in which subjects received a 2-dose primary vaccination with different doses/formulations of the A/Vietnam strain vaccine (i.e. either 3.75 µg, 7.5 µg, 15 µg or 30 µg in a non-adjuvanted formulation or 7.5 µg or 15 µg in an aluminum hydroxide [$AlOH_3$] adjuvanted formulation). The cross-reactive antibody response of subjects (N=42) who received a 2-dose primary vaccination with the 7.5 µg non-adjuvanted A/Vietnam strain vaccine are displayed in this table.

2 MN titre ≥ 20

3 ≥ 4-fold increase in MN titre

4 Geometric mean fold increase

Table Q3–2
Antibody response against clade 1, clade 2.1, clade 2.2 and clade 2.3 strains after booster vaccination with the 7.5 µg non-adj. A/Indonesia following a two-dose primary vaccination with 7.5 µg non-adj. A/Vietnam vaccine as measured by MN assay (study 810703 [1])

	Day	A/Indonesia/05/2005 (clade 2.1)	A/Vietnam/1203/2004 (clade 1)	A/turkey/Turkey/1/2005 (clade 2.2)	A/Anhui/1/2005 (clade 2.3)
Seroprotection [2]	0	0.0%	25.0%	8.3%	0.0%
	7	90.9%	90.9%	100.0%	90.9%
	21	100.0%	91.7%	91.7%	75.0%
Seroconversion [3]	7	90.9%	72.7%	100.0%	90.9%
	21	91.7%	66.7%	91.7%	91.7%
GMFI [4]	7	11.8	6.1	14.7	10.4
	21	14.3	7.0	17.8	12.6

1 Study 810703 is a Phase I clinical study in which a 12-17 month booster vaccination with the 7.5 µg non-adjuvanted formulation of A/Indonesia strain vaccine was administered to a subset of subjects who previously received a 2-dose primary vaccination in the Phase I/II study 810501 with different doses/formulations of the A/Vietnam strain vaccine (i.e. either 3.75 µg, 7.5 µg, 15 µg or 30 µg in a non-adjuvanted formulation or 7.5 µg or 15 µg in an aluminum hydroxide [$AlOH_3$] adjuvanted formulation). The results to the A/Indonesia booster vaccination in the subset of subjects (N=12) who received a 2-dose primary vaccination with the 7.5 µg non-adjuvanted A/Vietnam strain vaccine are displayed in this table.

2 MN titre ≥ 20

3 ≥ 4-fold increase in MN titre

4 Geometric mean fold increase

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2.4.3. Discussion on clinical efficacy

Some considerations have to be taken into account prior to the assessment of the efficacy of the pre-pandemic vaccine Vepacel:

- For pandemic and pre-pandemic vaccines, evaluation of clinical protection is only possible during a pandemic outbreak. It is therefore necessary to evaluate immunogenicity as a surrogate for clinical

efficacy. The requirements for the evaluation of immunogenicity parameters with the HI and SRH assay, which are commonly used for the assessment of the seasonal influenza vaccines, are laid down in EMEA/CHMP/VWP/263499/2006.

- High variability and low sensitivity of the HI assay results were observed during the clinical development program for this investigational vaccine. In consequence, it was agreed that the Applicant would evaluate the immune response with the MN assay and, additionally, file SRH assay results as supportive data.
- Because there are no correlates of protection established for the MN assay, the Applicant performed passive immune transfer studies in mice in order to validate a cut-off titre of 1:20 for seroprotection.

Design and conduct of clinical studies

This application is based on data from 5 clinical studies involving a total of 4535 vaccinated subjects, of whom 1750 were evaluated for immunogenicity after receiving the 7.5 µg dose of the investigational vaccine (1698 subjects vaccinated with the Vietnam strain and 52 with the Indonesia strain in the primary vaccination series). These studies were generally open label (except for the dose-finding trial 810501, which was partially blinded) and designed to evaluate immunogenicity and persistence of antibodies after a two dose priming schedule.

The fact that the clinical trials were open label and not placebo-controlled is a downside of this application, because it could have potentially introduced bias. However as the risk for bias was judged minimal and the same vaccine construct (with an H1N1 strain) has been extensively used during the latest pandemic, the design was considered overall acceptable.

Cross-reactivity was explored as well as the effects of homologous and heterologous booster immunisations with the full (7.5µg) or the half (3.75µg) dose at 6, 12-15 and 24 months after the primary vaccination. Furthermore, cellular immunity was studied in a subset of subjects in trials 810501, 810601 and 810705.

The population included into these trials consists mostly of healthy adults in two age strata from 18 - 59 and ≥60 years of age. In study 810705, cohorts of immunocompromised and chronically ill adult subjects were evaluated as well.

Efficacy data and additional analyses

Overall, of the three serological criteria specified for the evaluation of the initial vaccination in the relevant guidance, in most studies/study parts at least two could be fulfilled. In dose finding study 810501 with the non-adjuvanted 7.5 µg dose, all three criteria could be fulfilled in the MN as well as the SRH assay. In the pivotal study 810601, based on MN, all three requirements were fulfilled in adults and 2 of three were met in the elderly. In the SRH assay, adults fulfilled 2 out of three requirements and elderly all three. In study 810705, which is pivotal for safety, in the immunogenicity subset in part A, 2 of three criteria were met in adults and one criterion was met in the elderly with the MN assay. The SRH assay showed 2 of three criteria met in adults and one in the elderly. One of the possible reasons for the modest titre increases is the presence of cross-reactive antibodies, especially in older adults.

Geometric mean of fold increase and seroconversion were lower in the elderly overall possibly due to pre existing neutralizing antibody titre to H5N1 at baseline. This is in agreement with data previously reported, namely, that a percentage of the population, particularly the elderly, will have antibodies

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cross-reactive to H5N1 or other potential pandemic viruses without having been exposed to this virus. This situation of pre-existing titres occurs frequently with studies with trivalent seasonal influenza vaccines.

In the immunocompromised and chronically ill subjects of cohorts 2 and 3 in study 810705, substantial titre increases were seen in the MN as well as the SRH assay.

Cross-reactivity, antibody persistence at 6 months after the primary immunisation and the effects of a booster vaccination with a full or a half dose of homologous or heterologous strains at varying time points (6, 12-15, 24 months) are assessed as satisfactory, confirming the assessment previously made of the data for Pandemic-Influenza-Vaccine-H5N1-Baxter (formerly known as Celvapan). A substantial amount of cross reactive antibodies was shown against different H5N1 clades: clade 0 (A/Hong Kong), 2.1 (A/Indonesia), 2.2 (A/turkey/Turkey) and clade 2.3 (A/Anhui). These favourable characteristics displayed by the investigational vaccine are judged to be of even greater importance with regard to the evaluation in a pre-pandemic context. In a pre-pandemic vaccination setting it is to be expected that priming is not done with the exact antigenic characteristics of the strain ultimately responsible for the outbreak of the pandemic. The ability of a pre-pandemic vaccine to induce cross-reactive antibodies at baseline is considered very important. Of even greater importance in face of the commonly occurring antigenic drift and shift of influenza viruses is the feasibility of boosting the induced immune response with a half-dose of a heterogeneous strain until at least 2 years after the initial priming, as shown in study parts B, C and D of study 810601.

In study 810705, part E, the effects of a heterologous booster (7.5µg A/Indonesia) 12 – 24 months after the primary vaccinations were explored. At Day 21 after administration of the booster vaccination, seroprotection rates (MN titre ≥ 1:20) were 82.3% and 70.3% for the A/Indonesia (booster) strain and 85.8% and 80.2% for the A/Vietnam (primary vaccination) strain in the adult and elderly population, respectively. For the immunocompromised and chronically ill cohorts, the seroprotection rates were 65.7% and 70.8% against A/Indonesia and 71.6% and 77.5% against A/Vietnam, respectively. This substantial cross-reactivity is reassuring.

In study 810705, part F, the T-cell responses (against all influenza strains tested) were determined in immunocompromised subjects following vaccination with the inactivated whole virus H5N1 vaccine compared to baseline levels. They suggest that the vaccine is capable of priming naïve T-cells and creating a large influenza-specific pool of memory T-cells compared to baseline levels against both priming (A/Vietnam/1203/2004) and booster (A/Indonesia/05/2005) vaccine strains. Among immune-compromised subjects, this high level of T-cell response was maintained for at least 2 years and the response could also be boosted at 12 to 24 months after priming. These results indicate that vaccination with the inactivated whole virus H5N1 vaccine could be of benefit for immune-compromised individuals in developing T-cell mediated resistance against a range of H5N1 influenza strains up to levels comparable to those of healthy subjects.

During the H1N1v pandemic, an expert meeting was organised by the European Medicines Agency in February 2009 in order to discuss the different immunogenicity results of Celvapan and to assess if the vaccine is considered sufficiently immunogenic in all age groups. For this meeting not only the data from clinical trials with the H1N1v vaccine were presented, but also the immunogenicity data from clinical trials with the H5N1 strain, which supported the marketing authorisation of the mock-up vaccine (i.e. data from study 810501 and 810601). By taking into account all the data obtained with the different assay systems, the experts considered the vaccine sufficiently immunogenic to be used in all age groups, when administered in accordance with the approved dosage recommendation of two doses at an interval of at least 3 weeks.

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It is estimated that at least 566 000 patients have been vaccinated with Celvapan in Europe during the 2009/10 H1N1 pandemic with only very few cases of vaccine failures reported.

Additional expert consultation

During the evaluation, the CHMP asked the VWP to provide advice on the relevance of the choice of strain for Vepacel and the breadth of the vaccine's cross-reactivity across different H5N1 clades in support of its use in pre-pandemic settings.

The VWP was of the opinion that due to the high degree of HA genetic diversification reached so far, which may influence antigenicity and cross-clade protective immunity, it is currently not possible to request the Applicant to change the used strain A/Vietnam/1203/2004 (H5N1) to any other strain, as knowledge is not sufficient to establish the benefit of such update. In addition the applicant has provided some data on cross-reactivity and cross-protection for Vepacel, which in the view of the VWP support the ongoing marketing authorisation application. Therefore, at this stage a commitment from the Company for a specific strain update should not be requested.

Conclusion

The CHMP concurs with the VWP response. A substantial amount of cross-protective data has been shown but, in light of the continuing evidence for the evolution of clade 2 H5N1 viruses, it is up to the Applicant whether or not a future application for a strain change of the pre-pandemic license should be submitted to the European Medicines Agency for evaluation.

2.4.4. Conclusions on the clinical efficacy

The CHMP overall considers the clinical data submitted supportive of the indication claimed and no additional measures are necessary to address any issues or missing information related to efficacy data.

2.5. Clinical safety

This dossier contains clinical studies that have already been assessed in context of the MAA of Pandemic Influenza Vaccine H5N1 Baxter (formerly known as Celvapan) or at submission of the corresponding FUMs (i.e. clinical studies 810501, 810601, 810701, 810703).

Patient exposure

Safety data are available from five completed clinical studies (phase 1/2 study 810501, phase 3 study 810601, phase 1/2 study 810701, phase 2 study 810703 and phase 3 study 810705 Parts A to F). In these studies, 4535 subjects were exposed to at least one vaccine dose of the Vero cell-derived H5N1 influenza vaccine. In total, 4075 subjects received at least one dose of the vaccine formulation (7.5 µg H5N1 HA, non-adjuvanted, strain A/Vietnam/1203/2004) intended for pre-pandemic use, of whom 3979 received the full vaccination course of two doses of the proposed vaccine formulation, 21 days apart (posology recommended by the applicant for pre-pandemic immunization). The applicant submitted an additional supportive study (810802, Part A) during the procedure and this data did not change the overall safety evaluation of Vepacel.

In all five H5N1 studies, safety was assessed in terms of AEs that occurred after vaccination: the primary safety endpoint in all five studies was the occurrence of systemic reactions within 21 days after vaccination, and secondary safety endpoints included frequency and severity of injection site

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reactions following vaccination, fever, malaise and shivering within 7 days of vaccination, and frequency and severity of AEs during the entire study period.

Long-term 6-month follow-up data are available for a large number of subjects who received at least one dose of study vaccine in studies 810601 (503 subjects), 810701 (105 subjects), study 810703 (76 subjects) and 810705 (3323 subjects). The total number of subjects exposed is considered to be sufficient for a core dossier application as adverse reactions or events at a frequency of between 1/100 and 1/1000 are detectable (in compliance with guideline EMEA/CHMP/VWP/164653/2005 on clinical evaluation of new vaccines). Six-month follow-up data are available for a large proportion of the total study population.

Additional safety results in adult and elderly subjects and special risk groups who received a heterologous 7.5µg booster vaccination with Baxter's H5N1 influenza vaccine containing strain A/Indonesia/05/2005 12 to 24 months after a two-dose priming immunization with 7.5µg non-adjuvanted A/Vietnam/1203/2004 formulation (study 810705 Part E) as well as in adults who received a single priming dose and 12-month booster vaccination (study 810802 Part A), based on the clinical study reports (CSRs) which have become available since the original submission, have been submitted with the D120 responses. During Part E of study 810705, 205 healthy subjects (113 in Stratum A and 92 in Stratum B), 67 immunocompromised subjects, and 89 chronically ill subjects received a booster vaccination at 12 to 24 months with the H5N1 vaccine containing 7.5µg HA antigen of A/Indonesia/05/2005 strain. In study 810802, a total of 230 male and female subjects received a single priming vaccination on Day 0 with the whole virion, Vero cell-derived influenza vaccine containing 7.5µg of H5N1 hemagglutinin (HA) antigen strain A/Vietnam/1203/2004 in a non-adjuvanted formulation. On Day 360 (Month 12), subjects were randomized at a ratio of 1:1 to receive a booster vaccination with the H5N1 influenza vaccine containing either 3.75µg or 7.5µg H5N1 HA antigen strain A/Indonesia/05/2005 in a non-adjuvanted formulation. The CSR of Study Part A covers safety and immunogenicity results up to Day 21 after the booster vaccination.

Adverse events

Since all studies were open label (with the exception of study 810501 which was partially blinded, i.e. within the different dose escalation cohorts), no comparative data are available.

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. Severe fever was reported only in study 810705 in the largest subject population, at rates of 0.3% and 0.2% after the first and second vaccination respectively.

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.

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Serious adverse event/deaths/other significant events

Serious adverse reactions (SARs) occurred 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.

Serious/Adverse events after booster vaccination

This tolerability profile was confirmed by the safety data for the booster vaccination in all three populations in study 810705 Part E and for the priming and booster vaccination in healthy adults in study 810802 Part A, showing a low occurrence of local and systemic reactions after vaccination.

In study 810705 Part E, the rates of non-serious systemic reactions within 21 days after the booster vaccination were 10.6% and 14.3% (Strata A and B) in healthy subjects (Cohort 1), 11.9% in immunocompromised subjects (Cohort 2), and 20.2% in chronically ill subjects (Cohort 3). Symptoms were mostly mild or moderate, and transient in nature. Injection site reactions after the booster vaccination occurred in 19.5% and 3.3% (Strata A and B) of subjects in Cohort 1, 7.5% in Cohort 2, and 23.6% in Cohort 3.

A total of five SAEs were reported after the booster vaccination; four were judged to be unrelated, and one was possibly related (a case of herpes zoster infection) in Cohort 2. No deaths occurred during Part E of this study.

In study 810802, systemic reactions were experienced by 28.3% of subjects after the priming vaccination and by 18.2% and 25.0% after the booster vaccination with 3.75µg and 7.5µg HA antigen. Most systemic AEs were mild; two severe reactions (headache) were reported by two subjects after the priming vaccination. Fever was only reported after the booster vaccination, at rates of 3.0% and 1.0% for the 3.75µg and 7.5µg dose group. The most common symptoms of systemic reactions overall were fatigue, headache, muscle pain and malaise. Injection site reactions were reported by 18.7% of subjects after the priming vaccination, and by 10.1% and 18.0% after the booster vaccination with 3.75µg and 7.5µg HA antigen, and were mostly mild. Nine SAEs occurred in seven subjects during study Part A, none of which comprised an SAR or a death.

These safety results indicate that receiving a heterologous booster vaccination 12 to 24 months after a priming-vaccination is well tolerated. The safety profile after the booster vaccination with A/Indonesia/05/2005 (H5N1) is comparable to the safety profile after the first and second vaccination with either 7.5µg or 3.75µg of the A/Vietnam/1203/2004 strain (H5N1).

Laboratory findings

Based on non-clinical data that showed slightly elevated liver enzymes after repeated dose application of the H5N1 vaccine in rats, liver function tests (i.e. measurement of ALT values) were performed on a subpopulation of healthy subjects in study 810601. Analysis of these data did not indicate an association between vaccine administrations and raised ALT values. Unfortunately, liver function test were carried out on only 51 healthy subjects, which is only a small data collection.

Additional liver function test were performed in study 810705: ALT values were determined in approximately 100 immune compromised and 100 chronically ill subjects. Elevated ALT values were detected in approximately 15% of subjects in both cohorts. In the majority of cases, ALT values were also elevated at baseline, pointing towards a pre-existing condition.

Nevertheless, slightly elevated ALT values after vaccination, with normal values at baseline, were reported for 9/130 immune compromised subjects and 7/125 chronically ill subjects. The applicant stated in the Summary of Clinical Safety (section 2.7.4.4.1, page 78) that "there was no indication of

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an association between elevated ALT values and the study vaccine in either cohort". As was requested during evaluation, the Applicant has provided descriptions of the subjects who showed elevated ALT values in studies 810601 and 810705. The abnormalities in ALT values were only mild (not higher than Grade 1), all elevated ALT values were assessed as not related to vaccination and an alternative causality associated with pre-existing conditions or concomitant medication could be identified in nearly all cases. Therefore the data from study 810601 and 810705 do not indicate an association between elevated ALT values and the study vaccine. Furthermore, the risk of a potential adverse effect of vaccination on liver functions in children will be assessed by ALT investigation in a subset of approximately 200 healthy children aged 3-17 years in the ongoing paediatric study 810706. Overall an effect on liver function by an inactivated, unadjuvanted influenza vaccine that contains no preservatives is considered unlikely, thus additional measurements of ALT levels in healthy subjects (retrospectively or in planned clinical trials) are not deemed necessary at this stage.

Non-clinical data also identified a putative effect of vaccine administration on plasma creatine phosphokinase activity levels in rats (repeat dose toxicity study BAX0014), which was not investigated during the clinical studies. The slightly elevated plasma CPK activity values could however be due to the intramuscular administration to the rats of quite large volumes of vaccine. CPK levels were equally distributed at a blood draw after 2 weeks of recovery. Overall the CPK activity data from study BAX0014 are not indicative of a vaccine-related change.

Safety in special populations

The safety of the H5N1 vaccine was further demonstrated by its use in a vulnerable population of 319 immune-compromised patients and 300 patients with chronic disease conditions in study 810705. The H5N1 vaccine was shown to be safe and well tolerated in these patient groups with a safety profile similar to that observed in healthy adult and elderly subjects and of licensed seasonal influenza vaccines. Systemic reaction rates were 28.5% after the first and 16.7% after the second vaccination in the immune-compromised individuals and 36.7% after the first and 20.1% after the second vaccination in the chronically ill patients. Local reactions occurred at rates of 12.5% and 8.4% in immunocompromised subjects and 17.0% and 13.4% in chronically ill subjects after the first and second vaccination, respectively. Similar local and systemic reaction rates were observed after a 12-24 month heterologous booster vaccination. Similar to healthy adults and elderly subjects, the most frequently reported symptoms of local and systemic reactions in the immune-compromised and chronically ill populations were injection site pain, fatigue and headache. Adverse reactions were predominantly mild and transient. There was only one serious adverse reaction reported as possibly related (a case of herpes zoster infection in Cohort 2). No death occurred during this study.

Discontinuation due to adverse events

Study 810501

PART A: Two subjects withdrew their informed consent at the time of the second vaccination in Part A (Visit 3, Day 21) due to adverse events experienced after the first vaccination. These AEs were non-serious and of mild or moderate severity, however, they were considered by the investigator to be related to the vaccination and included:

- arthralgia, chills, eye discharge, fatigue, headache, hyperhidrosis, hypoesthesia, injection site pain, malaise, myalgia, generalized pruritus, insomnia for one subject and
- arthralgia, myalgia, papular rash for another.

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PART B: No subject withdrew their informed consent during study Part B (i.e. safety results obtained between Day 42 and Day 180) due to a safety issue.

Study 810601

PART A: Five subjects who withdrew their informed consent before the second vaccination at Visit 2 (Day 21 [±3 days]) stated adverse events after the first vaccination as the reason for their decision not to continue with the study. Two subjects experienced SAEs which were considered unrelated to vaccination and included

- abscess on face which required hospitalization for the one subject (Stratum B) and
- skin cancer which required surgery for another (Stratum A).

A third subject (Stratum A) experienced an AE which was which was considered possibly related to vaccination:

- moderate pyrexia.

A fourth and fifth subject (both Stratum B) experienced unrelated non-serious adverse events which were mostly mild and included

- diarrhea, arthralgia, myalgia, neck pain, headache and hyperhidrosis) for the one subject and
- bronchitis for another.

One subject (Stratum A) who returned to the second vaccination visit (Visit 2) but withdrew their informed consent before receiving a second vaccination reported AEs as the reason for withdrawal: severe malaise and mild fatigue three days after the first vaccination which were considered to be probably related to vaccination and which lasted seven days.

One subject (Stratum B) experienced a suspected serious adverse reaction (reactivation of malaria tertiana) eight days after the first vaccination. The investigator and the responsible medical director decided to discontinue the subject from the study to avoid interference with the immune response while the subject received treatment.

PART B: One subject who withdrew informed consent stated side effects after 2nd vaccination as the reason. This subjects was randomized to the 6 month booster but was not vaccinated.

Study 810701

No subjects withdrew from the study due to an AE.

Study 810703

In Part A, one subject withdrew from the study. The subject reported occurrence of nasopharyngitis (reported term: common cold) of 29 days duration and onset 5 days after vaccination. The investigator deemed the AE to be mild, and possibly related to the vaccination. The subject did not specify a reason for withdrawal from the study.

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Safety related to drug-drug interactions and other interactions

No interaction studies with other vaccines or medicinal products have been performed.

Post marketing experience

There are no postmarketing data available for the Vero cell-derived H5N1 influenza vaccine.

Data from post-marketing surveillance are available from a whole virion, Vero cell derived, H1N1 vaccine (Celvapan) which was used in several European countries during the 2009-10 H1N1 pandemic in paediatric and adult populations, including the elderly, risk groups and pregnant women.

A total of 11.755.200 doses of Celvapan were distributed to EU member states, however the EMA provided exposure data in their 22nd pandemic pharmacovigilance update report dated 19 August 2010 of at least 566,000 subjects vaccinated with Celvapan in the European Economic Area.

The following adverse reactions have been reported in the post-marketing experience in adults and children receiving Celvapan: anaphylactic reaction, hypersensitivity, febrile convulsion, hypoaesthesia, angioedema, pain in extremity and influenza-like illness. These adverse reactions are listed as class effects in the Vepacel SmPC post-marketing surveillance section accordingly. The safety profile of Celvapan was assessed as generally similar to that reported in Baxter's H1N1 clinical studies and comparable to that seen for seasonal flu vaccines. No fatal outcome with a possible causal relationship as assessed by the CHMP was reported.

2.5.1. Conclusions on the clinical safety

The safety data provided do not identify any apparent safety concerns regarding frequency and nature of adverse events. The profiles of adverse events after administration are not unusual and are comparable to other licensed influenza vaccines. The lack of (double) blinding studies, with the use of a control arm, which could theoretically introduce bias, its compensated by the extensive use during the latest pandemic of the H1N1 vaccine, which is also produced in Vero cells as well as the H5N1 influenza vaccine. For the H1N1 vaccine, the safety database from clinical studies includes 202 healthy adults and elderly and 3216 subjects from the pandemic observational study. Furthermore, it is estimated that more than 500,000 subjects received the vaccine during the recent H1N1 pandemic. The observed safety profile in the clinical studies and through the post-marketing pharmacovigilance data is excellent and similar to that of seasonal influenza vaccines.

For the H5N1 vaccine, safety data from clinical trials include approximately 4,800 adult and elderly subjects, of whom 319 are immunocompromised and 300 are chronically ill. The observed safety profile following primary vaccinations and booster shots is benign and comparable to seasonal vaccines.

Although differences in the procedure of safety data collection between clinical studies (H1N1 vs. H5N1) and postmarketing surveillance (only available for H1N1) are considered, the favourable safety profile evidenced by the large safety database of Celvapan (H1N1)v is considered supportive and confirms the overall favourable safety profile observed in several studies conducted with Baxter's H5N1 Vaccines, Vepacel and Pandemic Influenza Vaccine H5N1 Baxter, respectively.

This substantial safety database supports the feasibility of using a Vero cell-derived influenza vaccine in a pre-pandemic situation, where, as with seasonal influenza vaccination, a very good safety profile is mandatory because a protective effect may not be experienced by all vaccinees (strain mismatch etc).

Given that no major safety issues were encountered during the clinical studies, this dossier is acceptable based on the available data. All the adverse reactions reported from clinical trials and post-marketing in the safety database have been included in the Summary of Product Characteristics.

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2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan. A summary of the risk management plan is provided in Table 11.

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Table 11. Summary of the risk management plan

Safety concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks		
Anaphylactic reaction / Angioedema	Routine Pharmacovigilance: • Monitoring of adverse events from ongoing clinical studies and post-marketing sources. • Expedited reporting of anaphylactic reactions	Routine Risk Minimization: **Contraindications in SmPC (Section 4.3)** The use of Vepacel is contraindicated in patients with: "History of an anaphylactic (i.e. life-threatening) reaction to any of the constituents or trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero cell protein) of this vaccine. If vaccination is considered necessary, facilities for resuscitation should be immediately available in case of need (see Section 4.4)." **Cautions in SmPC (Section 4.4)** Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to trace residues (formaldehyde, benzonase, sucrose, trypsin, Vero cell protein)." "As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine." "Hypersensitivity reactions, including anaphylaxis, have been reported following use of a similar whole virion, Vero cell derived H1N1 influenza vaccine administered during a pandemic period. Such reactions have occurred both in patients with a history of multiple allergies and in patients

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Safety concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		with no known allergy."
Important Potential Risks		
Vaccination Reactions, including Immunologic Reactions /Disorders/ and / or AESIs (including neuritis, convulsion, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's (facial) palsy, demyelinating disorders)	Routine Pharmacovigilance: • Monitoring of adverse event reports from ongoing clinical studies and post-marketing sources. • Expedited reporting of all events of special interest (AESIs).	Section 4.8 will be updated as additional clinical and post market adverse events are reported
Low efficacy / laboratory confirmed vaccination failure	Routine Pharmacovigilance: • Monitoring of adverse event reports for cases that may represent poor vaccine efficacy including vaccination failure. • Expedited reporting of laboratory confirmed vaccination failure. (AESI)	Routine Risk Minimization: **Cautions in SmPC (Section 4.4)** "Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient. A protective immune response may not be induced in all individuals receiving the vaccine, (see Section 5.1)."
Administration of inappropriate / ineffective vaccine strains against current circulating virus	Routine Pharmacovigilance: • Monitoring of adverse event reports for cases that may represent poor vaccine efficacy including vaccination failure.	Routine Risk Minimization **Cautions in SmPC (Section 4.4)** "A protective immune response may not be induced in all individuals receiving the vaccine (see Section 5.1)."
Interaction with regular childhood vaccines	Routine Pharmacovigilance • Monitoring of adverse event reports for cases that may represent poor vaccine efficacy including vaccination failure in the paediatric population. • Monitoring of adverse event reports for cases that might result from co-administration of childhood vaccines.	Routine Risk Minimization **Interactions in SmPC (Section 4.5)** "There are no data on co-administration of Vepacel with other vaccines. However, if co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified."
Graft versus host disease	Routine Pharmacovigilance • Monitoring of adverse event reports for cases that may represent graft vs. host	None

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Safety concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
	disease.	
Transplant rejection	Routine Pharmacovigilance • Monitoring of adverse event reports for cases that may represent transplant rejection.	None
Immune thrombocytopenia	Routine Pharmacovigilance • Monitoring of adverse event reports for cases that may represent immune thrombocytopenia.	None
Important Missing Information		
No paediatric data	Routine Pharmacovigilance Additional Pharmacovigilance: • Ongoing Paediatric Study **810706**	Routine Risk Minimization: **Posology and method of administration in SmPC (Section 4.2)** "Paediatric population: There are currently no data available for Vepacel vaccination dose and schedule for subjects under 18 years old."
Limited information on safety in pregnant or lactating women.	Routine Pharmacovigilance • Monitoring of spontaneous reports in pregnant women from countries where Vepacel will be administered.	Routine Risk Minimization: **Fertility, pregnancy and lactation in SmPC (Section 4.6)** "The safety of Vepacel in pregnancy and lactation has not been assessed in clinical trials. Animal studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/fetal development, parturition or post-natal development. Healthcare providers should carefully consider the potential risks and benefits for each specific patient before prescribing Vepacel." "The use of Vepacel during pregnancy and lactation may be considered in a pre pandemic situation, taking into account official

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Safety concerns	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		recommendations."
Missing information regarding abnormal liver enzymes, and abnormal serum calcium levels in the paediatric population	Routine Pharmacovigilance • Monitoring of adverse event reports for cases that may represent abnormal liver function, or test results. • Monitoring of adverse event reports for cases that may represent abnormal serum calcium levels. Additional Pharmacovigilance • Paediatric Study 810706 includes investigation of ALT levels in a subset of approximately 200 healthy children aged 3-17 years	Routine Risk Minimization **Preclinical Safety Data in SmPC (Section 5.3)** "Non-clinical studies demonstrated minor alterations in liver enzymes and calcium levels in a repeat dose toxicity study in rats. Clinically significant alterations in liver enzymes and calcium levels have not been seen to date in human clinical studies."

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

The following additional risk minimisation activities were required

Continuous monitoring (i.e. monitoring of AESI including neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, GBS and/or Fisher syndrome, Bells (facial) palsy, and demyelinating disorders) and risk communication.

Regarding the PSUR cycle the CHMP concluded that during the Prepandemic phase, the PSUR cycle for Vepacel should follow the standard requirements

Vepacel is also indicated for used during a Pandemic phase. CHMP recommended the following for PSUR submissions in a Pandemic. During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation (EC) No 726/2004 will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for risk-benefit balance in a pandemic. Prompt analysis of cumulative safety information in light of extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated. In addition, duration a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared and the pre-pandemic vaccine is used, the MAH shall submit more frequent simplified periodic safety update reports with a format and a periodicity defined in the "CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (EMEA/49993/2008), and any subsequent update.

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2.7. Significance of paediatric studies

An EMA Decision on a modification of an agreed Paediatric Investigation Plan [P/67/2011] was adopted on 11 March 2011. A waiver is applied to infants and toddlers from birth to less than 6 months for the suspension for injection for intramuscular use on the grounds that the specific medicinal product is likely to be ineffective.

At the time of submission of the application, the Paediatric Investigation Plan (P/121/2010) was not yet completed as all measures were deferred until December 2012.

2.8. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The patient leaflet for Pre-Pandemic Influenza Vaccine Baxter (Vepacel) is essentially similar to Baxter's licensed mock-up vaccine "Pandemic Influenza Vaccine H5N1 Baxter".

Therefore, the readability test for the Pandemic Influenza Vaccine H5N1 Baxter (originally named Celvapan) is attached to this application.

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3. Benefit-Risk Balance

Benefits

Beneficial effects

The major benefits of Vepacel are:

- it can be produced swiftly in the event of a pre-pandemic situation and there is no need for high growth or attenuated reassortants;
- viruses isolated and passaged in Vero cell cultures retain their antigenic characteristics;
- it does not require additional adjuvant;
- it may have the potential to induce a stronger and broader cellular and humoral response due to the presence of the full set of viral proteins;
- it does not contains egg proteins and is therefore safe for people with allergies to eggs. Cell culture technology might also provide an advantage because it eliminates the dependence on embryonated hens' eggs, the availability of which could be a limiting factor in the event of a pandemic caused by a highly pathogenic avian virus.

The immunogenicity of Vepacel, which has been investigated in five completed clinical studies, demonstrates an immunogenicity profile close to the CHMP criteria, in all age groups studied and in at risk subjects. Cross-reactivity of the induced antibodies to heterologous influenza strains (different clades of H5N1) has been shown. Persistence of acceptable levels of antibody titres at 6 months after the primary immunisation was shown.

The feasibility of boostering the immune response with a full or a half dose of homologous or heterologous vaccine after a 6, 12-15 or 24 month interval was also demonstrated. The boosterability with a heterologous strain is of special relevance for the pre-pandemic setting, where it is highly likely that the antigenic characteristics of the influenza strain, against which the primary vaccination is targeted, may change very rapidly.

In study 810705 part F, the T-cell responses (against all influenza strains tested) were determined in immune-compromised subjects following vaccination with the inactivated whole virus H5N1 vaccine compared to baseline levels. They suggest that the vaccine is capable of priming naïve T-cells and creating a large influenza-specific pool of memory T-cells, supporting the use of the H5N1 vaccine in this highly susceptible patient population, particularly in pre-pandemic situations when H5N1 pandemic strains are circulating.

Uncertainty in the knowledge about the beneficial effects

Although the use of immunogenicity data as surrogates for protection is accepted for influenza vaccines in general, they do not provide a direct measurement of clinical protection.

The CHMP discussed the validity of the immunogenicity data because correlates of protection are not known for the functional MN assay and particularly with regard to the cut-off value for protection proposed by the Applicant (MN titre 1/20 instead of 1/40). Although some level of uncertainty still persists, the cut-off value chosen was considered acceptable because i) the results with the SRH assay confirmed the results with the MN assay; ii) a good level of cross-reactivity was shown; iii) the Applicant performed passive immune transfer studies in mice using human sera from the pivotal clinical study 810601, showing that a measured titre of 1:10 conferred 50% protection and 1:13 conferred 80% protection to the challenged animals.

Another uncertain element is the ability of the vaccine to raise an immunological response in very old patients. The Applicant provided a detailed overview of the age of the participants in the elderly group. As expected, immune response decreased with age and was lower in elderly subjects aged 75 years and above versus the subgroups aged 60-74 years. However due to the relatively low number of subjects aged ≥75 years (N=37) in the pooled dataset, it is difficult to draw definitive conclusions on the immunogenicity in this age group.

Some element of uncertainty is present for the immunocompromised patients, whose antibody response is lower than in the healthy subjects, albeit expected.

The relevance of the choice of strain with the regard to the present scenario of diverse circulating H5N1 clades was discussed. The CHMP concurs with VWP that at present the scientific knowledge is not sufficient to ascertain whether or not a strain change would entail an added benefit.

Risks

Unfavourable effects

Safety data are available from five clinical studies (phase 1/2 study 810501, phase 3 study 810601, phase 1/2 study 810701, and phase 2 study 810703 and 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. Other commonly reported systemic reactions were fatigue, malaise, chills, myalgia, hyperhidrosis, nasopharyngitis, arthralgia, pyrexia and

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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%), 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). 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 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.

The safety data provided do not identify any apparent safety concern regarding frequency and nature of adverse events. The profile of adverse events after administration is not unusual and is comparable to other licensed influenza vaccines. The safety profile in the investigated cohorts of immunocompromised and chronically ill subjects was favourable as well.

The proposed actions by the Applicant in the Risk Management Plan in case of pandemic are in line with the guidance CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorization Application for a Pandemic Influenza Vaccine (revision 1.1 - 24 September 2009). The identified risks are represented by anaphylactic reaction/Angioedema. This is acceptable based on the postmarketing spontaneous reports with Celvapan H1N1 of anaphylaxis and severe hypersensitivity including angioedema.

The potential Risks include:

- Vaccination Reactions, including Immunologic Reactions/Disorders and/or AESIs (including neuritis, convulsion, encephalitis, vasculitis, Guillain-Barre syndrome Bell's (facial) palsy, demyelinating disorders, laboratory confirmed vaccination failure)
- low/efficacy or vaccination failure;
- administration of inappropriate/ineffective vaccine strains against current circulating virus;

Benefit-risk balance

Importance of favourable and unfavourable effects

The importance of protection against influenza disease is well known. Influenza is a highly contagious respiratory disease that is characterized by a sudden onset of systemic symptoms such as chills, high fever, headache, myalgia and anorexia, frequently followed by pharyngitis, laryngitis and tracheobronchitis. Primary influenza pneumonia, which mainly occurs in young adults, can be fatal in less than 24 hours, and secondary bacterial pneumonia, for which incidence increases with age (>60 years), can also be fatal especially if there is an underlying disease.

While frequent and irregular epidemics during influenza seasons can sometimes be very severe, a pandemic outbreak of a highly virulent strain in a population lacking immunity could be catastrophic. Although the demonstration of protection against influenza disease is not possible in this setting, immunogenicity data are an accepted surrogate endpoint.

The clinical serology data and the preclinical serology and protection data obtained with Vepacel underline the positive impact of vaccination in a pre-pandemic setting. An immunologically naïve population can be primed against a virus strain expected to cause an influenza pandemic, and boostering with a homologous or a heterologous strain even years after the initial priming could be feasible. This strategy allows a fast response to the outbreak of a pandemic (provided closely related

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H5N1 influenza strains), since a substantial antibody response and therefore a high likelihood of protection are induced 2 to 3 weeks after one booster shot in primed individuals.

Unfavourable effects of the vaccination with Vepacel observed in clinical trials are similar to those seen with yearly seasonal influenza vaccinations. The most frequently reported systemic reaction after vaccination was headache. Other commonly reported systemic reactions like fatigue, malaise and myalgia were generally mild and of limited relevance. Most importantly, SARs occurred at low rate and were assessed to be only possibly related to vaccination.

Benefit-risk balance

Looking at the entire data package, the CHMP is of the opinion that the benefit of the vaccine is demonstrated with regard to its immunogenicity in healthy adults and elderly, and in at risk groups. In addition a substantial amount of cross-reactive antibodies against different H5N1 clades has been shown. In light of this, the choice of strain can be considered presently acceptable.

Furthermore, the excellent safety profile that was consistently observed in healthy adults, healthy elderly, immunocompromised and chronically ill subjects after either priming or booster vaccinations supports the favourable benefit-risk balance of Vepacel.

Discussion on the benefit-risk balance

The marketing authorisation application of Vepacel is supported by an overall solid non-clinical/clinical development program.

Immunogenicity results from the five clinical studies submitted in this dossier show a robust immune response in healthy adults, as well as an acceptable immune response in healthy elderly individuals, immunocompromised and chronically ill subjects. Acceptable cross-reactivity of the induced antibodies to heterologous influenza strains could be shown. Persistence of acceptable levels of antibody titres at 6 months after the primary immunisation was demonstrated. The feasibility of boostering the immune response with a full or a half dose of homologous or heterologous vaccine after a 6, 12-15, or 24 month interval was demonstrated. The boosterability with a heterologous strain is of special relevance for the pre-pandemic setting, where it is highly likely that the antigenic characteristics of the influenza strain against which the primary vaccination is targeted may change until the outbreak of a pandemic.

No major safety issues were encountered during the clinical studies and the adverse events reported are regarded as less relevant compared with the benefits that can be expected from avoiding cases of influenza (and influenza-associated complications) on an individual patient level and at the population level.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vepacel in the prophylaxis of H5N1 subtype of influenza A in either a pre-pandemic or pandemic situation in adults aged 18 years and older is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

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Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management System and PSUR cycle

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan and the Efficacy Follow-up Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

The PSUR cycle for the medicinal product should follow the standard requirements.

PSUR submission when Vepacel is used during an influenza pandemic:

During a pandemic situation, the frequency of submission of periodic safety update reports specified in Article 24 of Regulation (EC) No 726/2004 will not be adequate for the safety monitoring of a pandemic vaccine for which high levels of exposure are expected within a short period of time. Such situation requires rapid notification of safety information that may have the greatest implications for risk-benefit balance in a pandemic. Prompt analysis of cumulative safety information, in light of extent of exposure, will be crucial for regulatory decisions and protection of the population to be vaccinated. In addition, duration a pandemic, resources needed for an in-depth evaluation of Periodic Safety Update Reports in the format as defined in Volume 9a of the Rules Governing Medicinal Product in the European Union may not be adequate for a rapid identification of a new safety issue.

In consequence, as soon as the pandemic is declared and the pre-pandemic vaccine is used, the MAH shall submit more frequent simplified periodic safety update reports with a format and a periodicity

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defined in the "CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (EMEA/49993/2008), and any subsequent update.

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

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that A/H5N1 pre-pandemic influenza vaccine (whole virion, Vero cell derived, inactivated), Baxter is not to be qualified as a new active substance.

Paediatric Data

At the time of submission of the application, the Paediatric Investigation Plan (P/121/2010) was not yet completed as all measures were deferred.

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