Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for split virus, vero cell derived, inactivated influenza vaccine

Proprietary Product Name: Preflucel

Sponsor: Baxter Healthcare Pty Ltd

July 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Biological Entity
Decision:	Withdrawn
Date of Decision:	15 May 2012
Active ingredient(s):	Influenza Vaccine, Split Virion, Inactivated
Product Name(s):	Preflucel Suspension for Injection in a prefilled syringe Influenza Vaccine (Split Virion, Inactivated, Prepared in Vero Cell Cultures) 2011 Season
Sponsor's Name and Address:	Baxter Healthcare Pty Ltd PO Box 88 Toongabbie NSW 2146
Strength(s):	One vaccine dose of 0.5 mL contains 15 µg haemagglutinin (HA) antigen of each of the three (sub) types in tris buffered saline (TBS) in a non adjuvanted formulation. In total, 45 µg/dose target, 15 µg of the following strain: • A/California/07/2009 (H1N1) • A/Perth/16/2009 (H3N2) like strain (A/Victoria/210/2009) • B/Brisbane/60/2008 (B)
Container(s):	Prefilled syringe (System Readyject). The container is a colourless, siliconised, Type I, borosilicate glass syringe. The stopper consists of halogen butyl rubber, latex free, to fully eliminate any potential risk of allergic reactions that might be related to natural latex.
Pack size(s):	A pack of 1 prefilled syringe (1 dose) A pack of 10 prefilled syringes (10 doses)
Proposed indications:	The indication of Preflucel vaccine is prophylaxis of influenza infection in adults (18 years old and over) and elderly (older than 60 years of age).
Route(s) of administration:	Intramuscular injection (into the deltoid muscle)
Dosage:	Single dose (0.5 mL) of the vaccine
ARTG Number (s)	178756

Product Background

This AusPAR describes an application by the sponsor, Baxter Healthcare Pty Ltd, to register a new seasonal influenza vaccine with the trade name Preflucel. Preflucel is a trivalent inactivated formulation produced in Vero cell derived, double inactivated (formalin and ultraviolet [UV]), sucrose gradient purified split virion of the influenza A/H1N1, A/H3N2 and B virus strains recommended by the Australian Influenza Vaccine Committee (AIVC) for 2011.

The AIVC agreed to adopt the September World Health Organisation (WHO) recommendations for the 2011 season, namely:

- A (H1N1): an A/California/7/2007 (H1N1) like strain, 15 μg per dose
- A (H3N2): an A/Perth/16/2009 (H3N2) like strain, 15 μg per dose
- B: a B/Brisbane/60/2008 like strain, 15 μg per dose.

The development of the split virus process was based on that of Baxter's serum free, microcarrier based, Vero cell technology, which was originally developed for the manufacture of the whole virus influenza vaccine.

Vero cells have been utilised for over thirty years for production of polio and rabies vaccines. They have been approved for production of human vaccines by the WHO, US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Baxter has adapted the cell line for production of trivalent seasonal influenza vaccine using whole or split virions of a "wild type" virus (that is, virus circulating in nature), isolated in embryonated hens' eggs and provided by WHO collaborating centres.

The Vero cell derived split virus vaccine is identical to the previous whole virus vaccine, except that detergent (Triton-X 100) is used to break apart the lipid containing envelope, releasing and solubilising the H and N surface glycoproteins. Triton-X has been used since the 1970s in the production of vaccines and has undergone clinical testing, and is the splitting agent used in several egg derived split virus influenza vaccines.

The Vero cell technology was used to manufacture the Baxter Healthcare Pty Ltd influenza pandemic vaccine, which was evaluated and approved by TGA in 2010: Pandemic Influenza vaccine (H5N1) (Aust R 153381).

Regulatory Status

The international regulatory status of Preflucel at the time of initial dossier submission is summarised in Table 1.

Table 1: Summary of international regulatory status of Preflucel.

Country	Date of Submission	Submission status
Austria	17 June 2008	Approved 29 September 2010 Approved indication: Prophylaxis of influenza in adults and elderly. The use of PREFLUCEL should be based on official recommendations.
Czech Republic	17 June 2008	Approved 29 September 2010 Approved indication: Prophylaxis of influenza in adults and elderly. The use of PREFLUCEL should be based on official recommendations.

Submissions for registration were sent to Germany, Portugal, Poland, Belgium, Italy, Spain, Ireland, UK, Sweden, Finland, Norway, Denmark, Switzerland and the Netherlands on 5 November 2010. These submissions were still pending decisions at the time of initial dossier submission in Australia.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The Drug Substance is an aqueous solution containing Vero cell derived, formaldehyde and Ultraviolet (UV) inactivated, sucrose gradient purified, split virions of influenza type A, subtypes H1N1 and H3N2, and of type B. Additional components of the drug substance are Tween 80 (Polysorbate 80), Sodium Chloride and Tris (Trometamol).

One vaccine dose of 0.5 mL in a pre filled syringe contains 15 µg HA antigen (target) of each of the three (sub) types in Tris buffered saline.

The strains used for vaccine production are received from a WHO Collaborating Centre and are in accordance with WHO/EMA recommendations for the respective of seasonal influenza. For season 2010/2011, the following strains have been recommended:

- A/California/07/2009 (H1N1)
- A/Perth/16/2009 (H3N2) like strain (A/Victoria/210/2009)
- B/Brisbane/60/2008 (B)

The vaccine does not contain egg or chicken protein and is free of preservatives. Except for preparation of the Master Cell Bank, no animal or human serum components are used in the production of the vaccine.

Stability and Specifications

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The following maximum storage durations are claimed by Baxter:

- Purified Monovalent Virus Harvest (PMVH): 2 years at ≤ -60°C
- Monovalent Bulk (MVB): 2 years at +2 to +8°C

The test results of the stability study performed on PMVH and MVB. For PMVH, the stability test results for up to 6 months have been provided for Strain A/California/07/2009 and Strain A/Victoria/210/2009 and up to 12 months for Strain B/Brisbane/60/2008 for study number BH-66-00014.

For MVB, the stability test results for up to 9 months have been provided for Strain A/California/07/2009 and Strain A/Victoria/210/2009 and up to 12 months for Strain B/Brisbane/60/2008 for study number BH-66-00014.

The sterility tests show no growth on T0 for the three lots tested. The DS meets the established specifications for potency at the time points evaluated.

The applicant commits to completing the ongoing real time/real temperature stability study for PMVH (≤-60°C for 30 months) and for MVB (+2 to +8°C for 36 months).

Stability testing was performed over a 24 months period to ensure a higher margin of stability. Testing intervals have been set according to International Conference on Harmonisation (ICH) Q1A and Q5C. Stability studies were performed using the actual final container. The Split Virus Vaccine is stored at 2-8°C in syringes. The objective of this stability study is to demonstrate stability of the Final Container Product (FCP) for at least 1 year since change in strains is expected each year.

Stability studies at +2 to +8°C over 24 months were undertaken using one batch containing strains from season 2006/2007 [VNV5F01A (study no. L023/06-FS)], three batches containing strains from season 2007/2008 (VNV5G05A, VNV5G04B, VNV5G03A) and two FCP of season 2010/2011 (VNV5K002A and VNV5K002B). Stability testing updates for up to 9 months period of season 2010/2011 lots have been provided in the second evaluation round of the submission of this application.

The stability indicating parameters cover identity, potency and purity as well as general quality (pH measurement, visual inspection, and extractable volume) and safety parameters (Sterility and Endotoxin/Limulus Amebocyte Lysate (LAL)). In these studies the main stability indicating parameters is the HA content, measured by Single Radial Diffusion (SRD) test. The shelf life specification is identical with the acceptance criteria defined in the release specification of final product.

The results from the stability studies demonstrate a good stability of the vaccine. The antigen content of the FCP of lots involved in the above studies was generally not affected during storage at +2 +8°C. The HA content met the release criterion. All stability indicating parameter met the release criteria for these lots. Thus, Baxter claims a shelf life of 1 year for the Final Container Product for the Seasonal Influenza Preflucel Vaccine 2010/2011.

Appropriate validation data were submitted for the proposed specifications, which control identity, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Drug Product

Preflucel is an inactivated, trivalent virus vaccine for active immunisation against influenza virus. It contains Vero cell derived, formaldehyde and UV inactivated, sucrose gradient purified Split Virions of Influenza strains type A, subtype H1N1 and H3N2, and of type B as declared by WHO.

The product is presented in a pre filled syringe (suspension for injection; clear to opalescent suspension) consisting of borosilicate glass of hydrolytic type I for injectable solutions. One vaccine dose of 0.5 mL in a pre filled syringe (System Readyject) contains 15 µg HA antigen of each of the three (sub) types in TBS in a non adjuvanted formulation. The product is a single dose presentation and must be stored between +2°C and +8°C with a proposed shelf life of 1 year for the final container product.

No thiomersal or any other anti microbial agent is added as preservative to the vaccine. This influenza vaccine contains no egg or chicken protein nor serum specific proteins.

Appropriate validation data were submitted for the proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product.

Biopharmaceutics

Biopharmaceutic data were not required.

Summary

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The sponsor has responded to questions raised in a letter dated 31 May 2011 regarding Sterility, Container Safety issues and Manufacture and QC including viral safety issues. Responses have been evaluated and found to be satisfactory.

Issues of concern

A number of deficiencies and other issues requiring resolution before the product can be recommended for approval were identified during the evaluation and have been referred to the applicant for comment or resolution. These issues are detailed in the main body of the evaluation reports and are summarised at the end of the report.

There are no outstanding issues regarding the Manufacture and Quality Control Safety Aspects of Preflucel vaccine that should delay registration. However, the following outstanding details, as indicated in this report, should form part of the conditions of registration and be provided as part of the Lot Release process for any Preflucel to be marketed in Australia.

Outstanding requirements – provision of these details should form part of the Conditions of Registration:

1. Please provide the TGA with the complete protocol for the potency assay of plaque forming unit (PFU) in MDCK cells.
2. Please provide TGA with up to date ongoing stability data for all lots of PMVH and MVB (30 months and 36 months, respectively) once available.
3. Please provide TGA with up to date ongoing stability data for all lots of FCP for up to 24 months once available.
4. The complete shipping validation of Preflucel Vaccine product from the manufacturer to Australia will be required as part of the initial Lot Release for Australia.

III. Nonclinical Findings

Introduction

The submission contained nonclinical vaccine immunogenicity, viral challenge, (Good Laboratory Practice (GLP) compliant) acute and repeat dose toxicity (incorporating local tolerance investigations) and a reproductive, developmental and pre postnatal toxicity study in rats which was repeated (both GLP compliant). A series of studies from the published literature investigating the toxicity of excipients Polysorbate 80 and Triton X-100 were submitted, some of which had not been previously evaluated. A risk assessment of each of these excipients, which was based on these publications, was also submitted. Overall, the nonclinical studies met the general requirements of the relevant EMA vaccine and seasonal influenza vaccine nonclinical guidelines.

Immunogenicity

Immunogenicity studies were conducted in naïve animals, to model exposure to a seasonal influenza strain to which humans have had no prior exposure.

Antigens derived from Vero cell derived whole influenza vaccine and a currently registered egg derived split vaccine (Vaxigrip®) were found to be immunogenically equivalent (based on HA inhibition (HI) assay) in mice and chimpanzees (the latter based on Committee for Proprietary Medicinal Products (CPMP) criteria); however, the study in chimpanzees was conducted in 1996-1997. Equivalent antigenicity and immunogenicity (based on HI titres) were also found in both mice and guinea pigs whether the inactivation step involved formalin only or (the proposed) formalin/UV combination inactivation step.

A study with a trivalent Vero cell derived vaccine was conducted in ferrets (in 1997). Although the sample size was small (n = 6/group) the study indicated that the vaccine provided protection against (a homologous) H3N2 infection, based on lower incidence of

increased body temperature, protein concentrations in nasal washings, as well as on lower virus titres in nasal washings and higher HI titre against the challenge virus.

Four immunogenicity studies in unprimed mice and guinea pigs tested the antibody response to two consecutive intramuscular (IM) doses (separated by three weeks) of split trivalent H3N2/H1N1/B vaccines.

Significant antibody responses were detected by HI to non adjuvanted vaccine over a wide range of HA doses (0.008-5 µg) (Table 2). However, this was the only method used for determining antibody titre (an enzyme linked immunosorbent assay (ELISA) was not used). The mean HI titre did not always show any clear relationship to dose, and the mean titres in all studies were well below 1000.

Table 2: HA antigen doses in nonclinical immunogenicity/viral challenge studies.

Study	HA antigen doses (µg)	HA antigen doses (µg/kg)*	HA antigen doses (µg/m²)**	Animal/human dose multiples (µg/m²)
Trivalent whole vaccine				
Chimpanzee immunogenicity	45	1	30#	1#
Ferret challenge^	45	45	450	15
Trivalent split vaccine				
Mouse immunogenicity				
Studies EV06IPIM001, EV07IPIM001, EV07IPIM002	0.05, 0.5, 5	2.5, 25, 250	7.5, 75, 750	0.25, 2.5, 25
Study EV07IPIM003	0.008, 0.04, 0.2, 1, 5	0.4, 2.0, 10, 50, 250	1.2, 6, 30, 150, 750	0.04, 0.2, 1.0, 5.0, 25
Guinea pig immunogenicity				
Studies EV06IPIM001, EV07IPIM001, EV07IPIM002	0.05, 0.5, 5	0.125, 1.25, 12.5	0.875, 8.75, 87.5	0.03, 0.3, 2.9
Study EV07IPIM003	0.008, 0.04, 0.2, 1, 5	0.02, 0.1, 0.5, 2.5, 12.5	0.14, 0.7, 3.5, 17.5, 87.5	0.005, 0.02, 0.12, 0.6, 2.9
Humans	45	0.9	30.06	---

Bodyweights: Mouse 20 g, guinea pig 400 g, ferret 1 kg (body surface area 0.1 m²), chimpanzee 45 kg, human 50 kg.
*Body surface area conversion factors: mouse 3, guinea pig 7, ferret 10, human 33.4.
^Vaccine characteristics and method of manufacture was not stated; whole vaccine assumed
#Assumes similar surface area to that in humans

Overall, the vaccine was immunogenic in these animal models at doses (based on mg/m²) lower than the recommended antigen dose in humans. However, the doses in the animal studies were boosted at three weeks, and the three week titres were generally lower than at 6 weeks. There were no immunogenicity studies in aged animals.

Secondary Pharmacodynamics and Safety Pharmacology

The sponsor noted (in the Pharmacology Written Summary) that secondary and safety pharmacodynamic studies were not conducted "since the Influenza Split Virus Vaccine was well tolerated in all toxicology studies and since there is extensive experience with the use of influenza vaccines in humans showing that influenza vaccines are safe". The assessment of secondary and safety pharmacology for this product is therefore dependent on clinical data.

Pharmacokinetics

No vaccine pharmacokinetic studies were submitted, and they were not required according to the relevant EMA vaccine, pandemic influenza vaccine guidelines.

Relative exposure

Exposure ratios for the HA antigen (based on dose per body surface area) were adequate, as shown in Table 3.

Table 3: HA antigen exposure multiples in nonclinical toxicity studies in rats.

Study (report no.)	HA antigen dose (µg)	HA antigen dose (µg/kg)*	HA antigen dose (µg/m²)**	Animal/human HA exposure multiple (µg/m²)
Single dose toxicity (SPV0001L01)	45	181 (M) 254 (F)	1086 (M) 1524 (F)	36 (M) 51 (F)
Repeat dose toxicity (BAX0007)	36	114 (M) 153 (F)	684 (M) 918 (F)	23 (M) 31 (F)
repro + development + pre/postnatal toxicity (BAX0008)	36	115 (F)	690 (F)	23 (F)
repro + pre/postnatal toxicity (EWA0019)	36	116 (F)	696 (F)	23 (F)
Humans	45	0.9	30.06	---
*Bodyweights: human 50 kg. For rat BW data, see main body of the report **Body surface area conversion factors: rat 6, human 33.4.				

Polysorbate 80 is added to Preflucel as an anti aggregant (excipient). The concentration of Polysorbate 80 in the Baxter Split Virus Vaccine product proposed for registration is 0.10-0.15% (target 0.125%; maximum 0.75mg/0.5mL) in a human adult dose, resulting in a maximum human dose of 0.015 mg/kg for a 50kg adult. Polysorbate 80 is present in other (currently registered) products, and greater systemic as well as local exposures would potentially result at the maximum recommended dose with the other products than through Preflucel. The concentration of Polysorbate 80 in Preflucel also complies with the European Pharmacopeia (EP) and US Pharmacopeia (USP).

During the manufacturing process of the Split Virus Influenza Vaccine, Triton X-100 is added as a splitting agent. The amount of Triton X-100 present in the split virus influenza vaccine is ≤ 0.015 %. Therefore, a recommended clinical human dose of 0.5 mL would contain ≤0.075 mg Triton X-100, and would result in a single dose of ≤ 1.5 µg/kg for a 50 kg individual. Although the concentrations of Triton X-100 (Octoxynol-9) in a study in rabbits (submitted in response to a Section 31 request) were lower (maximum 0.01%) than those in Preflucel, Triton X-100 is present in other (currently registered) products either for viral inactivation or as a non ionic surfactant. The concentrations range up to <0.2 mg/mL (IM). A 0.5 mL (recommended) dose at that concentration would result in exposure to (0.5 x 200 =) 100 µg Triton X-100, which is equivalent to 2 µg/kg IM, for a 50 kg person. The local and systemic exposures with currently registered products are therefore greater at the recommended dose than with the proposed Preflucel formulation.

Toxicology

General toxicity

Vaccine related findings in the toxicity studies were local changes at the injections sites and draining lymph nodes.

During the in life phase of the repeat dose toxicity study, slight and transient injection site redness was seen in a few rats after they had received the first dose of vaccine. Mild inflammatory infiltrates had been detected at microscopic examination of the tissue at the injection site from rats killed three days after receiving a single dose of vaccine. These findings were not reported for the single dose toxicity study. This finding was not seen in rats killed fourteen days after dosing.

The vaccine related changes observed in the draining lymph nodes of rats that had received vaccine were considered by the sponsor to be a normal physiological response to vaccination and a sign that the animals were developing a strong specific immune response. Consistent with this explanation was the presence of high levels of circulating antibodies.

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies were not required for the Preflucel vaccine. This is consistent with EMA vaccine and seasonal influenza vaccine nonclinical guidelines.

Reproductive toxicity

The effect of Baxter's split virus influenza vaccine on reproduction and development in rats was investigated. In a developmental and reproductive toxicology study, female rats received IM injections on Days -42 and -14 before pairing and on GD (Gestation Day) 7 of either Baxter's split virus influenza vaccine, a reference vaccine, or a corresponding control article. After pairing and mating, selected offspring were raised to sexual maturity and euthanised at seven weeks of age. Any exposure the F1 offspring was *in utero* or via the milk.

There was no effect on the F0 females. The foetuses examined had no vaccine related visceral or skeletal abnormalities. A strong immune response of the maternal dams to vaccination was demonstrated by serological testing for vaccine specific antibodies. Sampling of the offspring also showed high levels of circulating antibody, demonstrating passive transfer of antibodies via the placental blood or milk.

The only evidence of a finding possibly related to the split virus vaccine was head or posture tilted to the left, which was noted on one or two occasions after six weeks of age in 5/20 F1 male and 2/20 F1 female offspring of dams that received the vaccine, compared with none in the control. A similar finding was also seen in 5/20 F1 males and 6/20 F1 females derived from dams exposed to the reference (marketed) vaccine, Fluzone. This was recorded a few days after blood sampling by puncture of the retro orbital sinus and the sponsor and a consultant procured to examine this issue considered it most likely that head or posture tilt was associated with either blood sampling or animal handling procedures at the time. However, there was no direct evidence for this in the study data and similar findings were not observed in concurrent control animals or in the dams when they were of a similar age and bled using the same technique during the early phase of this study, prior to their first exposure to vaccines. Data from other studies of a similar design, as well as data from concurrent studies at the same test facility, showed that head/posture tilt was an extremely rare event and could occur in the absence of blood sampling from the orbital sinus. An association to maternal exposure to the vaccines therefore could not be excluded and the finding was considered to be potentially adverse, even if the long term significance was not established.

A second investigative study was therefore undertaken, employing a study design with greater power (larger sample size) to determine whether any postural changes in the F1 offspring were reproducible. Blood sampling was not conducted by retro orbital sinus puncture in this study. Dams were either given the vehicle, Baxter's 2007/08 season vaccine, Baxter's 2008/09 season vaccine, or the marketed Fluzone reference vaccine.

Investigations conducted on the F1 offspring until weaning showed no other findings related to vaccination. The investigations included pre weaning reflex development, sensory examinations (motor activity, learning and memory), sexual maturation and gross pathology. In the second study, the observation period of the F1 generation was extended to ten weeks and there were detailed weekly physical examinations and intensive arena observations by a specialist on four occasions. Parameters shown to be unaffected by

administration of the candidate vaccine in the first study were not reassessed, to reduce animal usage. It was concluded that the postural changes were unrelated to treatment with Preflucel.

Pregnancy classification

The sponsor has proposed Category B1.[1] While most influenza vaccines currently registered in Australia are Category B2, the sponsor submitted two developmental toxicity studies in rats, which indicated no significant treatment related findings. On this basis, the proposed Category B1 is considered acceptable.

Use in children

The product is not indicated for paediatric use.

Nonclinical Summary and Conclusions

- The submitted nonclinical studies comprised vaccine immunogenicity (mice and guinea pigs), viral challenge (ferrets), and acute and repeat dose toxicity and local tolerance investigation of reproductive, developmental and pre postnatal toxicity study in rats. Toxicity studies were GLP compliant. References from the published literature were submitted to support the proposed limits for the excipients Polysorbate 80 and Triton X-100. Overall, the scope of the nonclinical studies met the general requirements of the relevant EMEA vaccine and seasonal influenza vaccine nonclinical guidelines.
- Identical as well as comparable influenza virus antigens from recent years to those contained in Preflucel were immunogenic (based on HA inhibition) in mice, guinea pigs and ferrets as well as in chimpanzees (seasons 1996/1997 and 1997/1998) at doses (based on mg/m^2) lower than the recommended antigen dose in humans. However, the doses in mice and guinea pigs were boosted at three weeks, and the titres at three weeks were generally lower than at six weeks. The immunogenicity and protective effect of Vero Cell Derived Whole Virus Vaccine was equivalent to the egg derived counterparts. Immunogenicity studies with the Split Virus Vaccines of seasons 2006/2007 and 2007/2008 in mice and guinea pigs showed comparable immunogenicity to the whole virus vaccines.
- No studies were submitted addressing the secondary and safety pharmacology of Preflucel and their assessment will therefore need to be based on clinical data.
- Slight and transient injection site redness was seen in some rats after they had received the first dose of vaccine in repeat dose toxicity study. Mild inflammatory infiltrates were detected under microscopic examination of the tissue at the injection site from rats killed three days after receiving a single dose of vaccine, but not after fourteen days.

[1] Definitions of the Australian categories for prescribing medicines in pregnancy:

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

- Vaccine related changes observed in the draining lymph nodes of rats were considered to be of equivocal toxicological significance, and were likely to reflect a normal physiological response to vaccination.
- Genotoxicity and carcinogenicity studies were not submitted, and were not required.
- In developmental and reproductive toxicology studies, female rats received IM injections of the HA antigen (at 23 fold the human dose on a mg/m^2 basis) on Days -42 and -14 before pairing and on GD 7, and selected F1 offspring were euthanised at seven to ten weeks of age. There was no effect on the F0 females. Sampling of the offspring also showed significant levels of circulating antibody, demonstrating passive transfer of antibodies via the placental blood or milk. Head or posture tilt was observed in F1 animals from dams vaccinated with either the proposed or a reference vaccine in one study, but not in another study designed for greater statistical power; these findings therefore were considered incidental and unrelated to maternal vaccination.
- The local and systemic exposures to Triton X-100 and Polysorbate 80 with currently registered products are greater at the recommended dose than with the proposed Preflucel formulation.

Conclusions and Recommendation

Immunogenicity was demonstrated (by HA inhibition) in various animal models at doses (based on mg/m^2) lower than the recommended antigen dose in humans. However, there were no studies of immunogenicity in aged animals. Unlike their proposed use in humans, the doses in mice and guinea pigs were boosted at three weeks, and the antigens used in most studies were equivalent but not identical to those in the proposed product. EMA immunogenicity will therefore ultimately rely on clinical data.

Apart from minor findings at the injection site, there were no toxicological findings that were likely to impact on the safety of Preflucel. The proposed Use in Pregnancy Category B1 is considered appropriate, based on negative findings in the submitted reproductive toxicity studies in rats.

There are no nonclinical objections to registration of Preflucel. Minor changes proposed by the nonclinical evaluator should be incorporated in the PI.

IV. Clinical Findings

Introduction

All study reports state that the trials were conducted according to the accepted Good Clinical Practice (GCP) requirements for the countries where the trials were conducted. These requirements are:

European trials:

- The ethical principles conveyed by the Declaration of Helsinki 1964 and as amended in following years until 1996;
- The EMA Note for Guidance on GCP (CPMP/ICH/135/95);
- Directive 2001/20/EC of the European Parliament and of the Council (4 April 2001);
- Commission Directive 2005/28/EC (April 2005); and
- Relevant national laws.

USA trials:

- US GCP requirements as set out in Title 21 of the US Code of Federal Regulations (CFR) parts 50 (informed consent), 54 (financial disclosure), 56 (IRB), 312 (IND), and 314 (NDA); and
- Local and national regulatory requirements.

Pharmacology

Not applicable for vaccines.

Efficacy

Baxter submitted six clinical studies in support of the application. Overall, the studies were planned and enrolled healthy adults aged over 18 years of age. No paediatric studies were done and the product is not intended for use in children (less than 18 years).

The product was developed in accordance with the following guidance documents for vaccine development:

1. Note for Guidance on Harmonisation of Requirements for Influenza Vaccines CPMP/BWP/214/96; and
2. FDA Guidance for Industry – Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007).

The European Union (EU; CPMP) Guidance has been adopted in Australia. Its requirements are set out in Table 4.

Table 4: Requirements of European Union guidance document for vaccine development as adopted in Australia.

Serological parameter	Compliance in	
	Adults 18-60 years	Elderly >60 years
Seroconversion rate (HI 0 ≥40 or ≥ 4 fold increase; SRH 0-≥25 mm² or ≥50% area increase)	>40% of subjects	>30% of subjects
Seroprotection rate (Rate of subjects achieving HI titre ≥40; SRH ≥25mm²)	>70%	>60%
Mean geometric fold increase in HI or SRH antibody titre	>2.5	>2.0

Pivotal Studies

Study 720601 was a Phase I/II single blind, randomised, active control study to compare the safety and immunogenicity of the investigational split virus, Vero cell derived influenza vaccine with a licensed egg derived vaccine in healthy male and female adults aged 18 years and older during the northern hemisphere 2006/2007 influenza season. The objective of the study was to assess safety and immunogenicity.

Two placebo controlled Studies 720703 and 720802 were conducted over two northern hemisphere influenza seasons (2007/2008 and 2008/2009) to evaluate efficacy in adults 18-49 years. The primary endpoint was the number of vaccinated subjects developing influenza infection with a virus that is antigenically similar to one of the strains contained in the vaccine, as confirmed by viral culture and typing of nasopharyngeal specimens. Secondary objectives were immunogenicity and safety.

Secondary endpoints also include number of vaccinated subjects developing influenza infections regardless of antigenic similarity to the strains contained in the vaccine.

Study 720801 was an active controlled study in which the investigational product was compared to a licensed egg derived vaccine in adults aged 50 years and older during the northern hemisphere 2008/2009 influenza season. Subjects were stratified into two groups 50-64 and >65 years (US requirements). The objective of the study was immunogenicity and safety.

Two studies investigated immunogenicity and safety in adults meeting the CPMP age ranges 18-59 and >60 years. Study 720901 was conducted in Austria in June 2009 using the strains recommended for the northern hemisphere 2009/2010 influenza season. Study 721001 was conducted in Austria in July 2010, but using the recommended strains for the Australian 2010/2011 influenza season.

Study 720601

Methods

Objectives

- To assess the safety and tolerability of Vero cell derived vaccine in comparison to egg derived vaccine in healthy subjects in two age strata: 18 to 49 and 50 years of age and older
- To assess the immunogenicity of Vero cell derived vaccine in comparison to egg derived vaccine for subjects in two age strata: 18 to 49 and 50 years of age and older

Study Design

A multicentre, single blind, randomised, controlled Phase I/II study conducted in nine centres in Germany, Austria and Poland from January 2007 to September 2007.

Study Participants

Study participants were healthy (defined as a physical condition such that the physician had no reservations administering influenza vaccine outside the scope of a clinical study) males and females aged 18 to 49 years (Stratum A) and 50 years or older (Stratum B).

The study was originally planned to be conducted in the USA. The US Centers for Disease Control and Prevention (CDC) currently recommends vaccination for persons aged >50 years. The study was then moved to Europe but the age groups was *not* changed to the CPMP recommendations of 18-59 and >60 years.

Women of childbearing age were eligible for the study as long as they had a negative urine pregnancy test within 24 hrs of the vaccination and to agree to both hormonal and barrier method of birth control for 60 days after vaccination.

Participants were excluded if they had had previous influenza vaccination for the 2006/2007 influenza season or an oral temp of ≥ 37.5°C at the time of vaccination. Exclusion criteria also included: a Body Mass Index (BMI) of >35; Type I diabetes; uncontrolled hypertension; active neoplastic disease; previous positive test for HIV, Hepatitis B Surface Antigen (HbsAg) or Hepatitis C (HCV); history of immunodeficiency or autoimmune disease or arthritis; cardiovascular disease requiring hospitalisation; significant electrocardigraphic abnormality at screening; any disease requiring therapy expected to affect immune response or history of inflammatory or degenerative neurological disease; vaccination within two weeks prior to study vaccination; blood transfusion or blood donation within 30 days prior to study vaccination; history of vaccine contraindicating event; rash, dermatological condition or tattoos which may interfere with injection site reaction rating; positive drug test; pregnancy or lactation, current participation in other clinical drug study, member of study team or in dependent relation with a study investigator.

Treatments

Test product: split virus, Vero cell derived seasonal influenza vaccine. One dose contains 15 µg HA antigen of each of the three influenza strains recommended by the WHO for the 2006/2007 season:

- A/H1N1: A/New Caledonia/20/99 (A/New Caledonia/20/99 like)
- A/N3H2: A/Hiroshima/52/2005 (A/Wisconsin/67/2005 like)
- B: B/Malaysia/2506/2004 (B/Malaysia/2506/2004 like)

Comparator product: a licensed egg derived vaccine – Inactivated Influenza Vaccine trivalent Types A and B (Split Virion) Vaxigrip [Sanofi Pasteur MSD] 2006/2007. One dose contains 15 µg HA antigen of each of three influenza strains:

- A/H1N1: A/New Caledonia/20/99-IVR-116 (A/New Caledonia/20/99 like)
- A/N3H2: A/Wisconsin/67/2005 (A/Wisconsin/67/2005 like)
- B: B/Malaysia/2506/2004 (B/Malaysia/2506/2004 like)

Only one lot of each product was used in the study. The vaccine was provided in pre filled syringes and administered as 0.5mL dose by IM injection into the deltoid muscle.

Study Duration

Each subject received a single vaccination on Day 0. Total duration of study participation for each subject was approximately 180 days and overall study duration was 9 months. Study visits was screening (Day -21 to 0), Day 0, Day 7, Day 21 and Day 180.

Outcomes/endpoints

Primary endpoint:

The number of subjects with oral temperatures of ≥ 38.0°C and onset within two days after vaccination.

Secondary endpoints:

Safety

- Fever ≥ 38.0°C within two days of vaccination that is associated with one or more of the following symptoms:
  - Malaise
  - Headache
  - Shivering
  - Vomiting
- Fever ≥ 38.0°C with onset within seven days after vaccination that persists for less than 24 hours
- Fever ≥ 38.0°C with onset within seven days after vaccination
- Malaise with initial onset within seven days after vaccination
- Shivering with initial onset within seven days after vaccination
- Headache with initial onset within seven days after vaccination
- Arthralgia with initial onset within seven days after vaccination

- Induration at the injection site larger than 50mm in diameter and persisting for more than three days
- Frequency and severity of occurrence of any injection site reactions and systemic reactions related to vaccination
- Frequency and severity of occurrence of any injection site reactions and systemic adverse events (AEs) observed during the entire 180 day follow up period.

Immunogenicity

- The rate of subjects achieving a reciprocal HI antibody titre of ≥ 40 against each of the three antigens in the vaccines at the Day 21 and Day 180 visits after vaccination.
- HI antibody titre against each of the three antigens in the vaccines measured at the Day 21 and Day 180 visits after vaccination
- Fold increases of HI antibody titre against each of the three antigens in the vaccines as compared to baseline.
- The rate of subjects with seroconversion to each of the three antigens contained in the vaccines at the Day 21 visit after vaccination.

Sample size

The primary endpoint of the study was the number of subjects experiencing fever within two days after vaccination. The sample size calculation was based on the assumptions of 1% fever rate with the control vaccine in both age strata and a 5% and 6% fever rate with the test vaccine in Stratum A and Stratum B respectively. The study had 85% power to detect a difference between the study groups with a sample size of 940 subjects (280 in Stratum A and 660 in Stratum B) randomised in a 3:1 ratio to receive test and control vaccine. Type 1 error was set to a 5% two sided level. It was assumed that there would be a 10% missing assessment in fever reactions two days after vaccination, and so 1000 subjects were planned to be randomised – 300 in Stratum A and 700 in Stratum B.

Of the 300 subjects in Stratum A – 225 would receive the Vero cell derived vaccine – this would provide a 90% change to detect at least one AE occurring at a frequency of 1% in this population.

Of the 700 subjects in Stratum B – 525 would receive the Vero cell derived vaccine – this would provide a 93% chance to detect at least one AE which has an underlying prevalence of 0.5%.

In order to detect an increase in fever rate in Stratum B from 1% to 7% against a two sided alternative hypothesis, 660 subjects randomised in a 3:1 ratio were needed to be enrolled. This sample size could provide approximately 87% power to detect such a rate increase if the type 1 error was set at 5%.

Note: age groups do not match CPMP recommendations for test groups which should be 18-50 and >60 years.

Randomisation

Subjects were randomised via an electronic data capture system in a 3:1 ratio to receive either the Vero cell derived or egg derived vaccine, respectively. Randomisation was carried out by the study sites and separate randomisations were prepared for each stratum.

Blinding (masking)

The study arms were single blinded as no attempt was made to repackage the two vaccines. Subjects participating in the study were blinded but study personnel could identify which product was administered.

Initially, a total of 180 subjects in stratum A were enrolled and randomly assigned in 3:1 ratio to receive vaccination on Day 0. These subjects were called Cohort 1. After all vaccinated subjects in Cohort 1 completed the Day 7 study visit, unblinded safety data was presented to an independent Data Safety Monitoring Board (DSMB) for review. The DSMB advised the sponsor to continue to enrol another 120 subjects in Stratum A and 700 in Stratum B. This second group was called Cohort 2.

Statistical methods

Primary endpoint

The number of subjects with body temperature of ≥ 38.0°C with onset within two days after vaccination was analysed in the two age strata combined and the study groups were compared by the Cochran Mantel Haenszel test, which adjusts for potential differences between aged strata. The analysis was carried out on the per protocol (PP) and intent to treat (ITT) analysis datasets.

Other safety endpoints

Point estimates and 95% Confidence Intervals (CI) were calculated for all safety endpoints. The rates of local and systemic reactions were compared by exact test for proportions for Stratum A and Stratum B separately.

Immunogenicity endpoints

Point estimates and 95% CI were calculated for the each of the immunogenicity endpoints.

Recruitment

Subjects were healthy adults recruited within planned timeframe. No information is provided on how the subjects were recruited.

Conduct of the study

Vaccinations were administered on Day 0 and vaccinations blood draws were performed by the investigator or assigned study personnel.

Blood samples were drawn from all subjects for serology at screening (prior to vaccination), Day 21 (± 2 days) and Day 180 (± 2 days).

Blood samples were drawn from all subjects for the following safety laboratory tests at screening, Day 7 (± 1 days), Day 21 (± 2 days), and Day 180 (± 2 days):

- Haemoglobin, white blood cell (WBC) and differential counts, platelets, glucose, creatinine, blood urea nitrogen, sodium, chloride, aspartate transaminase, alanine aminotransferease, alkaline phosphatise, bilirubin, and troponin.

The patients completed study diaries from Day 0 to Day 180. The diary was divided into Parts A, B, and C. Part A covered the period from vaccination to the Day 7 visit. Part B covered the period from Day 7 through Day 21 visit. Part C covered the period Day 21 though Day 180.

At Day 90 (± 10 days) subjects were contacted by telephone or email to remind them of their study participation and of the need to record pertinent data in the subject diary.

The following information was collected in the subject diary:

- Measurement of body temperature orally, once every evening from vaccination until the Day 7 visit
- Injection site reactions (injection site pain, tenderness, redness, swelling, induration)
- Systemic AE (fever, malaise, shivering, fatigue, headache, sweating, muscle pain, joint pain)
- Other adverse reactions
- Any medication taken after vaccination (including non steroidal anti inflammatory drugs and other over the counter drugs administered for therapeutic use)

Baseline data

940 subjects were vaccinated and had blood drawn for baseline safety screening and baseline HI antibody titres.

In Stratum A, there were 54.7% males and 45.3% females randomised to egg derived vaccine and 53.5% males and 46.5% females randomised to the Vero cell derived vaccine. The age ranged from 18 to 49 with a greater percentage (41.3% in egg derived and 49.6% in Vero cell derived) in the age group 18-25 years with even distribution in the following 5year age brackets.

In Stratum B, there were 43.9% males and 56.1% females randomised to egg derived vaccine and 48.3% males and 51.7% females randomised to the Vero cell derived vaccine. The age ranged from 50 to >75 years with a greater percentage (59.3% in egg derived and 58.3%in Vero cell derived) in the age group 50-60 years. Only 3.8% in egg derived and 4.2% in Vero cell derived were in age range 71-75 years and only 5.1% in egg derived and 4.2% in Vero cell derived were in age range >75 years.

The demographic characteristics of subjects were similar for both treatment groups in both age groups.

Baseline HI antibody titre

In Stratum A (18-49 years), >98% of subjects in each vaccine group had a seroprotective antibody titre (reciprocal HI titre ≥ 40) for the A/H3N2 strain, > 56% of subjects for the A/H1N1 strain. Only 23.3-31.1% had a seroprotective antibody titre for the B strain.

In Stratum B (≥ 50 years), >94% in each vaccine group had a seroprotective antibody titre for the A/H3N2 strain and >27% for the A/H1N1 strain. Only 13.0-19.1% had a seroprotective antibody titre for the B strain.

Numbers analysed

The full analysis dataset included all vaccinated subjects. A total of 940 subjects were vaccinated – 303 in Stratum A (18-49 years) and 637in Stratum B (≥ 50 years).

The ITT dataset included randomised and vaccinated subjects with available data for the respective analysis. A total of 940 subjects were included in the ITT dataset– 303 in Stratum A (18-49 years) and 637in Stratum B (≥ 50 years).

The PP analysis included all randomised and vaccinated subjects who met the inclusion/exclusion criteria, had no major protocol violations and for whom data for the respective analysis were available. A total of 939 subjects were included in the PP dataset– 303 in Stratum A (18-49 years) and 636 in Stratum B (≥ 50 years).

Results

Primary outcome

The primary outcome was the number of subjects with oral temperatures ≥ 38°C and onset within two days after vaccination.

A very low overall rate of fever with onset within two days after vaccination was observed in the Vero cell derived (10/707 subjects – 1.4%), and no fever cases were reported in the egg derived vaccine. The observed cases appeared to be randomly distributed between the study centres.

There was no significant difference between the vaccine groups as shown by comparison with the Cochran Mantel Haenzel test (p=0.686) in the ITT dataset; (p=0.0690) in the PP dataset. The sensitivity analysis, by which subjects in the ITT dataset without body temperature assessments were considered fever cases, also showed no significant difference between the vaccines regarding the primary endpoint (p=0.0562).

Immunogenicity

Immunogenicity testing was conducted at baseline (prior to vaccination) and at Day 21 and Day 180. Antibodies against the influenza virus strains used in the vaccines were determined by HI tests against egg derived antigens. Antibody titrations were done in duplicate: pre and post vaccination sera were titrated simultaneously. The titre assigned to each sample was the geometric mean of two independent determinations. For the purpose of the analysis, any HI result <1:10 (undetectable) was expressed as 1:5 and was considered negative.

Rate of subjects achieving a reciprocal HI antibody titre ≥ 40

The summary of the data is seen in Table 5. Table is for ITT dataset. PP population is similar.

Table 5: Rate of subjects achieving a reciprocal HI antibody titre ≥ 40.

Stratum A (18–49 years)				
Strain	**Day 21**		**Day 180**	
	Egg derived	Vero cell-derived	Egg derived	Vero cell-derived
A/H1N1	100.0%	99.6%	98.6%	96.9%
A/ H3N2	100%	99.6%	100%	100%
B	98.6%	92.9%	91.8%	75.3%
Stratum B (≥ 50 years)				
A/H1N1	100%	96.7%	89.0%	82.2%
A/ H3N2	100%	100%	100%	99.8%
B	93.6%	73.0%	61.0%	39.5%

Geometric mean of HIA titre (GMTs)

The summary of the data is seen in Table 6. Table is for ITT dataset. PP population is similar.

Table 6: Geometric mean of HIA titre.

Stratum A (18-49 years)				
Strain	**Day 21**		**Day 180**	
	Egg derived	Vero cell-derived	Egg derived	Vero cell-derived
A/H1N1	566.6	693.1	280.2	365.8
A/ H3N2	716.1	471.0	463.4	350.2
B	241.6	122.5	128.6	69.6
Stratum B (≥ 50 years)				
A/H1N1	234.5	215.7	107.2	89.3
A/ H3N2	612.2	423.3	348.6	257.6
B	111.6	56.3	39.8	24.1

Geometric mean fold increase of HIA titre

The summary of the data is seen in Table 7. Table is for ITT dataset. PP population is similar.

Table 7: Geometric mean fold increase of HIA titre.

Stratum A (18-49 years)				
Strain	**Day 21**		**Day 180**	
	Egg derived	Vero cell-derived	Egg derived	Vero cell-derived
A/H1N1	12.0	12.8	6.5	8.3
A/ H3N2	4.0	2.7	2.5	2.1
B	14.0	7.5	7.3	4.2
Stratum B (≥ 50 years)				
A/H1N1	9.3	7.9	5.0	3.8
A/ H3N2	4.6	2.9	2.7	1.8
B	8.6	4.0	3.1	1.8

Rate of subjects with seroconversion

The rate of subjects with seroconversion at Day 21 after vaccination in Stratum A and Stratum B is shown in Table 8.

Table 8: Rate of subjects with seroconversion at Day 21 after vaccination in Stratum A and Stratum B.

Stratum A (18-49 years) (Intent-To-Treat Dataset)				
Strain	**Egg derived**		**Vero cell derived**	
	n/N (%)	**95% C.I.**	**n/N (%)**	**95% C.I.**
A/H1N1	59/74 (79.7%)	(68.8%; 88.2%)	179/226 (79.2%)	(73.3%; 84.3%)
A/H3N2	46/74 (62.2%)	(50.1%; 73.2%)	88/226 (38.9%)	(32.5%; 45.6%)
B	67/74 (90.5%)	(81.5%; 96.1%)	173/226 (76.5%)	(70.5%; 81.9%)

Stratum B (≥50 years) (Intent-To-Treat Dataset)				
Strain	**Egg derived**		**Vero cell derived**	
	n/N (%)	**95% C.I.**	**n/N (%)**	**95% C.I.**
A/H1N1	126/156 (80.8%)	(73.7%; 86.6%)	358/476 (75.2%)	(71.1%; 79.0%)
A/H3N2	102/156 (65.4%)	(57.4%; 72.8%)	204/476 (42.9%)	(38.4%; 47.4%)
B	129/156 (82.7%)	(75.8%; 88.3%)	252/476 (52.9%)	(48.3%; 57.5%)

Reverse cumulative distribution

Reverse cumulative distribution of immune response at Day 21 classified by titre from 1:20 to 1:320 showed that both vaccines elicited a strong immune response in both age strata.

Secondary safety outcomes

The secondary safety outcomes are set out in Tables 9 and 10.

Table 9: Other safety endpoints, Stratum A (Full Analysis Dataset).

Safety Endpoint	Egg derived n/N (%) (95% C.I.)	Vero cell derived n/N (%) (95% C.I.)
Fever >=38.0°C within 2 days of vaccination that is associated with one or more of the following symptoms: Malaise, Headache, Shivering, Vomiting	0/75 (0.0%) (0.0%; 4.8%)	4/228 (1.8%) (0.5%; 4.4%)
Fever >=38.0°C with onset within 7 days after vaccination that persists for less than 24 hours	0/75 (0.0%) (0.0%; 4.8%)	7/228 (3.1%) (1.2%; 6.2%)
Malaise with initial onset within 7 days after vaccination	4/75 (5.3%) (1.5%; 13.1%)	14/228 (6.1%) (3.4%; 10.1%)
Shivering with initial onset within 7 days after vaccination	2/75 (2.7%) (0.3%; 9.3%)	11/228 (4.8%) (2.4%; 8.5%)
Headache with initial onset within 7 days after vaccination	10/75 (13.3%) (6.6%; 23.2%)	37/228 (16.2%) (11.7%; 21.7%)
Arthralgia with initial onset within 7 days after vaccination	2/75 (2.7%) (0.3%; 9.3%)	4/228 (1.8%) (0.5%; 4.4%)
Induration at the injection site larger than 50 mm in diameter and persisting for more than 3 days	1/75 (1.3%) (0.0%; 7.2%)	0/228 (0.0%) (0.0%; 1.6%)

Table 10: Other safety endpoints, Stratum B (Full Analysis Dataset).

Safety Endpoint	Egg derived n/N (%) (95% C.I.)	Vero cell derived n/N (%) (95% C.I.)
Fever >=38.0°C within 2 days of vaccination that is associated with one or more of the following symptoms: Malaise, Headache, Shivering, Vomiting	0/157 (0.0%) (0.0%; 2.3%)	3/479 (0.6%) (0.1%; 1.8%)
Fever >=38.0°C with onset within 7 days after vaccination that persists for less than 24 hours	1/157 (0.6%) (0.0%; 3.5%)	6/479 (1.3%) (0.5%; 2.7%)
Malaise with initial onset within 7 days after vaccination	11/157 (7.0%) (3.5%; 12.2%)	33/480 (6.9%) (4.8%; 9.5%)
Shivering with initial onset within 7 days after vaccination	3/157 (1.9%) (0.4%; 5.5%)	20/480 (4.2%) (2.6%; 6.4%)
Headache with initial onset within 7 days after vaccination	15/157 (9.6%) (5.4%; 15.3%)	48/480 (10.0%) (7.5%; 13.0%)
Arthralgia with initial onset within 7 days after vaccination	3/157 (1.9%) (0.4%; 5.5%)	17/480 (3.5%) (2.1%; 5.6%)
Induration at the injection site larger than 50 mm in diameter and persisting for more than 3 days	0/157 (0.0%) (0.0%; 2.3%)	0/480 (0.0%) (0.0%; 0.8%)

Local reactions

The number of local reactions was mostly mild with a few moderate reactions observed in both treatment groups. No local reactions were graded severe. The probability of occurrence of local reactions is given in Tables 11 and 12.

Table 11: Probability of occurrence of local reactions after vaccination, Stratum A (Full Analysis Dataset).

Study group	Local reactions occurred n/N	Probability of occurrence	95% C.I. of the probability of occurrence
Egg derived	27/75	36.0%	25.2%; 47.9%
Vero cell derived	89/228	39.0%	32.7% ; 45.7%

Table 12: Probability of occurrence of local reactions after vaccination, Stratum B (Full Analysis Dataset).

Study group	Local reactions occurred n/N	Probability of occurrence	95% C.I. of the probability of occurrence
Egg derived	39/157	24.8%	18.3% ; 32.4%
Vero cell derived	105/480	21.9%	18.3% ; 25.8%

There was no significant difference in rates of local reactions between the Vero cell derived and egg derived vaccine in either age stratum using the exact test (Stratum A: p=0.6827, Stratum B: p=0.4432).

There were no reports of induration at the injection site larger than 50 mm in diameter and persisting for more than three days after vaccination with the Vero cell derived vaccine in either age group.

Systemic reactions

The probability of occurrence of systemic reactions (excluding fever) after the vaccination is shown in Table 13.

Table 13: Probability of occurrence of systemic reactions (excluding fever) after the vaccination.

Stratum A (Full Analysis Dataset)			
Study group	Systemic reactions occurred n/N	Probability of occurrence	95% C.I. of the probability of occurrence
Egg derived	18/75	24.0%	14.9% ; 35.3%
Vero cell derived	65/228	28.5%	22.7% ; 34.8%

Stratum B (Full Analysis Dataset)			
Study group	Systemic reactions occurred n/N	Probability of occurrence	95% C.I. of the probability of occurrence
Egg derived	24/157	15.3%	10.0% ; 21.9%
Vero cell derived	108/480	22.5%	18.8% ; 26.5%

There was no significant difference in the rates of systemic reactions between the vaccine groups and age strata using the exact test (Stratum A: p=0.5507; Stratum B: p=0.0545).

Laboratory parameters

No comment is made in the study report about the laboratory parameters but review of tabulated lists of laboratory assessments does not demonstrate any consistent abnormalities or apparent differences between split virus vero cell derived seasonal influenza vaccine (VCIV) or egg derived split virus seasonal influenza vaccine (EIV).

Conclusions

- Company claim that both CPMP and FDA requirements have been met – however, the CPMP age ranges required are 18-59 and >60 years and FDA requirement is 18-64 and ≥ 65 years. Company claim that as CDC recommend vaccination in adults >50 years their age ranges were appropriate. However, no comment was made as to why recalculation based on CPMP was done. This was done for a later study
- Safety appears to be similar between VCIV and EIV

Study 720703

Methods

Primary objectives

- Demonstrate the efficacy of an investigational VCIC in preventing infection in an adult population with an influenza virus that is antigenically similar to one of the three strains in the vaccine
- Demonstrate the consistency of immunologic response among three different lots of an investigational VCIV

Secondary objectives

- Compare the safety of an investigational VCIV with a placebo
- Establish a correlation between the VCIV induced HI and immunity to infection

Study design

This is a randomised, multicentre, placebo controlled, double blind, Phase III clinical study. It was conducted at 35 centres in the USA between November 2007 and June 2008

Study participants

Healthy adults aged 18 to 49 years of age on day of screening. No explanation is provided on how healthy adults were recruited.

Inclusion criteria were minimal:

- Aged 18 to 49 years
- Understood the study and gave written informed consent
- Females capable of bearing children were required to have a negative pregnancy test within 24 hours of vaccination and to agree to use adequate contraception for at least 60 days following vaccination

Exclusion criteria were:

- all persons with any of the risk factors for complications from influenza infection as defined by the CDC:
  - pregnancy, chronic disorders of pulmonary or cardiovascular system including asthma (but not hypertension), chronic renal disorders, chronic haematological disorders, chronic metabolic disorders (including diabetes mellitus), immunosuppression (including that caused by medications or HIV), any condition that could compromise respiratory function or the handling of respiratory secretions or increase risk of aspiration (eg cognitive dysfunction, spinal cord injuries, seizure disorders or other neuromuscular disorders), residence in a nursing home or other chronic care facility, household contact with children aged

0-59 months or someone who is included in risk categories above, employment as a health care worker

- history of severe allergic reactions or anaphylaxis
- presence of oral temperature ≥ 37.5°C on the day of vaccination
- having a rash or dermatological condition or tattoos which may interfere with injection site reaction rating
- had previous live vaccine within four weeks or inactivated vaccine within 2 weeks of study entry or ever received season influenza vaccine for the 2007/2008 northern hemisphere influenza season

Treatments

Subjects allocated to treatment received a single 0.5 mL injection of the VCIV from one of three different lots, comprised of 15 μg HA each of the influenza virus types/subtypes:

- A/H1N1 (A/Solomon Islands/3/2006)
- A/H3N2 (A/Wisconsin /67/2005)
- B (B/Malaysia/2506/2004)

The investigational vaccine was supplied in pre filled syringes.

Control subjects were administered a phosphate buffered saline placebo packaged in syringes identical to those used for the investigational vaccine.

Study duration and compliance

All subjects were vaccinated on Study Day 1. Vaccination and placebo injections were administered by trained study site personnel.

Total length of study participation was approximately 180 ± 14 days for each subject.

Outcomes/endpoints

Primary endpoints

The co primary endpoints were:

- The number of subjects developing influenza infection with a virus that is antigenically similar to one of the vaccine strains, as confirmed by viral culture and typing of nasopharyngeal specimens, 21 days to 180 days after the date of vaccination
- The consistency of immune response produced by three different lots of Vero cell derived vaccine

Secondary endpoints

Efficacy:

- The number of subjects developing influenza infection, as confirmed by viral culture and typing and/or Reverse Transcription Polymerase Chain Reaction (RT PCR) analysis of nasopharyngeal specimens, 21 days to 180 days after the date of vaccination

Immunogenicity:

- HIA titre for each of the three antigens contained in the vaccine at Day 21

- The number of subjects with seropositive antibody titre [reciprocal HIA titre ≥ 40] for each of the three antigens contained in the vaccine at Day 21
- Fold increase of HIA titre for each of the three antigens contained in the vaccine at Day 21 as compared to baseline
- The number of subjects demonstrating seroconversion to each of the three antigens contained in the vaccine at Day 21

Safety:

- Frequency and severity of occurrence of any injection site reactions and systemic reactions related to vaccination
- Frequency and severity of occurrence of any injection site reactions and systemic adverse events (AEs) observed during the entire 180 day follow up period

Sample size

Each co primary endpoint was tested separately. Since both endpoints must be met, no adjustment for a Type 1 error was considered necessary.

Co primary endpoint 1

Sample size calculation was based on the following assumptions:

- Influenza infection rate of placebo recipients = 3%
- Vaccine efficacy for the three strains = 75%
- Randomisation rate = 1:1

Based on these assumptions the null hypothesis of vaccine efficacy (VE) <40% can be rejected with 85% power if 3362 subjects are evaluable. A drop-out rate of approx 7% was assumed and so 3600 subjects were planned to be enrolled.

Co primary endpoint 2

The planned 3600 subjects were randomised in a ratio of 1:1:1:3 to receive one of the three different lots of the Vero cell derived vaccine to placebo.

To assess consistency between different lots of the vaccine, the antibody response of the lots were compared pair wise in order to establish if they were equivalent regarding immune response after vaccination.

To show equivalence between two study lots, the 95% CI of the ratio of the geometric mean titre was calculated. This CI had to be entirely within 0.67 and 1.5. These two limits correspond on a natural log scale to the value of ± 0.41.

With a sample size of approximately 560 subjects receiving a specific lot of the influenza vaccine, the study had >90% power to show equivalence between two study lots. Therefore, the overall power for the nine pair wise comparisons (three strains and three lots) to show equivalence simultaneously is approximately 91%. The Type 1 error is set at a 5% two sided level. Adjustment of Type 1 error for multiple comparisons was not considered necessary as lot consistency was only proven if equivalence was shown in each of the three pair comparisons for all three strains.

Secondary analysis

The sample size of 1660 evaluable subjects per group is enough to prove the superiority of Vero cell derived vaccine versus placebo in the incidence rate of culture confirmed influenza with a power of 99%.

Safety

The sample size of 1800 subjects per group in the safety population enabled detection with a probability greater than 95% of all AEs with an underlying incidence rate of at least 1:600. For an AE of 5% incidence in the placebo group, a relative risk increase of 1.5 in the vaccine group can be detected with a power of 87%. For an AE of 10% incidence in the placebo group, a relative risk increase of 1.3 can be detected with a power of 80%, while for a 20% incidence rate there is a 83% power to detect a relative risk increase of 1.2.

Randomisation

Randomisation was performed centrally via an interactive voice response system. Randomisation was carried out in blocks with a block size ≥6 using the random number generator algorithm.

Blinding (masking)

The study medication was double blinded with the vaccine presented in identical pre filled syringes.

The study blind was broken after all subjects completed the Day 180 visit, all data was entered into the study database and the data was cleaned.

Statistical methods

Co-primary endpoint 1

The two-sided 95% CI of the VE was determined by first calculating the two sided 95% CI of the risk ratio of the Vero cell derived study group to the placebo group. The null hypothesis of VE <40% against the alternative hypothesis VE ≥40% was tested at a 5% two sided significance level.

Co-primary endpoint 2

Consistency between the lots was concluded if the two sided 95% CI for the ratio of geometric mean titres is contained in the range of [0.67, 1.5] for all three pair wise comparisons and for all strains. For each strain, pair wise difference between least square means of the log transformed titre values were estimated within an analysis of covariance (ANCOVA) framework for the fixed effect of lot and baseline HIA titre value as a covariate.

Secondary endpoints

Efficacy:

The two sided 95% CI of the risk ratio of the Vero cell derived study group to the placebo group was estimated.

Safety:

The relative risk (95% CI) between Vero cell derived vaccine and placebo group was estimated for local and systemic reactions related to vaccination. Point estimates and 95% CI were calculated for all safety endpoints. The probability of occurrence and 95% CI was calculated for all queried local and systemic reactions.

Recruitment

The subjects were healthy adults aged 18 to 49 years of age. No information is provided as to how the subjects were recruited.

Conduct of the study

The study was conducted at multiple sites in the USA.

All subjects were vaccinated on Study Day 1. Vaccination and placebo injections were administered by trained study site personnel.

Subjects were seen at Visit 1 (Screening and baseline: Day -14 to Day 1), Visit 2 (Day 1 vaccination day), Visit 3 (Day 21 ± 3), and Visit 4 (Day 180 ± 14 days). Unscheduled visits occurred whenever a subject developed symptoms of influenza like infection from Day 21 through Day 180 after the day of vaccination.

Subjects recorded measurement of body temperature orally, once every evening in a diary card from Day 1 to Day 7. They also recorded any adverse reactions and any concomitant medications taken from Day 1 to Day 21. Diaries were collected at Visit 3 (Day 21 ± 3).

Blood was drawn from all subjects for a determination of HIA on Day 1 (prior to vaccination) and Day 21.

If subjects developed influenza like infection they had physical exam and throat and nasopharyngeal swab for viral identification.

Results

Primary efficacy endpoint

The primary efficacy endpoint was the number of subjects developing influenza infection with a virus that is antigenically similar to one of the vaccine strains, as confirmed by viral culture and typing of nasopharyngeal specimens, 21 to 180 days after vaccination. Due to low virus replication resulting in insufficient titres for testing (HI assay using ferret reference antisera), the number of samples for which antigenic similarity could be evaluated was very limited. Furthermore, of those specimens tested, only the A/H1N1 strain was consistently similar to the vaccine strain (the B strain was a lineage mismatch).

Therefore, statistical analysis of efficacy with regard to antigenically similar strains was stated to not be meaningful and was performed instead for the number of subjects developing influenza infection disregarding antigenic similarity to the vaccine strains.

Overall, 35 (2.0%) of vaccinated subjects in the ITT analysis set developed culture confirmed influenza infection (CCII) and compared with 62 (3.4%) who received placebo.

Antigenic similarity was determined in 8 (0.4%) vaccinated subjects (A/H1N1: 2 (0.1%), A/H3N2: 6 (0.6%), and B: 0 (0%), and 13 subjects (0.7%) subjects who received placebo (A/N1H1: 7 (0.4%) A/N3H2: 6 (0.3%) and B 0 (0%).

The strain was not antigenically similar in 12 (0.7%) vaccinated (0 [0.0%]) A/H1N1, 3 [0.2%] A/H3N2, and 9 [0.5%] B), and 14 (0.8%) placebo subjects (0 [0.0%] A/H1N1, 6 [0.3%] A/H3N2, and 8 [0.4%] B).

Due to low virus replication and thereby insufficient titre for HI testing, similarity was not assessable in 7 (0.4%) vaccinated and 15 (0.4%) placebo subjects, and typing was not done for 8 (0.4%) and 20 (1.1%) of vaccinated and placebo subjects, respectively.

Analysis by logistic regression showed an effect of the log HIA titre at Day 21 ($p < 0.001$, odds decreasing with HIA titres increasing), a borderline age effect ($p=0.011$, odds decreasing with age), and a borderline effect of gender (male versus female) ($p=0.026$,

with higher odds in females) on subjects developing influenza infection (as confirmed by RMix or TradCx) with the A/H3N2 strain, and an age effect for the B strain (p <0.001, odds increasing with age).

The overall VE rate (disregarding antigenic similarity) was 42.8% (95% CI: 14.1 to 61.9).

Cultures positive for influenza virus were then analysed by RT-PCR for strain and subtype identification:

- For the A/H1N1 strain, 3 (0.2%) vaccinated subjects were CCII positive versus 10 (0.6%) with placebo;

  VE for the A/H1N1 strain was 69.6% (95% CI: -2.3 to 91.0)

- A total of 20 (1.1%) vaccinated subjects had CCII with the A/H3N2 strain versus 41 (2.3%) with placebo;

  VE for the A/H3N2 strain was 50.5% (95% CI: 16.5 to 70.7)

- For the B strain, 12 (0.7%) vaccinated subjects were positive for CCII versus 11 (0.6%) with placebo;

  VE for the B strain was -10.6% (95% CI: -144.8 to 50.0)

CCII rates and VE for the PP analysis set (n = 1544 VCIV, n = 1579 placebo) were similar to the ITT analysis.

The influence of demographic factors on subjects developing CCII was analysed by logistic regression. A significant effect of vaccination group (VCIV versus placebo) (p=0.006, with higher odds in the placebo group) and race (White versus non White) (p<0.001, with higher odds in Whites) was observed. Age and gender did not appear to influence rates of CCII.

Co Primary endpoint: Consistency of immune response in 3 different lots of VCIV

Immune responses for each strain were consistent across the three lots, as shown by comparison of the ratios of geometric mean HIA titres (GMTs) at Day 21 between individual lots for the immunogenicity analysis set.

The GMTs were all entirely within range 0.67 and 1.5 (required to show equivalence).

The results are shown in Table 14.

Table 14: Geometric mean HIA titres at Day 21 between individual lots for the immunogenicity analysis set.

Comparison Lot 2 versus Lot 1	Ratio of GMTs	95% CI
A/H1N1	1.22	1.07 – 1.39
A/H3N2	0.94	0.83 - 1.07
B	0.88	0.78 – 0.99
Comparison Lot 3 versus Lot 1	**Ratio of GMTs**	**95% CI**
A/H1N1	1.10	0.96 – 1.25
A/H3N2	0.99	0.87 – 1.13
B	0.91	0.81 – 1.02
Comparison Lot 3 versus Lot 2	**Ratio of GMTs**	**95% CI**
A/H1N1	0.90	0.79 – 1.02
A/H3N2	1.05	0.93 – 1.20
B	1.04	0.92 – 1.17

Lot consistency analysis results were similar in PP dataset. When placebo was excluded (sensitivity analysis), there were no substantial differences in GMT ratios to those obtained including the placebo group.

Day 21 GMTs and geometric mean fold increases in HIA titre (from Baseline to Day 21) also demonstrated a consistent immune response across all 3 lots for the immunogenicity analysis set (that is, all subjects with available Day 21 serology).

Secondary endpoints

The secondary efficacy endpoint was the number of subjects developing influenza infection, as confirmed by viral culture and typing and/or RT PCR analysis of nasopharyngeal specimens, 21 days to 180 days after the date of vaccination.

The overall VE rate was 33.9% (95% CI 8.8 to 52.2) when influenza infection was determined by viral culture and or RT-PCR. 58 (3.2%) subjects who were vaccinated developed influenza infection as compared with 89 (4.9%) who received placebo.

- A/H1N1 strain – VE was 63.8% (95% CI 3.6 - 86.4)

  5 (0.3%) vaccinated subjects tested positive for influenza infection with viral culture and/or RT-PCR versus 14 (0.8%) with placebo

- A/H3N2 strain – VE was 36.2 (95% CI 2.8 – 58.1)

  34 (1.9%) vaccinated subjects tested positive for influenza infection with viral culture and/or RT-PCR versus 54 (3.0%) with placebo

- B strain – VE was 8.3% (95% CI -68.5 – 50.0)

  19 (1.1%) vaccinated subjects tested positive for influenza infection with viral culture and/or RT-PCR versus 21 (1.2%) with placebo

An additional analysis of VE by study week was conducted due to the reported antigenic drift that occurred in the circulating A/H3N2 strain during the 2007/2008 season (confirmed by CDC). The cumulative VE in the A/H3N2 strain by week was calculated in order to detect if VE could have been affected by an epidemiological change during the influenza season. After the first two weeks (Study Week 6 and 7), when only a few infections occurred, VE for the A/H3N2 strain increased rapidly (from 49.3 to 74.7%) and stayed approximately at this level for three weeks. After week 12 VE for A/H3N2 dropped to 54.2%, remaining around this level until the end of the study. The lower limit of the 95% CI of cumulative VE rapidly increased each week as the number of infection increased, to 26.8% at Week 11 and was considerably lower the following week (15.1%). For the A/H1N1 strain, the efficacy decreased somewhat until Week 11 but remained around 70%. After Week 11, concurrent with the observed drop in efficacy of the A/H3N2 strain, no further infections occurred with the A/H1N1 strain. It is noted that the initial VE with the A/H3N2 stain was very close to the VE observed with the A/N1H1 stain until the suspected antigenic drift occurred.

Sensitivity and specificity analysis were also performed to determine the optimal HIA titre cut off differentiating infected from non infected subjects for each strain. An additional analysis was conducted to investigate HIA titres ≥ 40 vs <40, and ≥ 80 and <80 as a correlate of risk for CCII.

Number (%) of subjects with infection who had an HIA titre ≥ 40 at Day 21:

- A/H1N1: 7/2555 (0.3%)
- A/H3N2: 35/2701 (1.3%)
- B: 9/1709 (0.5%)

Risk Ratio (≥ 40 versus <40):

- A/H1N1: 0.44 (95% CI 0.15 – 1.24)
- A/H3N2: 0.40 (95% CI: 0.25 – 0.66)
- B: 0.68 (95% CI: 0.30 – 1.53)

Number (%) of subjects with infection who had an HIA titre ≥ 80 at Day 21:

- A/H1N1: 4/2201 (0.2%)
- A/H3N2: 28/2436 (1.1%)
- B: 5/1228: (0.4%)

Risk Ratio (≥ 80 versus <80)

- A/H1N1: 0.26 (95% CI 0.09 – 0.81)
- A/H3N2: 0.37 (95% CI: 0.23 – 0.61)
- B: 0.52 (95% CI: 0.20 – 1.34)

The maximum value (% sensitivity + % specificity) for the A/H1N1 strain was obtained with a cut off titre of 80 (132.0%). For the A/H3N2 and B strains, a cut off titre of 160 corresponded to the highest sum (% sensitivity + % specificity): 127.5% for A/H3N2 and 114.8% for B.

Immunogenicity Endpoints

The secondary immunogenicity endpoints were HIA titre, fold increase of HIA titre, number of subjects with a seropositive titre (reciprocal HIA titre ≥ 40), and number of subjects demonstrating seroconversion (≥ 4 fold increase in HIA titre from baseline or a reciprocal HIA titre ≥ 40 when there is no detectable HIA titre [reciprocal HIA titre < 10] at baseline). These results are outlined in Table 15.

Table 15: Immunogenicity results from Study 720703.

	GMT	fold increase	Seroprotective Titre at Day 21 (%)	Seroconversion at Day 21 (%)
A/H1N1				
VCIV	385.8	10.48	92.8	69.2
Placebo	40.2	1.05	52.5	2.8
A/H3N2				
VCIV	514.0	10.78	97.1	71.7
Placebo	47.3	1.03	57.0	1.4
B				
VCIV	83.4	6.52	75.9	57.0
Placebo	13.3	1.03	21.8	1.2

Safety

A total of 1829 subjects received vaccination of VCIV and 1841 received placebo injection.

Serious adverse events (SAEs) occurred in 10 (0.5%) subjects with the VCIV and 14 (0.8%) with placebo.

Two SAEs were considered related to the VCIV (one severe case of hypersensitivity and one case of acute disseminated encephalomyelitis).

Systemic and local reactions

A total of 593/1829 (32.4%) subjects experienced non serious systemic reactions within 7 days after vaccination compared to 337/1841 (18.3%) who received placebo. Of those who received VCIV, 399 (21.8%) subjects experienced mild, 165 (9.0%) moderate and 29(1.6%) severe systemic reactions.

Systemic reactions were predominantly mild and transient.

Fever (related and unrelated) was reported in a total of 25 (1.4%) subjects who received VCIV – 6 (0.3%) mild, 12 (0.7%) moderate and 7 (0.4%) severe – compared to 10 (0.5%) who received placebo – 4 (0.2%) mild, 3 (0.2%) moderate and 3 (.2%) severe.

A total of 958 (52.4%) subjects who received VCIV experienced non-serious local reactions within 7 days after vaccination – 832 (45.5%) mild, 98 (5.4%) moderate, and 5 (0.3%) severe, compared to 246 (13.4%) subjects who received placebo – 229 (12.4%) mild, 6 (0.3%) moderate, and 0 subjects reported sever events.

During the entire follow up period (180 days) in the VCIV group, a total of 961 (52.2%) subjects experienced non serious local reactions – 834 (45.6%) mild, 99 (5.4%) moderate, and 5 (0.3%) severe, with 23 subjects with severity unknown – compared to 255 (13.9%) subjects who received placebo – 237 (12.9%) mild, 7 (0.4%) moderate, and 0 severe, with severity unknown in 11 subjects. These results are shown in Table 16.

Table 16: Relative risk: VCIV versus placebo.

	RR VCIV	95% CI
Of any local reactions within 7 days after vaccination	392.0%	346.5 to 444.2
Mild	365.7%	321.0 to 417.2
Moderate	1644.0%	739.4 to 3662.2)
Severe	0	
Of any local reactions during entire follow-up period	379.3	336.1 to 428.8
Mild	354.2	311.6 to 403.2
Moderate	1423.6	675.6 to 3004.8
Severe	0	
Of any systemic reaction within 7 days after vaccination	177.1	157.6 to 199.2
Mild	174.6	150.5 to 202.7
Moderate	167.8	132.0 to 213.3
Severe	364.9	10.5 to 781.8
Of any systemic reactions during entire follow-up period	158.9	142.8 to 177.0
Mild	162.8	141.1 to 188.0
Moderate	144.9	117.2 to 179.1
Severe	213.9	119.5 to 383.1

In the VCIV group, all severe local reactions were injection site pain. The most commonly reported specifically queried AEs are shown in Table 17.

Table 17: Summary of adverse events.

Adverse event	VCIV N=1829		Placebo N=1841	
	n	%	n	%
Tenderness	848	46.4	200	10.9
Injection site pain	598	32.7	140	7.6
Headache	327	17.9	223	12.1
Muscle pain	275	15.0	99	5.4
Fatigue	194	10.6	116	6.3
Malaise	137	7.5	75	4.1
Shivering	101	5.5	39	2.1
Joint pain	96	5.2	43	2.3
Swelling	61	3.3	15	0.8
Redness	57	3.1	17	0.9
Induration	29	1.6	3	0.2
Sweating	72	3.9	35	1.9
Vomiting	56	3.1	36	2.0
Fever within 7 days of vaccination	23	1.3	12	0.7
Fever with onset later than 7 days of vaccination	10	0.5	5	0.3

Systemic and local reactions were consistent between lots, as shown in Table 18.

Table 18: Number of subjects with non serious AEs related to vaccination during the entire follow up period by treatment group (Study 720703: Safety Analysis Set).

	Number (%) of Subjects				
	Lot 1	Lot 2	Lot 3	Total VCIV	Placebo
Reactions	**(N=609)**	**(N=608)**	**(N=612)**	**(N=1829)**	**(N=1841)**
Local	313 (51.1)	320 (52.6)	328 (53.9)	961 (52.5)	255 (13.9)
Systemic	204 (33.3)	210 (34.5)	216 (35.5)	630 (34.4)	399 (21.7)
a Planned follow-up period is of 180 days					

Conclusions

- It is noted that age range of study is 18-49 years rather than 18-59 as recommended by European and US guidelines
  - *The sponsor commented that the US age ranges are adults 18-64 and elderly: 65 and older, and the US recommendations for influenza vaccinations applying for age groups of 50 and older. This recommendations prevented inclusion of adults 50 years of age and older and elderly in a placebo controlled efficacy study conducted in the US.*
- Primary efficacy endpoint – Analysis of VE based on antigenically similar strains was not possible due to the high number of circulating strains that were antigenically mismatched with the vaccine strains or that could not be analysed for determination of antigenic match
- Overall VE (disregarding antigenic similarity was 42.8% (≥ 40 is required)
  - 69.6% for A/N1H1
  - 50.5% for A/H3N2
  - 8.3% for B – due to complete lineage mismatch (confirmed by CDC)
- The VCIV induced a significant immune response for all three strains
- Immune response and AEs were consistent across all 3 lots tested
- AEs were well tolerated and consistent with expected influenza vaccine

Serious related AE

1. Hypersensitivity

A 24 year old male subject received VCIV and on the same day was treated in the Emergency Room (ER) for an anaphylactic reaction: throat swelling, itching, mild trouble breathing, skin rash, redness of the conjunctiva, moderate trouble swallowing, and tachycardia. The subject was treated in the ER with steroid and antihistamine and was considered recovered when seen four days later. AE term later revised to allergic reaction.

2. Acute disseminated encephalomyelitis (ADEM)

A 32 year old African American male subject received VCIV and six weeks later developed symptoms including: injection site pain with tingling, burning, itching and numbness spreading down from this right lateral arm to antecubital region. Neurological examination suggested axillary nerve irritation as most likely secondary to the injection. Over the next few weeks, the subject developed increasing symptoms of numbness and tingling in right lateral deltoid, bicep, anterior forearm and thumb. Electromyography (EMG) revealed evidence of a mild right median nerve neuropathy at the wrist consistent with clinical diagnosis of carpal tunnel syndrome. Worsening symptoms over the next few months resulted in magnetic resonance imaging (MRI) that revealed multifocal areas of T2 prolongation throughout the brain, brain stem and corpus callosum with some mild atrophy in the posterior corpus, two small enhancing lesions within the brain, and right sided lesion at about C4-C5 (cervical spine); these observations were consistent with demyelinating process. Differential diagnosis was reported as ADEM versus multiple sclerosis. At time of reporting follow-up to AE in trial, ADEM was considered ongoing and unchanged. Three months later, the subject was diagnosed with multiple sclerosis.

Study 720801

Methods

Objectives

- To demonstrate the effectiveness on surrogate endpoints (seroprotection and seroconversion as measured by the HI assay) of an investigational VCIV in adults 50 years of age and older
- To describe the safety of an investigational VCIV in adults 50 years of age and older

Study design

This is a randomised, double blind, two arm, active controlled, Phase III clinical study conducted at 30 centres in the US. An approved EIV was used as the active comparator.

Subjects were stratified into two groups. Stratum A were subjects aged 50-64 years and Stratum B were subjects 65 years of age and older.

Study was originally designed with these Strata to meet the FDA requirements for elderly patients defined as 65 years of age and older. Once the study was completed, the data was reanalysed to meet EU Guidelines of 18-60 and >60 years.

Study participants

Study participants were healthy adults aged 50 years and older. No information is provided as to how subjects were recruited.

Inclusion criteria were:

- 50 years and older

- able to understand study and give informed consent
- if female and capable of bearing children, had a negative urine pregnancy test prior to vaccination and agreed to employ adequate birth control

Exclusion criteria included:

- no history of severe allergic reactions or anaphylaxis to egg protein or any other component of VCIV or EIV
- an oral temperature of ≥ 37.5°C on the day of vaccination
- presence of a rash or dermatological condition or tattoos which may interfere with injection site reaction rating
- receiving a blood transfusion or immunoglobulins within 90 days of study entry
- receiving a live vaccine within four days or inactivated vaccine or subunit vaccine within two weeks of study entry
- previous vaccination against influenza for the 2008/2009 northern hemisphere influenza season
- had a functional or surgical asplenia
- diagnosed immunodeficiency (pathological/pharmacological/radiotherapeutic)
- known or suspected drug use
- previous investigational drug within six weeks of study entry
- member of team conducting study or in dependent relationship with study investigator

Treatments

Study Drug: Split virus VCIV containing 15 µg HA of each of the three influenza strains, as recommended by the WHO and CDC for the 2008/2009 northern hemisphere season:

- A/H1N1/Brisbane/59/2007
- A/H3N2/Uruguay/716/2007 (A/Brisbane/10/2007-like)
- B/Florida/4/2006

Active comparator: Inactivated Influenza Vaccine Trivalent Types A and B (Split Virion) Fluzone 2008/2009 (EIV) manufactured by Sanofi-Pasteur, Inc. One dose of Fluzone contained 15 µg HA of each of the three influenza strains:

- A/H1N1/Brisbane/59/2007
- A/H3N2/Uruguay/716/2007 (A/Brisbane/10/2007-like)
- B/Florida/4/2006

Additionally, the FDA required the study participants allocated to the study drug to be offered an approved influenza vaccine after breaking the blind following the Day 21 visit.

The vaccine offered at Day 21 was Afluria (Inactivated Influenza Virus Vaccine Trivalent Types A and B (split virion); CSL Limited. One dose of Afluria contained 15 µg HA of each of the three influenza strains:

- A/H1N1/Brisbane/59/2007
- A/H3N2/Uruguay/716/2007 (A/Brisbane/10/2007-like)
- B/Florida/4/2006

All vaccines were administered at a dose of 0.5 mL by IM injection in the deltoid muscle.

Study duration

For each subject Part A of the study (double blind) was 21 days (± 3 days); Part B (open label follow up) was 159 days (± 14 days). Total study duration = ~180 days.

Outcomes/endpoints

Immunogenicity

Co primary endpoints

- The rate of subjects vaccinated with VCIV that demonstrate seroconversion via HI antibody titre at Day 21 after vaccination to each of the three antigens contained in the vaccine
- The rate of subjects vaccinated with VCIV that achieve a reciprocal HI antibody titre of 40 or higher 21 days after vaccination for each of the three antigens contained in the vaccine

Secondary Endpoints

- HI antibody titre for each of the three antigens contained in the vaccine at Day 21 after vaccination.
- Fold increases of HI antibody titre for each of the three antigens contained in the vaccine at Day 21 after vaccination as compared to baseline.

Safety

- Rate of subjects experiencing any injection site reactions and systemic reactions until the Day 21 visit after vaccination.
- Rate of subjects experiencing any systemic AEs during the entire 180 days follow up period regardless of assessed relationship to the vaccine.

Sample size

Immunogenicity

The planned recruitment was 3195 adults aged 50 years and older. Subjects were to be recruited in two groups:

- Stratum A = 1980 subjects aged 50-64 years
- Stratum B = 1215 subjects 65 and older

Sample size calculation for Stratum A was based on the assumption that the rate of seroconversion for the least immunogenic strain contained in the vaccine is at least 44%.

The null hypothesis was that the rate of seroconversion was less than 40%. A sample size of 1600 would provide at least 90% power to reject the null hypothesis. With an assumed dropout rate of approx 10%, 1760 subjects were planned to be vaccinated with VCIV in Stratum A. With 8:1 randomisation, total enrolment for Stratum A was 1980.

Sample size calculation for Stratum B was based on the assumption that the rate of seroconversion for the least immunogenic strain contained in the vaccine is at least 35%.

The null hypothesis was that the rate of seroconversion was less than 30%. A sample size of 960 would provide at least 91% power to reject the null hypothesis. With an assumed dropout rate of ~10%, 1080 subjects were planned to be vaccinated with VCIV in Stratum A. With 8:1 randomisation, total enrolment for Stratum A was 1215.

The type 1 error for the hypotheses tests is set at a 2.5% one sided level.

Safety

The sample size of 1760 subjects vaccinated with VCIV in Stratum A would enable detection with a probability of ~95% all AEs with an underlying incidence rate of at least 1:600.

The sample size of 1080 subjects vaccinated with VCIV in Stratum B would enable detection with a probability of ~83% all AEs with an underlying incidence rate of at least 1:600.

Randomisation

Subjects were randomised in a ratio of 8:1 to receive VCIV or EIV. Central randomisation was done via an Interactive Voice Response System and separate randomisation lists were provided for each stratum. Randomisation was carried out in blocks of >9 using a random number generator algorithm.

Blinding (masking)

The vaccines were provided in pre filled syringes, containing one single dose of 0.5 mL, pre labelled with a randomisation code. No attempt was made to repackage EIV into a syringe identical to the VCIV. To preserve the study blind, the person at the study site who performed the vaccinations was not to be involved in any study data collection activities.

The study blind was broken when the last subject completed Part A of the study (Day 21).

For subjects who received VCIV and accepted the offer to be vaccinated, this was done in an open label manner, with a US FDA approved influenza vaccine (Afluria) after Day 21.

Statistical methods

The primary analysis was performed on the ITT dataset and, as supportive evidence, on the PP dataset. The analysis was performed for each stratum and each strain contained in the vaccine separately.

Co primary endpoint 1

The two sided 95% exact CI of the proportion of subjects that achieve seroconversion 21 days after vaccination was calculated for both treatment groups.

Co primary endpoint 2

The two sided 95% exact CI of the proportion of subjects that achieve a reciprocal HI antibody titre of 40 or higher 21 days after vaccination was calculated for both treatment groups.

Secondary immunogenicity endpoints

Point estimates and 95% CI was calculated:

- HI antibody titre for each of the three antigens contained in the vaccine at Day 21 after vaccination

- Fold increases of HI antibody titre at Day 21 as compared to baseline. For the fold increase, the 95% CI of the geometric mean was calculated for both treatment groups, assuming a lognormal distribution

Safety

Safety analysis was performed on the safety analysis dataset which comprised all vaccinated subjects. The proportion and 95% exact CI was calculated for both treatment groups.

The proportion of subjects experiencing local reactions and systemic reactions in the two treatment groups were compared by likelihood ratio chi square test.

Recruitment

Subjects were healthy adults aged over 50 years recruited within planned timeframe. No details are provided as to how subjects were recruited.

Conduct of the study

Vaccinations were administered as single 0.5 mL dose per intramuscular injection of either VCIV or EIV by study staff not involved in data collection as vaccines were not in identical prefilled syringes. Vaccination occurred on Day 1.

Subjects were provided with subject diaries on Day 1 and collected on Day 21. Subjects recorded the following information:

- Measurement of body temperature orally, once every evening from vaccination day (Day 1) to Day 8
- Injection site reactions: injection site pain, redness, swelling, induration
- Systemic AEs: fever, malaise, shivering, fatigue, headache, sweating, muscle pain, joint pain
- Any medication taken from Day 1

A new subject diary was provided at Day 21 and collected at the end of the study (Day 180). This diary only collected information on AEs and concomitant medication.

Results

After study was completed, the data was re-analysed to provide support for EU submission.

The study was designed and conducted in US in line with FDA "Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines". This guidance sets age ranges to be included as: adults < 65 and adults ≥ 65 years of age.

The addendum to the study report reanalysed the data to meet the CPMP guideline that sets the age ranges as 18-59 years and ≥ 60 years.

In the reanalysis no explanation is provided as to the effect of this reanalysis on the statistical power of the study.

The results presented here are from the reanalysis as it relates to the CPMP guidance adopted in Australia (see Table 19).

Table 19: Number of subjects in different analysis sets (Study 720801: All Randomised Subjects).

Age Stratum	Analysis Set	VCIV	EIV	Total
50-59 years	Safety	1272	151	1423
	ITT	1248	143	1391
	PP	1203	136	1339
60+ years	Safety	1570	215	1785
	ITT	1548	212	1760
	PP	1479	205	1684

Safety = all vaccinated subjects
ITT = all randomised and vaccinated subjects with immunogenicity data available at baseline and day 21 for at least one strain
PP = all randomised and vaccinated subjects who fulfilled the inclusion/exclusion criteria, had no major protocol deviations and who completed Part A of the study and had immunogenicity data available at baseline and Day 21 for at least one strain

Immunogenicity Analysis

Co primary endpoint 1: Seroconversion

The rate of subjects vaccinated with VCIV that demonstrate seroconversion via HI antibody titre at Day 21 after vaccination to each of the three antigens contained in the vaccine (Table 20). The CPMP requirement is >40% for age <60 years and >30% for >60 years.

Table 20: Proportion of subjects demonstrating seroconversion at Day 21.

Stratum A (50-59 years) (Study 720801: Intent-to-Treat Analysis Set)						
	VCIV			**EIV**		
Strain	**n/N**	**%**	**95% CIa**	**n/N**	**%**	**95% CIa**
A/H1N1	631/1248	50.6	47.75 to 53.4	90/143	62.9	54.5 to 70.9
A/H3N2	875/1248	70.1	67.5 to 72.6	125/143	87.4	80.8 to 92.4
B	613/1248	49.1	46.3 to 51.9	88/143	61.5	53.0 to 69.5
a Clopper-Pearson exact CI						
Stratum B (60+ years) (Study 720801: Intent-to-Treat Analysis Set)						
	VCIV			**EIV**		
Strain	**n/N**	**%**	**95% CIa**	**n/N**	**%**	**95% CIa**
A/H1N1	576/1548	37.2	34.8 to 39.7	101/212	47.6	40.8 to 54.6
A/H3N2	926/1548	59.8	57.3 to 62.3	154/212	72.6	66.1 to 78.5
B	580/1548	37.5	35.0 to 39.9	120/212	56.6	59.6 to 63.4
a Clopper-Pearson exact CI						

PP dataset results were similar.

Co primary endpoint 1: Seroprotective HI assay

The rate of subjects vaccinated with VCIV that achieve a reciprocal HI antibody titre of 40 or higher 21 days after vaccination for each of the three antigens in the vaccine (Table 21). The CPMP requirement is >70% for age <60 years and >60% for >60 years.

Table 21: Proportion of subjects with seroprotective antibody titre.

Stratum A (50-59 years) (Study 720801: Intent-To-Treat Analysis Set)							
		VCIV			**EIV**		
Strain	**Day**	**n/N**	**%**	**95% CIa**	**n/N**	**%**	**95% CIa**
A/H1N1	1	376/1248	30.1	27.6 to 32.8	40/143	28.0	21.0 to 33.0
	21	960/1248	**76.9**	74.5 to 79.2	124/143	**86.7**	81.7 to 91.0
A/H3N2	1	508/1248	40.7	38.0 to 43.5	62/143	43.4	38.1 to 51.6
	21	1124/1248	**90.1**	88.3 to 91.7	136/143	**95.1**	92.4 to 98.1
B	1	580/1248	46.5	43.7 to 49.3	68/143	47.6	35.5 to 48.9
	21	1092/1248	**87.5**	85.5 to 89.3	137/143	**95.8**	89.6 to 96.5
a Clopper-Pearson exact CI							
Stratum B (60+ years) (Study 720801: Intent-To-Treat Analysis Set)							
		VCIV			**EIV**		
Strain	**Day**	**n/N**	**%**	**95% CIa**	**n/N**	**%**	**95% CIa**
A/H1N1	1	512/1548	33.1	30.7 to 35.5	68/212	32.1	25.8 to 38.8
	21	1100/1548	**71.1**	68.7 to 73.3	169/212	**79.7**	73.7 to 84.9
A/H3N2	1	856/1548	55.3	52.8 to 57.8	106/212	50.0	43.1 to 56.92
	21	1406/1548	**90.8**	89.3 to 92.2	204/212	**96.2**	92.7 to 98.4
B	1	734/1548	47.4	44.9 to 49.9	95/212	44.8	38.0 to 51.8
	21	1281/1548	**82.8**	80.8 to 84.6	197/212	**92.9**	88.6 to 96.0
a Clopper-Pearson exact CI							

Secondary immunogenicity endpoints

- HI antibody titre for each of the three antigens contained in the vaccine at Day 21 after vaccination.
  - CPMP requirement = at least 4 fold increase
- Fold increases of HI antibody titre for each of the three antigens contained in the vaccine at Day 21 after vaccination as compared to baseline.
  - CPMP requirement = >2.5 for age <60 years and >2.0 for >60 years.

These are illustrated in Table 22.

Table 22: Descriptive statistics of HIA titre values.

Stratum A (50 - 59 years) (Study 720801: ITT Analysis Set)							
Vaccine Group	**Strain**	**Day**	**N**	**GMT**	**95% CIa**	**GMT of Fold Increase from Baseline**	**95% CIa**
VCIV	A/H1N1	1	1248	17.6	16.4 to 18.8		
		21	1248	91.1	83.7 to 99.0	5.18	4.77 to 5.63
	A/H3N2	1	1248	23.3	21.5 to 25.3		
		21	1248	225.4	206.5 to 246.0	9.67	8.86 to 10.55
	B	1	1248	29.1	26.9 to 31.4		
		21	1248	133.6	124.3 to 143.6	4.59	4.25 to 4.97
EIV	A/H1N1	1	143	16.2	13.3 to 19.6		
		21	143	123.8	100.1 to 153.0	7.66	5.96 to 9.84
	A/H3N2	1	143	22.1	17.6 to 27.7		
		21	143	305.8	241.7to 387.1	13.86	11.10 to 17.29
	B	1	143	27.5	22.0 to 34.3		
		21	143	185.6	153.5 to 224.5	6.76	5.33 to 8.58
a CIs based on the t-distribution applied for log-transformed data (then back computed)							
Stratum B (60+ years) (Study 720801: ITT Analysis Set)							
Vaccine Group	**Strain**	**Day**	**N**	**GMT**	**95% CIa**	**GMT of Fold Increase from Baseline**	**95% CIa**
VCIV	A/H1N1	1	1548	19.0	17.9 to 20.1		
		21	1548	63.5	59.3 to 67.9	3.35	3.14 to 3.57
	A/H3N2	1	1548	37.0	34.4 to 39.8		
		21	1548	227.1	210.7 to 244.7	6.14	5.71 to 6.59
	B	1	1548	30.1	28.2 to 32.2		
		21	1548	96.3	90.3 to 102.7	3.20	3.00 to 3.40
EIV	A/H1N1	1	212	18.2	15.7 to 21.1		
		21	212	73.0	62.9 to 84.8	4.01	3.41 to 4.72
	A/H3N2	1	212	34.6	28.4 to 42.3		
		21	212	371.5	307.8to 448.4	10.73	8.62 to 13.34
	B	1	212	27.6	23.2 to 32.9		
		21	212	159.5	135.8 to 187.2	5.78	4.77 to 6.99
a CIs based on the t-distribution applied for log-transformed data (then back computed)							

Conclusions

All CPMP criteria for seroprotection, seroconversion and significant increase in GMT ratio are met.

Safety: Part A (Day 1 to Day 21)

Systemic Reactions

Overall there was a higher trend toward slightly higher systemic reaction rates after vaccination with VCIV compared to EIV in the younger adults (Stratum A) – 41.5% compared to 34.4% respectively and in Stratum B – 30.1% versus 23.7% respectively.

One subject had a SAE considered trial related. The subject, aged 50-59 yrs, had an allergic reaction one day after vaccination with VCIV and resolved within 5 days.

Local Reactions

Local reactions after vaccinations with VCIV or EIV occurred at a frequency of 37.1% or 31.8% respectively in Stratum A and 23.9% or 27.4% respectively in Stratum B.

The majority of injection site reactions were mild. The commonest reaction was injection site pain.

A list of the specifically queried AEs is shown in Table 23.

Table 23: Number (%) of subjects with specifically queried symptoms of non serious local and systemic reactions related to vaccination (Study 720801: Safety Analysis Set).

	Stratum A (50 - 59 years)				Stratum B (60+ years)			
Adverse Event	VCIV (N=1272)		EIV (N=151)		VCIV (N=1570)		EIV (N=215)	
	n	%	n	%	n	%	n	%
Swelling	50	3.9	3	2.0	67	4.3	5	2.3
Induration	34	2.	4	2.6	45	2.9	7	3.3
Redness	47	3.7	4	2.6	62	3.9	7	3.3
Injection Site Pain	437	34.4	47	31.1	307	19.6	52	24.2
Fever Within 7 Days After Vaccination	27	2.1	3	2.0	23	1.5	0	0
Fever Later Than 7 Days After Vaccination	3	0.2	1	0.7	4	0.3	0	0
Malaise	251	19.7	19	12.6	205	13.1	15	7.0
Shivering	118	9.3	7	4.6	103	6.6	4	1.9
Fatigue	251	19.7	20	13.2	190	12.1	20	9.3
Headache	232	18.2	24	15.9	157	10.0	15	7.0
Sweating	85	6.7	3	2.0	48	3.1	4	1.9
Muscle Pain	216	17.0	19	12.6	160	10.2	14	6.5
Arthralgia (Joint Pain)	106	8.3	9	6.0	71	4.5	6	2.8

Part B: Day 21 to Day 180

A separate analysis of the Part B safety was presented but the analysis is for the US age brackets and is complicated by the additional vaccination that was offered to the subjects who received the VCIV.

The rate of any systemic AE over the entire study period was similar between vaccine groups.

There were six deaths during the trial, all considered unrelated to the trial but one death was from unknown causes (five months after vaccination with VCIV).

There were 116 SAEs during the follow up period. Seven cases were classified as unlikely related by the investigators: myocardial infarction and atrial fibrillation, vertigo, orthostatic hypotension (VCIV only) and acute myocardial infarction, sick sinus syndrome, ileus, and angina pectorum and delirium (VCIV + EIV).

Study 720802

Methods

Primary objective

To demonstrate the efficacy of an investigational VCIV to prevent infection in an adult population with an influenza virus that is antigenically similar to one of the three strains in the vaccine.

Secondary objectives

- To compare the safety of an investigational VCIV with placebo
- To establish a correlation between the VCIV induced HIA and immunity to infection

Study design

This is a multicentre, randomised, placebo controlled, double blind Phase III clinical study conducted at 36 centres in the US between December 2008 and June 2009.

Study Participants

Healthy adults aged 18-49 years of age. No information is provided as to how subjects were recruited. Inclusion/exclusion criteria were similar to other studies.

Inclusion criteria:

- 18-49 years of age inclusive on day of screening
- Understand the study and procedures required and provide written informed consent
- Be accessible by telephone or email to receive reminders
- If female have negative urine pregnancy test within 24 hours of vaccination and agree to adequate birth control during trial

Exclusion criteria:

- Any risk factors for complications from influenza infection as defined by the US CDC (see Study 720703)
- Unable to lead independent life
- History of severe allergic reaction or anaphylaxis
- Oral temp of ≥ 37.5°C on the day of vaccination
- Rash or dermatological condition or tattoos which could interfere with injection site reaction rating
- Received a blood transfusion, blood products or immunoglobulins with 90 days of study entry
- Received a live vaccine within four weeks or inactivated or subunit vaccine within two weeks of study entry
- Received previous influenza vaccination for the 2008/2009 influenza season
- Functional or surgical asplenia
- Known or suspected drug abuse
- Received another investigational product within six weeks of study entry
- Member of team conducting study or in dependent relationship with investigator

Treatments

All subjects received a single 0.5 mL IM injection into the deltoid muscle of the trivalent seasonal VCIV containing either 15 µg of HA of the A/H1N1, A/H3N2 and B antigens designated for the 2008/2009 northern hemisphere influenza season or placebo.

Based on WHO and CDC recommendations for 2008/2009, the VCIV contained:

- A/H1N1/Brisbane/59/2007
- A/H3N2/Uruguay/716/2007 (A/Brisbane/10/2007-like)
- B/Florida/04/2006

The placebo consisted of phosphate buffered saline.

Study duration

Subjects were vaccinated on Day 1. Therefore the total duration of the trial was 180 days ± 14 days for each subject.

Outcomes/endpoints

Primary endpoints

The number of subjects developing influenza infection, as confirmed by viral culture and typing of nasopharyngeal specimens, with a virus that was antigenically similar to one of the strains contained in the vaccine in the period between Day 21 and the end of the study (May 2009).

Secondary endpoints

Efficacy

The number of subjects developing influenza infection, as confirmed by viral culture and typing of nasopharyngeal specimens regardless of whether the isolate is antigenically matched to one of the strains contained in the vaccine in the period between Day 21 and the end of the study (May 2009).

Immunogenicity

- HIA titre for each of the three antigens contained in the vaccine at Day 22
- Number of subjects with seroprotective antibody titre (reciprocal HIA titre ≥ 40) for each of the three antigens contained in the vaccine at Day 22
- Fold increase of HIA titre for each of the three antigens contained in the vaccine at Day 22 as compared to baseline
- Number of subjects demonstrating seroconversion to each of the three antigens contained in the vaccine at Day 22

Safety

- Frequency and severity of occurrence of any injection site reactions and systemic reactions related to vaccination
- Frequency and severity of occurrence of any injection site reactions and systemic AEs observed during the entire 180 day follow up period

Sample size

The sample size was calculated on the primary efficacy endpoint, with the following assumptions:

- Influenza infection rate of placebo recipients = 2.5%
- Vaccine efficacy for the three strains = 70%
- Randomisation ratio = 1:1

With these assumptions, the null hypothesis of VE <40% could be rejected with 90% power if 3360 subjects per treatment were evaluable. A dropout rate of 6% was assumed and so 7200 subjects were planned for enrolment.

A sample size of 3,600 subjects per group in the safety population enabled detection with a probability greater than 95% of all AEs with an underlying incidence rate of at least

1:1200. For an AE of 5% incidence in the placebo group, a relative risk increase of 1.3 in the vaccine group could be detected with a power of 78%.

Randomisation

Subjects were randomised in a ratio of 1:1 with VCIV or placebo on Day 1. Randomisation was performed centrally via an automated system. Randomisation was in blocks of >2 using a random number generator algorithm.

Blinding (masking)

The VCIV and placebo was packaged in pre filled syringes, labelled with a kit number and containing one single dose of 0.5 mL. To preserve the blinding, the person at the study site who performed the vaccinations was not to be involved in any study data or assessment activities. The blind was broken when all subjects had completed the Day 181 visit, the database was cleaned and locked and the antigenic similarity of all virus strains isolated during the study had been determined.

Statistical methods

Efficacy

The primary analysis was performed on the ITT dataset. The VE estimates and their 95% CI were calculated from the hazards ratios of the Cox regression.

Secondary analysis was done of the per protocol dataset (PP). In addition, the influence of demographic factors (age and gender) was analysed by Cox's proportional hazards regression.

Immunogenicity

Point estimates and 95% CI were calculated for HIA titres at Day 22 and GMTs (95% CI) of fold increases from baseline to Day 22 were calculated.

For proportion of subjects with seroprotective antibody titre and proportion of subjects demonstrating seroconversion the Clopper Pearson exact 95% CI of the estimates was calculated.

Safety

The relative risk (95% CI) between the VCIV and placebo groups was estimated for local and systemic reactions related to vaccination.

Point estimates and 95% CI were calculated for all safety endpoints.

Recruitment

No information was provided on how subjects were recruited.

Conduct of the study

All subjects were vaccinated on Day 1. Before leaving the site, the subjects were given a diary to record the following information:

- Oral temperature recorded every evening from vaccination on Day 1 to Day 8
- Any AEs during the 21 days following vaccination

Blood was drawn from all subjects for HIA determination on Day 1 and Day 22.

After Day 22, the subjects were instructed that should they develop symptoms of influenza infection – fever plus at least one of following – sore throat, cough, muscle ache, headache, fatigue, nausea or blood shot eyes or any two of preceding symptoms in absence of fever – they should contact the clinic for an unscheduled visit within 48 hours of onset of

symptoms. At clinic visit, throat and nasopharyngeal swabs for culture and typing were taken.

Subjects were contacted by clinic staff every 7-14 days until end of study to remind subjects to record AEs and check for evidence of influenza infection. Contact was by telephone or email.

At Day 181 all subjects were seen again at the clinic for collection of subject diaries, final evaluation and follow up of any AEs.

Results

Primary endpoint

The number of subjects with influenza cases was lower for the VCIV than for the placebo group and the VE estimates exceeded ≥ 40% overall and against all matching strains (Table 24).

Table 24: Vaccine efficacy estimates for culture confirmed influenza infections (R-Mix or TradCx) for matching strains (Study 720802: ITT Analysis Set).

Strain	Number (%) of Subjects with Influenza Cases		Vaccine Efficacy (%)	95% CIa
	VCIV	Placebo		
A/H1N1	11(0.3)	52(1.4)	79.0	59.7 to 89.0
A/H3N2	2(0.1)	4(0.1)	50.0	-173.0 to 90.8
All A Strains	13(0.4)	56(1.5)	77.0	57.9 to 87.4
B	0(0.0)	4(0.1)	100.0	4.1 to 100.0
Total	13(0.4)	60(1.7)	78.5	60.8 to 88.2
a CI estimated within the Cox regression framework				

Results for PP dataset were similar.

Testing for the effect of demographic factors found that age and gender did not seem to influence occurrence of influenza infection.

Secondary endpoint: Efficacy

Vaccine efficacy estimates are summarised in Table 25.

Table 25: Vaccine efficacy estimates for culture confirmed influenza infections (R-Mix or TradCx) for matching strains (Study 720802: ITT Analysis Set).

Strain	Number (%) of Subjects with Influenza Cases		Vaccine Efficacy (%)	95% CIa
	VCIV	Placebo		
A/H1N1	11(0.3)	52(1.4)	79.0	59.7 to 89.0
A/H3N2	2(0.1)	4(0.1)	50.0	-173.0 to 90.8
B	8(0.2)	18(0.5)	55.7	-1.9 to 80.7
Total	21(0.6)	74(2.0)	71.9	54.3 to 82.7
a CI estimated within the Cox regression framework				

Immunogenicity endpoints

HIA titre and fold increases are shown in Table 26. The CPMP requirement is for HIA titre – at least 4x increase, Fold increase: >2.5 for age <60yrs; >2.0 for age >60yrs.

Table 26: Descriptive statistics of HIA titre values (Study 720802: Immunogenicity Analysis Set).

Vaccine Group	Strain	Day	N	GMT	95% CIa	GMT of Fold Increase from Baseline	95% CIa
VCIV	A/H1N1	1	3473	17.5	16.7 to 18.2	-	-
		22	3473	194.1	184.4 to 204.3	11.11	10.52 to 11.74
	A/H3N2	1	3473	22.2	21.2 to 23.3	-	-
		22	3473	299.7	285.2 to 314.9	13.51	12.85 to 14.20
	B	1	3473	39.8	38.0 to 41.7	-	-
		22	3473	301.7	290.5 to 313.4	7.58	7.22 to 7.97
Placebo	A/H1N1	1	3459	16.7	16.0 to 17.4	-	-
		22	3459	17.7	17.0 to 18.4	1.06	1.04 to 1.08
	A/H3N2	1	3459	22.1	21.1 to 23.2	-	-
		22	3459	22.4	21.3 to 23.5	1.01	1.00 to 1.02
	B	1	3459	38.1	36.3 to 39.8	-	-
		22	3459	39.3	37.6 to 41.2	1.03	1.02 to 1.05
a CIs based on the t-distribution applied for log-transformed data (then back computed)							

The proportion of subjects with seroprotective antibody titre is shown in Table 27. The CPMP requirement is >70% for age <60yrs; >60% for age >60yrs.

Table 27: Proportion of subjects with seroprotective antibody titre: HIA titre >=40 (Study 720802: Immunogenicity Analysis Set).

		VCIV			Placebo		
Strain	Day	n/N	%	95% CIa	n/N	%	95% CIa
A/H1N1	1	1024/3473	29.5	28.0 to 31.0	954/3459	27.6	26.1 to 29.1
	22	3055/3473	88.0	86.8 to 89.0	1032/3459	29.8	28.3 to 31.4
A/H3N2	1	1368/3473	39.4	37.8 to 41.0	1332/3459	38.5	36.9 to 40.2
	22	3240/3473	93.3	92.4 to 94.1	1343/3459	38.8	37.2 to 40.5
B	1	1958/3473	56.4	54.7 to 58.0	1904/3459	55.0	53.4 to 56.7
	22	3373/3473	97.1	96.5 to 97.7	1943/3459	56.2	54.5 to 57.8
a Clopper-Pearson exact CI							

The proportion of subjects demonstrating seroconversion at Day 22 is shown in Table 28. The CPMP requirement is >40% for age <60yrs; >30% for age >60yrs.

Table 28: Proportion of subjects demonstrating seroconversion at Day 22 (Study 720802: Immunogenicity Analysis Set).

	VCIV			Placebo		
Strain	n/N	%	95% CIa	n/N	%	95% CIa
A/H1N1	2446/3473	70.4)	68.9 to 71.9	42/3459	1.2	0.9 to 1.6
A/H3N2	2746/3473	79.1	77.7 to 80.4	32/3459	0.9	0.6 to 1.3
B	2282/3473	65.7	64.1 to 67.3	45/3459	1.3	1.0 to 1.7
a Clopper-Pearson exact CI						

Additional analysis

Sensitivity and specificity analysis were preformed on the ITT analysis set to determine the optimal HIA titre cut off differentiating infected from non infected subjects for each strain with maximum values obtained with a reciprocal cut off HIA titre of 60 for the A/H1N1 (127.0%) and the A/H3N2 (138.7%) strains, and of 120 for the B strain (152.7%).

The risk ratio data indicated a substantial risk reduction for the vaccinated subjects developing an influenza infection with the A/N1H1 when they had achieved a reciprocal HIA titre of ≥15.

The risk ratio (≥15 versus ≤15) was 0.418 (95% CI 0.27 – 0680) for A/H1N1, 0.303 (95% CI 0.070 – 1.311 for A/H3N2, and 0.154 (95% CI 0.027 – 0.870) for B strain, showing a good separation of the infected from the non infected population at a cut off HIA titre of ≥15.

Analysis of Youden's index (sensitivity + specificity -1), which was calculated for the different reciprocal HIA titre cut off values, suggested that a reciprocal HIA titre of 15 may represent an appropriate correlate of protection. Obtaining reciprocal HIA titres of ≥30 demonstrated no further improvement.

Safety

Deaths – There were two deaths in VCIV group, both unrelated to the trial.

SAEs – There were 29 SAEs reported in the VCIV group of which none were considered trial related, and 27 reported in the placebo group of which only one "hypertensive crisis" was considered to be trial related.

Local and systemic reactions are shown in Table 29.

Table 29: Number (%) of subjects with specifically queried symptoms of local and systemic non serious reactions related to the vaccination (Study 720802: Safety Analysis Set).

Adverse Event	VCIV (N=3623)		Placebo (N=3620)	
	n	%	n	%
Swelling	100	2.8	10	0.3
Induration	125	3.5	14	0.4
Redness	114	3.1	27	0.7
Injection Site Pain	1567	43.3	274	7.6
Tenderness	5	0.1	0	0.0
Fever Within 7 Days After Vaccination	72	2.0	27	0.7
Fever Later Than 7 Days After Vaccination	9	0.2	11	0.3
Malaise	522	14.4	278	7.7
Shivering	225	6.2	104	2.9
Fatigue	635	17.5	430	11.9
Headache	646	17.8	487	13.5
Sweating	168	4.6	102	2.8
Muscle Pain	652	18.0	227	6.3
Arthralgia (Joint Pain)	224	6.2	110	3.0

Conclusions

- VE >40% was demonstrated against all matching strains
- Immunogenicity results indicated compliance with CPMP requirements for all strains

Study 720901

Methods

Primary objective

- To assess the immunogenicity to each of the three antigens contained in a trivalent seasonal influenza vaccine with strain composition according to WHO/CPMP recommendation for the 2009/2010 season in an adult and elderly population.

Secondary objective

- To assess the safety and tolerability of a trivalent seasonal influenza vaccine with strain composition according to WHO/CPMP recommendation for the 2009/2010 season in an adult and elderly population.

Study design

This is an open label, unrandomised, Phase III clinical study conducted in one single centre in Austria from June to July 2009.

Study participants

Subjects were healthy adults aged over 18 years of age who meet the following inclusion and exclusion criteria.

Inclusion criteria:

- Were generally healthy and aged 18 years or older at the time of screening
- Understood the study and could comply with all procedures and gave written informed consent
- If female of childbearing potential had a negative urine pregnancy test and agreed to employ adequate birth control measures for the duration of the study

Exclusion criteria:

- Had a history of severe allergic reaction or anaphylaxis
- Had an oral temp of ≥37.5^{o}C on the day of vaccination
- Had received a seasonal influenza vaccine within six months of study entry
- Had history of or current significant neurological, cardiovascular, pulmonary (including asthma), hepatic, metabolic, rheumatic, autoimmune, haematological or renal disorder at study entry
- Had any inherited or acquired immunodeficiency
- Previously had a disease or currently undergoing treatment within 30 days prior to study entry which could be expected to influence immune response.
- Had a functional or surgical asplenia
- Known or suspected drug abuse
- Member of team conducting study or in a dependent position to a study team member
- If female, pregnancy or lactating at time of study entry
- Had participated in any other clinical study involving investigational products within 30 days of study entry

Treatments

All subjects received inactivated split virus non adjuvanted seasonal influenza vaccine (VCIV). It contained formaldehyde and UV inactivated, split virions of influenza types/subtypes N/H1N1, A/N4H2 and B according to WHO/EU recommendations for the 2009/2010 northern hemisphere influenza season:

- A/H1N1/Brisbane/59/2007
- A/N3H2/Uruguay/716/2007
- B/Brisbane/60/2008

All subjects received one single injection of 0.5 mL vaccine dose (15 µg of each antigen) IM into the deltoid muscle.

Study duration

The study duration was approximately 21 days for each subject. The overall study ran for approximately four weeks.

Outcomes/endpoints

Primary endpoint

Number of subjects demonstrating seroconversion (defined as either a HIA titre of ≥40 in case of negative pre vaccination level (HIA titre <1:10) or a minimum fourfold antibody titre increase if the pre vaccination level is ≥1:10) to each of the three antigens contained in the vaccine 21 days after vaccination.

Secondary endpoints

- Number of subjects achieving an HIA titre of ≥1:40 for each of the three antigens contained in the vaccine 21 days after vaccination
- HIA titre for each of the three antigens contained in the vaccine 21 days after vaccination
- Fold increase of HIA for each of the three antigens contained in the vaccine 21 days after vaccination as compared to baseline

Safety

- Number of subjects with fever (≥38°C) for 24 hours or more or malaise or shivering with onset within seven days after vaccination
- Number of subjects with indurations larger than 50 mm in diameter and persisting for more than three days or ecchymosis with onset within days after vaccination
- Number of subjects with systemic reactions and injection site reactions observed until 21 days after vaccination
- Number of subjects with AEs observed until 21 days after vaccination

Sample size

Approximately 110 subjects were planned to be enrolled into the study and stratified into 2 age groups – Stratum A – aged 18-59 years and Stratum B – aged 60 years and older on day of screening.

A dropout rate of <10% was assumed so that at least 50 subjects would have evaluable immunogenicity results at end of study.

With this sample size, the exact two-sided 95% CI of the rate of subjects with antibody response associated with protection 21 days after vaccination does not extend more than 15% from the observed rate.

Randomisation

There was no randomisation as this was an open label, uncontrolled study.

Blinding (masking)

There was no blinding as this was an open label, uncontrolled study.

Statistical methods

Primary endpoint - seroconversion

The rate of subjects demonstrating seroconversion to each of the three antigens contained in the vaccine 21 days after vaccination and their exact 95% CIs were calculated by the Clopper-Pearson method, separately for each age stratum.

The analysis was performed on the ITT and the PP datasets.

Point estimates and exact 95% CIs were calculated for all secondary immunogenicity endpoints separately for each age stratum and for all safety endpoints.

Recruitment

No information is provided as to how subjects were recruited.

Conduct of the study

Study was conducted according to standards set out in European Directives and ICH-GCP.

Study procedures and visits are shown in participant flow chart.

Baseline data

- In Stratum A (18-59 years) there were 34 female and 21 males, with the majority (60%) in the 18-29 age group and both weight and height normally distributed.
- In Stratum B (60+ years) there were 31 female and 24 males, with the largest percentage in the 66-70 age group and both weight and height normally distributed.

Numbers analysed

All analysis was done on the ITT dataset – all patients vaccinated with baseline and post vaccination HIA titre measurements for at least one strain. The PP dataset contained all ITT subjects who fulfilled the inclusion and exclusion criteria and had no major protocol deviations. The safety dataset was all subjects who had been vaccinated.

For this study, the ITT and PP dataset was the same as the safety dataset (= 110).

Results

Primary endpoint – Seroconversion

Seroconversion after the vaccination is shown in Table 30.

Table 30: Number of seroconversion 21 days after the vaccination as compared to baseline as measured by HIA assay (Study 720901: ITT dataset).

	Stratum A (18-59 years)			Stratum B (60+ years)		
Strain	**n/N**	**%**	**95% C.I.**	**n/N**	**%**	**95% C.I.**
A/H1N1/Brisbane 59/2007	39/55	70.9	57.1; 82.4	20/55	36.4	23.8; 50.4
A/H3N2/Uruguay/716/2007	33/55	60.0	45.9; 73.0	26/55	47.3	33.7; 61.2
B/Brisbane/60/2008	35/55	63.6	49.6; 76.2	21/55	38.2	25.4; 52.3
'Seroconversion' is defined as either an HIA of ≥ 1:40 in case of a negative pre-vaccination sample [HIA titre < 1:10] or a minimum fourfold HIA titre increase if the pre-vaccination sample is positive [HIA titre ≥ 1:10] to each of the three antigens contained in the vaccine 21 days after vaccination.						

Secondary immunogenicity endpoints

Antibody responses associated with protection are shown in Table 31.

Table 31: Number of subjects with antibody response associated with protection (>=1:40) measured by HIA (Study 720901: ITT dataset).

		Stratum A (18-59 years)			Stratum B (>=60 years)		
Strain	Day	n/N	%	95% C.I.	n/N	%	95% C.I.
A/H1N1/Brisbane 59/2007	1	31/55	56.4	42.3 - 69.7	22/55	40.0	27.0 - 54.1
	21	52/55	**94.5**	84.9 - 98.9	47/55	**85.5**	73.3 - 93.5
A/H3N2/Uruguay/716/2007	1	48/55	87.3	75.5 - 94.7	52/55	94.5	84.9 - 98.9
	21	55/55	**100.0**	93.5 - 100.0	55/55	**100.0**	93.5 - 100.0
B/Brisbane/60/2008	1	18/55	32.7	20.7 - 46.7	15/55	27.3	16.1 - 41.0
	21	55/55	**100.0**	93.5 - 100.0	43/55	**78.2**	65.0 - 88.2

Geometric means of HIA titre are shown in Table 32.

Table 32: Geometric mean of HIA titre 21 days after the vaccination (Study 720901: ITT dataset).

		Stratum A (18-59 years)			Stratum B (60+ years)		
Strain	Day	N	GMT	95% C.I.	N	GMT	95% C.I.
A/H1N1/Brisbane 59/2007	1	55	40	26.7; 59.9	55	25.1	19.1; 32.9
	21	55	340.8	238.8; 486.4	55	101	74.8; 136.4
A/H3N2/Uruguay/716/2007	1	55	88.5	68.3; 114.6	55	97.9	76.9; 124.5
	21	55	358.4	281.4; 456.5	55	406.6	293.2; 563.8
B/Brisbane/60/2008	1	55	17.6	13.4; 23.2	55	15.5	11.9; 20.3
	21	55	144.7	113.4; 184.5	55	69.6	52.3; 92.8

Safety

There were no deaths or SAEs during this study (Table 33).

Table 33: Number of subjects with specifically queried symptoms of non serious injection site reactions and non serious systemic reactions related to the vaccination (Study 720901: Subjects included in the safety dataset).

		Stratum A (18-59 yrs)			Stratum B (≥ 60 yrs)		
Reported Term	Preferred Term	n/N	%	95% C.I.	n/N	%	95% C.I.
Swelling	Injection site swelling	1/55	1.8	0.0, 9.7	2/55	3.6	0.4%, 12.5%
Induration	Injection site induration	2/55	3.6	0.4, 12.5	3/55	5.5	1.1%, 15.1%
Redness	Injection site erythema	2/55	3.6	0.4, 12.5	4/55	7.3	2.0%, 17.6%
Injection Site Pain	Injection site pain	10/55	18.2	9.1, 30.9	6/55	10.9	4.1%, 22.2%
Tenderness	Injection site pain	23/55	41.8	28.7, 55.9	13/55	23.6	13.2%, 37.0%
Ecchymosis	Injection site haemorrhage	1/55	1.8	0.0, 9.7	2/55	3.6	0.4%, 12.5%
Malaise	Malaise	14/55	25.5	14.7, 39.0	13/55	23.6	13.2%, 37.0%
Shivering	Chills	10/55	18.2	9.1, 30.9	11/55	20.0	10.4%, 33.0%
Fatigue	Fatigue	15/55	27.3	16.1, 41.0	9/55	16.4	7.8%, 28.8%
Headache	Headache	19/55	34.5	22.2, 48.6	8/55	14.5	6.5%, 26.7%
Sweating	Hyperhidrosis	7/55	12.7	5.3, 24.5	10/55	18.2	9.1%, 30.9%
Muscle pain	Myalgia	9/55	16.4	7.8, 28.8	8/55	14.5	6.5%, 26.7%
Joint pain	Arthralgia	9/55	16.4	7.8, 28.8	5/55	9.1	3.0%, 20.0%
Fever with onset later than Day 7 after vaccination	Pyrexia	0/55	0.0	0.0, 6.5	0/55	0.0	0.0%, 6.5%

The VCIV demonstrated a higher incidence of fever rates occurring within 7 days and lasting less than 24 hours. Fever rates were 9.1% and 14.5% in adult and elderly subjects occurring within 7 days after vaccination with all but 1 subject with fever recovering within 24 hours. Systemic reactions occurred at rates of 52.7% and 43.6% in adult and elderly subjects and injection site reactions of 43.6% and 27.3%. These results are higher than seen in the larger studies and no explanation is provided in the study report or clinical summary.

Conclusion

- VCIV complies with CPMP guideline for all strains
- Increased systemic and local reactions were seen in both age groups without explanation.

Study 721001

There is only very brief information about this study with only a summary Study Report and no synopsis. Information is taken from summary report and study tabulation lists.

Methods

Objectives

- To assess the immunogenicity and safety of Preflucel, a Vero cell derived seasonal influenza vaccine in an adult (18-59 years) and elderly (60+ years) population. Preflucel contained the strains recommended for the 2010/2011 influenza season.

Study design

This was an open label, non randomised, uncontrolled, Phase III study conducted at a single centre in Austria from July to August 2010.

Study participants

Very little information is provided about the participants. They are stated to be healthy volunteers aged 18 years and over. No inclusion or exclusion criteria are provided.

Treatments

All subjects received a single injection into the deltoid muscle of 0.5 mL Preflucel – inactive influenza vaccine (split virus, Vero cell derived) containing 15 µg antigen of each of the three influenza strains:

- A/H1N1/California/07/2009
- A/H3N2/Victoria/210/2009 (an A/Perth/16/209 like virus)
- B/Brisbane/60/2008

Study duration

The study duration was approximately 21 days for each subject. Overall study ran for approximately four weeks.

Outcomes/endpoints

Primary endpoint

Number of subjects demonstrating seroconversion (defined as either a HIA titre of ≥40 in case of negative pre vaccination level (HIA titre <1:10) or a minimum fourfold antibody titre increase if the pre vaccination level is ≥1:10) to each of the three antigens contained in the vaccine 21 days after vaccination.

Secondary endpoints

- Number of subjects achieving an HIA titre of ≥1:40 for each of the three antigens contained in the vaccine 21 days after vaccination
- HIA titre for each of the three antigens contained in the vaccine 21 days after vaccination

- Fold increase of HIA for each of the three antigens contained in the vaccine 21 days after vaccination as compared to baseline

Safety

- Number of subjects with fever (≥38°C) for 24 hours or more or malaise or shivering with onset within 7 days after vaccination
- Number of subjects with indurations larger than 50 mm in diameter and persisting for more than three days or ecchymosis with onset within days after vaccination
- Number of subjects with systemic reactions and injection site reactions observed until 21 days after vaccination
- Number of subjects with AEs observed until 21 days after vaccination

Sample size

A total of 110 subjects were enrolled in two age strata of 18-59 and >60 years. It was assumed that the dropout rate would be less than 10%, and therefore at least 50 subjects in each age stratum would have evaluable immunogenicity results after vaccination. With this sample size, the exact two sided 95% CI of the rate of subjects with antibody response associated with protection 21 days after the vaccination does not extend more than 15% from the observed rate.

Randomisation

There was no randomisation as this was an open label, uncontrolled study.

Blinding (masking)

There was no blinding as this was an open label, uncontrolled study.

Statistical methods

No information is provided about the statistical methods but assume they are same as for Study 720901.

Recruitment

No information is provided as to how subjects were recruited

Conduct of the study

No information is provided on ethical standards of the Study. Study procedures and visits are shown in participant flow chart.

Baseline data

In Stratum A (18-59 years), there were 25 female and 30 males, mean age was 33.9 ± 10.6 years (range 21-59 years). 96.4% were White and 3.6% were Asian, mean weight 72.9 ± 12.2 Kg and mean height 173.0 ± 9.2 cm.

In Stratum B (60+ years), there were 29 female and 26 males; mean age was 54.0 ± 4.9 years (range 60-81 years). 100% were White, mean weight 80.9 ± 17.9 Kg and mean height 170.7 ± 7.6 cm.

Numbers analysed

The following datasets were used for the analysis.

- ITT dataset: all subjects vaccinated with baseline and post vaccination HIA titre measurements for at least one strain (n = 110).

- PP dataset: all ITT subjects who fulfilled the inclusion and exclusion criteria and had no major protocol deviations (n = 109).
- Immunogenicity dataset: all subjects vaccinated and had pre and post vaccination immunogenicity data available (n = 109).
- Safety dataset: all subjects who had been vaccinated (n = 110).

Results

Primary endpoint – Seroconversion

Seroconversion after the vaccination is shown in Table 34.

Table 34: Proportion of subjects demonstrating seroconversion at Day 22 (Study 721001: Immunogenicity dataset).

	Stratum A (18-59 years)			Stratum B (60+ years)		
Strain	**n/N**	**%**	**95% C.I.**	**n/N**	**%**	**95% C.I.**
A/H1N1/California	41/55	74.5	61.0; 85.3	36/54	66.7	52.5; 78.9
A/H3N2/Victoria	15/55	27.3	16.1; 41.0	16/54	29.6	18.0; 43.6
B/Brisbane	34/55	61.8	47.7; 74.6	16/54	29.6	18.0; 43.6
'Seroconversion' is defined as either an HIA of ≥ 1:40 in case of a negative pre-vaccination sample [HIA titre < 1:10] or a minimum fourfold HIA titre increase if the pre-vaccination sample is positive [HIA titre ≥ 1:10] to each of the three antigens contained in the vaccine 21 days after vaccination.						

Secondary immunogenicity endpoints

Subjects with seroprotective antibody titre and HIA values are shown in Tables 35 and 36.

Table 35: Proportion of subjects with seroprotective antibody titre - Reciprocal HIA titre ≥ 40 (Study 721001: Immunogenicity Analysis Set).

Stratum A (18-59 years)				
		Preflucel		
Strain	**Timepoint**	**n/N**	**%**	**95% CIa**
A/H1N1/California	Day 1	26 / 55	47.3	33.7; 61.2
	Day 22	50 / 55	90.9	80.0; 97.0
A/H3N2/Victoria	Day 1	51 / 55	92.7	82.4; 98.0
	Day 22	55 / 55	100.0	93.5; 100.)
B/Brisbane	Day 1	19 / 55	34.5	22.2; 48.6
	Day 22	53 / 55	96.4	87.5; 99.6
a Clopper-Pearson exact CI				
Stratum B (60+ years)				
		Preflucel		
Strain	**Timepoint**	**n/N**	**%**	**95% CIa**
A/H1N1/California	Day 1	17 / 54	31.5	19.5; 45.6
	Day 22	48 / 54	88.9	77.4; 95.8
A/H3N2/Victoria	Day 1	54 / 54	100.0	93.4; 100.0
	Day 22	54 / 54	100.0	93.4%; 100.0
B/Brisbane	Day 1	22 / 54	40.7	27.6; 55.0
	Day 22	42 / 54	77.8	64.4; 88.0
a Clopper-Pearson exact CI				

Table 36: Descriptive Statistics of HIA Titre Values, (Study 721001: Immunogenicity Analysis Set).

Stratum A (18-59 years)						
Strain	Timepoint	N	GMT	95% CIa	GM of Fold Increase from Baseline	95% CIa
A/H1N1/California	Day 1	55	24.5	17.2; 34.8		
	Day 22	55	209.8	149.4; 294.6	8.6	6.1; 12.1
A/H3N2/Victoria	Day 1	55	99.1	79.2; 124.1		
	Day 22	55	209.8	172.5; 255.1	2.1	1.8; 2.5
B/Brisbane	Day 1	55	18.8	13.3; 26.6		
	Day 22	55	99.1	80.1; 122.6	5.3	3.7; 7.6
a CIs based on the t-distribution applied for log-transformed data (then back-computed)						
Descriptive Statistics of HIA Titre Values, Stratum B (60+ years)						
Strain	Timepoint	N	GMT	95% CIa	GM of Fold Increase from Baseline	95% CIa
	Day 1	54	22.7	17.7; 29.2		
A/H1N1/California	Day 22	54	119.1	81.3; 174.4	5.2	3.8; 7.2
A/H3N2/Victoria	Day 1	54	135.4	113.6; 161.5		
	Day 22	54	315.9	243.2; 410.5	2.3	1.8; 3.0
B/Brisbane	Day 1	54	26.5	19.5; 36.0		
	Day 22	54	64.3	48.3; 85.6	2.4	1.8; 3.2
a CIs based on the t-distribution applied for log-transformed data (then back-computed)						

Safety

There were no deaths or SAEs during this study (Table 37).

Fever occurring within 24 hours after vaccination occurred in no subjects in Stratum A and in four subjects in Stratum B (7.3%, 95% CI 2.0 – 17.6). All fevers occurred within 24 hours after vaccination and resolved within 8 hours after onset.

Systemic reactions (systemic AEs classified as related to vaccination) occurred at rates of 25.5% (95% CI 14.7 to 39.0) in Stratum A and 20.0% (95% CI 10.4 to 33.0) in Stratum B.

Injection site reactions occurred less frequently in older subjects: 36.4% versus 23.6% in Stratum A and B respectively.

Table 37: Number (%) of subjects with specifically queried symptoms of local and systemic non serious reactions within 21 days (Study 721001: Safety Analysis Set).

	Stratum A (18-59 years) (N = 55)			Stratum B (60+ years) (N = 54)		
Adverse Event	n	%	95% CIa	n	%	95% CIa
Injection Site Swelling	1	1.8	0.0; 9.7	3	5.5	1.1; 15.1
Injection Site Induration	1	1.8	0.0; 9.7	1	1.8	0.0; 9.7
Injection Site Redness	1	1.8	0.0; 9.7	0	0.0	0.0; 6.5
Injection Site Pain	16	29.1	17.6; 42.9	8	14.5	6.5; 26.7
Fever Later Than 7 Days After Vaccination	0	0.0	0.0%; 6.5	0	0.0	0.0; 6.5
Malaise	4	7.3	2.0; 17.6	1	1.8	0.0; 9.7
Shivering	1	1.8	0.0; 9.7	1	1.8	0.0; 9.7
Fatigue	8	14.5	6.5; 26.7	5	9.1	3.0; 20.0
Headache	5	9.1	3.0; 20.0	5	9.1	3.0; 20.0
Sweating	4	7.3	2.0; 17.6	0	0.0	0.0; 6.5
Muscle Pain	5	9.1	3.0; 20.0	1	1.8	0.0; 9.7
Arthralgia (Joint Pain)	4	7.3	2.0; 17.6	1	1.8	0.0; 9.7
a Clopper-Pearson exact CI						

Clinical studies in special populations

No special populations were studied.

Analysis performed across trials (pooled analyses and meta analysis)

An overview of immunogenicity for Preflucel is shown in Table 38.

Table 38: Overview of immunogenicity Day 21 results Preflucel.

Study (Influenza season)	Age group (Years)	Number of subjects	Seroprotection rate A/H1N1 A/H3N2 B	Seroconversion rate A /H1N1 A/H3N2 B	GM fold increase A/H1N1 A/H3N2 B
CHMP Criteria for adults 18-60 years			>70%	>40%	>2.5
720601 (2006/2007)	18-59	484a	98.3% 99.8% 82.9%	79.9% 38.7% 66.9%	10.9 2.7 5.5
720801 (2007/2008)	50-59	1248	76.9% 90.1% 87.5%	50.6% 70.1% 49.1%	5.18 9.67 4.59
720703 (2007/2008)	18-49	1744	92.8% 97.1% 75.9%	69.2% 71.7% 57.0%	10.48 10.78 6.52
720802 (2008/2009)	18-49	3473	88.0% 93.3% 97.1%	70.4% 79.1% 65.7%	11.11 13.51 7.58
720901 (2009)	18-59	55	94.5% 100.0% 100.0%	70.9% 60.0% 63.6%	8.5 4.1 8.2
721001 (2010)	18-59	55	90.9% 100.0% 96.4%	74.5% 27.3% 61.8%	8.6 2.1 5.3
CHMP Criteria for adults >60 years			>60%	>30%	>2.0
720601 (2006/2007)	≥60	220b	95.9% 100.0% 71.8%	68.9% 47.9% 46.6%	6.4 3.2 3.8
720801 (2007/2008)	≥60	1548	71.1% 90.8% 82.8%	37.2% 59.8% 37.5%	3.35 6.14 3.20
720901 (2009)	≥60	55	85.5% 100.0% 78.2%	36.4% 47.3% 38.2%	4 4.2 4.5
721001 (2010)	≥60	54	88.9% 100.0% 77.8%	66.7% 29.6% 29.6%	5.2 2.3 2.4
A N=483 for GM fold increase and seroconversion measurements.					
B N=219 for GM fold increase and seroconversion measurements.					

Supportive studies

No supportive studies were submitted.

Evaluator's overall conclusions on clinical efficacy

A major concern with these studies is the age ranges stratified in the studies were 18-49 and >50 years. The company claim the rationale for this was the US CDC recommendation for influenza vaccination is for all adults >50 years. However, the US and CPMP guidelines clearly state that the required age ranges for proof of efficacy and safety should be 18-64 and >65 years for USA and 18-59 and >60 years for CPMP. In Study 720801, the company re-analysed the data to present results in the CPMP age stratifications. The lack of the appropriate age ranges makes the interpretation of the efficacy unnecessarily difficult.

Study 720601 demonstrated similar efficacy to an egg derived vaccine.

The company repeatedly claims compliance with the CPMP guideline without explanation for the different age ranges. However, only in the Clinical Overview does the company

present the immunogenicity data reanalysed for the CPMP age groups. This is shown in Table 38.

VCIV was immunogenic in all six clinical studies in adult and elderly subjects. CPMP criteria were met for all three strains in all six studies with the exception of the following:

- Seroconversion in adults aged 18-59 years in Study 720601 with a rate slightly below 40% for the H3N2 strain (38.7%), however >99% of subjects had an antibody titre ≥40 at baseline for this strain
- Seroconversion in adults aged 18-59 years in Study 721001 with a rate below 40% for the A/H3N2 strain (27.3%)
- GM fold increase in adults aged 18-59 years in Study 721001 with a fold increase below >2.5 for the A/H3N2 strain (2.1)
- Seroconversion in adults aged >60 years in Study 721001 with a rate below >40% for the B strain (29.6%)

The company only listed the first of these exceptions and makes no comment on the last three.

In the CPMP guideline it is not required to meet all three criteria of all strains so it is correct that the results meet the CPMP criteria.

Safety

Introduction

Overall, the Vero cell derived vaccine was well tolerated in the healthy adults enrolled in the studies. Two very large studies were conducted in adults aged 18 to 49 years and one study in > 50 year old adults. A total of 9222 received the VCIV. The safety profile of the VCIV was similar to the approved vaccines used as active comparators.

Patient exposure

With the exception of Study 720903, the overall exposure to Preflucel in completed clinical studies is shown in Table 39.

Table 39: Overall Exposure to Preflucel in Completed Clinical Studies.

Subject Age (years)	Influenza Season	Study#	Phase	Number of subjects vaccinated	
				VCIV	Control
≥18	2006-2007	720601	I/II	708	232(EIV)
18 to 49	2007-2008	720703	III	1829	1841 (placebo)
≥50	2007-2008	720801	III	2842	366 (EIV)
18 to 49	2008-2009	720802	III	3623	3620 (placebo)
≥18	2009-2010	720901	III	110	No control
≥18	2010-2011	721001	III	110	No control

Adverse events

In all the studies, the AE monitoring was similar. Local and systemic reactions expected for a vaccine were included in all studies and subjects kept diaries for the duration of the trials.

Two studies compared VCIV with approved egg derived vaccines (Studies 720601 and 720801). The AE profiles were similar for the two vaccines (Tables 40 and 41).

Table 40: Number (%) of subjects with specifically queried symptoms of local and systemic non serious reactions related to the vaccination in EIV controlled studies (18-59 years) (Studies 720601 and 720801).

Adverse Event	VCIV (N=1760)		EIV (N=312)	
	n (%)b	95% CIa	n (%)b	95% CIa
Swelling	69 (3.9)	3.1 to 4.9	10 (3.2)	1.5 to 5.8
Induration	53 (3.0)	2.3 to 3.9	15 (4.8)	2.7 to 7.8
Redness	65 (3.7)	2.9 to 4.7	10 (3.2)	1.5 to 5.8
Injection Site Pain	577 (32.8)	30.6 to 35.0	88 (28.2)	23.3 to 33.5
Fever Within 7 Days After Vaccination	35 (2.0)	1.4 to 2.8	4 (1.3)	0.4 to 3.2
Fever Later Than 7 Days After Vaccination	3 (0.2)	0.0 to 0.5	1 (0.3)	0.0 to 1.8
Malaise	283 (16.1)	14.4 to 17.9	28 (9.0)	6.0 to 12.7
Shivering	142 (8.1)	6.8 to 9.4	11 (3.5)	1.8 to 6.2
Fatigue	301 (17.1)	15.4 to 18.9	31 (9.9)	6.9 to 13.8
Headache	290 (16.5)	14.8 to 18.3	38 (12.2)	8.8 to 16.3
Sweating	103 (5.9)	4.8 to 7.1	5 (1.6)	0.5 to 3.7
Muscle Pain	243 (13.8)	12.2 to 15.5	27 (8.7)	5.8 to 12.3
Arthralgia (Joint Pain)	123 (7.0)	5.8 to 8.3	10 (3.2)	1.5 to 5.8
a Clopper-Pearson CI b For subjects vaccinated twice in study 720801 only symptoms occurred before the second blood draw are included				

Table 41: Number (%) of subjects with specifically queried symptoms of local and systemic non serious reactions related to the vaccination in EIV controlled studies (60+ years) (Studies 720601 and 720801).

Adverse Event	VCIV (N=1789)		EIV (N=287)	
	n (%)b	95% CIa	n (%)b	95% CIa
Swelling	73 (4.1)	3.2 to 5.1	13 (4.5)	2.4 to 7.6
Induration	50 (2.8)	2.1 to 3.7	8 (2.8)	1.2 to 5.4
Redness	65 (3.6)	2.8 to 4.6	10 (3.5)	1.7 to 6.3
Injection Site Pain	342 (19.1)	17.3 to 21.0	68 (23.7)	18.9 to 29.0
Fever Within 7 Days After Vaccination	30 (1.7)	1.1 to 2.4	0 (0.0)	0.0 to 1.3
Fever Later Than 7 Days After Vaccination	4 (0.2)	0.1 to 0.5	6 0 (0.0)	0.0 to 1.3
Malaise	218 (12.2)	10.7 to 13.8	16 (5.6)	3.2 to 8.9
Shivering	111 (6.2)	5.1 to 7.4	4 (1.4)	0.4 to 3.5
Fatigue	216 (12.1)	10.6 to 13.7	24 (8.4)	5.4 to 12.2
Headache	177 (9.9)	8.5 to 11.4	20 (7.0)	4.3 to 10.6
Sweating	60 (3.4)	2.6 to 4.3	7 (2.4)	1.0 to 5.0
Muscle Pain	169 (9.4)	8.1 to 10.9	16 (5.6)	3.2 to 8.9
Arthralgia (Joint Pain)	77 (4.3)	3.4 to 5.4	7 (2.4)	1.0 to 5.0
a Clopper-Pearson CI b For subjects vaccinated twice in study 720801 only symptoms occurred before the second blood draw are included				

Two studies compared VCIV with placebo (Studies 720703 and 720802). Both these studies were conducted in subjects aged 18-49 years of age. Summary of local and systemic non serious AEs are shown in Table 42.

Table 42: Number (%) of subjects with specifically queried symptoms of local and systemic non serious reactions related to the vaccination (18-59 years) (Studies 720703 and 720802).

Adverse Event	VCIV (N=5452)		Placebo (N=5461)	
	n (%)	95% CIa	n (%)	95% CIa
Swelling	161 (3.0)	2.5 to 3.4	25 (0.5)	0.3 to 0.7
Induration	154 (2.8)	2.4 to 3.3	17 (0.3)	0.2 to 0.5
Redness	171 (3.1)	2.7 to 3.6	44 (0.8)	0.6 to 1.1
Injection Site Pain	2166 (39.7)	38.4 to 41.0	413 (7.6)	6.9 to 8.3
Fever Within 7 Days After Vaccination	95 (1.7)	1.4 to 2.1	32 (0.6)	0.4 to 0.8
Fever Later Than 7 Days After Vaccination	19 (0.3)	0.2 to 0.5	23 (0.4)	0.3 to 0.6
Malaise	659 (12.1)	11.2 to 13.0	353 (6.5)	5.8 to 7.1
Shivering	326 (6.0)	5.4 to 6.6	143 (2.6)	2.2 to 3.1
Fatigue	827 (15.2)	14.2 to 16.1	548 (10.0)	9.3 to 10.9
Headache	972 (17.8)	16.8 to 18.9	711 (13.0)	12.1 to 13.9
Sweating	240 (4.4)	3.9 to 5.0	137 (2.5)	2.1 to 3.0
Muscle Pain	927 (17.0)	16.0 to 18.0	326 (6.0)	5.4 to 6.6
Arthralgia (Joint Pain)	320 (5.9)	5.3 to 6.5	153 (2.8)	2.4 to 3.3
a Clopper-Pearson CI				

Two studies (720901 and 721001) were conducted to assess immunogenicity and safety in adult and elderly populations using the vaccine strains relevant to the 2009/2010 and 2011 influenza seasons.

The higher level of systemic and local reactions seen in Study 720901 is not discussed in the individual study report or the clinical summary; however it is noted in the Risk Management Plan (RMP) and was thought by the company to be due to an effect of the manufacturing process. The company states that this is the reason for not proceeding with the paediatric clinical program. The company stated that as a result of this study the manufacturing process was changed to standardise the protein/Triton X-100 rate in order to better control the split rate in the relatively short timeframe following production of the monovalent bulk.

The RMP was written prior to Study 721001 being conducted. No comment on this change or the results is given the in the very brief study report or the clinical summary so it is unclear if this cause for the results in Study 72901 is justified.

Serious adverse events and deaths

Deaths

There were a total of 10 deaths in the six clinical studies conducted. All of these were judged by the investigator and the company to have been unrelated to the VCIV.

There was one stillbirth (Study 720703) and two spontaneous abortions (Study 720802) in subjects receiving VCIV and one induced abortion (Study 720802) due to drug exposure in a subject who received placebo. All were unclassified or considered unrelated to the trial product by the investigators.

Serious Adverse Events (SAEs)

SAEs occurred in 122 (1.4%) subjects in the pooled clinical trials. The only events classified as related to the VCIV were:

- One case of hypersensitivity occurring in Study 720703
- One case of disseminated encephalomyelitis, later confirmed as a case of multiple sclerosis in Study 720703. While the investigator judged the event to be unrelated to

the VCIV, the company classified it as possibly related due to the temporal association and lack of alternative aetiologies

- One case of severe hypersensitivity in Study 720801
- One case of hypertensive crisis in Study 720802 was classified as possibly related to VCIV

The Delegate notes that unrelated events were deleted – these are the SAEs classified as related to the VCIV.

A summary of all treatment emergent adverse events is shown in Table 43.

Table 43: Overall number of subjects with treatment emergent AEs (Studies 720601, 720703, 720801 and 720802).

	Number (%) of Subjects		
	(VCIV N=9001)	EIV (N=599)	Placebo (N=5461)
Deaths[a]	10 (0.1%)	0 (0.0%)	0 (0.0%)
Serious AEs[b]	122 (1.4%)	26 (4.3%)	41 (0.8%)
Treatment-related Non-Serious Systemic AEs	3121 (34.7%)	145 (24.2%)	1273 (23.3%)
Non-Serious Moderate or Severe Systemic AEs	2480 (27.6%)	191 (31.9%)	1422 (26.0%)
Any Non-Serious Systemic AEs	5377 (59.7%)	370 (61.8%)	3021 (55.3%)
Non-Serious Moderate or Severe Local AEs	356 (4.0%)	14 (2.3%)	15 (0.3%)
Any Non-Serious Local AEs	3633 (40.4%)	169 (28.2%)	565 (10.3%)
a 8 occurred within the follow-up period and 2 after the follow-up period b For study 720802, all SAEs reported before 12 August 2009 are included in this table			

The two open label studies (Studies 720901 and 721001) demonstrate consistent safety profiles to the comparative studies.

Laboratory findings

In only one study (Study 720601) was laboratory safety parameters measured. No comment is made in the study report about the laboratory parameters but review of tabulated lists of laboratory assessments does not demonstrate any consistent abnormalities or apparent differences between VCIV and EIV.

Safety in special populations

The company claim that as subjects with possible renal, hepatic or cardiac impairment could be recruited into Study 720801 and the results did not indicate any serious AEs, the product is thereby safe in these subjects. However, no laboratory safety parameters were done in this study and no analysis was done in these special populations. There can therefore be no confidence in the safety of the product in special populations.

Immunological events

One case of disseminated encephalomyelitis, later confirmed as a case of multiple sclerosis, occurred in Study 720703. While the investigator judged the event to be unrelated to the VCIV, the company classified it as possibly related due to the temporal association and lack of alternative aetiologies.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Post marketing experience

No post marketing information is provided by the company as they state that the product Preflucel is not marketed yet.

The sponsor has relied on efficacy data on vaccines which are identical to the proposed new product but differ only in the strain content of the vaccine. It would appear strange that they wish to rely on efficacy data but not on the safety data from these similar products.

At the very least it would seem appropriate to provide some post marketing experience with these products.

Delegate's comments: At submission of the dossier, no post marketing data were available. Following the Section 31 questions, the sponsor provided the first Periodic Safety Update Report (PSUR) report (29 September 2010 through 28 February 2011). The estimated number of subjects exposed to Preflucel amounted to 64,930. No safety signal was identified during the full reporting period. The positive benefit-risk balance of the product remained unchanged. Based on evaluation of the safety information in this PSUR, no change of the Reference Safety Information (RSI) of the product was recommended. No other post marketing data than that from the period covered by the PSUR is available for Preflucel.

Product Information (PI) with respect to safety

The PI appears to contain typical information on the safety aspects of the product.

Evaluator's overall conclusions on clinical safety

Preflucel appears to have a similar safety profile as other seasonal influenza vaccines.

Clinical Summary and Conclusions

Clinical aspects

Clinical efficacy

Main clinical studies

Six clinical studies were included in the submission. A comparison to a licensed egg derived vaccines demonstrated similar efficacy and safety. Two active comparator trials assessing efficacy in preventing influenza infection were hampered by low infection rates and very low antigenic similarity between isolated influenza virus and the strains contained in the VCIV. The trial conducted in the 2007/2008 northern hemisphere influenza season was also complicated by a major mismatch for the H3N2 and B strains from the strains contained in the VCIV.

Despite these problems, the sponsor has presented data from the six studies that indicate the product has similar efficacy to licensed influenza vaccines and the seroprotection and seroconversion criterion used, are in accordance with the CPMP guidelines and appear adequate.

Immune response and adverse events were consistent across all three lots tested.

Clinical studies in special populations

No data is presented on the use of the product in children. The product is not intended for use in children.

Data is presented in elderly populations (>60 years) with acceptable immunogenicity data.

No other special populations are included.

Clinical safety

Patient exposure

Over 9000 subjects were included in six clinical studies.

Adverse events

AEs appear similar to other approved seasonal influenza vaccines.

Serious adverse events and deaths

There were very few AEs considered related to the VCIV and no deaths considered related. The SAEs considered related were all allergy or hypersensitivity reactions, which are to be expected from a vaccine.

Laboratory findings

There were no abnormal laboratory findings of concern.

Safety in special populations

The only special population considered was the elderly and the vaccine appears to have acceptable safety profile.

Immunological events

One possible immunological SAE was seen in over 9000 patients.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Benefit risk assessment

Benefits

The benefit of the product is the benefit of an effective preventative vaccine against influenza. Annual vaccination against the best estimation of the season's dominant influenza strains has been shown to be an effective measure in protecting the general public against the possibility of epidemic influenza.

A particular benefit of VCIV is for individuals with hypersensitivity to egg and/or chicken proteins as the product does not contain either egg or chicken proteins.

Risks

The risks of the product relate to the possibility of adverse reactions. The most commonly reported AEs are generally mild or moderate in severity and usually resolved in a few days with minimal medical intervention. The most common AEs were injection site pain, transient induration, headache, fever, fatigue, malaise, shivering, muscle pain, joint pain and sweating.

The incidence of AEs appears similar to other approved seasonal influenza vaccines.

The incidence of severe anaphylaxis and hypersensitivity reactions were not investigated in the studies as subjects who may have been predisposed to such reactions were excluded from the trials.

Safety Specification

The RMP includes Studies 720903 and 720701 that were not included in the clinical studies in the submission. Study 721001, which is proposed in the RMP, was completed and included in the submission.

The pooled safety analysis therefore does not include Studies 72901 or 721001 (220 subjects).

Serious AEs are rare but can occur, for example, anaphylaxis and hypersensitivity reactions. Appropriate warnings should be included in the PI and CMI.

The safety profile observed in the clinical studies is consistent with the Safety Specification in the Risk Management Plan except as noted above.

Balance

Given the large subject populations included in the dossier the balance of risk versus benefit appears favourable to Preflucel.

Conclusions

It was considered that Preflucel meets the requirements for a seasonal influenza vaccine.

The safety profile was considered acceptable.

Based on the evaluation of the submitted clinical studies, the product was supported for inclusion in the Australian Register of Therapeutic Goods (ARTG).

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a RMP that was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor provided a summary of Ongoing Safety Concerns that are shown at Table 44.

Table 44: Important identified, potential risks and missing information for Preflucel.

Risks	Safety Concern
Important Identified Risks	
Hypersensitivity reactions, including anaphylaxis, to the active substances or to any of the excipients or residues	Development of unexpected immunopathology
Use of PREFLUCEL in patients with febrile illness or acute infection	Receiving PREFLUCEL while having febrile illness or acute infection may exacerbate a patient's current condition or lead to complications. Immunization should be postponed in these types of patients.
Important Potential Risks:	
Occurrence of neuritis, convulsion, encephalitis, vasculitis, Guillain-Barre syndrome Bell's (facial) palsy, demyelinating disorders	Development of unexpected pathology
Lack of effect and/or vaccination failure in special populations including immunocompromised patients, chronically ill patients or others with altered immune responses	Lack of protection against influenza virus
Important Missing Information	
Lack of pediatric data	Safety in infants and children
Lack of data on pregnant or lactating women	Safety in pregnant or lactating women
Lack of data on immunocompromised patients, chronically ill patients or others with altered immune responses	Safety in immunocompromised patients, patients with chronic diseases or others with altered immune responses

OPR reviewer comment:

The above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance Plan

The sponsor has proposed to undertake routine pharmacovigilance for each of the identified safety concerns. In the RMP evaluated, the sponsor had also proposed to undertake a number of clinical studies as additional pharmacovigilance activities for the important identified risk: 'hypersensitivity reactions' and the important missing information: 'lack of paediatric data'. The initially proposed studies in the RMP were Studies 720903, 721001, 720701 and a Phase I/II Double Blind Clinical Study of Effectiveness and Safety of VCIV in Infants, Children, and Adolescents aged 6 Months to 17 Years.

Subsequent information from the sponsor in response to the Section 31 request for information states that Studies 720903 and 721001 have been completed and that no paediatric studies are ongoing or have been finalised. Therefore, it would appear that none of the studies proposed in the RMP evaluated are still considered to be additional pharmacovigilance activities.

Instead, the sponsor stated (in response for a TGA request for information) that an updated Australian RMP is in process and it is anticipated that it will be submitted to the TGA on 30 August 2011. The summary of this RMP has been provided which lists the following pharmacovigilance activities for each safety concern (Table 45). It is noted that

the additional pharmacovigilance activities described below have been requested by the EU.

While in principle the above proposed activities appear to be acceptable, as no further information on the proposed activities has been provided it is difficult to make a final assessment of the proposed activities at this point in time.

It is anticipated that when the updated RMP is submitted it will contain more detailed information on the proposed activities, including the objectives and rationales for each action and further measures that may be taken based on the results of the proposed actions. Furthermore, it is expected that the updated RMP will provide a discussion of why 'ocular reactions' has now been included as an identified risk in the RMP. Upon receipt of the updated RMP, the OPR will make an assessment of the appropriateness of the proposed activities.

Furthermore, the advice from the Advisory Committee on the Safety of Medicines (ACSOM) stated that the committee expressed concern that one trial (Study 720901), which was discussed in the RMP safety specification, suggested a slightly greater reactogenicity (that is, increased immediate short term reactions to vaccines) in comparison with egg derived protein influenza vaccines. Based on this, ACSOM advised that a cautious approach be adopted to ensure appropriate post market surveillance of Preflucel and that in future updates from the sponsor about the status of the further hypersensitivity studies, information be sought to ascertain whether the higher incidence of fever was limited to the batch in Study 720901.

The advice received from ACSOM will be used when evaluating the updated RMP to determine if the proposed pharmacovigilance activities for hypersensitivity reactions are adequate to monitor this risk.

Table 45: Summary of updated RMP for Preflucel.[2]

Safety Concern	Proposed Pharmacovigilance Activities
Identified Risks	
Hypersensitivity reactions, including anaphylaxis, to the active substances or to any of the excipients or residues	Routine Pharmacovigilance • Expedited reporting of severe hypersensitivity and anaphylaxis reactions Additional Pharmacovigilance • Severe hypersensitivity and anaphylaxis reactions will be separately discussed and evaluated in the PSUR
Use of PREFLUCEL in patients with febrile illness or acute infection	Routine Pharmacovigilance
Ocular Reactions	Routine Pharmacovigilance Additional Pharmacovigilance • Ocular reactions will be separately discussed and evaluated in the PSUR
Potential Risks	
Vaccination Reactions including Immunologic Reactions / Disorders and / or AESIs (neuritis, convulsion, encephalitis, vasculitis, Guillain-Barre syndrome, Bell's (facial) palsy, demyelinating disorders)	Routine Pharmacovigilance Additional Pharmacovigilance • AESIs will be separately discussed and evaluated in the PSUR • Expedited reporting of events of special interest (AESI)
Lack of effect and/or vaccination failure, especially in special populations (including immunocompromised patients, chronically ill patients or others with altered immune responses)	Routine Pharmacovigilance • TBD Title – Effectiveness Study, in adults aged 50 years and older. Strain Composition 2011/2012 Additional Pharmacovigilance • An evaluation of lack of efficacy in immunocompromised patients will be provided in the PSUR • Closely monitor all AR reports of vaccination failure
Important Missing Information	
Lack of safety information in infants and children	Routine Pharmacovigilance
Lack of data on pregnant or lactating women	Routine Pharmacovigilance Additional Pharmacovigilance • All reports of PREFLUCEL exposure in pregnant and lactating women will be followed-up in the postmarketing setting and a cumulative presentation and discussion will be provided in the PSUR
Lack of data in immunocompromised patients, elderly, and special patient groups (subjects with renal, hepatic, or cardiac impairment)	Routine Pharmacovigilance Additional Pharmacovigilance • Efficacy for these patients will be separately discussed in Special Patient Groups in the PSUR

[2] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs; and
- Meeting other local regulatory agency requirements.

OPR reviewer comment:

Risk Minimisation Activities

As the sponsor is only proposing to undertake routine risk minimisation activities,[3] there was no risk minimisation plan.

OPR reviewer comment:

This was considered acceptable.

Potential for medication errors

The sponsor has stated:

> *The potential for medication error with the Preflucel is highly unlikely because a healthcare provider administers the vaccine as a single dose syringe.*

OPR reviewer comment:

This was considered acceptable.

Summary of Recommendations

The ability of the RMP evaluator to make recommendations to the Delegate has been impaired by the significant changes to the RMP in the sponsor's response and the corresponding lack of information provided to assess.

As part of the TGA request for information, the sponsor was requested to provide an update on the status of the proposed studies in the pharmacovigilance plan. The sponsor's response was that the proposed studies were no longer relevant and provided a table of the newly proposed pharmacovigilance plan. However, no further information was provided to allow an assessment of these activities. The sponsor stated that an updated RMP will be available by 30 August 2011.

At the time of this evaluation there was nothing to suggest that the newly proposed activities will not be suitable, however, they must first be evaluated by OPR before any recommendations regarding the RMP can be made.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data submitted in this application have been evaluated by the Office of Laboratories and Scientific Services (OLSS) in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

It is considered that there are no outstanding issues regarding the Manufacture and Quality Control Safety aspects of Preflucel vaccine which should delay registration. However, some outstanding details should form part of the conditions of registration and be provided as part of the Lot Release process for any Preflucel to be marketed in Australia (see *Quality Findings* on page 6 of this AusPAR).

[3] 'Routine risk minimisation' activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Nonclinical

The nonclinical evaluator considers that the immunogenicity was demonstrated in various animal models at doses (based on mg/m^2) lower than the recommended antigen dose in humans. However, there were no studies of immunogenicity in aged animals. Unlike their proposed use in humans, the doses in mice and guinea pigs were boosted at three weeks, and the antigens used in most studies were equivalent but not identical to those in the proposed product. The immunogenicity will therefore ultimately rely on clinical data. The evaluation concluded that apart from minor findings at the injection site, there were no toxicological findings that were likely to impact on the safety of Preflucel. The proposed Use in Pregnancy Category B1 was considered as appropriate based on negative findings in the submitted reproductive toxicity studies in rats.

There were no nonclinical objections to registration of Preflucel. Minor changes to the PI were proposed by the nonclinical evaluator.

Clinical

Six studies were submitted in the initial submission with one additional study (Study 720903) submitted with the sponsor's response. Due to the late submission, Study 720903 was not evaluated by the clinical evaluator, and this study is briefly discussed in this Overview.

The initial submitted six studies include two placebo controlled studies (pivotal studies: Study 720802 and Study 720703), two active controlled studies (Study 720601 and Study 720801), and two open labelled uncontrolled studies (Study 720901 and Study 721001). All studies are conducted according to acceptable GCP requirements. The same investigational vaccine formulation was used in these studies, but the viral strain compositions were different and were based on the WHO recommendation for the respective influenza season. In all six studies, the HI assay was used to measure antibody titres 21 days after vaccination. These studies were conducted in healthy adults over 18 years of age. These studies are briefly discussed below with the focus on the results of the primary endpoints.

Study 720802

Study 720802 was a multicentre, randomised, placebo controlled, double blind Phase III study conducted at 36 centres in the USA between December 2008 and June 2009. The primary objective was to evaluate the VE of an investigational VCIV to prevent infection with an influenza virus that is antigenically similar to one of the three strains in the vaccine. The study was conducted in healthy adults aged 18-49 years of age. The VCIV safety, immunogenicity, and the correlation between VE and HI antibody titre were assessed as secondary objectives.

The primary endpoint was defined as the number of subjects developing influenza infection, as confirmed by viral culture and typing of nasopharyngeal specimens, with a virus that is antigenically similar to one of the strains contained in the vaccine in the period between 21 days after vaccination in the study and 15 May 2009. Primary analysis was by the ITT set. First subject enrolled at 1 December 2008 and the last subject completed the study at 26 June 2009.

The immunogenicity endpoints, including seroprotection rate (SPR), seroconversion rate (SCR), geometric mean titre (GMTs), GMT fold increase (GMFI) were evaluated as secondary endpoints. These immune responses were measured for three antigens at Day

21. The EU CHMP (Committee for Medicinal and Products for Human Use)[4] and US FDA[5] have laid down the set of acceptance immunogenicity criteria (SCR, SPR, GMFI) to determine if a seasonal influenza vaccine is considered as 'effective'.

A total of 7250 healthy adults (18-49 years) were randomly assigned in a 1:1 ratio to one injection of either saline placebo or VCIV (which contains 15 µg of HA of the A/H1N1, A/H3N2 and B antigens designated for 2008/2009 northern hemisphere season) during the 2008-09 seasons. A total of 3623 subjects were vaccinated with VCIV and 3620 received placebo. The ITT dataset included 3619 subjects in the VCIV group and 3617 in placebo group. Primary analysis was performed on the ITT dataset. The overall protective VE for antigenically matched influenza infection was shown to be 78.5% (95% CI 60.8–88.2). The proportion of culture confirmed infections reported in the VCIV group was substantially lower than in the placebo group. The protective VE against culture confirmed influenza was 79% against strain A/H1N1, 50% against strain A/H3N2, and 100% against strain B. Protective efficacy for all influenza viruses, irrespective of the method of detection or antigenic match, was more than 70%. The null hypothesis (VE <40%) was thus rejected when the primary efficacy endpoint was considered. The vaccine efficacy remained consistent throughout the influenza season.

The immunogenicity analysis showed that the immune responses (SPR, SCR, GMFI) fulfilled the CHMP criteria defined for the assessment of vaccine effectiveness.[2] In terms of the correlation between VE and HI antibody titre, analysis showed that an HI titre of at least 1:15 appears to provide a reliable correlate of cell culture derived influenza vaccine induced protection; no additional benefit was noted with titres greater than 1:30. Analysis of Youden's index (sensitivity + specificity -1), which was calculated for the different reciprocal antibody titre cut off values, suggested that a reciprocal HI titre of 15 may represent an appropriate correlate of protection.

AEs were mainly mild and transient. Generally, non serious local AEs were reported more often by the VCIV group (45.0%) than by the placebo group (8.6%). As of 12 August 2009, treatment emergent SAEs were reported by similar numbers of subjects who received VCIV (0.8%) and those who received placebo (0.7%). One SAE, 'hypertensive crisis' was assessed as possibly related, but the subject was injected with placebo. All other SAEs were considered unlikely or not related to the vaccination. Two deaths occurred in the VCIV group but were considered as not related to vaccination.

Study 720703

Study 720703 was a randomised, multicentre, placebo controlled, double blind, Phase III study conducted at 35 centres in the USA between November 2007 and June 2008. The subjects were healthy adults aged 18 to 49 years of age. The co primary endpoints were defined as:

1. The number of subjects developing influenza infection with a virus that is antigenically similar to one of the vaccine strains, as confirmed by viral culture and typing of nasopharyngeal specimens, 21 days to 180 days after the date of vaccination; and

[4] European Medicines Agency, "Note for Guidance on Harmonisation of Requirements for Influenza Vaccines", March 1997, Web, accessed 29 May 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf>.

[5] US Food and Drug Administration, "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines", May 2007, Web, accessed 29 May 2012 <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091985.pdf>.

2. The consistency of immune response produced by three different lots of VCIV.

The secondary immunogenicity endpoints include SPR, SCR GMT and GMFIs at Day 21.

For the co primary endpoint 1, the two sided 95% CI of the VE was determined by first calculating the two sided 95% CI of the risk ratio of the VCIV group to the placebo group. The null hypothesis of VE < 40% against the alternative hypothesis VE ≥40% was tested at a 5% two sided significance level. For the co primary endpoint 2, consistency between the lots was concluded if the two sided 95% CI for the ratio of GMTs is contained in the range of [0.67, 1.5] for all three pair wise comparisons and for all strains.

A total of 3670 subjects were randomised, with 3609 included in the efficacy analysis (1792 received VCIV and 1817 received placebo). Due to low virus replication resulting in insufficient titres for testing, the number of samples for which antigenic similarity could be evaluated was very limited: antigenic similarity was not assessable in 7 VCIV vaccinated subjects (0.4%) and 15 placebo subjects (0.4%), and typing were not done for 8 subjects in VCIV group (0.4%) and 20 subjects in placebo group (1.1%). Furthermore, of those specimens tested, only the A/H1N1 strain was consistently similar to the vaccine strain (the B strain was a lineage mismatch). Therefore, statistical analysis of VE with regard to antigenically similar strains was not considered as meaningful. Instead, the number of subjects developing influenza infection was analysed disregarding antigenic similarity to the vaccine strains.

Overall, 35 of vaccinated subjects in the ITT analysis set (2.0%) developed CCII and compared with 62 who received placebo (3.4%). Disregarding antigenic similarity, the overall VE was 42.8% (95% CI: 14.1 to 61.9). The VEs for the A/H1N1 strain was 69.6% (95% CI: -2.3 to 91.0), for the A/H3N2 strain was 50.5% (95% CI: 16.5 to 70.7), and for the B strain was -10.6% (95% CI: -144.8 to 50.0). VE ≥ 40% was not shown for the B strain due to a lineage mismatch between the vaccine strain and circulating strains in the US during 2007/2008 season.

Immune responses for each strain were consistent across the three different lots of VCIV, as shown by comparison of the ratios of GMTs at Day 21 between individual lots for the immunogenicity analysis set. The GMTs were all entirely within range 0.67 and 1.5 which was required to show equivalence. The results of SCRs, SPRs, GMFIs at Day 21 fulfilled the CHMP criteria for all three antigens. An additional VE analysis by study week was also presented which confirmed antigenic drift during that season.

Safety analysis included 1829 subjects in VCIV group and 1841 subjects in placebo group. A total of 52.4% subjects in the VCIV group had non serious local reaction compared to 13.3% in the placebo group. In the VCIV group, all severe local reactions were injection site pain. Systemic reactions were predominantly mild and transient. There was one unrelated death (head trauma) and one unrelated stillbirth. SAEs occurred in 10 (0.5%) subjects in the VCIV group and 14 subjects (0.8%) in the placebo group. Two SAEs occurred in two subjects in VCIV group were considered as vaccine related: hypersensitivity in a 24 year old male subject and an ADEM in a 32 year old African American male. Adverse reactions in subjects vaccinated with VCIV appear to be consistent with the AEs expected for seasonal influenza vaccine.

Study 720601

Study 720601 was a Phase I/II, single blind, randomised, active controlled study. The study compared the safety and immunogenicity of the investigational VCIV with a licensed EIV, Vaxigrip by Sanofi Pasteur MSD 2006/2007, in healthy subjects in two age strata: 18 to 49 and >50 years of age. The study was conducted during the northern hemisphere 2006/2007 influenza season.

The primary endpoint was the number of subjects with oral temperatures ≥38°C and onset within two days after vaccination. The immunogenicity endpoints, including SPR, SCR, GMTs, GMFI, were evaluated as secondary endpoints. These immune responses were measured for three antigens and at both the Day 21 and Day 180 post vaccination.

A total of 1077 subjects enrolled with 940 subjects vaccinated (Full Analysis Dataset = 940) There were 303 subjects in Stratum A (18-49 years) and 637 in Stratum B (≥ 50 years). The ITT dataset (n = 940) included randomized and vaccinated subjects with available data for the respective analysis. The PP dataset (n = 939) included all randomised and vaccinated subjects who met the inclusion/exclusion criteria, had no major protocol violations and for whom data for the respective analysis were available.

There was a very low overall rate of fever with onset within two days after vaccination with VCIV (1.4%), and no fever cases were reported in the group received EIV. No significant difference was shown between the two groups by analysis in the ITT and the PP dataset. The sensitivity analysis, by which subjects in the ITT dataset without body temperature assessments were considered fever cases, also showed no significant difference between the vaccines regarding the primary endpoint.

With regards to the immunogenicity endpoints (SPR, SCR, and GMFI), the reanalysis based on CHMP age strata showed that immune responses to VCIV have met CHMP criteria except the SCR in 18-59 age group for H3N2 strain which was slightly below 40% (38.7%). The Day 180 results provided some evidence with regards to persistence of the immune response.

Safety appears to be similar between VCIV and EIV, as there were no significant differences in rates of local and systemic reactions between the two vaccine groups in either age stratum. No deaths occurred in this study. There were a total of 34 SAEs that were all considered as unrelated to the study product.

Study 720801

Study 720801 was a randomised, double blind, active controlled Phase III study conducted in 30 centres in the USA. The study compared the immunogenicity and safety of the investigational VCIV to a licensed EIV (Fluzone® 2008/2009) in adults aged 50 years and older during the northern hemisphere 2008/2009 influenza season.

The investigational vaccine is the split virus VCIV containing 15 µg HA of each of the three influenza strains, as recommended by the WHO and CDC for the 2008/2009 northern hemisphere season. The active comparator is Fluzone 2008/2009, the EIV manufactured by Sanofi-Pasteur, Inc. One dose of Fluzone contained 15 µg HA of the same three influenza strains as that contained in the investigational VCIV, which are the three influenza strains recommended by the WHO and CDC for the 2008/2009 northern hemisphere season.

This study consisted of Part A and Part B. Part A began when the first subject consented to participate and ended when the last subject completed the Day 21 visit. Part B began after the first subject completed the Day 21 visit and ended when the last subjects completed the Day 180 visit. Part B included an administration of one 0.5 mL of Afluria 2008/2009 (an EIV by CSL Limited). Part B assessed safety only.

SCRs and SPRs at Day 21 were evaluated as co primary endpoints while GMTs and GMFIs were assessed as secondary immunogenicity endpoints. A total of 3210 subjects were randomised in 8:1 ratio to receive either VCIV or EIV. A total of 2842 subjects received VCIV and 366 received EIV. The primary analysis was performed on ITT dataset. Subjects were stratified into two age groups: 50-64 and >65 years (based on FDA requirements). After study completion, data was reanalysed according to the age range defined in the CHMP guideline (18-59 years and > 60 years). The reanalysis showed that vaccination

with 2008/2009 strains of VCIV induced strong immune responses and the immunogenicity assessments (SPR, SCR and GMFI by HI assay) against three viral antigens fulfilled the criteria laid down in the CHMP guideline.

In Part A of the study (Day 0 to Day 21), local reactions after vaccinations with VCIV or EIV occurred at a frequency of 37.1% or 31.8% respectively in Stratum A and 23.9% or 27.4% respectively in Stratum B. The majority of injection site reactions were mild. The commonest reaction was injection site pain. There was a trend toward slightly higher rates of systemic reaction after vaccination with VCIV than with EIV in both age groups (Stratum A: 41.5% versus 34.4% and Stratum B: 30.1% versus 23.7%). One subject had a SAE considered trial related. This was a subject (aged 50-59 yrs) who had an allergic reaction one day after vaccination with VCIV and the reaction resolved within five days. There was one death in Study Part A and six deaths in Study Part B, all were considered as unrelated to vaccination.

Study 720901

Study 720901 was an open label, non randomised, Phase III study conducted in one single centre in Austria from June to July 2009. The primary objective was to assess the immunogenicity to each of the three antigens contained in the VCIV. The strain composition is according to WHO/CPMP recommendation for the northern hemisphere 2009/2010 season. The study was conducted in an adult and elderly population.

The primary endpoint was SCR and secondary endpoints included SPR, GMT, and GMFI.

All immune responses were measured at Day 21 after vaccination. A total of 110 subjects were enrolled in the study with 55 in the 18-59 age group and 55 in ≥ 60 age group. The number of the subjects in the ITT, PP, and safety dataset were the same (n = 110). The immunogenicity analysis showed that SCR, SPR, and GMFI at 21 days following VCIV vaccination met the CHMP criteria for all three strains.

There were no deaths or SAEs during this study. Systemic reactions occurred at rates of 52.7% and 43.6% in adult and elderly subjects. There was a higher incidence of fever occurring within seven days after vaccination (9.1% and 14.5% in adult and elderly subjects). All fever cases, except one subject, recovered within 24 hours. The injection site reactions occurred at 43.6% and 27.3% in adult and elderly subjects. The rates of systemic and local reactions in this study are higher than that seen in other studies, and these higher rates were thought to be due to an effect of the manufacturing process.

The company stated that as a result of this study the manufacturing process was changed to standardise the protein/Triton X-100 rate in order to better control the split rate in the relatively short timeframe following production of the monovalent bulk.

Study 721001

Study 721001 was an open label, non randomised, uncontrolled Phase III study conducted at a single centre in Austria from July to August 2010. The study vaccine (Preflucel) contained the viral strains recommended for the Australian 2010/2011 influenza season. The study assessed the immunogenicity and safety of Preflucel (a VCIV) in an adult (18-59 years) and elderly (60+ years) population. The primary endpoint was SCR at Day 21 and the secondary endpoints included SPR and GMT at Day 21. A total of 110 healthy adults enrolled in the study with equal numbers for the age group of 18-59 (n = 55) and ≥ 60 (n = 55). With three antigens, three measures of immune responses (SPR, SCR, and GMFI), and two age groups (18-59 and ≥ 60), there were a total of 18 immunogenicity measures to be assessed against CHMP criteria. The results showed that all the CHMP criteria, except the following, have been met:

- SCR in adults aged 18-59 years was below 40% for A/H3N2 strain (27.3%)

- SCR in adults aged >60 years was below 40% for B strain (29.6%)
- GMFI in adults aged 18-59 years was below 2.5 for A/H3N2 strain (2.1)

The immunogenicity criteria laid down in CHMP guideline for a strain change[6] were fulfilled because the guideline only require that at least one of the assessments (SCR, SPR or GMFI) met or exceeded the indicated criterion per each strain.

Safety analysis showed that injection site reactions occurred less frequently in older subjects (36.4% in Stratum A versus 23.6% in Stratum B). Systemic reactions related to vaccination occurred at rates of 25.5% (95% CI 14.7 to 39.0) in Stratum A and 20.0% (95% CI 10.4 to 33.0) in Stratum B. Fever occurring within 24 hours after vaccination occurred in no subjects in Stratum A and in four subjects in Stratum B (7.3%, 95% CI 2.0 – 17.6). All fevers occurred within 24 hours after vaccination and resolved within 8 hours after onset. There were no deaths or SAEs during this study.

Study 720903

Study 720903 was submitted late in the evaluation process and is briefly mentioned here. It is an open label study conducted in healthy adults aged 18 to 59 years. The study assessed the safety and immunogenicity of a VCIV (with strain composition 2009/2010) and the impact of age of the MVB and impact of the protein/Triton X-100 ratio which has not previously been standardised. A total of 211 subjects received one of two lots of the VCIV:

- Cohort 1 (n = 110): subjects were vaccinated with a VCIV lot manufactured according to the standard process using a fixed Triton-X-100 concentration during the splitting process, with an MVB age of 42-44 weeks (all three strains);
- Cohort 2 (n = 101): subjects were vaccinated with a VCIV lot manufactured using a standardized protein to Triton X-100 ratio during splitting of the A/H3N2 and B strains; the MVB age was 8 weeks for the A/H3N2 and B strains, and 55 weeks for A/H1N1.

The primary endpoints were the number of subjects with fever, malaise or shivering with onset within seven days after vaccination and the number of subjects with injection site indurations ≥ 50 mm and persisting for more than three days or ecchymosis with onset within seven days after vaccination.

SCR, SPR, GMT, GMFI were assessed as secondary endpoints.

The safety analysis showed that there were fewer systemic adverse reactions associated with the lot used in Cohort 1 than with the lot used in Cohort 2. The proportion of subjects with fever, malaise or shivering with onset within seven days after vaccination (primary safety endpoint) was 11.8% in Cohort 1 versus 25.7% in Cohort 2. Fever with onset within 24 hours after vaccination and lasting 24 hours or less occurred in 1.8% of subjects in Cohort 1 and 9.9% in Cohort 2. All fevers in Cohort 1 were mild. In Cohort 2, fever was rated mild (five subjects) and moderate (five subjects). There was no fever related to vaccination that started later than seven days after vaccination. Malaise was reported in 4.5% of subjects in Cohort 1 and in 18.8% of subjects in Cohort 2. Shivering was reported in 5.5% of subjects in Cohort 1 and in 11.9% of subjects in Cohort 2. Indurations >50 mm in diameter with onset within seven days after vaccination and persisting for more than

[6] European Medicines Agency, "Note for Guidance on Harmonisation of Requirements for Influenza Vaccines", March 1997, Web, accessed 29 May 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf>.

three days, or ecchymosis with onset within seven days after vaccination were reported by three subjects in Cohort 1 (2.7%) and 2 subjects in Cohort 2 (2.0%).

The immunogenicity analysis showed that both lots of the VCIV were immunogenic and the immune responses (SPR, SCR, GMT, and GMFI at Day 21) fulfilled the FDA and CHMP immunogenicity criteria for all three strains in both cohorts. The immune response was comparable between Cohort 1 and 2.

These results suggest that ageing of the MVB can favourably influence the reactogenicity profile of the product. The older product (MVBs manufactured 42-44 weeks, Cohort 1) resulted in a safety profile comparable to that observed in previous large studies (N>9,000) with the Baxter's VCIV. When younger B and A/H3N2 MVBs (eight weeks of age) were included in the vaccine (Cohort 2), standardisation of the ratio protein:Triton-X during the splitting process did not lead to improvement in the reactogenicity profile. Immunogenicity appeared unaffected by either vaccine age (Cohort 1) or the newly defined standardisation of protein/Triton-X 100 ratio (Cohort 2).

Overall, the study concluded that the reactogenicity of the VCIV was improved with increasing age of the MVBs, but was not similarly influenced by standardisation of the protein to Triton X ratio during the splitting process.

Risk Management Plan

The submitted RMP version 5 (28 April 2010) was evaluated. The sponsor's summary of the Ongoing Safety Concerns was considered acceptable by the RMP evaluator. The sponsor proposed to undertake routine pharmacovigilance for each of the identified safety concerns, and to undertake a number of clinical studies as additional pharmacovigilance activities.

As part of a TGA request for information, the sponsor was requested to provide an update on the status of the proposed studies in the pharmacovigilance plan. In the sponsor's response, it was stated that that the proposed studies were no longer relevant. A table of the newly proposed pharmacovigilance plan was provided with no detailed information to allow an assessment of these activities. The sponsor stated that an updated RMP will be available by the end of August 2011.

The RMP evaluator has noted the concerns expressed by the ACSOM with regards to the higher reactogenicity of the VCIV in Study 720901. Based on this, the committee advised that a cautious approach be adopted to ensure appropriate post market surveillance. The RMP evaluator would take this into account when evaluating the updated RMP.

The Delegate agreed with the RMP evaluator that the updated RMP would need to be evaluated before any recommendations can be made. The Delegate intended to recommend registration approval of Preflucel based on the evaluated RMP version with the updated RMP listing as one of the post approval commitments. The sponsor was required to follow up with any recommendations that OPR may make after the evaluation of the updated RMP.

Risk-Benefit Analysis

Delegate Considerations

The submitted six clinical trials were conducted over five influenza seasons, and these trials studied more than 9000 adults with greater than 1700 subjects in the ≥ 60 years age group. The efficacy of the investigational vaccine (Preflucel) was shown to be 78.5% in the season of 2008/2009 in the pivotal study (Study 720802). In the 2007/2008 season, which was determined to have been a mismatch year for the recommended H3N2 and B strains due to antigenic shift, the vaccine efficacy was shown to be 42.8% (Study 720703).

The assessment of immunogenicity in the six studies showed that the immune responses of VICV against various influenza viral strains (over different influenza seasons) satisfied the immunogenicity criteria laid down by the CHMP guideline. Preflucel has also demonstrated to have an acceptable safety profile in these studies, and the safety profile appears to be similar to that of licensed egg derived influenza vaccines. The higher rates of systemic and local reactions with Preflucel observed in Study 720901 will require further investigation although manufacture changes were made to improve reactogenicity profile, and these reactions will need to be closely monitored during the post marketing surveillance.

It was acknowledged that there was uncertainty as to the value of using HI assay to measure the immunogenicity of Vero cell derived vaccine. The protective efficacy of Preflucel and the correlation between HI titers and vaccine efficacy demonstrated in Study 720802 has provided some assurance.

No paediatric studies were conducted and the product is not intended for use in children. Lack of data in special populations, such as immunocompromised subjects, pregnant and lactating women, have been identified in the RMP, and relevant information are included in the PI.

The sponsor (Baxter) indicated that they have no plan to undertake a clinical study in Australia if strains change for the southern hemisphere 2012 influenza vaccine. They justify this plan by stating that Preflucel has been shown to be safe and efficacious independent of strain composition in the submitted clinical trials, and these clinical trials have evaluated 11 different strains in 7 clinical studies over 5 influenza seasons in more than 9000 adults. Baxter intends to closely monitor spontaneous AEs where the vaccine is marketed to ensure the safe use of the vaccine. The delegate considers this justification acceptable.

The sponsor was asked to incorporate all recommendations from quality, toxicology, RMP, and clinical evaluation areas.

With regard to the proposed indication, it was recommended to amend the statements to the followings:

> "*For the prevention of seasonal influenza cause by Influenza Virus Type A and B in adults and elderly.*
>
> *The use of Preflucel should be based on official recommendations."*

It was recommended that more detailed description of the trial information should be included, such as the study design, primary efficacy endpoints.

Under "Interaction with other medicines", it is recommended to include the following statement:

> "*No data are available on the concomitant administration of Preflucel with other vaccines."*

Based on the evaluated data on quality, safety and efficacy, the Delegate considers that the risk-benefit balance of Preflucel for the prevention of seasonal influenza in adults and elderly is favourable, and therefore recommended the granting of the marketing authorization of Preflucel for the prevention of seasonal influenza cause by Influenza Virus Type A and B in adults and elderly. The use of Preflucel should be based on official recommendations.

Prior to the approval, the PI should be amended to the satisfaction of the TGA.

Conditions of registration include:

- Satisfying the requirements listed under the heading "Quality" (on page 68 of this AusPAR);
- Submission of the reports of ongoing studies; and
- Submission of the update RMP and satisfying the RMP requirements as evaluated by the OPR.

The advice of the Advisory Committee on Prescription Medicines (ACPM) is requested for this application, specifically with regards to the acceptability of the sponsor's justification for not conducting a clinical trial in Australia if strains change for the southern hemisphere 2012 influenza vaccine.

Response from Sponsor

Introduction

Baxter accepted the Delegate's recommendation to revise the wording of the indication as follows:

> *For the prevention of seasonal influenza caused by influenza virus type A and B in adults and elderly. The use of Preflucel should be based on official recommendations.*

Baxter agreed with the Delegate's proposal to include outstanding quality items as conditions of approval. However, as agreed with the quality evaluator, Baxter will clarify some of these concerns directly with the evaluator and hence will not discuss further in this pre ACPM response.

Baxter wished to discuss the following two points:

1. Higher reactogenicity observed in Study 720901
2. Reanalysis by EU age strata in Study 720801

1. Reactogenicity

The Delegate commented that:

> *'The RMP evaluator has noted the concerns expressed by the ACSOM with regards to the higher reactogenicity of the VCIV in Study 720901'.*

Baxter concurred with the Delegate's intention to recommend registration of Preflucel based on the evaluated updated RMP version which discusses the higher reactogenicity observed in the above mentioned clinical study.

An updated RMP was attached to the sponsor's response. The updated RMP included safety measures to ensure adequate post marketing surveillance for the expedited reporting of severe hypersensitivity and anaphylaxis reactions. The events will be summarised and discussed in the PSURs that will be submitted to TGA in accordance with the standard conditions of approval. In addition, the following cautionary wording is already included in the PI document (refer to Precautions section of the PI):

> *As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.*

Moreover, 64,930 doses of Preflucel were distributed during the 2010/2011 influenza season in Austria and Czech Republic after initial licensure. During the reporting period for the first PSUR (29 September 2010 through 28 February 2011), no safety signal was identified. The positive benefit-risk balance of the product remained unchanged.

Based on the evaluation of the safety information in this PSUR, no change of the RSI of the product was recommended in the EU.

In conclusion, Baxter will closely monitor post marketing vaccinations, with the actions of routine pharmacovigilance detailed in the RMP and the separate discussion and evaluation in the forthcoming PSURs.

2. Reanalysis by EU age strata in Study 720801

Study 720801 was conducted in the US and, in line with FDA guidelines,[7] data were analysed according to the following age strata:

- 50 to 64 years of age
- 65 years of age and older.

The addendum to the Clinical Study Report (CSR) for Part A of Study 720801 includes an additional analysis of primary and secondary immunogenicity and safety endpoints according to the following age strata in accordance with the EU guidelines:[8]

- 50 to 59 years of age
- 60 years of age and older.

In this addendum to the Clinical Safety Report for Study 720801 (Part A), subjects aged 50-59 are defined as Stratum A, and subjects aged 60 years and over as Stratum B.

The clinical evaluator commented that the reanalysis of clinical Study 720801 (efficacy study on seroprotection and seroconversion surrogate endpoints) provided in the addendum does not explain the effect of the reanalysis on the statistical power of the study.

Indeed, there was no power estimation for the reanalysis by EU age strata. The reason for this is that the criteria in the EU guidelines are formulated in terms of point estimates and there are no conditions for the lower limits of CIs.

From a efficacy point of view, reassigning subjects to EU age strata results in a small increase in the point estimates of the seroconversion rates (due to the fact that the seroconversion rate in the subgroup of subjects with age at baseline between 60 and 64 years is expected to be lower than for subjects in EU stratum A, and higher than for subjects in US Stratum B). Therefore, the power of the comparison against the threshold values prescribed by the guidelines is also slightly higher in case of the EU age stratification.

From a safety standpoint, the sample size of 1272 subjects in the study group immunised with Preflucel in EU Stratum A (safety population) enables detection, with a probability of approximately 88%, of all AEs with an underlying incidence rate of at least 1:600. The sample size of 1570 subjects in the study group immunised with Preflucel in EU Stratum B enables detection with a probability of approximately 93%, of all AEs with an underlying incidence rate of at least 1:600.

[7] US Food and Drug Administration, "Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines", May 2007, Web, accessed 29 May 2012 <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091985.pdf>.

[8] European Medicines Agency, "Note for Guidance on Harmonisation of Requirements for Influenza Vaccines", March 1997, Web, accessed 29 May 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf>.

In conclusion, the additional analyses of immunogenicity of Part A of Study 720801 confirm the strong immunogenicity of Preflucel in adults and elderly subjects, when stratified according to EU guidelines. All CHMP criteria for seroprotection, seroconversion and GMT ratio for all strains were met (all 18 of 18 CHMP criteria).

Note that Preflucel has been approved in 14 European countries. During the European evaluation, there were no major concerns raised with regards to the reanalysis performed in accordance to the age strata specified in the EU guidelines.

Conclusion

Baxter concurred with the Delegate's overall comments, in particular with the recommendation to include the following as conditions of registration:

- Satisfactory response to the six quality outstanding details listed in the Delegate's overview; and
- Updated RMP which discusses the higher reactogenicity observed in clinical study 720901.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

Six trials were evaluated which incorporated an immunological endpoint. The studies were conducted in accordance with the TGA adopted EU guidelines and over five influenza seasons in more than 9000 adults. Satisfactory efficacy and immunogenicity of the vaccine was demonstrated.

It was accepted by the committee that for a seasonal influenza vaccine the strains for each year were set by the World Health Organisation and that at least some of these change each year. As the submitted studies have assessed 11 different strains, and included at least one pertinent strain, H1N1/09, it was not thought to be essential to study the strains specifically recommended for the year that the vaccine is to be used.

Safety

There were no particular safety signals of concern noted. The committee noted that this was a Vero cell based vaccine rather than egg based which should reduce the number of egg related adverse events. However, the rate of local systemic adverse events in general appeared slightly higher with vero cell derived vaccine than the egg based vaccine comparator in some of the submitted studies. A small number of serious adverse events were also reported, including allergy and acute disseminated encephalomyelitis. It was also noted that there were no interaction studies with other vaccines submitted. Extensive post market monitoring should be carried out.

The Delegate's restatement of the indication to conform to other vaccines was supported.

Specific conditions of registration which may be considered include:

- the implementation of the latest version of the Australian specific RMP
- resolution of any outstanding pharmaceutical issues

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of safety and efficacy submitted in the application package for influenza vaccine (split virion,

inactivated, prepared in vero cell cultures) 2011 season (Preflucel) would support the safe and effective use of this product.

Outcome

On 15 May 2012, Baxter Healthcare Pty Ltd wrote to the TGA, asking for the application for Preflucel to be withdrawn before a decision was made.

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Reference/Publication #