Table 31: Specifically queried symptoms of local and systemic reactions (other than malaise and shivering) related to the 1st vaccination (full analysis dataset)

Reported Term	Preferred Term	Age group	
		18-59 yrs	≥60 yrs
		n/N (%) 95% C.I.	n/N (%) 95% C.I.
Swelling	Injection site swelling	2/281 (0.7%) (0.1% ; 2.5%)	4/280 (1.4%) (0.4% ; 3.6%)
Induration	Injection site induration	6/281 (2.1%) (0.8% ; 4.6%)	5/280 (1.8%) (0.6% ; 4.1%)
Redness	Injection site erythema	1/281 (0.4%) (0.0% ; 2.0%)	2/280 (0.7%) (0.1% ; 2.6%)
Injection Site Pain	Injection site pain	44/281 (15.7%) (11.6% ; 20.4%)	16/280 (5.7%) (3.3% ; 9.1%)
Ecchymosis	Injection site hemorrhage	4/281 (1.4%) (0.4% ; 3.6%)	0/280 (0.0%) (0.0% ; 1.3%)
Fatigue	Fatigue	23/281 (8.2%) (5.3% ; 12.0%)	21/280 (7.5%) (4.7% ; 11.2%)
Headache	Headache	27/281 (9.6%) (6.4% ; 13.7%)	27/280 (9.6%) (6.5% ; 13.7%)
Sweating	Hyperhidrosis	12/281 (4.3%) (2.2% ; 7.3%)	14/280 (5.0%) (2.8% ; 8.2%)
Muscle pain	Myalgia	11/281 (3.9%) (2.0% ; 6.9%)	9/280 (3.2%) (1.5% ; 6.0%)
Joint pain	Arthralgia	4/281 (1.4%) (0.4% ; 3.6%)	14/280 (5.0%) (2.8% ; 8.2%)
Fever with onset later than Day 7 after vaccination	Pyrexia	0/281 (0.0%) (0.0% ; 1.3%)	0/280 (0.0%) (0.0% ; 1.3%)

Table 32: Specifically queried symptoms of local and systemic reactions (other than malaise and shivering) related to the 2nd vaccination (full analysis dataset)

Reported Term	Preferred Term	Age group	
		18-59 yrs	≥60 yrs
		n/N (%) 95% C.I.	n/N (%) 95% C.I.
Swelling	Injection site swelling	1/269 (0.4%) (0.0% ; 2.1%)	4/270 (1.5%) (0.4% ; 3.7%)
Induration	Injection site induration	2/269 (0.7%) (0.1% ; 2.7%)	4/270 (1.5%) (0.4% ; 3.7%)
Redness	Injection site erythema	0/269 (0.0%) (0.0% ; 1.4%)	5/270 (1.9%) (0.6% ; 4.3%)
Injection Site Pain	Injection site pain	37/269 (13.8%)	8/270 (3.0%)

		(9.9% ; 18.5%)	(1.3% ; 5.8%)
Ecchymosis	Injection site hemorrhage	1/269 (0.4%) (0.0% ; 2.1%)	1/270 (0.4%) (0.0% ; 2.0%)
Fatigue	Fatigue	18/269 (6.7%) (4.0% ; 10.4%)	12/270 (4.4%) (2.3% ; 7.6%)
Headache	Headache	14/269 (5.2%) (2.9% ; 8.6%)	17/270 (6.3%) (3.7% ; 9.9%)
Sweating	Hyperhidrosis	7/269 (2.6%) (1.1% ; 5.3%)	9/270 (3.3%) (1.5% ; 6.2%)
Muscle pain	Myalgia	6/269 (2.2%) (0.8% ; 4.8%)	9/270 (3.3%) (1.5% ; 6.2%)
Joint pain	Arthralgia	6/269 (2.2%) (0.8% ; 4.8%)	12/270 (4.4%) (2.3% ; 7.6%)
Fever with onset later than Day 7 after vaccination	Pyrexia	0/269 (0.0%) (0.0% ; 1.4%)	0/270 (0.0%) (0.0% ; 1.4%)

The probability of occurrence of systemic reactions (including fever) within 21 days after the first vaccination was 22.8% in adults and 23.3% in elderly subjects. The majority of subjects reported no fever within 7 days after the first and second vaccinations in both age strata. After the first vaccination, the occurrence of fever was 2.2% in the group of adults, and 1.1% in the elderly. After the second vaccination, the occurrence of fever within 7 days after vaccination was 0.4% and 0.7% in adults and elderly. No fever case lasted more than 2 days. Of the few fever cases reported, most were mild. There was no severe fever in either age stratum after either vaccination.
The probability of occurrence of malaise after the first vaccination was 6.4% in both age strata; after the second vaccination**,** 3.7% in adults, and 4.1% in elderly subjects. Malaise after the first vaccination in adults was reported mostly as mild (5.3%), 2 were moderate (0.7%), and 1 (0.4%) severe. The rates of malaise by severity were generally similar in elderly subjects (5.7% mild and 0.7% moderate), and none severe. After the second vaccination, mild or moderate malaise was reported in 6 (2.2%), and 4 adult subjects (1.5%), respectively, and 10 (3.7%) and 1 elderly subject (0.4%), respectively. The probability of occurrence of shivering after the first vaccination was 3.6% in adults and 4.6% in elderly; the rates were lower after the second vaccination: 1.1% and 1.9%, adult and elderly subjects, respectively. Reports of shivering were predominantly mild, with a few moderate cases reported, none were severe.
Local reactions after the first vaccination occurred at a rate of 17.1% in adults aged 18-59 years, and 8.6% in subjects 60 years and older, and in 14.5% and 6.3% of subjects after the second vaccination, respectively. Most of the local reactions were mild after each vaccination (15.7% and 8.2% after the first, and 13.8% and 5.9% after the second vaccination, respectively).

The follow-up data to 6 months after the first vaccination for all subjects were available during the procedure. None of the 503 subjects experienced systemic reactions and new adverse reaction in the period between day 42 and day 180. All systemic symptoms or diagnosis of AEs reported between Day 42 and 180 were considered unrelated to vaccination.

Systemic reactions within 21 days after the 6-months booster dose were mostly mild. One subject experienced moderate reactions (chills, nasophryngitis, arthralgia and headache) in the group of adults. There were no severe systemic reactions.

- Serious adverse event/deaths/other significant events

Study 810501
During the 42 day and 180 day follow-up of the study, no SAEs related to the vaccination, deaths or other significant AEs were reported.

Study 810601
A total of 9 SAEs were reported during the 42 day follow-up of the study. Eight SAEs were considered unrelated to vaccination. One SAE (malaria tertiana reactivation) was judged related to vaccination by the investigator. The subject has a history of malaria tertiana since August 2006 and experienced an episode of reactivation of malaria tertiana previously in November 2006.

Within 21 days after the 6-month booster dose three subjects reported severe AEs (2 adults and 1 elderly subject), who suffered from nasopharyngitis, uveitis and spinal stenosis.

- Laboratory findings

Alanine aminotransferase (ALT) values were tested in a subpopulation (N=51) in study 810601.
There were no clinically significant increases in ALT. Slightly elevated ALT values were detected in 3 subjects. All elevated ALT values were assessed as not related to vaccination by an independent DMC and the responsible investigators.

- Safety in special populations

A comparison of injection site reactions between the two age strata in Study 810601 showed that injection site pain was reported more often by the younger population than by the elderly. Joint pain and sweating was reported less often by the younger population than by the elderly.

- Safety related to drug-drug interactions and other interactions

Not applicable

- Discontinuation due to adverse events

810501: Two subjects stated adverse events experienced after the first vaccination as the reason for withdrawing their informed consent. These AEs were non-serious and were of mild or moderate severity, however, they were considered by the investigator to be related to the vaccination and included arthralgia, chills, eye discharge, fatigue, headache, hyperhidrosis, hypoesthesia, injection site pain, malaise, myalgia, generalized pruritus and insomnia for one subject and arthralgia, myalgia, papular rash for another.

810601: One subject reported an AE as the reason for withdrawal. This subject experienced severe malaise and mild fatigue 3 days after the first vaccination which were considered to be probably related to vaccination and which lasted 7 days.

- Post marketing experience

Not applicable

2.5 Pharmacovigilance

Pharmacovigilance system
The Rapporteur considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Detailed description of the Pharmacovigilance system

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

Risk Management Plan
The routine and additional PhV activities proposed by the applicant are in accordance with CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccines. Minor modifications requested during the initial evaluation have been included by the Applicant in the response document.

A clinical trial in children is currently discussed at the Paediatric Committee. After approval the Applicant is requested to submit the final study protocol as well as timelines. Further it is planned to include 300 patients with a chronic illness and 300 immunocompromised subjects as well as 450 vaccinees aged 61 years or older in a clinical trial which will be submitted to support the authorisation of a pre-pandemic H5N1 vaccine. A total of app. 4500 male and female subjects will be enrolled into three different cohorts. The study has been initiated in May 2008 and milestones and timelines have been provided.

The MAA submitted a risk management plan.

Summary of the risk management plan for Celvapan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
1. Limited clinical data on vaccine safety and efficacy	• Pre-pandemic Phase III study in adult and elderly populations and specified risk groups (810705) • Pre-pandemic paediatric study (810706) • Pandemic observational study in subjects exposed to the vaccine through policies by governments or health authorities (810704) • Routine pharmacovigilance activities	• SmPC Section 5.1: "Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as 'novel' antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical immunogenicity, safety and reactogenicity data obtained with mock-up vaccines are relevant for the pandemic vaccines." • Completion of additional clinical studies (810705, 810706, and 810704) will permit development of more accurate SmPC.
2. Immunogenicity	• Monitoring of adverse events from ongoing clinical studies for any indication of abnormal immunogenicity • Special reporting (7-day expedited reporting) of death or life-threatening reactions, and events of special interest (including neuritis, convulsion, severe allergic reaction,	• Caution in SmPC Section 4.4: "Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance(s), to any of the excipients and to trace residues e.g. formaldehyde, benzonase, or sucrose.

	encephalitis, thrombocytopenia, vasculitis, Guillain-Barré syndrome and Bell's palsy) • Routine pharmacovigilance activities	As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine." • Review of adverse events of special interest in the observational study (810704)
3. Low efficacy	• Pandemic observational study (810704) • Monitoring of adverse event reports for cases that may represent poor vaccine efficacy • Routine pharmacovigilance activities	• Development of pandemic virus vaccine with relevant strains(s)
4. Effects of vaccine on liver function	• Investigation of ALT levels, as a marker of altered liver function, will be included in subgroups of Cohort 2 (immunocompromised patients) and Cohort 3 (chronically ill patients) of study 810705 (pre-pandemic Phase III study in adult and elderly populations and specified risk groups). Further, in order to assess the risk of a potential negative effect of vaccination on liver functions in children, ALT investigation will also be included in a subset of the planned study 810706 (pre-pandemic paediatric study) • Routine pharmacovigilance activities • Monitoring of adverse event reports for abnormalities in liver function	• SmPC Section 5.3: "Non-Clinical studies demonstrated alterations in liver enzymes and calcium levels in repeat dose toxicity studies in rats. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies."
5. Effects of vaccine on serum calcium levels	Serum calcium levels will be examined in subgroups of subjects of Cohort 1 (healthy subjects aged >18 years), Cohort 2 (immunocompromised patients) and Cohort 3 (chronically ill patients) of study 810705 (pre-pandemic Phase III study in adult and elderly populations and specified risk groups) • Routine pharmacovigilance activities • Monitoring of adverse event reports for abnormalities in liver function	• SmPC Section 5.3: "Non-Clinical studies demonstrated alterations in liver enzymes and calcium levels in repeat dose toxicity studies in rats. Such alterations in liver function have not been seen to date in human clinical studies. Alterations in calcium metabolism have not been examined in human clinical studies."
6. Lack of	• Pre-pandemic paediatric study	• Cautions in SmPC Section 4.2:

paediatric data	(810706) • Pandemic observational study in subjects exposed to the vaccine through policies by governments or health authorities (810704) • Routine pharmacovigilance activities	"There is no data on CELVAPAN vaccination dose and schedule for subjects under 18 years old and for subjects with co-morbidities (e.g. immunosuppressed subjects). In a pandemic situation administration of the vaccine in those populations shall follow national recommendations." • Planned studies in children may lead to more detailed information in the SmPC in the future.
7. Lack of data on pregnancy and lactation	• Completion of reproductive toxicology studies • Routine pharmacovigilance activities	• Caution in SmPC Section 5.3: "As of yet data from non-clinical studies concerning reproduction and development are not available."
8. Lack of information on safety in individuals in various risk groups including patients with chronic disease and immunocompromised patients	• Study 810705 (pre-pandemic Phase III study in adult and elderly populations and specified risk groups) • Pandemic observational study in subjects exposed to the vaccine through policies by governments or health authorities (810704) • Routine pharmacovigilance activities	• None
9. Pharmacovigilance monitoring during declared pandemic	• Enhanced PV activities including web based event collection and collection of consumer reports • Special reporting (7-day reports) for death or life-threatening reactions and events of special interest (including neuritis, convulsion, severe allergic reaction, encephalitis, thrombocytopenia, vasculitis, Guillain-Barré syndrome and Bell's palsy) • Abbreviated PSUR with 14-day PSUR reporting cycle • Safety Data Exchange Agreements with countries purchasing vaccine	• None

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The production process of Celvapan Active Substance and Medicinal product is well defined and is sufficiently validated. All manufacturing sites are in compliance with current GMP requirements. Several non-compliance issues with the Ph. Eur regarding the Vero cell bank system and the omission of the classical extraneous agent testing, which were initially raised as major concerns, have been addressed by the Applicant. The Applicant has committed to further address some minor outstanding issues as follow-up measure.

Non-clinical pharmacology and toxicology

Consistent pharmacology data has been generated to support the potency of the vaccine, independent of the manufacturing scales and animal species tested, although a large body of data are from mice. The pharmacological program is in line with the Guideline on "core dossier approach to registration of pandemic influenza vaccines" (CPMP/VEG/4717/03), which specifies that immunogenicity data derived from small animals that well respond to the human influenza vaccine are normally expected and that challenge experiments should be conducted if possible.

Non-clinical toxicological testing program comprises a literature-based risk assessment of Tween 80 (Polysorbate 80), a non-GLP rabbit pyrogenicity study, a GLP single-dose toxicity study and a GLP pivotal repeat-dose toxicity study in which local tolerance assessment is included. This program is considered to sufficiently meet the requirements of Regulatory Guideline on "core dossier approach to registration of pandemic influenza vaccines" (CPMP/VEG/4717/03).

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

Efficacy

Clinical trials on protective efficacy for the mock-up vaccine are not possible. Therefore a detailed characterisation of the immunological response has been performed.

In the dose-response study 810501 four vaccine formulations adjuvanted with alum (3.5µg, 7.5µg, 15µg and 30µg) and 2 non-adjuvanted vaccine formulations (7.5, and 15µg) were evaluated in healthy adults of 18-45 years of age. Based on the MN and SRH assay using the homologous vaccine strain (A/Vietnam) the highest immune responses were achieved and all CHMP requirements were fulfilled following the first and second immunisation with the non-adjuvanted 7.5µg vaccine formulation. Moreover cross-neutralisation experiments indicate a high responsiveness for the original prototype A/HongKong strain and a moderate cross-neutralising response for the further evolved strain A/Indonesia. The neutralising antibody responses against all three virus strains persist over 6 months with low to moderate decline rates.

In the pivotal trial 810601 the immunogenicity of the 7.5µg vaccine was investigated in healthy adults of 18-59 years of age and elderly 60 years of age and older. Following two vaccinations and based on the MN assay all three requirements were fulfilled in the age group of adults and 2 out of 3 requirements were met in the elderly. With regards to the group of adults a seroneutralisation rate of 72.5%, a seroconversion rate of 60.8% and a 4.7 fold GM increase was achieved. In the elderly a seroneutralisation rate of 74.1%, a seroconversion rate of 26.7% and a 2.8 fold increase was obtained. The results of the MN assay were generally confirmed by the SRH assay. Following two vaccinations 2 out of 3 three CHMP requirements were fulfilled in adults and all three 3 requirements were met in the elderly. In the group of the adults a seroprotection rate of 63.3%, a seroconversion rate of 60.2% and a 4.6 fold GM increase was achieved. In the elderly a seroprotection rate of 67.7%, a

seroconversion rate of 62.4% and a 4.6 fold increase was obtained. Data on 6 months persistence of antibodies indicate a moderate decline in antibody responses.

Similar results were obtained in study 810701, where adults between 21 and 45 years of age received 2 doses of 3.75µg HA or 7.5µg HA of strain A/Indonesia/05/2005. With regard to the MN assay all three requirements were met regardless which antigen dose were administered. Based on the SRH assay nearly all CHMP criteria were fulfilled. While in the 3.75µg group a seroprotection rate of 71.2% was reached, it was slightly below the CHMP criterion for SPR in the 7.5µg group (69.2%).

Based on the MN and SRH assay the immunogenicity results obtained with the non-adjuvanted 7.5µg vaccine formulation are consistent throughout the three clinical studies suggesting that the Vero cell derived, inactivated whole virion H5N1 vaccine is suitable immunogenic.

Safety

The safety data provided does not raise any safety concerns as regards frequency and nature of adverse events. The most commonly observed adverse reactions after administration of Celvapan were injection site pain, which was reported post dose 1 and 2. More rarely, local reactions such as injection site erythema and induration, as well as systemic reactions such as headache, fatigue, malaise, myalgia, chills, pharyngolaryngeal pain, pyrexia and arthralgia were reported after the first and second vaccination with the Vero cell-derived whole virion H5N1 pandemic vaccine. Symptoms normally abated without treatment after a few days. In general less systemic and local reactions were reported after the second vaccination compared to the first vaccination. The profile of adverse events after administration is not unusual and comparable to other licensed influenza vaccines. Considering that the vaccine will be used in a pandemic situation the frequency and nature of the adverse events is acceptable.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user/readability testing is considered acceptable. Information on several outstanding issues regarding the user testing was provided by the Applicant and was found to be satisfactory.

Risk-benefit assessment

Clinical context

It is not known which strain (in terms of H and N type) will trigger the next human influenza pandemic. Celvapan is a mock-up influenza vaccine, whose scientific development is based on the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) and the guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03).

Benefits

The benefit of Celvapan can only be assessed during a pandemic and following insertion of an appropriate final pandemic strain into the vaccine. At present the potential benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination.

Based on the MN and SRH assays the immunogenicity results obtained with the non-adjuvanted 7.5µg vaccine formulation are consistent throughout the three clinical studies suggesting that vaccine is suitable immunogenic

Therefore the expected benefit of Celvapan is to provide some protection against clinically-apparent infection and/or possibly against development of severe disease in case of an influenza pandemic. It is unlikely that Celvapan containing the antigens from the strain derived from A/Vietnam/1203/2004 would provide adequate protection if used during a pandemic. In line with the developed core dossier concept, a variation would therefore have to be submitted to introduce the WHO/EU recommended strain, prepared from the influenza virus causing the pandemic, prior to use of Celvapan.

Risks

Celvapan is commonly or very commonly associated with a range of local and systemic adverse reactions but these are not often of severe intensity and the safety profile would not preclude the use of the vaccine in healthy adults aged 18-60 years or > 60 years.

The current safety database is considered to be sufficient to describe adverse reactions that occur uncommonly and to give an indication of any rare events. However, there are some adverse reactions known to be very rarely associated with influenza vaccines and it is currently not possible to predict if higher rates might be observed with Celvapan compared with, for example, seasonal influenza vaccines.

Balance

The overall B/R of Celvapan is positive.

A risk management plan was submitted in accordance with the CHMP-recommended core RMP for these types of vaccines when intended only for use during an actual pandemic.

The clinical and pharmacovigilance specific obligations identified for Celvapan can only be fulfilled if and when a pandemic is officially declared. The data which could form the basis of an annual reassessment will therefore only be available after the pandemic has occurred. Since a review of these specific conditions would provide no relevant information in the absence of a declared pandemic situation, an annual review of the exceptional circumstances status should be initiated only in case the Pandemic is declared.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Celvapan for the prophylaxis of influenza in an officially declared pandemic situation, in accordance with official guidance, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.