SCIENTIFIC DISCUSSION

1. Introduction

Influenza is characterised by the occurrence of frequent, unpredictable epidemics, and much less frequent, worldwide pandemics. Influenza pandemic occurs when a novel influenza virus emerges against which the vast majority of the world's population has no immunity. If such a virus demonstrates the ability to transmit efficiently from person to person, the result is a global outbreak of disease that affects a high percentage of individuals in a short period of time and is likely to cause substantially increased morbidity and mortality in all countries of the world.

Experience with previous known influenza pandemics (1918, 1957 and 1968), has shown that a pandemic spreads in 2-3 waves (the first being less intense than the second one) over a total period of 13 to 23 months. There is evidence that as the volume and speed of international travel has increased during the 20th century that successive pandemics have disseminated worldwide in ever decreasing amounts of time.

Although the great majority of deaths in current influenza epidemics occur among the elderly, a large proportion of influenza-related deaths in the 20th century pandemics were among those under 65 years of age.

EMEA/CHMP have established a fast track assessment procedure for pandemic influenza vaccines, as described in the *Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure* (CPMP/VEG/4986/03). The procedure involves the submission and evaluation of a core pandemic dossier during the interpandemic period, followed by a fast track assessment of the data for the recommended pandemic strain as a variation to the MAA. The dossier requirements for the core dossier are laid down in the *Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisations Application* (CPMP/VEG/4717/03).

Focetria is a pandemic influenza vaccine, surface antigen, inactivated, adjuvanted with MF59C.1. It is an egg-derived, monovalent vaccine, manufactured with the same process and has the same adjuvant used for a nationally authorised seasonal Influenza vaccine "Fluad", a trivalent influenza vaccine licensed in 12 countries through a Mutual Recognition Procedure (MRP).

The applicant had submitted a data package for Focetria, based on the requirements laid down in the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03.

In the initial MAA, the applicant referred to the influenza strains H5N3 and H9N2. With the response document, the applicant has submitted a new application for changing the main reference strain from the H9N2 to the Reverse Genetic (RG) strain A/Vietnam/1194/2004 (H5N1), which now has to be regarded as the mock-up strain of this dossier.

From an epidemiological point of view it is very unlikely that influenza strain A/Vietnam /1194/2004 would be the next pandemic strain, since the virus will either undergo further antigenic drift or the pandemic will be caused by another subtype of influenza vaccines (antigenic shift). Antigenic shift and drift are natural phenomena related to all influenza viruses. For example, additional mutations will be required to enable the virus to transmit effectively from human to human. It is highly unlikely, therefore, that Focetria containing the antigens from the strain derived from A/Vietnam /1194/2004 will provide adequate protection when using during a pandemic. In line with the developed core dossier concept as described in the guideline (CPMP/VEG/4986/03), 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 Focetria in a pandemic situation. This will assure that the pandemic vaccine will induce a satisfactory immune response to the influenza virus causing the pandemic.

As further expanded in section 3.6 of this report, Focetria has not been developed for prophylactic use during the pre-pandemic period (interpandemic and pandemic alert period).

2. Quality aspects

Introduction

Focetria is manufactured with the same process and has the same adjuvant used for Fluad, a trivalent seasonal influenza vaccine nationally authorised through a MRP for several years in 12 EU countries and currently on the market. The MF59C.1 adjuvant contained in Focetria and Fluad is an oil-in-water emulsion, composed mainly of squalene that is an intermediate metabolite in the synthesis of cholesterol.

The formulation proposed for Focetria, selected based on the Clinical Trials performed using pandemic strains, contains 7.5 µg HA of antigen/dose. It is 6-times lower than the total amount of HA present in a conventional trivalent seasonal influenza vaccine, that is 15 µg HA per strain (or 45µg HA/dose).

The vaccine is presented as a suspension for injection in a pre-filled syringe (single dose) or in vials, single dose or multi-dose. The vaccine in multi-dose vials is formulated with Thiomersal.

Active Substance

The Drug Substance is the Monovalent Pooled Harvest (MPH) of Pandemic Influenza vaccine, surface antigen, inactivated. It is a buffered suspension containing predominantly the purified outer membrane proteins, Haemagglutinin (HA) and Neuraminidase (NA), of a pandemic influenza virus strain recommended by the WHO-EU for the Pandemic.

- Manufacture

The manufacturing process of Monovalent Pool Harvest (MPH) involves the cultivation of the pandemic influenza virus strain in embryonated chicken eggs, harvesting of allantoic fluid, concentration by ultrafiltration and formaldehyde inactivation, followed by whole virus purification using sucrose gradient centrifugation and diafiltration.
The HA and NA antigens from the surface of the purified whole virus are solubilised by treatment with a detergent cetyltrimethylammonium bromide (CTAB). The solubilised antigens are then separated from the non-solubilised components of the virus by centrifugation. The resultant supernatants are treated with polystyrene based resin to remove CTAB. The polystyrene resin is removed by filtration and the resulting MPH is filter sterilised.

Preparation and control of Virus Seeds
The reference virus (H5N1 NIBRG-14) was manufactured by Reverse Genetics (RG) technology and provided by NIBSC, UK, an authorized WHO reference laboratory.

According to Ph.Eur. the Working Seed (WS) is obtained after no more than 15 passages from the approved reference virus. Aliquots of Master Seed (MS) are aseptically filled into sterile sealed vials, and stored in a freezer at a temperature lower than -60 ^{o}C.

The WS is obtained after only one passage from the MS using SPF eggs. WS is QC tested and the vials are stored at a temperature lower than -60 ^{o}C. WS is tested for HA and NA identity, absence of mycoplasma, sterility, infectivity, HA titre and egg infectivity to assure identity and microbial quality.

Virus cultivation
The virus is grown in pre-incubated, candled, fertile hens eggs. The virus inoculum is prepared from the WS at a dilution calculated to ensure total egg infection and maximum virus yield and it is injected into the allantoic cavity of each production egg. After inoculation, the eggs are incubated at an optimum temperature and time for maximum virus yield. After incubation, the eggs are cooled to 2-8°C and thereafter fed directly into the Harvesting room.

Harvesting of Allantoic Fluid

The allantoic fluid (AF) is collected into the harvesting vessel. The resultant fluid is then clarified by centrifugation, collected in a refrigerated tank, which is then connected to an ultrafiltration system to concentrate the allantoic fluid.

Inactivation
An aqueous solution of formaldehyde is added to the clarified concentrated allantoic fluid. The content of the tank is then transferred to a sanitised and temperature controlled inactivation vessel and stirred throughout the inactivation period. The inactivation cycle depends upon the characteristics of specific virus strains. The inactivation temperature is selected in order not to compromise antigenicity.

Purification
The virus is removed from the inactivated allantoic fluid using continuous flow ultracentrifuges. The virus is collected using a sucrose density gradient, which concentrates and purifies the virus through isopycnic centrifugation.

The purified virus Pool is diluted with PBS and then diafiltered. A clarifying filtration takes place with pre-filters and filters of different pore sizes. The filtered product represents the Whole Virus Concentrate, and it is sampled for testing. A Polysorbate 80 solution is added to the Whole Virus Concentrate and the product is stored waiting for the Split test results.

Haemagglutinin and Neuraminidase solubilisation
Following the split test results, CTAB Solution is added to the Whole Virus Concentrate to solubilise the HA and NA antigens. The product is then centrifuged under continuous flow and the supernatant collected.
A polystyrene resin, is added to the Subunit Supernatant Pool to absorb the CTAB. Afterwards, the product undergoes a clarifying filtration to remove the resin, and a stabilizer solution is added and the product is then filtered into a stainless steel tank.

Filling, storage and transportation
After the filtration described above, the monovalent pool is transferred to Rosia, where it is sampled for Bioburden, and sterile filtered into a sterile container. The Monovalent Pooled Harvest is sterile filtered. The filtered Monovalent Pooled Harvest (i.e. the active substance) is sampled for release testing and stored at 2-8°C in a stainless steel tank.

Process Validation and/or Evaluation
Consistency of production was demonstrated by data provided on three H5N1 full-scale batches and further supported by batch analysis results of the inter-pandemic vaccine production campaigns of previous years.
MPHs are manufactured in compliance with GMP and according to requirements of the Ph.Eur. Studies have been carried out to evaluate the effectiveness of the antigen production process to inactivate potential viral, bacterial and mycoplasma contamination in addition to influenza viruses.
The formaldehyde inactivation step has been evaluated for three consecutive production egg harvests.
The optimum quantities of polysorbate 80 and of CTAB to allow complete splitting of the virus vaccine strain is determined in the QC laboratory, prior to application to production lots. The optimal conditions are determined on the basis of the electrophoresis patterns, the haemagglutinin and the neuraminidase activity identified in the lots. Tests are performed to determine the levels of potential impurities, which may arise in Monovalent Pooled Harvest. Limits are applied to these impurities.
Transportation between Novartis Siena and Rosia sites is carried out using validated procedures.

Characterisation
The active substance complies with Ph.Eur. monograph for Influenza Vaccine, Surface Antigen, Inactivated. It is a sterile suspension containing predominantly the purified outer membranes proteins: HA and NA of the influenza virus strain. The crystal structure of HA has been determined to atomic resolution for the native HA, for the HA bound to a number of different receptor analogues, for proteolytic fragments of HA which have gone through the conformational changes required for mediating membrane fusion, and for HA complexed with neutralizing antibody.

Influenza virus NA structure has been determined with structural studies of NA in complex with specific monoclonal antibodies, by electron microscopy, X-ray crystallography amino acid sequencing and gene sequencing.

The concentrations of potentially contaminant substances (formaldehyde, citrates and CTAB) are controlled during the process or in the MPH. Limits are applied. Polysorbate 80 is also used as an excipient of MF59C.1 adjuvant and is not considered as a residual of production but is nevertheless tested on the MPH. It is concluded that the impurities in Focetria active substance are sufficiently controlled.

- Specifications

The MPH complies with the Ph.Eur. monograph 01/2006:0869 on Influenza Vaccine (Surface Antigen, Inactivated).

The MPH is tested for release for Haemagglutinin Identity and Content (SRID), Neuraminidase Identity (ELISA), Viral inactivation, Purity (SDS-PAGE), Sterility, CTAB, Polysorbate 80, Barium, Citrates, Endotoxin, Formaldehyde, Ovalbumin Content and Appearance.

Specifications have been selected to be as much as possible in accordance to the Ph.Eur. monograph for the influenza vaccine (surface antigen inactivated).
Specification for Haemagglutinin identity and content, Neuraminidase Identity, Viral Inactivation, Purity, Sterility comply with Ph.Eur. for the Monovalent Bulk. A limit for Endotoxin and Ovalbumin is set up on the Active Substance to ensure that the Ph.Eur. specification for the Final Lot (i.e. monovalent at 7.5 µg HA/dose) is met.
Due to the presence of the adjuvant in the finished product, the test for formaldehyde is performed on the Monovalent Pooled Harvest. Ovalbumin is also controlled on the active substance. The acceptance limits have been set to ensure that the Ph.Eur. limits for the finished product (i.e. monovalent at 7.5 µg HA/dose) are not exceeded. The concentrations of the other substances used during manufacture of the vaccine (i.e. CTAB, citrates, Polysorbate 80) are controlled in the active substance. The limit for the citrates is calculated considering the content of HA on the Final Lot. It has to be noted that Polysorbate 80 is also used as an excipient of MF59C.1 adjuvant
All the relevant analytical methods have been validated or qualified for the active substance. It is acceptable that some analytical validations have been performed on the inter-pandemic strains, as the methods are not strain specific.

- Stability

The applicant has provided stability data up to 9 months for three full-scale batches of H5N1 Monovalent Pooled harvest as well as data collected with the inter-pandemic antigens produced in previous years. The data are consistent with shelf-life of 1 year for the active substance when stored at 2-8°C. The applicant committed to complete the stability study for H5N1 MPH.
At least one batch of the MPH in its container will be stability tested. A stability protocol up to 24 months at 2-8°C was provided. The key stability-indicating parameter are the HA content and purity, measured with the same methods and acceptance limits used at release.

Finished Product

The finished product is a combination of MPH, MF59C.1 adjuvant bulk and buffer solutions. The Mock-up vaccine application is based on the H5N1 Reverse Genetics Strain NIBRG 14, which is derived from the highly pathogenic avian influenza strain A/Vietnam/1194/2004. It should be noted that this mock-up vaccine will have to be varied to introduce the actual pandemic strain, as designated by WHO/EU, when the pandemic is declared.

The MF59C.1 adjuvant is an oil-in-water emulsion, composed mainly of squalene that is an intermediate metabolite in the synthesis of cholesterol. Squalene is a commercially available natural product distilled from shark liver oil. It is then redistilled and supplied by qualified manufacturers. MF59C.1

The process for the Final Bulk preparation consists is a simple mixing operation. In case of formulation with preservative a Thiomersal solution is added. The formulated suspension is filled into syringes or vials. The potency of the vaccine is expressed as the concentration of the HA protein.

The vaccine is presented as a suspension for injection in an emulsion in a pre-filled syringe (single dose) or in vials, single dose or multi-dose. Vaccine in multi-dose vials is formulated with Thiomersal.

Description and Composition of the finished product:

Each 0.5 ml dose of vaccine has the following composition:

Active Ingredient:

HA and NA antigens from the influenza virus strain recommended by WHO/EU for the Pandemic	≥ 7.5 µg HA

Adjuvant MF59C.1:

Squalene	9.75 mg
Polysorbate 80	1.175 mg
Sorbitan trioleate	1.175 mg

Other Ingredients:
Sodium chloride
Potassium chloride
Potassium dihydrogen phosphate
Disodium phosphate dihydrate
Magnesium chloride hexahydrate
Calcium chloride dihydrate
Thiomersal (included only in multi-dose vials)
Sodium citrate
Citric acid
Water for injections

- Pharmaceutical Development

Focetria contains the same adjuvant and is manufactured with the same process used for Fluad. Fluad a surface antigen, trivalent inactivated, inter-pandemic influenza vaccine, adjuvanted with MF59C.1, is currently the only influenza vaccine with an adjuvant on the market, and has been approved in 2000 through a Mutual Recognition Procedure in 12 EU countries. Fluad is also licensed and marketed in other European countries and outside Europe.

Formulation Development
The finished product is a combination of MPH, MF59C.1 adjuvant bulk and buffer solutions. The present core pandemic dossier describes the H5N1 mock-up vaccine.
The MF59 adjuvant has been used in pre-clinical and clinical studies for a range of different vaccines.
From the 1999 Fluad has been formulated using adjuvant containing citrate buffer to improve adjuvant stability, designated as MF59C.1. This formulation has been the one used for Focetria.
Both the aqueous and citrate formulations of MF59 were used in preclinical and clinical studies. A clinical study has been successfully completed which demonstrates equivalence between the citrate and water formulations of Fluad.

Manufacturing Process Development

The first production of Focetria with the H5N3 strain was in 1999. The manufacturing process was the same of the seasonal influenza vaccine Fluad. Successively, Focetria was produced with the H9N2 strain in 2004 and with the H5N1 strain in 2005, with the same manufacturing process approved for Fluad in 2005.
From 2000, some changes in formulation and manufacturing process were introduced for Fluad and approved through the relevant MRP variations. However these differences, as already demonstrated for the variations submitted for Fluad, do not affect the quality, safety and efficacy of the product.
Thiomersal was previously used in the production of the active substance (as reagent during the process and as preservative at the final stage) and of the finished product (as preservative). Thiomersal was removed in two steps: in the first one it was removed from the active substance and finished product as preservative (remaining as traces); in the second one it was removed completely (in 2003).
Clinical trials performed to compare Fluad formulations (with and without preservative) and of the stability studies confirmed that the presence of Thiomersal, as a preservative in Fluad, does not have any impact on the quality, immunogenicity and safety of the product. For that reason, the current licensed Fluad in pre-filled syringe is a thiomersal-free product.
Focetria with H5N3 strain was produced before 2003 with the preservative, while Focetria with H9N2 and H5N1 strains were produced in 2004 and 2005 without any preservative.

- Adventitious Agents

In addition to inactivation of influenza virus, the Ph.Eur., requires that the formaldehyde inactivation process be shown to be capable of inactivating avian leucosis viruses and mycoplasma. Studies have been carried out to evaluate the effectiveness of the antigen production process to inactivate potential viral, bacterial and mycoplasma contamination in addition to influenza viruses.
CTAB, as detergent, could contribute to virus inactivation. Its capacity to inactivate mycoplasma has been validated.
Sucrose gradient centrifugation could contribute to virus removal as well as the centrifugation steps, which follow the Polysorbate 80/CTAB treatment.

With respect to the transmission of TSE, the only animal derived starting materials are eggs (used in production of the active substance) and squalene (used in the MF59C. 1 adjuvant). There is no scientific evidence to suggest that eggs are likely to present any risk of contamination from TSE-agents. Copy of the Declaration of compliance with the annex to Directive 75/ 318/ EEC, as amended by directive 1999/ 82/ EEC relating to TSE was submitted.
Regarding squalene, derived from shark liver, it does not present any risk of potential contamination from TSE agents as well.
With regards to the use of reverse genetics strains, which may be prepared using materials from ruminant origin (foetal calf serum, bovine trypsin, Vero Cells), the TSE compliance was performed by NIBSC.

- Manufacture of the Product

Description of Manufacturing Process and Process Controls

Final Bulk Vaccine Process
The Buffer A, Solution B and Thiomersal solution are prepared in Rosia. The Monovalent Pools are prepared at the Siena facility and transported to Rosia where they are sterilised by filtration to produce the MPH. The MF59C.1 Adjuvant Bulk is received from the manufacturing site and is sterilised by filtration.
The components are added to the Final Bulk container (buffer solution, water for injection, MPH, stabilizer solution and MF59). The required quantity of Thiomersal solution is only added in case of formulation with preservative. After the addition is completed, the bulk is stirred to allow adequate mixing. The pH of the Final Bulk is checked and samples are taken for Final Bulk release control testing [i.e. HA identity and content, Endotoxin, Total protein (other than HA), Osmolality, Ovalbumin Content, Thiomersal (if appropriate)]. The Final Bulk is then aliquoted by aseptic transfer into sterile containers (each container is subsequently sampled and tested for sterility), and stored at 2-

8°C. The in-process controls are appropriate for the preparation of the Final bulk and of the Final Lot in its final container.
The adjuvant MF59C.1 is produced in Germany and transported to Italy, where it is filtered and used to formulate the Final Bulk. Bioburden is controlled before the sterilizing filtration, while sterility and other in-process parameters are monitored after filtration and before the addition into the Final Bulk mixing tank.

Filling and packaging Process (Final lot syringes and Final lot vials)
Filling operations are carried out at the Rosia manufacturing site. Syringes and vials are filled by a validated, aseptically procedure which is also registered for Fluad. The packed product is stored at 2-8°C until released.

- Product Specification

The Final Lot is tested for release for Haemagglutinin Identity and Content (SRID), Sterility, Endotoxin, Appearance, Abnormal toxicity, Squalene identity and content (HPLC), Particle size distribution, pH, Thiomersal (only for multi-dose vials) and Extractable volume.

The release tests are the same approved for the inter-pandemic Fluad vaccine (except for the haemagglutinin content - 7.5µg/dose vs. 15 µg for each strain/dose) and fulfil the Ph.Eur. requirements for surface antigen influenza vaccine.

The specifications might differ from the Ph.Eur. monograph for the influenza vaccine (surface antigen inactivated) due to the presence of the MF59C.1 that could interfere with some analytical methods.

The specification for Haemagglutinin identity and content complies with Ph.Eur. for the Final Lot. This test is also performed in the Final Bulk. In case the quantity of relevant materials to carry out the assay is insufficient (a real possibility in a Pandemic emergency), this test will be performed only on the Final Bulk and will not be repeated in the final lot. The specifications for squalene content and identity and for particle size distribution are specific to control the MF59C.1 adjuvant into the vaccine. Thiomersal is controlled when it is used as a preservative in the Final Bulk formulation.

The Test for free formaldehyde is performed earlier in the process, on the Monovalent Pooled Harvest, rather than on the Final Bulk vaccine or the Final Lot, as required by Ph.Eur. The MF59C.1 adjuvant in the finished product interferes with the performance of this test.

All the relevant analytical procedures have been validated or qualified for the finished product.

All excipients used during production and in the formulation of Monovalent Pooled Harvest, MF59C.1 adjuvant and Final bulk Vaccine comply with Ph.Eur., except for squalene (in-house specifications).

Batch analysis
Batch analysis results of three H5N1 full production scale lots show consistent production and are consistent with results obtained for the seasonal Fluad vaccine.

- Stability of the Product

Stability data for the pre-filled syringes of Focetria H5N1 are provided (3 full-scale batches for 9 months) and are consistent with stability results of the seasonal MRP approved Fluad vaccine justifying the proposed shelf life of 1 year when stored at 2-8°C. The applicant committed to complete the stability study for pre-filled syringes as well as for mono-dose and multi-dose vials.
The proposed shelf life for the adjuvant MF59C.1 of 3 years when stored at 2-8 °C is sufficiently supported by data.

3. Non-clinical aspects

Introduction

Focetria is an inactivated monovalent influenza vaccine, adjuvanted with MF59C.1. The vaccine is based upon virus surface antigens (haemagglutinin and neuraminidase), propagated in eggs, of strain: H5N1 A/Vietnam/1194/2004 (H5N1).

Focetria is manufactured with the same process and has the same adjuvant used for Fluad, a trivalent seasonal influenza vaccine, nationally approved *via* MRP. The MF59C.1 adjuvant contained in Focetria and Fluad is an oil- in- water emulsion, composed mainly of squalene. Taking this into consideration the applicant submitted a reduced non-clinical package for Focetria; this is in accordance with the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03.

For the non-clinical part of the dossier, the applicant has compiled data emerging from non-clinical studies with the adjuvant alone and in combination with different antigens, performed over the last 15 years. The non-clinical data supporting the approval of Fluad and the MF59 non-clinical data package represent the principal support to this application.

GLP

The relevant studies were carried out in compliance with GLP.

Pharmacology

- Primary pharmacodynamics

Ferret challenge study

A ferret challenge study was performed to determine the protective efficacy of the pandemic mock up vaccine against challenge with homologous live avian influenza A/NIBRG-14 (H5N1) virus strain and to evaluate its immunogenicity.

In order to perform the study, the ferrets were primed with an H3N2 Influenza virus, vaccinated twice with the A/Vietnam/1194/2004 (H5N1) containing mock-up vaccine and then challenged with the reassortant avian influenza A/NIBRG-14 (H5N1) virus. Two different doses of the mock up vaccine, 7.5 and 15 µg HA/dose were tested; MF59 adjuvant served as control. The use of a heterologous priming infection in ferrets mimics the human condition where individuals are not naïve to influenza virus per se, but are naïve to pandemic virus strains.

The following observations were made:

- Both the 7.5µg and 15µg vaccine formulations reduced viral shedding in nasal washes and induced seroconversion against Influenza A/NIBRG-14 (H5N1) virus antigen, when compared to the negative control article.
- No seroconversion was observed in the negative control animals.
- The 15µg vaccine formulation was associated with greater reductions in viral shedding and higher titres of Influenza A/NIBRG-14 (H5N1) virus HA antibodies, compared to the 7.5µg vaccine formulation.
- Body temperature elevations were lowest in the animals that were given the 15µg vaccine (as determined from the temperatures measured in the afternoon).
- There were no statistically significant differences between treated and control animals in symptom scores, weight loss or leukocyte counts.

Mouse immunogenicity assay

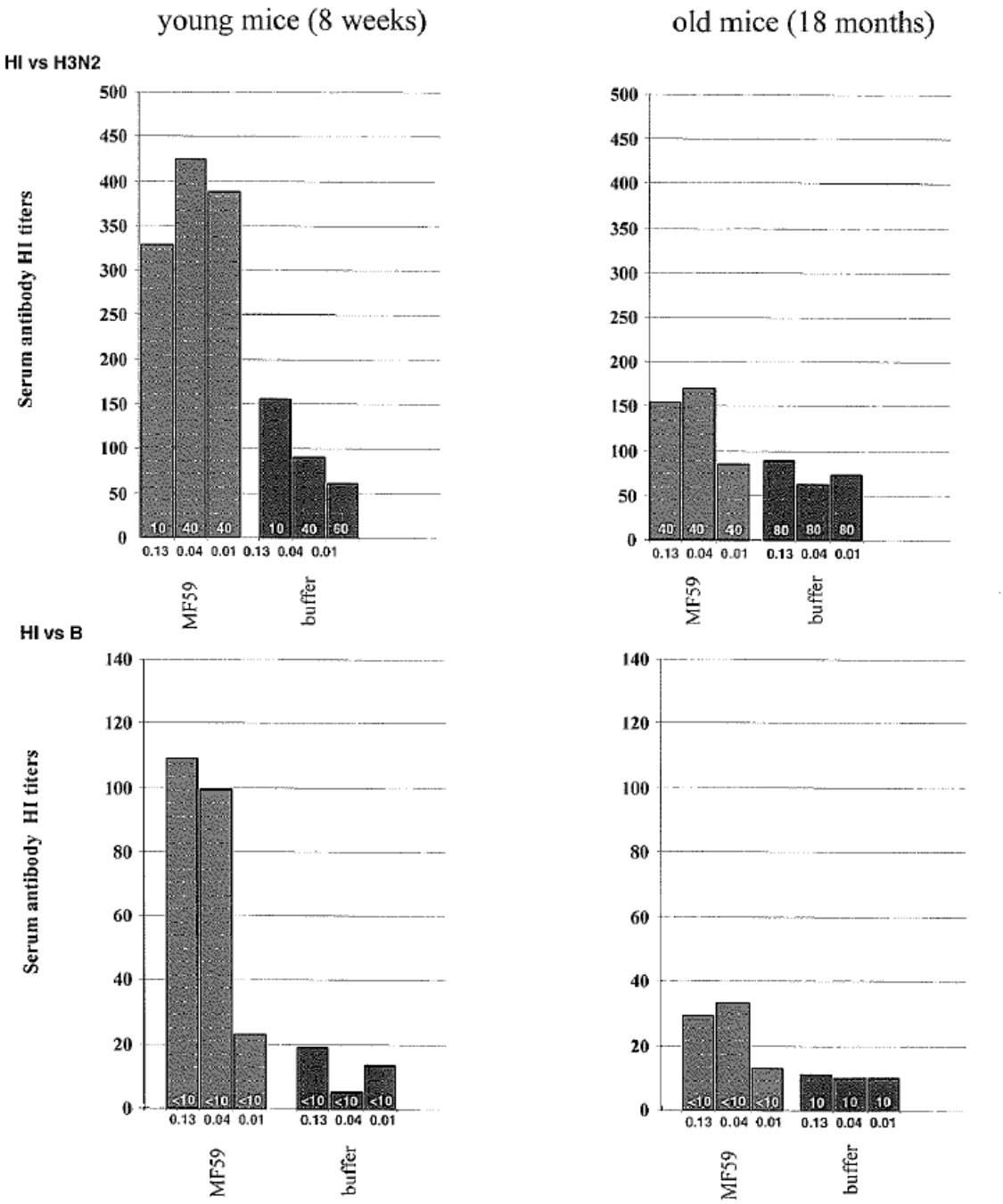
The applicant has performed immunogenicity and influenza challenge studies in mice. The results of a recent study, which confirmed the ability of MF59 to enhance the antibody response (ELISA and haemagglutination inhibition [HI]) in young adult (8 weeks-old) and in old BALB/c mice (18 months-old) is summarised below. The study evaluated the dose-response when various amounts of influenza trivalent subunit vaccine were combined with fixed amounts of MF59 (1:1 volume-to-volume ratio),

keeping constant the volume of injection. Titration of haemagglutinin (HA) specific immunoglobulin G antibodies was performed from each mouse.

The details of the study and the results are summarised in the table below:

Mouse /group of test article and vaccine formulation	**Doses (subcutaneous) / days of immunisation**	**Findings (Antibody titres determined by ELISA and haemagglutination inhibition [HI])**
10 Young and old mice/group A/New Caledonia/20/99 (H1N1) alone and + MF59, A/Panama/2007/99 (H3N2) alone and + MF59 B/Shandong/7/97 (B) alone and + MF59	0.4, 0.13, 0.04, 0.01, 0.003, and 0.001 µg each mouse was immunised on days 1 and 21	MF59 significantly enhances the HA-specific antibody response in ELISA and HI assays for all antigens in both young and old mice allowing the reduction of the amount of HA by 100 folds or more to get antibody response induced by the non-adjuvanted vaccine.

Summary HI titres after the second vaccination



- Secondary pharmacodynamics

Secondary pharmacodynamic studies were not performed. This approach is in accordance with the relevant guidelines, note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95) and the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03.

- Safety pharmacology programme

Safety pharmacology studies with Focetria were not performed. This approach is in accordance with the relevant guidelines, CPMP/SWP/465/95 and CPMP/VEG/4717/03. However, during the early development of MF59C.1 adjuvant, safety pharmacological endpoints were included in two repeat-dose dog toxicology studies conducted to evaluate the safety profile of vaccine formulations with antigens that are unrelated to this dossier. Both studies included a MF59C.1 group and a saline/buffer

control group. Cardiovascular and neurological parameters were evaluated in the studies. An overview of the study designs and results is provided below.

Cardiovascular and neurological evaluations during repeat-dose studies with MF59 in dogs

Test materials and Intramuscular dosing schedule	**Numbers of Animals (M/F)**	**Cardiovascular and neurological evaluation**
0.5 ml saline (control) or 1:1 saline: MF59, 3 injections On days 1, 16 and 29	2/2	Cardiovascular -No relevant changes noted Neurology -All dogs showed normal reaction
0.5 ml buffer (control) or 1:1 buffer: MF59, 3 injections On days 1, 15 and 29	2/2	Cardiovascular -No treatment-related abnormalities Neurology -No abnormalities detected

* Evaluated pre-test, and prior to necropsy. Animals were necropsied 1week post-last dose.

- Pharmacodynamic drug interactions

Such studies are not required according to CPMP/SWP/465/95 and CPMP/VEG/4717/03.

Pharmacokinetics

Pharmacokinetic or classic absorption, distribution, metabolism and excretion (ADME) studies with Focetria or Fluad or MF59C.1 have not been performed. In accordance with the relevant guidelines (guideline on non-clinical testing vaccine CPMP/SWP/465/95 and guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004), it is considered acceptable that a complete ADME study has not been conducted because they are considered not relevant for a vaccine.

The main component of MF59C.1 is squalene. It is an intermediate in the biosynthesis of cholesterol and is a constituent in dietary product (vegetable and fish oil).

Clearance study performed in rabbits injected intramuscularly with labeled squalene (125I) demonstrated that it is rapidly cleared and only 5% remains at the injection site for approximately 5 days after injection.

From data available and considering the route of administration, the low volume and the frequency of human administration, the use of squalene does not constitute a risk factor in clinical use.

Toxicology

- Single dose toxicity / Repeat dose toxicity

Focetria an inactivated monovalent influenza vaccine, adjuvanted with MF59C.1., manufactured with the same process and has the same adjuvant used for Fluad thus no single dose toxicity/ repeat dose toxicity studies are required according CPMP/VEG/4717/03. Nevertheless the applicant submitted a repeat-dose toxicity study in rabbits, with seasonal trivalent vaccine + MF59W.1 (Fluad). The human dose of Fluad was administered as two intramuscular injections 14 days apart. There were no systemic adverse effects and the vaccine was tolerated locally, although transient local effects have been shown.

- Genotoxicity

No genotoxicity studies were conducted; this is in line with the relevant guidelines CPMP/SWP/465/95 and CPMP/VEG/4717/03.

- Carcinogenicity

No carcinogenicity studies were conducted; this is in line with the relevant guidelines CPMP/SWP/465/95 and CPMP/VEG/4717/03.

- Reproduction Toxicity

No reproduction toxicity studies were conducted with Focetria, this is in line with the relevant guidelines CPMP/SWP/465/95 and CPMP/VEG/4717/03.

- Local tolerance

Focetria development is based on the manufacturing process of Fluad, a Novartis' trivalent, seasonal influenza vaccine (surface antigen, inactivated, adjuvanted with MF59C.1) currently on the market. No local tolerance studies with Focetria are required according CPMP/VEG/4717/03. However, the repeat-dose toxicity study with Fluad in rabbits included an evaluation of local tolerability. There were no clinical signs of any injection site reactions (including Draize score).

Macroscopic examination of injection site muscle from animals treated two days previously indicated an increased frequency of slight focal haemorrhage in the Fluad group, compared with each component administered separately. Complete recovery was observed in animals treated 16 days previously.

Histological examination of the injection site 2 days post-injection revealed interstitial inflammation), interstitial haemorrhage, and/or muscle fiber degeneration in almost all animals. These observations were more notable in the Fluad group. However at 16 and 30 days after injections degenerative changes and inflammatory were still present but to a lower degree and without relevant differences between control and treated groups.

Ecotoxicity/environmental risk assessment

Focetria is an inactivated viral vaccine, and only a surface antigen. Squalene is an intermediate in the biosynthesis of cholesterol and is a constituent in dietary product (vegetable and fish oil).

There is no environmental risk for the product itself.

4. Clinical aspects

Introduction

Clinical trials on protective efficacy for the mock-up vaccine cannot be performed. Therefore a detailed characterisation of the immunological response to the mock-up vaccines is required. The vaccine virus strains chosen for these studies should allow simulating a situation where the target population for vaccination is immunologically naïve.

The criteria for these studies are laid down the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03. With no other criteria to suggest at present, mock-up vaccine should be able to elicit sufficient immunological response to meet all three of the current standards set for existing vaccines in adults or older adults laid down in CPMP/BWP/214/96.

In adults aged 18-60 years:

- Number of seroconversions or significant increase in anti-haemagglutinin antibody titre > 40%
- Mean geometric increase > 2.5;
- Proportion of subjects achieving an HI titre $\geq$ 40 or SRH titre $\geq$ 25 mm^2 > 70%.

In adults > 60 years:

- Number of seroconversions or significant increase in antihaemagglutinin antibody titre > 30%
- Mean geometric increase > 2.0;
- Proportion of subjects achieving an HI titre $\geq$ 40 or SRH titre $\geq$ 25 mm^2 > 60%.

In addition neutralising antibodies should be present. The development program for Focetria is based on this guideline.

Early investigations were performed with H5N3 and H9N2 strains.

Since the avian influenza strain H5N1 strain considered as a possible candidate to cause the next influenza pandemic, the applicant decided to base the mock-up dossier on studies performed (immunogenicity and safety) with A/Vietnam/1194/2004 (H5N1) strain containing vaccine.

GCP

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

Pharmacokinetics

Pharmacokinetic studies were not performed in accordance with the note for guidance on clinical evaluation of new vaccines (CPMP/EWP/463/97) and the Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03.

Pharmacodynamics

In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to vaccines. The detailed characterisation of the immunological response to the mock-up vaccines is the surrogate parameter for efficacy (CPMP/VEG/4717/03) and these data are discussed below.

Clinical efficacy

Two dose ranging studies evaluating safety and immunogenicity in young adults have been performed with adjuvanted candidate vaccines. In these trials two different mock-up strains, H5N3 and H9N2, have been used. A total of 161 subjects were enrolled and vaccinated in these studies. Eighty subjects received at least one dose of different formulations of the adjuvanted vaccine and 81 subjects received at least one dose of a comparator non-adjuvanted vaccine.

The pivotal study V87P1 was conducted in healthy adults aged 18 to 60 years and subjects > 61 with an adjuvanted candidate vaccine containing the mock-up strain H5N1 (A/Vietnam/1194/2004).

Dose response studies

Study V7P37

Study V7P37 was an observer blind, randomised comparative dose ranging study to evaluate safety/reactogenicity and immunogenicity of an adjuvanted influenza vaccine containing the mock-up strain H5N3 as compared to a non-adjuvanted split influenza vaccine containing H5N3.

Fifty-five healthy adults, between 18-40 years old were enrolled in the study. Subjects were randomised to receive adjuvanted H5N3 vaccine (7.5 µg, 15 µg or 30 µg HA per dose) or the same dose of a non-adjuvanted comparator vaccine according to a 2-dose schedule (day 0, day 21).

Immunogenicity was assessed by microneutralisation assay (MN), haemagglutination inhibition assay (HI), and single radial haemolysis (SRH). Blood samples were drawn at day 0, 21, and 42. Antibody cross-reactivity was assessed against heterovariant H5N1 influenza strains.

Results: Before immunization all participants had serum HI titres of less than 1:10. After the first and after the second vaccine dose, GMTs of antibody to MF59C.1-adjuvanted vaccine were significantly higher than to non-adjuvanted vaccine. There was no dose response relationship, in particular, within the adjuvanted mock-up strain groups. The highest response was achieved in the two groups with the lowest antigen concentration. At 7·5 µg the MF59C.1- adjuvanted influenza vaccine gave the highest GMT on day 42.

Immunisation with candidate vaccine (adjuvanted influenza vaccine) seroconversion rates between 18-60%, were achieved. Interestingly higher seroconversion rates were achieved with the lower antigen content. Seroconversion rate was significantly higher in the adjuvanted groups compared to the non-adjuvanted group, but the dose response was not significant.

Seroprotection rates were between 18 and 60% in the adjuvanted vaccine groups, where higher seroprotection rates were achieved with the lower antigen content. Seroprotection rate was significantly higher in the adjuvanted groups compared to the non-adjuvanted group, but the dose response was not significant.

Immunogenicity results after two doses with candidate vaccine ± MF59C.1 (mock-up strain H5N3)

Assay		GMTs and (95% CI)					
		7.5µg		15µg		30µg	
		Adjuvant	No adjuvant	Adjuvant	No adjuvant	Adjuvant	No adjuvant
HI	GMT	35 (18-67)	5 (2.59-9.64)	26 (14-51)	5 (2.67-9.35)	10 (5.34-19)	6.16 (3.19-12)
	% SC	60 (26-88)	0 (0-31)	40 (12-74)	0 (0-28)	18 (2-52)	10 (0-45)
MN	GMT	32 (23-45)	11 (7.68-15)	26 (19-37)	11 (8.26-16)	29 (21-40)	14 (11-20)
	% SC	80 (44-97)	10 (0-45)	100 (69-100)	18 (2-52)	100 (72-100)	30 (7-65)
SRH H5N3	GMT	92 (60-141)	4 (2.6-6.15)	77 (50-119)	13 (8.29-19)	72 (48-109)	7.83 (5.09-12)
	% SC	100 (69-100)	0 (0-31)	100 (69-100)	45 (17-77)	100 (72-100)	30 (7-65)
SRH H5N1	GMT	41 (30-56)	4 (2.93-5.45)	38 (28-52)	5.31 (3.95-7.13)	33 (25-45)	4 (2.93-5.45)
	% SC	90 (55-100)	0 (0-31)	80 (44-97)	0 (0-28)	82 (48-98)	0 (0-31)

Study V7P37E1

In the extension study **V7P37E1**, 28 subjects who completed study V7P37 were revaccinated approximately 17 months after primary vaccination in order to evaluate the immunogenicity of an additional vaccine dose as previously formulated, with and without MF59C.1 adjuvant.

Of the 28 subjects, 26 were included in the immunogenicity analyses; 15 of these individuals were previously vaccinated with the adjuvanted formulations, while the remaining 11 had received the comparator vaccine. Immunogenicity was assessed by MN, HI and SRH. Serum samples were collected before and 3 weeks after revaccination.

Results: At baseline none of the subjects had detectable antibodies as tested by HI and/or MN. By SRH, subjects immunised with any dose of adjuvanted candidate vaccine still had detectable antibodies against both A/H5N3 and A/H5N1. Non-adjuvanted vaccine recipients had detectable antibodies only in the group immunised with the 15 µg dose, and against A/H5N3 only. At re-vaccination with adjuvanted candidate vaccine H5N3 GMTs increased significantly when compared to non-adjuvanted vaccine. MF59C.1-adjuvanted H5N3 vaccine induced antibodies that cross-protected against not only the H5N1 strains from 1997-1998, but also against the more recent and virulent strains isolated in 2003 and 2004 in Vietnam and Hong Kong, which exhibit some antigenic drift as compared to the original strains.

Immunogenicity results after three doses with candidate vaccine ±MF59C.1 (mock-up strain H5N3)

Assay		7.5 µg		15 µg		30 µg	
		Adjuvant N=6	No-Adj. N=3	Adjuvant N=3	No-Adj. N=6	Adjuvant N=6	No-Adj. N=2
HI	GMT (95% CI)	25 13-49	5 1.98-13	10 3.96-25	5 2.6-9.63	32 16-61	5 1.61-16
MN	GMT (95% CI)	325 158-668	7.66 2.77-21	181 65-501	15 7.45-31	202 99-416	47 13-163
SRH	GMT (95% CI)	138 98-195	47 29-77	134 82-218	45 32-64	137 97-194	68 37-123

Study DIMD 04-019

Study DMID 04-019 was double blind study to evaluate the safety and immunogenicity of an adjuvanted influenza vaccine containing the mock-up strain H9N2 as compared to a non-adjuvanted split influenza vaccine containing the same strain. Young healthy adults, 18 to 34 years old were included in the study. Four dose levels of adjuvanted candidate vaccine (3.75 µg, 7.5µg, 15 µg and 30 µg HA/dose) were compared to the related non-adjuvanted formulations. A total of 48 subjects received 4-dose levels of adjuvanted candidate vaccine (3.75 µg, 7.5µg, 15 µg and 30 µg HA/dose) and 48 subjects received the comparator non-adjuvanted vaccine. Twelve individuals were included in each vaccine group.

Two vaccine doses were administered, four weeks apart. Immunogenicity was assessed by HI test, and, in a subset of subject by using microneutralization (MN) test; blood samples were drawn at baseline, and 28 days after each vaccination (day 28, and 56).

Results:

Immunogenicity results after two doses with candidate vaccine ± MF59C.1 (mock-up strain H9N2)

Parameter	3.75 µg		7.5 µg		15 µg		30 µg	
	Adjuvant N=12	Non-adj N=12	Adjuvant N=12	Non-adj 7N=12	Adjuvant N=12	Non-adj N=12	Adjuvant N=12	Non-adj 30 µg N=12
GMT (95% CI)	181.0 (108.0-303.1)	35.9 (19.7-65.4)	128.0 (70.0-233.9)	28.5 (19.7-41.2)	143.7 (90.0-229.4)	25.4 (12.4-52.0)	45.3 (27.8-73.7-)	161.3 (109.6-237.3)
% SC (95% CI)	91.7 (61.5-99.8)	66.7 (34.9-90.1)	91.7 (61.5-99.8)	50.0 (21.1-78.9)	100.0 (73.5-100)	50.0 (21.1-78.9)	100.0 (73.5-100)	66.7 (34.9-90.1)
% SP (95% CI)	100 (73.5-100)	41.7 (15.2-72.3)	91.7 (61.5-99.8)	16.7 (2.1-48.4)	91.7 (61.5-99.8)	33.3 (9.9-65.1)	100.0 (73.5-100)	66.7 (34.9-90.1)

A better antibody response against the vaccine antigen (A/Chick/G9 strain) was seen with the adjuvanted candidate vaccine at all dosages than the respective nonadjuvanted vaccines. GMTs after vaccination with adjuvanted candidate vaccine were consistently higher when compared to non-adjuvanted vaccine and reached seroprotective levels for all dosages. The seroconversion rate (4-fold increase) and seroprotection rate (> 40) after 2 doses of adjuvanted candidate vaccine ranged between 91% and 100% depending on the dosage. The non-adjuvanted vaccine was poorly immunogenic even at the highest dose of 30 µg.

- Main study

Study V87P1

Study V87P1 is a partially-blind randomised multicentre study designed to evaluate the reactogenicity and immunogenicity of two doses of pandemic monovalent (surface antigen adjuvanted with MF59C.1) influenza vaccines (Focetria) administered at different doses (7.5 µg, 15 µg of A/H5N1 antigen) in non-elderly and elderly subjects.

METHODS

Study Participants

A total of 486 subjects were enrolled, 313 aged 18-60 years (adults) and 173 aged 61 years and over (elderly). Among the adults 157 and 156 subjects received Focetria containing 7.5 µg and 15 µg of A/H5N1 influenza antigen, respectively. Among the elderly 87 and 86 subjects received Focetria containing 7.5 µg and 15 µg of A/H5N1 influenza antigen (HA), respectively.

Treatments

Subjects were randomised to receive vaccination Focetria at different doses (7.5 µg and 15 µg HA) adjuvanted with MF59.C1. The subjects were vaccinated at day 0 and day 21. A subset of the population will receive a booster dose at day 202.

Objectives

The primary objective was to evaluate the immune response (in term of anti-haemagglutinin antibody) of two doses of pandemic adjuvanted mock-up vaccine (H5N1), 3 weeks after the second dose.

The secondary objectives were

- To demonstrate non-inferiority of the antibody response elicited, as determined by using HI test, by doses of Focetria containing 7.5 µg of A/H5N1 HA vs. two doses of Focetria containing 15 µg of A/H5N1 HA, in terms of post-immunisation GMT, 3 weeks after the second immunization.
- To evaluate immunogenicity of one dose of Focetria containing either 7.5 µg or 15 µg of A/H5N1 HA, as measured by HI, in compliance with CPMP/VEG/4717/03, and by MN (in a subset of subjects).
- To evaluate the safety of the administration of two doses of Focetria containing either 7.5 µg or 15 µg of A/H5N1 HA according to the safety parameters routinely used for seasonal influenza vaccines (see below).

Outcomes/endpoints

The co-primary endpoints were defined as follows:

Non-elderly adult subjects 18-60 years (i.e., ≥ 18 and < 61)

- Number of seroconversions[1] or significant increase in antibody titre[2] > 40%
- Mean geometric increase > 2.5
- The proportion of subjects achieving an HI titre ≥ 40 should be > 70%·

Elderly subject 61 years and over (i.e., ≥ 61)

- Number of seroconversions[1] or significant increase in antibody titre[2] > 30%
- Mean geometric increase > 2.0
- The proportion of subjects achieving an HI titre ≥ 40 should be > 60%

1 Seroconversion is defined as negative pre-vaccination serum (< 10) / post-vaccination titre ≥ 40.
2 Significant increase in antibody titre is defined as at least a fourfold increase from non-negative pre-vaccination serum (≥ 10)

Statistical methods / Sample size

There was no statistical null hypothesis associated with the primary immunogenicity objective, which was analyzed descriptively.

The null hypothesis for the secondary immunogenicity objective stated that a regimen consisting of two doses of Focetria influenza vaccine containing 7.5 µg each does not comply with the non-inferiority assumption that the lower limit of the 95% confidence interval (CI) of the post-immunization (day 43) GMT ratio is > 0.5, by using HI test, when compared to two doses of Fluad-H5N1 influenza vaccine containing 15 µg.

- H0: GMT7.5 / GMT 15 ≤ 0.5
- H1: GMT7.5/ GMT 15 > 0.5

The target sample size was at least 520 subjects overall (at least 260 aged 18-60 years and260 aged 61 and over). The planned sample size accounted for a 10% dropout rate, in order to achieve a minimum of 460 evaluable subjects (230 in each vaccine group).

The sample-size calculation was based on the secondary immunogenicity objective of non-inferiority between two doses of Fluad-H5N1 influenza vaccine containing 7.5 µg vs. two doses of Fluad-H5N1 influenza vaccine containing 15 µg, as measured by HI test.

A 0.025 one-sided alpha level, a clinically relevant value of 0.5 in terms of the ratio of post-immunization GMTs (day 43, visit 3) between the two vaccines (i.e., a difference of 0.301 in terms of log10 [GMTs] between vaccines) and a power of 80% were chosen.

RESULTS

Numbers analysed

A total of 486 subjects were enrolled, 313 aged 18-60 years (adults) and 173 aged 61 years and over (elderly). Among the adults 157 and 156 subjects received Focetria influenza vaccine containing 7.5 µg and 15 µg of A/H5N1 influenza antigen, respectively. Among the elderly 87 and 86 subjects received Focetria influenza vaccine containing 7.5 µg and 15 µg of A/H5N1 influenza antigen, respectively.

Out of the 486 enrolled subjects, 464 subjects were included in the Per-Protocol population (PP) analyses.

For the Focetria 7.5µg and the Focetria 15µg groups, 151 and 150 adult subjects and 84 and 79 elderly subjects, all respectively, were included in the immunogenicity analyses. Within each age stratum demographic and other baseline characteristics were similar between the groups.

Number of subjects: planned (actually enrolled)

Vaccine group	**Focetria 7.5**	**Focetria 15**	
Vaccine	7.5 µg/dose, adjuvanted	15 µg/dose, adjuvanted	Total
Adults (18-60 years)	130 (157)	130 (156)	260 (313)
Elderly (≥ 61 years)	130 (87)	130 (86)	260 (173)
Total	260 (244)	260 (242)	520 (486)

Outcomes and estimation

Vaccine immunogenicity was assessed on all subjects using the SHR, HI, and MN assays.
An analysis of sera by SRH at day 43 has (adults: 297 subjects; elderly: 161 subjects) been performed.

The tables below give an overview of the immunogenicity results for the adult and elderly population.

Evaluation of immunogenicity criteria according CPMP/VEG/4717/03 in adults, percentages of subjects (n/N[a]), GMAs, and GMRs with 95% CIs before and after 7.5 µg and 15 µg Focetria vaccination

		Total immunogenicity population	Subset seronegative at baseline

Time point	Assessment Parameters	7.5 µg N=149	15 µg N=148	7.5 µg N=133	15 µg N=128
Pre-vaccination (day 1)	GMA (95%CI)	4.79 (4.34-5.3)	5.21 (4.72-5.76)	4 (4-4)	4 (4-4)
	Seroprotection[b] (95%CI%)	5% (2-10)	9% (5-15)	0% (0-3)	0% (0-3)
Post-1st dose (day 22)	Seroprotection[b] (95%CI%)	41% (33-49)	51% (42-59)	36% (28-45)	46% (37-55)
	GMR[c] (95%CI)	2.42 (2.02-2.89)	**2.76 (2.31-3.3)**	**2.53 (2.09-3.07)**	**3.19 (2.62-3.88)**
	Serocon.[e] /sign. increase[f] (95%CI%)	39% (31-47)	**42% (34-50)**	36% (28-45)	**46% (37-55)**
Post-2nd dose (day 43)	Seroprotection[b] (95%CI%)	**86% (79-91)**	**85% (78-90)**	**84% (77-90)**	**84% (76-90)**
	GMR[d] (95%CI)	**7.85 (6.7-9.2)**	**6.81 (5.81-7.98)**	**8.93 (7.65-10)**	**8.56 (7.31-10)**
	Serocon.[e] /sign. increase[f] (95%CI%)	**85% (79-91)**	**80% (72-86)**	**84% (77-90)**	**84% (76-90)**

bold indicated that CHMP requirement was achieved: Serocon./sign. increase = seroconversion/significant increase.

[a] n/N number of subjects of the population (N) who met SRH definition of seroprotection, seroconversion, or significant increase;

[b] Seroprotection is defined as SRH area ≥ 25 mm^2;

[c] GMR = geometric mean of ratios of SRH areas (day 22/day 1);

[d] GMR = geometric mean of ratios of SRH areas (day 43/day 1);

[e] Seroconversion is defined as negative pre-vaccination serum (<4 mm^2) and post-vaccination SRH area ≥ 25 mm^2;

[f] Significant increase is defined as at least a 50% increase in SRH area.

Evaluation of immunogenicity criteria according CPMP/VEG/4717/03 in elderly, percentages of subjects (n/N[a]), GMAs, and GMRs with 95% CIs before and after 7.5 µg and 15 µg Focetria vaccination:

		Total immunogenicity population		Subset seronegative at baseline	
Time point	Assessment Parameters	7.5 µg N=83	15 µg N=78	7.5 µg N=65	15 µg N=52
Pre-vaccination (day 1)	GMA (95%CI)	6.05 (4.92-7.43)	7.72 (6.24-9.56)	4 (4-4)	4 (4-4)
	Seroprotection[b] (95%CI%)	11% (5-20)	24% (15-35)	0% (0-6)	0% (0-6)
Post-1st dose (day 22)	Seroprotection[b] (95%CI%)	53% (42-64)	58% (46-69)	45% (32-57)	42% (29-57)
	GMR[c] (95%CI)	**2.85 (2.22-3.66)**	**2.4 (1.86-3.11)**	**3.38 (2.47-4.63)**	**3.12 (2.19-4.44)**

	Serocon.[e] /sign. increase[f] (95%CI%)	**45% (34-56)**	**42% (31-54)**	**45% (32-57)**	**42% (29-57)**
Post-2nd dose (day 43)	Seroprotection[b] (95%CI%)	**81% (71-89)**	**81% (70-89)**	**77% (65-86)**	**73% (59-84)**
	GMR[d] (95%CI)	**5.02 (3.91-6.45)**	**3.94 (3.04-5.1)**	**6.7 (5.09-8.82)**	**6.06 (4.44-8.28)**
	Serocon.[e] /sign. increase[f] (95%CI%)	**71% (60-81)**	**68% (56-78)**	**77% (65-86)**	**73% (59-84)**

bold indicated that CHMP requirement was achieved: Serocon./sign. increase = seroconversion/significant increase.

[a] n/N number of subjects of the population (N) who met SRH definition of seroprotection, seroconversion, or significant increase;

[b] Seroprotection is defined as SRH area ≥ 25 mm^2;

[c] GMR = geometric mean of ratios of SRH areas (day 22/day 1);

[d] GMR = geometric mean of ratios of SRH areas (day 43/day 1);

[e] Seroconversion is defined as negative pre-vaccination serum (<4 mm^2) and post-vaccination SRH area ≥ 25 mm^2;

[f] Significant increase is defined as at least a 50% increase in SRH area.

In the baseline seronegative subset (261 adults; 117 elderly) of the total immunogenicity population, there was a tendency for slightly higher GMRs and higher percentages demonstrating seroconversion than in the total immunogenicity population. At day 43 all CHMP immunogenicity criteria were met. The results show that in subjects without detectable antibody titres at baseline the immunes response after two Focetria vaccinations with 7.5 µg or 15 µg doses met all three CHMP immunogenicity criteria as requested by the EMEA/CPMP/VEG/4717/03.

An analysis of sera samples assayed by MN has performed on the full immunogenicity population (301 adults; 163 elderly) for all time points (day 1, day 22, day 43). The immune responses at day 43 were high with 83% and 58% of adult and elderly recipients of 7.5 µg Focetria demonstrating at least 4-fold increases above baseline. At this time point GMTs respectively increased 11 and 4.53-fold above baseline. The immune responses to 7.5 µg and 15 µg Focetria were similar.

In the baseline seronegative subset (280 adults; 120 elderly) of the total immunogenicity population, there was a tendency at day 43 for slightly higher GMRs and higher percentages demonstrating at least 4-fold increases than in the total immunogenicity population, especially in the elderly. However, slightly fewer elderly subjects attained postvaccination titres of at least 1:20, 1:40, and 1:80 with similar percentages attaining these titres after the second vaccination in adults regardless of baseline seronegativity. The immune responses to 7.5 µg and 15 µg Focetria were similar in baseline seronegative subjects.

Evaluation of MN assay in adult population: reciprocal titres assessed by MN

		Total immunogenicity population		Subset seronegative at baseline	
Time point	MN	7.5 µg N=151	15 µg N=150	7.5 µg N=141	15 µg N=139
Pre- vaccination (day 1)	≥1:20 (95% CI)	7% (3-12)	7% (4-13)	0% (0-3)	0% (0-3)
	≥1:40 (95% CI)	3% (1-7)	3% (1-7)	0% (0-3)	0% (0-3)
	≥1:80 (95% CI)	1% (0-4)	1% (0-4%)	0% (0-3)	0% (0-3)
Post-1st dose (day 22)	≥1:20 (95% CI)	52% (44-60)	58% (50-66)	49% (40-57)	55% (47-64)
	≥1:40 (95% CI)	34% (26-42)	43% (35-51)	30% (22-38)	40% (31-48)
	≥1:80 (95% CI)	20% (14-27)	23% (16-30)	16% (11-13)	23% (16-31)
Post-2nd dose (day 43)	≥1:20 (95% CI)	91% (86-95)	88% (82-93)	91% (85-95)	88% (81-93)
	≥1:40 (95% CI)	85% (78-90)	81% (73-87)	84% (77-89)	81% (73-87)
	≥1:80 (95% CI)	66% (58-74)	63% (55-71)	65% (56-72)	64% (55-72)

Evaluation of MN assay in elderly population, reciprocal titres assessed by MN

		Total immunogenicity population		Immunogenicity of subset of total population who were seronegative at baseline	
Time point	MN	7.5 µg N=84	15 µg N=79	7.5 µg N=59	15 µg N=61
Pre- vaccination (day 1)	≥1:20 (95% CI)	30% (20-41)	23% (14-34)	0% (0-6)	0% (0-6)
	≥1:40 (95% CI)	18% (10-28)	14% (7-24)	0% (0-6)	0% (0-6)
	≥1:80 (95% CI)	8% (3-16)	11% (5-21)	0% (0-6)	0% (0-6)
Post-1st dose (day 22)	≥1:20 (95% CI)	63% (52-73)	59% (48-70)	47% (34-61)	51% (38-64)
	≥1:40 (95% CI)	49% (38-60)	51% (39-62)	32% (21-46)	41% (29-54)
	≥1:80 (95% CI)	33% (23-44)	37% (26-48)	20% (11-33)	30% (19-43)
Post-2nd dose (day 43)	≥1:20 (95% CI)	89% (81-95)	82% (72-90)	85% (73-93)	79% (66-88)
	≥1:40 (95% CI)	79% (68-87)	76% (65-85)	69% (56-81)	72% (59-83)
	≥1:80 (95% CI)	54% (42-65)	58% (47-69)	42% (30-56)	56% (42-68)

- Clinical studies in special populations

Elderly

In study V87P1 seventy-three subjects aged 61 years and over (elderly) were enrolled.

For the elderly population, there was no difference between the Focetria 7.5 µg and 15 µg groups in the attainment of the three CHMP criteria (CPMP/BWP/214/96) for the A/Vietnam/1194/2004-like (H5N1) influenza antigen both using the SRH. Three out of the three CHMP criteria were met in subjects receiving two doses of either the 7.5 µg or the 15 µg Focetria using the SRH assay.

Paediatric population

Neonates and infants are not included in the population studied during the clinical development and such a situation is expected to be common for the pandemic vaccines. Therefore this does not represent an obstacle to the current authorisation. However this situation is reflected in the SPC, recommendation for injection in infants is left to national official recommendations during the pandemic period.

- Discussion on clinical efficacy

The development of Focetria benefits is based on the experience with Fluad, Novartis' seasonal trivalent adjuvanted influenza vaccine. The MF59C.1 adjuvant contained in the vaccine is an oil- in-water emulsion, composed mainly of squalene. Focetria is manufactured with the same process and has the same adjuvant used for Fluad.

Initial dose finding studies with an adjuvanted candidate vaccine containing mock-up strains H5N3 or H9N2 showed that a dose as low as 3.75 µg HA elicits adequate seroprotection in healthy adults. All three immunogenicity criteria defined by CHMP (CPMP/BWP/214/96) were fulfilled. However these results are based on a very small number of individuals (10-12 individuals per vaccine group).

The studies also confirmed that adjuvant MF59C.1 significantly enhances specific immune response to influenza vaccines. In fact, this result is consistent across studies and tests used (HI, MN, SRH). It is also evident that two doses of candidate vaccine are necessary to induce a proper immune response.

Subsequently, the dossier was shifted to a H5N1 mock-up file and further data were provided for this vaccine in order to establish efficacy Focetria.

For 7.5 µg and 15 µg HA group, seroconversion rate and seroconversion factor in the adult and the elderly population were in compliance with CHMP requirements (CPMP/BWP/214/96). In both age groups, the GMTs induced by Focetria (7.5 µg HA) was non-inferior to the GMTs induced by the vaccine containing 15 µg HA.

Seroprotection rates in adults and elderly calculated using the SRH assay met the set CHMP requirements. These results were sustained also by the microneutralisation assay.

A subset of patients will be followed up for long-term immunogenicity data; samples will be tested after 6 and 12 month. The applicant commits to submit these results with the final study report.

Paediatric studies were not included in the clinical development program. These studies are not required according CPMP/VEG/4717/03 at this time point. Recommendations for immunisation of the paediatric population are left to national official recommendations during the pandemic period.

Clinical safety

- Patient exposure

Study V87P1

Overall 485 subjects of the 486 enrolled were exposed to the investigational vaccines and included in the safety analyses. Among the adults, one subject did not receive any dose and 7 subjects did not receive the second dose. Among the elderly, 7 subjects did not receive the second dose.

- Adverse events

Adults

Summary of local reactions after any vaccination - Adults

Type of Reaction		Number (%) of subjects		
		Focetria 7.5 N=156	**Focetria 15 N=156**	**Total N=312**
Erythema	any	18 (12%)	20 (13%)	38 (12%)
	> 50 mm	1 (1%)	0	1 (<1%)
Induration	any	32 (21%)	28 (18%)	60 (19%)
	> 50 mm	1 (1%)	1 (1%)	2 (1%)
Swelling	any	15 (10%)	21 (13%)	36 (12%)
	> 50 mm	2 (1%)	0	2 (1%)
Ecchymosis	any	5 (3%)	8 (5%)	13 (4%)
	> 50 mm	0	0	0
Pain	any	88 (56%)	101 (65%)	189 (61%)
	Severe	3 (2%)	2 (1%)	5 (2%)

Summary of systemic reactions after any vaccination – Adults

Type of Reaction		Number (%) of subjects		
		Focetria 7.5 N=156	Focetria 15 N=156	Total N=312
Systemic reactions				
Chills	any	16 (10%)	17 (11%)	33 (11%)
	Severe	3 (2%)	0	3 (1%)
Malaise	any	22 (14%)	26 (17%)	48 (15%)
	Severe	3 (2%)	3 (2%)	6 (2%)
Myalgia	any	54 (35%)	47 (30%)	101 (32%)
	Severe	4 (3%)	0	4 (1%)
Arthralgia	any	21 (13%)	23 (15%)	44 (14%)
	Severe	3 (2%)	1 (1%)	4 (1%)
Headache	any	37 (24%)	42 (27%)	79 (25%)
	Severe	2 (1%)	4 (3%)	6 (2%)
Sweating	any	10 (6%)	9 (6%)	19 (6%)
	Severe	0	1 (1%)	1 (<1%)
Fatigue	any	25 (16%)	29 (19%)	54 (17%)
	Severe	2 (1%)	3 (2%)	5 (2%)
Nausea	any	5 (3%)	15 (10%)	20 (6%)
	Severe	0	0	0
Coughing	any	9 (6%)	7 (4%)	16 (5%)
	Severe	0	1 (1%)	1 (<1%)
Wheezing	any	8 (5%)	4 (3%)	12 (4%)
	Severe	1 (1%)	0	1 (<1%%)
Chest tightness	any	5 (3%)	2 (1%)	7 (2%)
	Severe	2 (1%)	0	2 (1%)
Diffi. breathing	any	4 (3%)	2 (1%)	6 (2%)
	Severe	0	0	0
Sore throat	any	10 (6%)	14 (9%)	24 (8%)
	Severe	0	1 (1%)	1 (<1%)
Facial edema	any	2 (1%)	2 (1%)	4 (1%)
	> 50 mm	0	0	0
Red eye	any	8 (5%)	6 (4%)	14 (4%)
	Severe	0	0	0
Fever	≥ 38°C	2 (1%)	4 (3%)	6 (2%)
	≥ 40°C	0	0	0

The percentages of adults experiencing each local reaction, systemic reaction and other indicators of reactogenicity (i.e., staying home due to a reaction and using analgesics or antipyretics medication) were generally similar between the Focetria 7.5 µg and 15 µg groups and overall.

The most frequently experienced local reaction was pain.

The most frequently experienced systemic reactions were myalgia and headache, followed by chills, malaise, arthralgia and fatigue.

Twenty-one adults, 7 % of the overall adult population, experienced symptoms consistent with oculo-respiratory-symptoms (ORS). All reactions were mild except for one adult who reported moderate red

eye on day 2. This is in the same range as other reports on ORS in clinical studies with influenza vaccines.

Local and systemic reactions were mostly mild or moderate in severity. Each severe local reaction and each severe systemic reaction was experienced by no more than 2% of adults overall.

- Serious adverse event/deaths/other significant events

No serious adverse events or death were reported.

- Safety in special populations

Elderly

Summary of local reactions after any vaccination - Elderly

Type of Reaction		**Number (%) of subjects**		
		Focetria 7.5 N=87	**Focetria 15 N=86**	**Total N=173**
Erythema	any	5 (6%)	5 (6%)	10 (6%)
	> 50 mm	0	0	0
Induration	any	3 (3%)	10 (12%)	13 (8%)
	> 50 mm	0	0	0
Swelling	any	3 (3%)	4 (5%)	7 (4%)
	> 50 mm	0	0	0
Ecchymosis	any	3 (3%)	1 (1%)	4 (2%)
	> 50 mm	0	0	0
Pain	any	17 (20%)	22 (26%)	39 (23%)
	Severe	0	1 (1%)	1 (1%)

Summary of systemic reactions after any vaccination – Elderly

Type of Reaction		Number (%) of subjects		
		Focetria 7.5 N=87	Focetria 15 N=86	Total N=173
Systemic reactions				
Chills	any	5 (6%)	9 (10%)	14 (8%)
	Severe	1 (1%)	1 (1%)	2 (1%)
Malaise	any	5 (6%)	10 (12%)	15 (9%)
	Severe	1 (1%)	1 (1%)	2 (1%)
Myalgia	any	10 (11%)	12 (14%)	22 (13%)
	Severe	0	1 (1%)	1 (1%)
Arthralgia	any	6 (7%)	13 (15%)	19 (11%)
	Severe	1 (1%)	1 (1%)	2 (1%)
Headache	any	10 (11%)	10 (12%)	20 (12%)
	Severe	0	0	0
Sweating	any	4 (5%)	5 (6%)	9 (5%)
	Severe	1 (1%)	0	1 (1%)
Fatigue	any	4 (5%)	10 (12%)	14 (8%)
	Severe	1 (1%)	0	1 (1%)
Nausea	any	3 (3%)	5 (6%)	8 (5%)
	Severe	0	0	0
Coughing	any	4 (5%)	7 (8%)	11 (6%)
	Severe	1 (1%)	1 (1%)	2 (1%)
Wheezing	any	2 (2%)	3 (3%)	5 (3%)
	Severe	0	0	0
Chest tightness	any	0	4 (5%)	4 (2%)
	Severe	0	1 (1%)	1 (1%)
Diff. breathing	any	2 (2%)	2 (2%)	4 (2%)
	Severe	0	0	0
Sore throat	any	4 (5%)	3 (3%)	7 (4%)
	Severe	0	0	0
Facial edema	any	1 (1%)	0	1 (1%)
	> 50 mm	0	0	0
Red eye	any	2 (2%)	5 (6%)	7 (4%)
	Severe	0	0	0
Fever	≥ 38°C	0	0	0
	≥ 40°C	0	0	0

The percentages of elderly subjects experiencing each local reaction, systemic reaction and other indicators of reactogenicity were generally similar between the Focetria 7.5 µg and 15 µg groups and overall.

The most frequently experienced local reaction was pain.

The most frequently experienced systemic reactions in the elderly were myalgia, headache and arthralgia followed by chills, malaise, and fatigue.

Overall, 6 elderly subjects, 3.5% of the overall elderly population, experienced symptoms consistent with ORS. All reactions were mild except for one elderly who reported severe coughing at 6 hours and

on day 2 after the first dose. This is in the same range as other reports on ORS in clinical studies with influenza vaccines.

Local and systemic reactions were mostly mild or moderate in severity

- Safety related to drug-drug interactions and other interactions

No data on co-administration of the mock-up vaccine with other vaccines are available. This is reflected in the SPC under section 4.5.

- Discontinuation due to adverse events

None

Supportive studies

The dose finding studies V7P37 (and extension study V7P37E1) and DMID 04-019 include 161 subjects of which 80 subjects received at least one dose of different formulations of the adjuvanted candidate vaccine and 81 subjects received at least one dose of a comparator non-adjuvanted vaccine. The total number of 176 doses of adjuvanted candidate vaccine and 172 doses of non-adjuvanted control vaccine were administered.

In study V7P37 and extension study V7P37E1, pain was the most frequently reported local reaction in the adjuvanted group. At each dose level the frequency is higher compared to the control group, in addition there appeared to be a dose response relationship.

The most frequently reported systemic reaction is headache, followed by myalgia and fatigue. No dose response relationship or marked difference with the control group can be observed.

In study DMID 04-019 tenderness was most frequently reported, and pain and tenderness were both more frequently reported as in the non-adjuvanted group after each dose. After the second dose, erythema and induration are also more frequently reported in the adjuvanted group.

Headache was the most common systemic reaction. There was no obvious difference between the groups or dose levels.

A limited number of subjects reported one or more unsolicited events, 4 subjects in study V7P37, 2 in the adjuvanted candidate vaccine (H5N3) 15 µg group, one in the adjuvanted candidate vaccine (H5N3) 7.5 µg group and one after the second dose of the non-adjuvanted 7.5 µg dose group. In extension study V7P37E1 a total of two subjects, both in the adjuvanted candidate vaccine (H5N3) 30 µg group, reported 3 non-serious adverse events (fever and headache, injection site pain), which were considered to be probably related to the vaccine.

In study DMID 04-019 in total 160 AEs were reported, 105 of which onset after the first vaccination and 55 after the second vaccination. The most frequently reported systemic reaction after vaccination with the adjuvanted candidate vaccine was headache (up to 50% of subjects in group containing 30 µg non-adjuvanted vaccine.

Reports of severe common reactions were limited to one subject receiving 15 µg non-adjuvanted vaccine who experienced severe malaise and nausea.

- Discussion on clinical safety

The dose finding studies were too small to evaluate common adverse events.

Thus, the safety analysis is based on the pivotal study with H1N5 candidate vaccine.

The observed rate of adverse events was lower than expected. Reactogenicity was generally higher for adults compared to elderly, and after the first than the second dose. No major differences were observed between the Focetria 7.5 µg and 15 µg groups.

The MF59C.1 adjuvant is also included in the currently licensed Fluad seasonal influenza vaccine. Additional available information on adjuvant safety from clinical studies and Post-Marketing surveillance have been provided and support the favourable safety profile of Focetria.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan.

Since Focetria is indicated for use in an officially declared pandemic situation, the Pharmacovigilance Plan will additionally be updated to be in compliance with the CHMP recommendations for the Pharmacovigilance Plan for Pandemic Influenza Vaccines.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Adverse events of special interests (AESI)	- Prospective cohort study during pandemic - Routine pharmacovigilance with active follow-up to obtain sufficient information - Special PSUR reporting requirements in the pandemic situation	Mention in Section 4.8 of the SPC
Safety profile of the final pandemic vaccine	- Prospective cohort study during pandemic - Routine pharmacovigilance - Special PSUR reporting requirements in the pandemic situation	N/A
Immunogenicity of the final pandemic vaccine	- Prospective cohort study during pandemic (subset of subjects)	N/A
Inadequately studied patients groups	- Prospective cohort study during pandemic - Routine pharmacovigilance - Special PSUR reporting requirements in the pandemic situation	N/A

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The present application is for a core pandemic dossier, based on data generated with 3 mock-up strains: H5N1, H9N2 and H5N3. The data with the two latter strains is supportive to the data generated with the RG H5N1 strain, derived from A/Viet Nam/1194/2004.

Due to the possible constrains in a pandemic situation, the applicant provided additional information with regard to the optimisation of the manufacturing process, alternative testing for extraneous agents, alternative testing to assay the potency (e.g. HA content) of the vaccine, the supply of SPF and production eggs and production of MF59. This additional information was regarded as satisfactory.

During the evaluation of Focetria, no major objections were identified. Minor concerns have been adequately addressed, however several commitments are made by the applicant, and several follow-up measures are defined to provide further information post-approval. In conclusion all quality issues are resolved.

Non-clinical pharmacology and toxicology

The non-clinical package for Focetria, this is in accordance with the relevant guidelines, namely the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03), the note for guidance on preclinical pharmacological testing and toxicological testing of vaccines guidelines pertaining to the non-clinical testing requirements for vaccines (CPMP/SWP/465/95) and the guideline on adjuvants in vaccines for human use (CPMPVEG/17/03/2004).

The challenge testing in the ferret shows that the formulation of vaccine containing either 7.5 µg or 15 µg of A/NIBRG-14 (H5N1) antigen per dose is both immunogenic and efficacious in reducing the viral load and viral shedding. The various disease markers indicate the protective effects of vaccination with the formulation of the vaccine used.

Immunogenicity studies in young and old mice showed that immunisation with both adjuvanted candidate vaccine and non-adjuvanted vaccine, elicited a dose-related antigen-specific antibody response, even in mice seropositive at baseline. The presence of MF59 adjuvant resulted in a more immunogenic and therefore more efficacious product, in both young and old mice.

Efficacy

The development of Focetria is based on the experience with Fluad, Novartis' seasonal, trivalent adjuvanted influenza vaccine. The MF59C.1 adjuvant is an oil- in- water emulsion, composed mainly of squalene. Focetria is manufactured with the same process and has the same adjuvant used for Fluad.

Initial dose finding studies with an adjuvanted candidate vaccine containing mock-up strains H5N3 or H9N2 showed that a dose as low as 3.75 µg HA elicits adequate seroprotection in healthy adults. All three immunogenicity criteria defined by CHMP (CPMP/BWP/214/96) were fulfilled. However these results are based on a very small number of individuals (10-12 individuals per vaccine group).

The studies confirm that adjuvant MF59C.1 significantly enhances specific immune response to influenza vaccines. In fact, this result is consistent across studies and tests used (HI, MN, SRH). It is also evident that two doses of candidate vaccine are necessary to induce a proper immune response.

Subsequently, the dossier was shifted to a H5N1 mock-up file and further data were provided for this vaccine in order to establish efficacy Focetria.

Immunogenicity of the mock-up strain A/Vietnam/1194/2004 (H5N1) was determined in 458 subjects (297 adults; 161 elderly) by using by single radial haemolysis (SRH) and haemagglutination inhibition assay. In addition to SRH, an analysis of serum samples assayed by microneutralisation assay (MN) has been repeated on the full immunogenicity population (301 adults; 163 elderly). Subjects received 2 doses of Focetria containing 7.5 µg or 15 µg influenza antigen (HA).

For 7.5 µg and 15 µg HA group, seroconversion rate and seroconversion factor in the adult and the elderly population were in compliance with CHMP requirements (CPMP/BWP/214/96). In both age groups, the GMTs induced by Focetria (7.5 µg HA) were non-inferior to the GMTs induced by the vaccine containing 15 µg HA. Seroprotection rates in adults and elderly calculated using the SRH assay met the set CHMP requirements. These results were sustained also by the microneutralisation assay.

Paediatric studies were not included in the clinical development program. These studies are not required according CPMP/VEG/4717/03 at this time point. Recommendations for immunisation of the paediatric population are left to national official recommendations during the pandemic period.

From an epidemiological point of view it is very unlikely that influenza strain A/Vietnam /1194/2004 would be the next pandemic strain, since the virus will either undergo further antigenic drift or the pandemic will be caused by another subtype of influenza vaccines (antigenic shift). Antigenic shift and drift are natural phenomena related to all influenza viruses. For example, additional mutations will be required to enable the virus to transmit effectively from human to human. It is highly unlikely, therefore, that Focetria containing the strain derived from A/Vietnam /1194/2004 will provide protection when using during a pandemic. In line with the developed core dossier concept, a variation would have to be submitted to introduce the WHO/EU recommended strain prepared from the influenza virus causing the pandemic, prior to use of Focetria in a pandemic. This will assure that the vaccine will induce a satisfactory immune response to the pandemic influenza virus.

For the same scientific reasons, and in absence of any studies demonstrating that antibodies elicited by Focetria containing the strain derived from A/Vietnam /1194/2004 will react with other H5N1 subtypes (in the neutralising antibody assay), this vaccine has not been demonstrated to have a role in use in the prepandemic period. No predictions can be made of the immunogenicity of Focetria against strains other than A/Viet Nam/1194/2004.

Safety

The observed rate of adverse events was lower than expected. The most frequently experienced local reaction in adults as well as in elderly was pain. The most frequently experienced systemic reactions in adults were myalgia and headache, followed by chills, malaise, arthralgia and fatigue.

In elderly the most frequently experienced systemic reactions were myalgia, headache and arthralgia followed by chills, malaise, and fatigue.

Local and systemic reactions were mostly mild or moderate in severity.

The safety profile of the vaccine, as it is revealed by the clinical studies performed, is satisfactory, especially in a pandemic situation.

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

- User consultation

The applicant performed readability testing ("user consultation") and a satisfactory report has been provided.

The applicant performed a readability testing on the English version of the package leaflet (PL) by a structured questionnaire. The sample was composed of 20 subjects (19/20 were female): ten adults were recruited in round 1 and ten in round 2. The composition of the target group was acceptable. They were asked 14 questions on the content of PL and 3 questions to obtain their feedback on the general layout and appearance of the PL. The PL was up-dated with recommended changes after round 1. The questionnaire was sufficient with regards to the number of questions and the different aspect of the PL and the evaluation and question rating system was acceptable.
In general, there were no difficulties for the respondents to find and understand different parts of the PL.
After 2 rounds the PL was considered to meet the criteria for readability testing as set out in the MHRA's Guidance on the User Testing of Patient Information Leaflets (June 2005).
In conclusion, the main objectives of the user consultation have been achieved, namely to assess the readability of the PL, to identify problems regarding comprehensibility and usefulness of the information and to describe possible changes to the PL to improve readability.

Risk-benefit assessment

An influenza pandemic is a global outbreak of influenza disease that occurs when a new type A influenza strain emerges in the human population, causes serious illness, and then spreads easily from

person to person worldwide. Though there may be no vaccines available yet at the beginning of a pandemic, efficacious and safe vaccines are regarded as an important tool to counteract this severe threat to public health, allowing protection from (severe) disease or death. The formulation of a pandemic vaccine has to take into account that, in contrast to seasonal influenza, all people will be immunologically naïve for the circulating pandemic strain. This naivety is expected to make it more difficult to elicit a protecting immune response in vaccinees. However, it may deserve some further discussions, what serological status and background immunity against new haemagglutinins may be characteristic for a naïve population.

With this background the applicant developed Focetria, a monovalent, inactivated and adjuvanted vaccine, containing 7.5µg haemagglutinin (HA) (virus surface antigen) from the influenza strain A/Vietnam /1194/2004 (H5N1) per 0.5 ml dose. The evaluation of the clinical efficacy was mainly based on the quantification of SRH and HI titres in vaccinees and subsequent analysis of the derived parameters seroprotection rate, seroconversion rate and factor, what generally is accepted as surrogate markers for efficacy of influenza vaccines.

Two dose ranging studies evaluating safety and immunogenicity in young adults have been performed with adjuvanted candidate vaccines with influenza pandemic reference virus strains (H5N3 and H9N2). Subsequently, the dossier was shifted to a H5N1 mock-up file and further data were provided for this vaccine in order to establish efficacy of the mock-up vaccine.

Clinical trials on protective efficacy for the mock-up vaccine cannot be performed. Therefore a detailed characterisation of the immunological response to the mock-up vaccines is required. The vaccine virus strains chosen for these studies should allow simulating a situation where the target population for vaccination is immunologically naïve. The criteria for these studies are laid down the Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application, CPMP/VEG/4717/03. All three CHMP criteria are fulfilled by vaccines containing 7.5 µg haemagglutinin (HA) from the influenza strain A/Vietnam /1194/2004 (H5N1) per 0.5 ml dose.

The safety profile of the mock-up vaccine is acceptable.

In the submitted core pandemic dossier, the applicant reported as required according CPMP/VEG/4717/03, the findings from non-clinical tests and clinical trials using the mock-up strain derived from the avian influenza strain A/Vietnam /1194/2004 (H5N1).

From an epidemiological point of view it is very unlikely that influenza strain A/Vietnam /1194/2004 would be the next pandemic strain, since will either undergo further antigenic drift or the pandemic will be caused by another subtype of influenza vaccines (antigenic shift). Thus in the event of a pandemic, the applicant would have to file a variation to the existing marketing authorisation to introduce the exact matching pandemic vaccine strain.

During the pandemic, the applicant will collect safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation (specific obligation).

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

During the pandemic, the applicant will conduct a prospective cohort study as identified in the pharmacovigilance plan (specific obligation).

Recommendation

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

The CHMP recommends granting this marketing authorisation for Focetria under exceptional circumstances, because in the present stage of knowledge comprehensive scientific information required for the vaccine containing the actual pandemic strain cannot be gathered.

The missing scientific information relates to the safety and effectiveness of the pandemic vaccine. These data can only be obtained once the actual strain causing the pandemic is included in the vaccine and during actual use of the vaccine. Therefore, the company has agreed the following specific obligations:

- To collect, during the pandemic, clinical safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation.
- To conduct, during the pandemic, a prospective cohort study as identified in the Pharmacovigilance plan.