European Medicines Agency

London, 24 September 2009
Doc. Ref.: EMEA/CHMP/503605/2009

CHMP ASSESSMENT REPORT
FOR

FOCETRIA

Common Name:
Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179A) [1]

Procedure No. EMEA/H/C/710

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

[1] This vaccine was initially developed as a Pandemic Mock-up file using H5N1 as the Pandemic strain

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission history

The applicant Chiron S.r.l. submitted on 12 January 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Focetria as an H5N1 mock-up vaccine, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The applicant's name Chiron S.r.l was changed into Novartis Vaccines and Diagnostics S.r.l in October 2006 further to the Novartis acquisition. As a consequence the applicant of this application now is Novartis Vaccines and Diagnostics S.r.l.

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The CHMP issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Focetria on 22 February 2007. The commission decision was issued on 2 May 2007.

The Applicant applied for the following indications:
Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

On 22 September 2009 the Marketing Authorisation Holder (MAH) applied for a variation according to Article 8 of the Commission Regulation (EC) No. 1085/2003 in order to update the composition of the strain of Focetria to those officially recommended by WHO and CHMP for the Pandemic Influenza A (H1N1)v, and this is the following:

A/California/7/2009 (H1N1)v like strain (X-179A)

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 15 December 2006 (EMEA/420093/2005). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:

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

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

Rapporteur:	Dr Antonio Addis	Co-Rapporteur:	Dr Barbara van Zwieten-Boot

CHMP Peer reviewer(s): Dr Christian Schneider

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 12 January 2006.
- Accelerated Assessment procedure was agreed-upon by CHMP on 15 December 2005.
- The procedure started on 1 February 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 April 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 31 March 2006. In accordance with Article 6(3) of Regulation (EC) No. 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The BWP discussed Focetria during their meeting on 19-20 April 2006 and adopted a BWP report to the CHMP.
- During the meeting on 24-27 April 2006, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 April 2006.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2006 and 24 October 2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 January 2007.
- The VWP discussed Focetria during their meeting on 9-11 January 2007 and adopted a Report to the CHMP.
- The BWP discussed Focetria during their meeting on 15-16 January 2007 and adopted a Report to the CHMP.
- During the CHMP meeting on 22-24 January 2007, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 January 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 February 2007.
- The BWP discussed Focetria during their meeting on 12-14 February 2007 and adopted a Report to the CHMP.
- During the meeting on 19-22 February 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Focetria on 22 February 2007. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 22 February 2007.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 2 May 2007

- On 23 July 2009 an opinion on a Type II variation on quality aspects (II-01) was adopted by the CHMP to up-date manufacturing specifications. The European Commission adopted a positive Commission Decision for variation II-01 on 12 August 2009.

- On 18 August 2009 an interim Opinion on a rolling review (RR/01) was adopted by the ETF[2]/CHMP to include information supporting the paediatric use of Focetria.

- On 1 September 2009 an interim Opinion on a rolling review (RR/02) was adopted by the ETF/CHMP to include a revision of the Pharmacovigilance and Risk Management Plan to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

- On 1 September 2009 an interim Opinion on a rolling review (RR/03) has been adopted by the ETF/CHMP to include information on the drug substance to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

- On 21 September 2009 an interim Opinion on a rolling review (RR/04) was adopted by the ETF/CHMP to include information on the drug product to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

- On 22 September 2009, Novartis submitted a variation (PU-05) to introduce the pandemic strain A/California/7/2009 (H1N1)v like strain X-179.

- On 24 September 2009, the CHMP adopted a positive Opinion on a variation (PU-05) to change the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

2 SCIENTIFIC DISCUSSION

2.1. Introduction

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which most or all humans are immunologically naïve emerges to cause clinically apparent illness, and then spreads easily from person to person worldwide

In April 2009, a new strain of human influenza A(H1N1)v was identified and characterised. On 11 June 2009 the WHO declared Phase 6 of the influenza pandemic. The declaration reflected sustained transmission of the virus from person to person in several WHO regions. WHO and other international agencies are calling the disease **pandemic (H1N1)v 2009**. For the virus the nomenclature **influenza A(H1N1)v** (where v indicates variant) has been chosen.

The attack rate for the A(H1N1)v virus strain is expected to be higher than for recently circulating seasonal strains because of the lower levels of pre-existing immunity in the population. Current estimates for the attack rate associated with the influenza A(H1N1)v virus over the first major wave of infection in 2009–10 vary from approximately 10-30 % in different geographical areas. As a result, the actual numbers of clinically apparent infections, cases that require hospitalisation and deaths in the pandemic period is expected to be higher than in recent years for seasonal influenza. These estimates may change (upwards or downwards) during the course of the pandemic.

So far in this pandemic there has been a marked under-representation of infections in people over 65 years of age, who make up only 2% of reported cases.

[2] EMEA Task Force

In Europe, among the reported cases the cases tend to be young, the median age being 25 years in those who acquired the infection during travel, and 13 years in those domestically infected. Nearly 80% of cases are in individuals under 30 years of age. Deaths have occurred in previously healthy subjects as well as in those with underlying conditions or pregnancy that would predispose them to complications of influenza. For more information about the known clinical features of the disease caused by influenza A(H1N1)v virus please see the updated Risk Assessment report from ECDC under:
http://ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf

Specific guidance has been developed for the fast track assessment procedure for pandemic influenza vaccines[3], which can only be used once WHO/EU have officially declared the pandemic (WHO Phase 6). The procedure involves the submission and evaluation of a core pandemic dossier (mock-up) during the inter-pandemic period, followed by a fast track assessment of the data for replacing the mock-up vaccine strain with the recommended pandemic strain as a variation to the MAA.

This guidance is based on a *Proof of Principle* approach by which safety and immunogenicity data would be generated with mock-up vaccines containing subtypes of influenza A to which the majority of the population is naïve. These principles are based on:

- The immune responses to a specific mock-up vaccine containing a strain to which subjects within a specific age range were immunologically naïve is expected to predict responses to the same vaccine construct containing an alternative strain of the same subtype or an alternative subtype of influenza A in a comparable population.

- The safety data generated with a specific mock-up vaccine in clinical studies is expected to predict the safety profile observed with the same vaccine construct containing an alternative strain of the same subtype or an alternative subtype of influenza A in a comparable population.

On the basis of these assumptions the mock-up/core dossier construct allows for insertion of the pandemic strain into a vaccine construct based on all the data obtained with the corresponding mock-up vaccine together with specific data relating to the pandemic strain. This approach rests on the premise that the final pandemic vaccine is produced in the same way (i.e. with regards to the formulation, manufacturing process and control methods) as approved for the mock-up vaccine. Therefore the strain change variation contains mainly the quality data that are new and relevant for the pandemic influenza vaccine virus.

Novartis received a Marketing Authorisation (core pandemic dossier) for Focetria in line with the above mentioned guidance. 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 EU countries through a Mutual Recognition Procedure (MRP). Focetria is indicated for prophylaxis of influenza in an officially declared pandemic situation and for use in accordance with official guidance.

On 22 September 2009 Novartis applied for a variation in order to update to the composition of the strain of Focetria to A/California/07/2009 (H1N1)v officially recommended by WHO and CHMP for the Pandemic Influenza.

Focetria is based on a the proposed new strain, A/California/7/2009 (H1N1)v like strain (X179A), which complies with the WHO[4] and CHMP[5] recommendations for the emergent novel A(H1N1)v

[3]Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure (CPMP/VEG/4986/03).
Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisations Application (CPMP/VEG/4717/03).

[4] http://www.who.int/csr/resources/publications/swineflu/vaccine_recommendations/en/index.html

influenza vaccine composition. In support of the strain change to A/California/07/2009 (H1N1)v, Novartis submitted quality data in accordance with the quality requirements for a novel influenza A(H1N1)v vaccine, the *Guideline On Dossier Structure And Content For Pandemic Influenza Vaccine Marketing Authorisation* (CPMP/VEG/4717/03 Rev. 1) and *EMEA fast track procedure for community human influenza inactivated vaccines annual strain(s)* (CHMP/BWP/99698/07).

The same manufacturing process, with the exception of strain-dependent parameters, and safety precautions were applied to the production of H5N1 and A(H1N1)v, which includes the release and shelf-life specifications. The MAH provided quality data in support of this variation to demonstrate that the vaccine containing A/California/07/2009 (H1N1)v is comparable from the Quality point of view to the Mock-up containing H5N1 A/Vietnam/1203/2004.

Recently, preliminary data on immunogenicity data obtained three weeks after administration of a single dose of an investigational MF59 adjuvanted MDCK cell culture A(H1N1)v vaccine to healthy adults has been made available. The results suggest a good immune response however further assessment and additional data are necessary before drawing final conclusion.

Data from ongoing and planned clinical trials and from studies as specified in the agreed pharmacovigilance/risk management plan using the Focetria vaccine construct with the influenza A(H1N1)v strain are reviewed on an ongoing basis. These studies will allow obtaining further safety, immunogenicity and efficacy data for the influenza A(H1N1)v pandemic vaccine.

The Focetria SPC summarises the existing clinical data and will be updated on an ongoing basis as new data are submitted from the ongoing and planned clinical studies with vaccine containing the pandemic influenza A(H1N1)v strain and/or the same vaccine constructs.

2.2 Quality aspects

The quality section is divided into two parts of which chapter 3.2.1 describes quality characteristics pertaining to the initial Mock-up vaccine (developed with A/Vietnam/1203/2004 (H5N1) NIBRG-14 and chapter 3.2.2. describes quality characteristics submitted in support of the strain change variation to introduce the new pandemic strain A/California/07/2009 (H1N1)v like strain X179A.

2.2.1 Mock-up vaccine (A/Vietnam/1194/2004 (H5N1) NIBRG-14)

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[6] or multi-dose. The vaccine in multi-dose vials is formulated with thiomersal.

[5] EU recommendation for the emergent novel H1N1 influenza vaccine composition (EMEA/CHMP/BWP/3408312009 Rev 1). http://www.emea.europa.eu/pdfs/human/bwp/34083109enrev1.pdf

[6] The MAH has withdrawn the single-dose vial presentation.

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 for the mock-up procedure (H5N1 NIBRG-14) was manufactured by Reverse Genetics (RG) technology and provided by NIBSC, UK, an authorised 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 °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 °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 stabiliser 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 neutralising 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 MAH 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 MAH 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.

Medicinal 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.

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[7] or multi-dose. Vaccine in multi-dose vials is formulated with Thiomersal.

Description and Composition of the finished product:

[7] The MAH has withdrawn the single-dose vial presentation.

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 * propagated in eggs	≥ 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. The same changes in the formulation and manufacturing process approved for FLUAD were submitted for Focetria mock-up variation and approved on 23 July 2009.

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, stabiliser 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 sterilising 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. 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 MAH 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.

2.2.2 Pandemic Strain Variation (A/California/7/2009 (H1N1)v like strain (X179A))

With regard to the quality requirements for a novel influenza A(H1N1)v vaccine, the *Guideline On Dossier Structure And Content For Pandemic Influenza Vaccine Marketing Authorisation* (CPMP/VEG/4717/03 Rev. 1) and *EMEA fast track procedure for community human influenza inactivated vaccines annual strain(s)* (CHMP/BWP/99698/07) are applicable. The same quality requirements and safety precautions apply to production of H5N1 and A(H1N1)v.

The proposed influenza strain for Focetria is: A/California/7/2009 (H1N1)v like strain (X-179A). This vaccine strain complies with the WHO[8] and CHMP[9] recommendations for the emergent novel A(H1N1)v influenza vaccine composition and therefore is accepted.

8 http://www.who.int/csr/resources/publications/swineflu/vaccine_recommendations/en/index.html

The MAH provided quality data in support of this variation to ensure that the manufacture of the drug substance and drug product is appropriately controlled. Adequate release and shelf-life specifications have been set.

Active substance
Information is presented on the source and passage level history of the primary seed virus as well as on the preparation and qualification of the working seed virus lots for the strain.

The Primary virus Seed needed to produce the pandemic A(H1N1)v influenza vaccine was provided by a WHO authorised Reference Laboratory. The pandemic H1N1 virus seed was obtained using the conventional reassortment techniques. The Master Seed was obtained after not more than fourteen passages from the approved Primary Virus Strain by cultivation in the allantoic cavity of SPF eggs. The Working Seed is obtained after only one passage from the Master Seed.

The production method as well all the in-process and release tests for Master and Working Seeds are unchanged with respect to the previous A/Vietnam/1194/2004 (H5N1) and are in compliance with Ph.Eur. requirements.

No changes have been applied to the production process concerning Working Seed growth with respect to A/Vietnam/1194/2004 (H5N1).

Process validation data (inactivation of virus particles and splitting efficiency) have been submitted for three batches. Specific inactivation kinetic studies were carried out. The optimum quantities of polysorbate 80 and of CTAB to allow complete splitting of the X-179A strain were determined using the Split Test in the QC laboratory, prior to application to production lots.

Satisfactory data are presented to demonstrate that the inactivation process is sufficiently validated.

The MAH has demonstrated the effectiveness of the antigen production process to inactivate ALV and the Bovine Adenovirus Type III (BAV 3).

The approved specifications for the drug substance have not been changed.

Validation studies for the SRD assay were performed for the new virus strain A/California/7/2009 (H1N1)v like strain (X-179A). Sufficient assay validation data were provided to assure acceptable performance of SRD assay to quantify HA content in the monovalent bulk.

Batch analysis results of monovalent pooled harvest (3 batches) were provided. All batches have been tested according to the approved specifications. The results of production batch analysis demonstrate reproducibility of the manufacturing process for the product.

Three batches of monovalent pooled harvest have been placed on stability. The proposed 12 month shelf life at 2-8°C for the A(H1N1)v monovalent pooled harvest is supported by extensive data from seasonal H1N1 monovalent pooled harvests and H5N1 monovalent pooled harvests. The company committed to finalise the ongoing studies with A(H1N1)v strain and to report any unexpected results generated during the ongoing stability studies, in case of a confirmed out-of-specification or unexpected trend not supporting the registered shelf-life.

Medicinal Product
The manufacturing process and quantitative composition of the drug product remain unchanged. Each 0.5 ml dose of vaccine has the following composition:

9 EU recommendation for the emergent novel H1N1 influenza vaccine composition (EMEA/CHMP/BWP/3408312009 Rev 1). http://www.emea.europa.eu/pdfs/human/bwp/34083109enrev1.pdf

Active Ingredient:
Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain:
A/California/7/2009 (H1N1)v like strain used (X-179A) ≥ 7.5 micrograms**
* propagated in eggs
** expressed in microgram haemagglutinin.

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

The drug product is presented in pre-filled syringes and multidose vials. Thiomersal is included in multidose dose vials only. The approved specifications for final bulk and drug product have not been changed for the A(H1N1)v vaccine.

Batch analysis results of final bulk and final containers (three commercial scale lots for each the multi dose vials and for the pre-filled syringes) were provided and show consistent production. All batches have been tested according to the approved specifications.

The first three commercial batches of Focetria in both presentations (pre filled syringe and multi dose vial) have been placed on stability. The company will perform the stability studies to support the registered shelf life of 12 months at 2-8 C. In accordance with the relevant guideline for influenza vaccines, the MAH committed to report any unexpected results generated during the stability studies, in case of a confirmed out-of-specification or unexpected trend not supporting the registered shelf-life.

Overall, the information presented in Modules 2.3 and 3 was considered in accordance with the above-mentioned guidelines and therefore acceptable.

2.3 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.

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 MAH 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 MAH 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.

The MAH further provided interim data concerning a non-clinical study in mice aimed at confirming the immunogenicity of vaccine formulation containing A(H1N1)v antigens made using the Focetria process, with and without MF59 adjuvant, when administered using different regimens.
These interim data seem to confirm that the use of the MF59 adjuvanted vaccine increase the antibody titres and reduces the amount of antigen necessary for the response. The MAH committed to present the final report as soon as the non clinical study will be ended, as outlined in the Letter of Undertaking.

GLP

The relevant studies were carried out in compliance with GLP.

Pharmacology

- Primary pharmacodynamics

Information from non-clinical studies with (H5N1) antigen:

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.

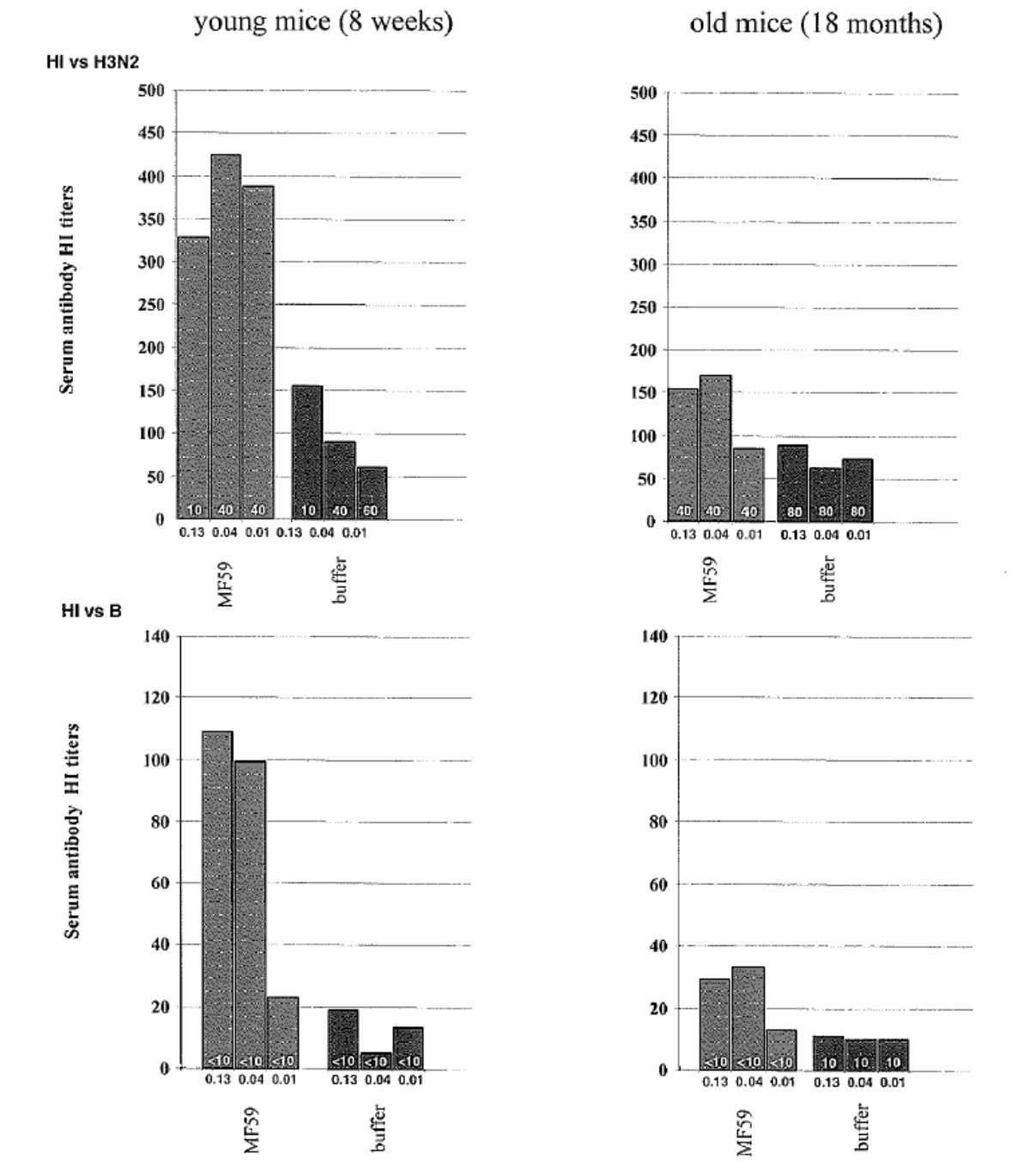
Mouse immunogenicity assay

The MAH has performed immunogenicity studies in mice. The results of a previous 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)v 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



Information from non-clinical studies with A(H1N1)v antigen:

Interim immunogenicity data from a non-clinical study in mice (Focetria Mouse Study No. BB-0910). with a vaccine formulation containing antigens made using the Focetria process, with and without MF59 adjuvant, containing antigen from an A/California/07/2009 H1N1-like strain have been provided and assessed.

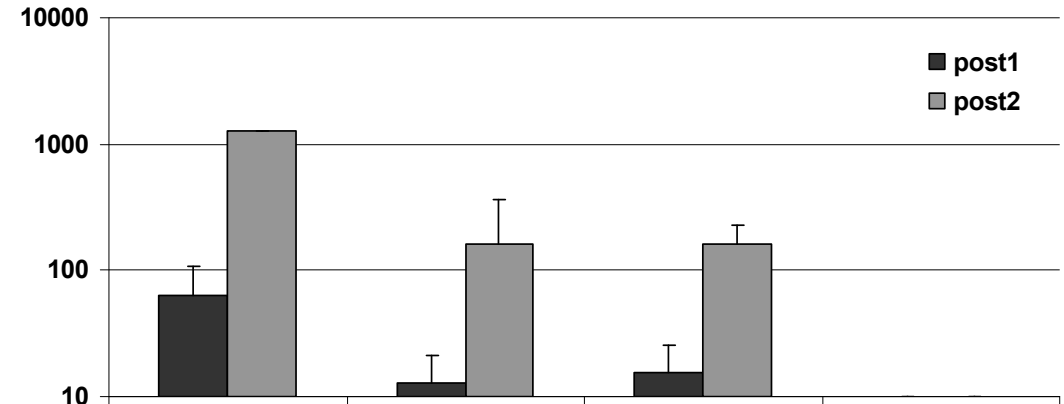
The study investigated different vaccine regimens administered to a total of 70 mice. Nine groups of immunologically naïve BALB/c female mice received intramuscular injections of phosphate buffered saline (PBS; control group) or antigen with or without MF59. Different vaccination schedules and antigen amounts (0.5 µg with and without MF59 and 1.0 µg without MF59) were investigated. Mice were 6-7 weeks old at study initiation. The serological immune response was analysed using ELISA

and haemagglutination inhibition (HI) assays. Individual animal sera were analysed and Geometric Mean Titres (GMTs) calculated.

Animals that received 0.5 µg of antigen with MF59 adjuvant had higher titres than those receiving 0.5 or 1.0 µg of antigen alone (Figure 1 and Figure 2).

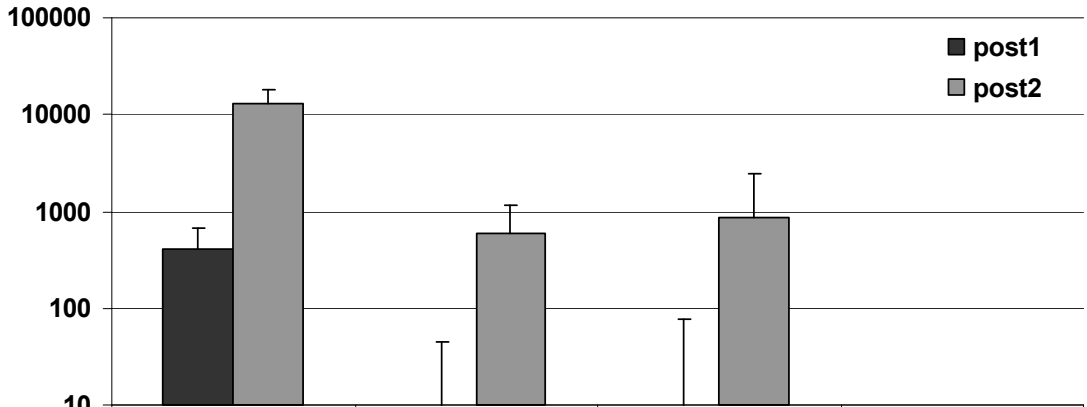
A single dose of 0.5 µg + MF59 elicited titres of 1:63; a titre of 1:40 is associated with protection in humans from seasonal influenza. A second dose of adjuvanted vaccine increased titres to 1:1280. Two doses of non-adjuvanted antigen were required to elicit titres of 1:160.

Figure 1: HI titres 2 weeks post-1st dose and 1 week post-2nd dose



	A/H1N1 0.5 µg + MF59	A/H1N1 1.0 µg	A/H1N1 0.5 µg	PBS
post1	63	13	15	10
post2	1280	160	160	10

Figure 2: ELISA titres 2 weeks post-1st dose and 1 week post-2nd dose



	A/H1N1 0.5 µg + MF59	A/H1N1 1.0 µg	A/H1N1 0.5 µg	PBS
post1	404	8	7	2
post2	12979	582	869	2

An extensive program of clinical and non-clinical studies has demonstrated that the addition of MF59 adjuvant to influenza antigens increases antibody titres (HI and ELISA) and reduces the amount of antigen necessary to elicit a response. The results from this mouse study are consistent with results

from similar studies conducted with the parent seasonal vaccine Fluad, and an H5N1 pandemic vaccine formulation.

- 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 MF59 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 MF59 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 labelled 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 MAH 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

The adjuvant MF 59 was tested alone in reproduction toxicity in rats and rabbits, and in conjunction with influenza and other antigens.

Developmental Toxicity (Embryo-Foetal and Teratogenic Potential) Study of a Vaccine (Antigen and Adjuvant Components) Administered Intramuscularly to Crl:CD BR VAF/Plus Female Rats. Range-Finding Study (Study No. 1303-002)

Table: Study No. 1303-002 - Test and control articles

Group	Number of females	Intramuscular injection
I	45	1.0 mL of saline (control) (0.5 mL in each of two separate sites)
II	45	0.5 mL of MF59 (2× clinical dose)*

*
The clinical dose of MF59 is 0.25 mL

In this GLP study, up to 0.5 ml of MF59 was administered IM either 5 (Caesarean section group) or six (natural delivery group) times. Two maternal deaths and a brief reduction in feed consumption were probably related to treatment. A slight increase (over historical incidence) of incomplete ossification of the sternebrae, pubes and/or ischia in foetuses was seen. However, the MF59 dose administered to rats was equivalent to twice the standard clinical dose of 0.25 ml. On a bodyweight basis, each 2× clinical dose in a 0.3 kg rat is approximately 200 times higher than the same dose in a 60 kg human and rats received 5 or 6 doses during the study. MF59 was not considered teratogenic or foetotoxic based on the study results.

Developmental Toxicity (Embryo-Foetal Toxicity and Teratogenic Potential) Study of Vaccine (Antigen and Adjuvant Components) Administered Intramuscularly to New Zealand White Rabbits (Study No. 1303-001P)

In this pilot GLP study, developmental toxicity (embryo-foetal toxicity and teratogenic potential) in female New Zealand White (NZW) rabbits was evaluated following intramuscular administration of MF59 alone or in combination with antigens. This study was used to select doses for a subsequent definitive study. Saline (control) or MF59 was injected intramuscularly on days 6 through 28 of presumed gestation.

Dose levels were as follows:

Table: Study No. 1303-001P - Test and control articles

Group*	Number of females	Clinical dose equivalent	Intramuscular injection
I	5	-	0.5 mL of saline (control)
III	5	0.25 ×	MF59W.1 diluted with saline
IV	5	0.50 ×	MF59W.1 diluted with saline

* Groups II and V received antigen and are therefore not presented here

There were no treatment-related effects on clinical observations, body weight, feed consumption or necropsy observations. No Caesarean-sectioning or litter parameters were affected. The litter averages for corpora lutea, implantations, litter sizes, resorptions, percent male foetuses and percent resorbed conceptuses were comparable among groups. There were no dead foetuses, and no litter consisted of only resorbed conceptuses. One late resorption occurred in a litter in group III (0.25× MF59). There were no gross foetal external alterations.

This study was performed to select doses for a definitive study. The definitive study did not have an MF59-alone group, therefore the data is not presented here, however the same dosing schedule with 0.5× and 1.0× MF59 combined with antigens had no effect on litter parameters and was not teratogenic in rabbits.

Study NoUBA00021: Intramuscular reproductive and developmental toxicity of Fluad H5N1 in rabbits, including a postnatal evaluation.

In addition to the above studies, a reproduction toxicity study in rabbits that was included in the submission for the MAA of the withdrawn prepandemic vaccine Aflunov (called “Fluad H5N1” in the study report), which however has the same composition as Focetria.

The object of this study was to assess the potential effects of Fluad H5N1 on reproductive and developmental toxicity in female rabbits and their foetuses or pups when administered by intramuscular injection at the 2 x clinical dose of 7.5 µg, before mating and during gestation. The study design is summarised below:

Group	Number of rabbits	Dosage (µg)/Injection volume (mL)[a]		Evaluations
		Day of study 1,15 and 29	Day of gestation 7 and 20	
Rabbits assigned to Caesarean-sectioning (day 29 of gestation)				Maternal and embryofetal toxicity and teratogenic potential
1	20	0/0.5	0/0.5	
2	20	15/0.5	15/0.5	
Rabbits assigned to natural delivery (day 29 of lactation)				
3	20	0/0.5	0/0.5	
4	20	15/0.5	15/0.5	

a Group 1 and 3 animals were administered saline as a control article. Group 2 and 4 animals were administered Aflunov (total volume 0.5 ml containing 15 µg antigen and 0.25 ml MF59 adjuvant). After 35 days on study, rabbits were mated (gestation day 0). Group 1 and 2 animals were euthanized at the end of the gestational period, on or about day 29.

The design of this study was considered sufficient to assess both reproductive and developmental toxicity. Under the conditions of this study, Fluad H5N1 is well-tolerated, does not cause maternal or embryofoetal toxicity, is not teratogenic, and has no effects on post-natal development. Additionally, the vaccine is immunogenic in maternal rabbits, in foetuses until to the first 4 weeks of life in F1 pups.

Considering that the study on "Reproductive and developmental toxicity of Fluad H5N1 in rabbits, including a postnatal evaluation", tested relatively high multiples of human doses for a vaccine product (five exposures to levels approximately 30-fold the expected clinical exposure to 7.5 µg on a body weight basis) it was supposed that Fluad H5N1 is safe also in the human use from this point of view.

Overall, animal data did not suggest an increased risk with respect to fertility, embryo-foetal development and teratogenicity following the administration of MF-59 adjuvant in pregnant animals. From these animal studies, there are no specific reasons for concerns in pregnancy.

- 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 fibre 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.

2.4 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 (Single Radial Haemolysis) 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 MAH decided to base the mock-up dossier on studies performed (immunogenicity and safety) with A/Vietnam/1194/2004 (H5N1) strain containing vaccine.

Additional clinical data with H5N1 has been submitted and evaluated since the initial approval (see paediatric and supportive studies sections).

GCP

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

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 microneutralisation (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 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 immunisation.
- 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-immunisation (day 43) GMT ratio is > 0.5, by using HI test, when compared to two doses of Focetria 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 Focetria influenza vaccine containing 7.5 µg vs. two doses of Focetria influenza vaccine containing 15 µg.

A 0.025 one-sided alpha level, a clinically relevant value of 0.5 in terms of the ratio of post-immunisation 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 (SRH) 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 immune 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

Study V87P6

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age and was submitted in support of the A(H1N1)v pandemic strain variation. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 µg haemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart.

Study V87P6 was a prospective, randomised, controlled, observer-blind phase II study that performed over a period of approximately 19 months at one study site in Finland.

The objectives for this study were as follows:

Immunogenicity

Primary: To evaluate the magnitude of antibody responses to two doses of Focetria influenza vaccine, each containing 7.5µg of H5N1 antigen administered 3 weeks apart in subjects of different ages.
Secondary: To evaluate the magnitude of antibody response to a 12 months booster dose of Focetria influenza vaccine, containing 7.5µg of H5N1 antigen in subjects of different ages.
To evaluate the persistence of specific antibodies 12 months after primary immunisation in subjects of different ages.
To evaluate the cross-protection of a Focetria influenza vaccine, containing 7.5µg of H5N1 antigen in subjects of different ages.

Safety
Primary: To evaluate the safety and tolerability of two 0.5mL intramuscular (IM) injections of Focetria influenza vaccine containing 7.5µg of A/H5N1 influenza antigen, administered 3 weeks apart.
Secondary: To evaluate the safety and tolerability of one 0.5mL IM injection of Focetria influenza vaccine containing 7.5µg of A/H5N1 influenza antigen, administered 12 months after the second dose.
To evaluate the safety profile of Focetria influenza vaccine when compared to FLUAD.

Study design:
This is a prospective, randomised, controlled, observer-blind phase II study that performed over a period of approximately 19 months at one study site in Finland. Approximately 469 subjects aged 6 months to 17 years were planned to be enrolled and followed, in three age-groups as follows:

- Cohort 1: toddlers aged 6 to <36 months (stratified 6 to <12, 12 to <24, 24 to <36 months).
- Cohort 2: children aged 3 to <9 years (stratified in 3 to < 6 and 6 to <9 years).
- Cohort 3: adolescents aged 9 to <18 years (stratified in 9 to <14 and 14 to <18 years).

Subjects in cohort 1 were stratified in three age groups; subjects in cohort 2 and 3 were stratified in two age groups each.
Each age group has been randomised in a 3:1 ratio to receive either two 0.5ml doses of Focetria influenza vaccine (applicable for all age groups) or two 0.25ml (subjects <3 years of age) or 0.5ml (subjects > 3 years of age) doses of FLUAD influenza vaccine.
All subjects have been vaccinated either with the prepandemic influenza vaccine Focetria, which is an egg-derived, surface-antigen, inactivated, influenza vaccine, adjuvanted with MF59C.1 (MF59), identical to the authorised interpandemic FLUAD with the exception of antigen composition and dose, or with the seasonal influenza vaccine FLUAD, a licensed, egg-derived, surface-antigen, inactivated, influenza vaccine, adjuvanted with MF59C.1 (MF59), containing the antigens proposed for the current season 2007/2008.
So far FLUAD is not licensed for children below 18 years of age.

Vaccines have been administered 3 weeks apart intramuscularly (IM) into the deltoid muscle (preferably of the non-dominant arm) or anterolateral thigh (depending on the muscle mass). Subjects in the Focetria group will receive one booster vaccination 12 months after the second dose.

Sample size
A total of 472 subjects have been enrolled in three cohorts:

- Cohort 1: 201 toddlers aged 6 to <36 months,
- Cohort 2: 136 children aged 3 to <9 years,
- Cohort 3: 134 adolescents aged 9 to <18 years

Subjects have been randomised in a 3:1 ratio to Focetria and to Fluad.
The study report presented immunogenicity and safety results up to visit 8 (day 403), 3 weeks after the booster injection.
For all age cohorts (6 to <36 months, 3 to <9years and 9 to <18 years), randomisation assignments were supplied to designated unblinded study personnel in sealed envelopes.
Randomisation lists were prepared by Novartis Vaccines Biostatistics and Clinical Data Management (BCDM) department.
The number of subjects enrolled for each age cohort is summarised in the below table under Number

of Subjects (planned and analyzed) section.

Number of Subjects analyzed (planned):

	Cohort 1 (aged 6 to <36 months)	**Cohort 2 (aged 3 to <9years)**	**Cohort 3 (aged 9 to <18years)**	**Total**
Fuad-H5N1	145 (150)	96 (100)	93 (100)	334 (350)
Fluad	56 (51)*	40 (34)**	41 (34)**	137 (119)
Total	201 (201)	136 (134)	134 (134)	**471 (469)**

*Subjects received 0.25mL doses of Fluad,**Subjects received 0.5mL doses of Fluad, and all subjects of the Focetria group will receive 0.5mL doses.

The demographic and other baseline characteristics were balanced between the two vaccine groups and within each of the three age cohorts (6 to <36months, 3 to <9years, and 9 to <18 years).
Overall, the premature withdrawal rate was comparatively higher in MF59-PanH5N1 IV group across all age cohorts, mostly due to withdrawal of consent from day 43 to day 202.

Percentages of Subjects Prematurely Terminating the Study - All Randomized Set

Vaccine Group	**Toddlers**		**Children**		**Adolescents**	
	Focetria	**Fluad**	**Focetria**	**Fluad**	**Focetria**	**Fluad**
Enrolled (n)	145	56	96	40	94	41
Completed study	84%	100%	88%	95%	88%	98%
Premature withdrawals	16%	0	13%	5%	12%	2%
AE or death	[a]<1%	0	2%	3%	0	0
Withdrew consent	11%	0	8%	0	6%	2%
Lost to follow-up	3%	0	2%	3%	3%	0
Protocol deviation	0	0	0	0	1%	0
Unable to Classify	[a] <1%	0	0	0	1%	0

[a]<1% = 1 subject

Higher percentages of toddlers, children and adolescents in the Focetria group than the Fluad group had major protocol deviations, mostly due to the failure of subjects to provide a blood draw immediately before the booster vaccination and 21 days afterwards.
In toddlers most of the reasons for protocol deviations in both vaccine groups were related to blood draws and/or vaccinations either not given within the protocol-specified time window or at all.

Serology

Blood was collected from all subjects on days 1, 22, 43 and for the Focetria group blood was also collected on days 382 and 403 for the evaluation of immunogenicity. The measures of immunogenicity, collected for all evaluable subjects of the Focetria group include:

- Geometric mean titres/area (GMTs/GMAs) and geometric mean ratios (GMRs) on days 1, 22, and 43, 382 and day 403 as determined by HI, SRH, and MN.
- Percentage of subjects achieving seroconversion or significant increase in antibody titer on days 22, 43, 382, and 403 as measured by HI and SRH.
- Percentage of subjects with MN titres ≥1:20, ≥1:40, ≥1:80 on day 1, day 22, and day 43.

- Percentage of subjects achieving at least a four-fold rise in antibody titer on days 22, 43, 382, and 403 as measured by MN.
- Percentage of subjects achieving a titer ≥40/ area ≥25mm^2 on days 22, 43, 382 and 403 as determined by HI and SRH.

Serum samples have been assessed by means of strain-specific HI, MN and SRH tests against A/H5N1.
HI and MN assays have been performed at Novartis Vaccines, Clinical Serology Laboratory, Marburg, Germany.
SRH test has been performed at Dipartimento di Fisiopatologia, Medicina Sperimentale e Sanità Pubblica, Laboratorio di Epidemiologia Molecolare, Università di Siena, Siena, Italy.
Other influenza specific assays might be conducted with these serum samples.
The detection limit of the HI assay is 10. All sera were tested in duplicate, if an individual result is below detection limit it will be set to 5 in the laboratory. The geometric mean value of the duplicate test values was received from the lab and used for analysis.
Regarding the SRH assay the diameter of the haemolytic zones observed including the well were provided by the laboratory. Zone areas (including the inner well) were calculated via the circle area function. The inner well has a diameter of 2.256 mm thus the area of the inner well is 4mm². Repeated measurements on the same sample are aggregated via the geometric mean of the respective areas. All areas below the lower limit of detection will be set to 4 for the immunogenicity analysis.
Individual MN titres below detection limit were set to half that limit (i.e. to a value of 10) for further analysis.

In the interpretation of HI and SRH immunogenicity results, CHMP criteria (CPMP/BWP/214/96) have been used as the reference

Immunogenicity results:

After the first vaccination containing 7.5µg of H5N1 antigen, toddlers (6 to <36 months of age), children (3 to <9 years of age), and adolescents (9 to <18 years of age) met either one or two of the CHMP criteria (GMR, seroconversion or significant increase, and seroprotection) for non-elderly adults (i.e., 18 to 60 years old) when assessed by HI and SRH assay.

After the second vaccination, administered 3 weeks after the first, each age cohort met all three of these CHMP criteria whether assessed by HI or SRH assay.
Although GMTs/GMAs decreased (significantly, based on the 95% CIs) from 21 days after primary vaccinations (day 43) to the booster vaccination (day 382), antibodies remained detectable, when assessed by HI and SRH assays. Between 26% and 46% of each age cohort were seroprotected at day 382 when assessed by HI and HI assay between 61% and 88% of each age cohort were seroprotected when assessed by SRH.

After the booster vaccination, all age cohorts met all three of the CHMP criteria when assessed by HI and SRH assays. The GMTs/GMAs by HI and SRH were highest after the booster vaccination across all age cohorts.

As assessed by HI and SRH serology assays, naïve populations needed two vaccinations of MF59-adjuvanted H5N1 vaccine to meet the CHMP criteria while the same population only needed one booster vaccination to meet all three CHMP criteria.

Results by age-group with the HI assay:

In toddlers aged 6 to<36 months HI assay on sera collected 21 days after the second vaccination, showed a 129-fold increase in GMT over day 1. Although GMTs decreased significantly from 21 days after primary vaccinations (day 43) to the booster vaccination (day 382), antibodies were still detectable (GMT 24) and 21 days after booster vaccination a 55-fold increase in titres was observed that exceeded the CHMP requirement. At 21 days after booster vaccination (day 403), 98% toddlers achieved the seroconversion or significant increase. After booster vaccination 99% of toddlers were seroprotected

In children 3 to <9 years of age twelve months after the primary vaccinations 26% of children were seroprotected, indicating some persistence of antibodies. Regardless of pre-booster titer, 21 days after booster vaccination, a large increase in titres (73-fold) was observed and 95% of subjects achieved seroconversion or significant increase. After the booster vaccination 98% of children were seroprotected

In adolescents 9 to <18 years of age GMTs decreased significantly from 21 days after primary vaccinations (day 43) to the booster vaccination (day 382), but antibodies were still detectable (GMT = 12). Twelve months after the two primary vaccinations, 30% of the adolescents were seroprotected, indicating some persistence of antibody titres. After booster vaccination a large increase in titres (39-fold) was observed. At 21 days after booster vaccination (day 403), adolescents again exceeded the CHMP criterion with 91% of subjects achieving seroconversion or significant increase. After the booster vaccination, 91% of the adolescents were seroprotected

Geometric Mean Titres and Geometric Mean Ratios (with 95% CIs) by HI Assay (Persistence after Primary Vaccinations; Focetria) – Full Analysis Set

	Toddlers	**Children**	**Adolescents**
	N=117	**N=84**	**N=81**
GMT Day 1	5.14 (4.87-5.41)	5 (5-5)	5.17 (4.83-5.54)
GMT Day 43	700 (598-819) N=116	577 (450-740)	364 (260-510)
GMT Day 382	24 (18-33)	11 (8.18-14)	12 (8.92-16)
GMR Day 382 to Day 43	0.035 (0.027-0.047) N=116	0.019 (0.014-0.025)	0.033 (0.023-0.048)

Ns in the cells are entered when they differ from those in the column headers

Geometric Mean Titres and Geometric Mean Ratios (with 95% CIs) by HI Assay (Booster Vaccination; Focetria) – Full Analysis Set

	Toddlers	**Children**	**Adolescents**
	N=113	**N=83**	**N=81**
GMT Day 382	25 (18-34)	10 (7.93-14)	12 (8.92-16)
GMT Day 403	1365 (1166-1598)	766 (613-958)	472 (335-667)
GMR Day 403 to Day 382	55 (41-75)	73 (53-101)	39 (26-60)

Similar results have been obtained with SRH and MN assays. In view of the MN results, 99% of the subjects reached an MN titre ≥1:40 at day 43 across all age groups.

Geometric Mean Areas and Geometric Mean Ratios (with 95% CI) by SRH Assay (Booster Vaccination; Focetria) – Full Analysis Set

	Toddlers	Children	Adolescents
	N=118	**N=84**	**N=82**
GMA Day 382	38 (35-41)	28 (24-32)	26 (23-30)
GMA Day 403	107 (103-111)	91 (86-95)	86 (81-91)
GMR Day 403 to Day 382	2.83 (2.63-3.04)	3.25 (2.85-3.7)	3.24 (2.86-3.67)

Percentages Showing Seroconversion or Significant Area Increase as Defined by CHMP for SRH Assay (Focetria) – Full Analysis Set

	Toddlers	Children	Adolescents
	N=135	**N=91**	**N=90**
Seroconversion or Significant Increase Day 22	44% (36-53)	56% (45-66) N=90	57% (46-67)
Seroconversion or Significant Increase Day 43	98% (95-100) N=133	100% (96-100)	99% (94-100)
Seroconversion or Significant Increase Day 403 (Booster vaccination effect)	100% (97-100) N=118	99% (94-100) N=84	98% (91-100) N=82

Ns in the cells are entered when they differ from those in the column headers

Percentages Showing Seroprotection (CHMP) by SRH Assay (Focetria) – Full Analysis Set

	Toddlers	Children	Adolescents
	N=137	**N=91**	**N=90**
Day 1	3% (1-7)	0% (0-4)	4% (1-11)
Day 22	47% (38-55) N=135	54% (44-65) N=90	59% (48-69)
Day 43	100% (97-100) N=133	100% (96-100)	100% (96-100)
Day 382 (persistence after primary vaccinations)	88% (81-93) N=122	71% (60-80) N=85	61% (50-72) N=82
Day 403 (Booster vaccination effect)	100% (97-100) N=118	100% (96-100) N=84	100% (96-100) N=82

Ns in the cells are entered when they differ from those in the column headers

- Discussion on clinical efficacy

The development of Focetria is based on the experience of 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 were necessary to induce a proper immune response against H5N1.

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.

In view of results from paediatric data generated with Focetria (H5N1), the CHMP pointed out that although there are no established criteria for the interpretation of immune responses to influenza vaccines in children the measured responses following two doses were high and consistent across the age groups and the different assays. Post-vaccination titres are higher than those observed in adults.

It has to be noted that immune responses in healthy children aged 6 months-17 years, after administration of two doses, comfortably exceeded the CHMP criteria applied to seasonal vaccines.

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 oedema	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 oedema	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

Study V87P6

In total, 471 out of the 472 enrolled paediatric subjects were vaccinated and were therefore included in the safety population and data up to day 403 is presented in the study report

Toddlers 6 to <36 months of age:

A total of 201 toddler subjects were enrolled and randomised in this age cohort, all were vaccinated according to the randomisation list (145 received Focetria and 56 received Fluad). All subjects provided some post vaccination safety data and were therefore included in at least one safety analysis. Overall reactogenicity was highest after the first vaccination and decreased after the second vaccination.

A total of 76% [110/145] of Focetria and 75% [42/56] of Fluad recipients after first injection and 68% [94/139] of Focetria and 63% [35/56] of Fluad recipients, after second vaccination reported at least one solicited local or systemic reaction, which by definition onset within 7 days of vaccination.

The CHMP noted that there is a high proportion of subjects who reported adverse events of any type. Such reactogenicity does not seem to be related to the full dose of MF59 because similar proportion is observed in Fluad, in recipient of half dosage of Fluad. The proportion of subjects reporting events is dependent upon the active surveillance post immunisation. The CHMP considered that a comparison across different products and age groups performed using a subset of events including objective measurements such as body temperature did not raise any concern.

Most solicited reactions were mild or moderate, with no more than 2% of each solicited local or systemic reaction classified as severe in either vaccine group. They mostly were transient with few continuing past the day 7 observation window and none continued at the end of the study.

Erythema (21 % [12/56] to 33% [46/139] after any injection and tenderness (21%[12/56] to 29%[16/56] after any injection) were the most common solicited local reactions and irritability (20%[11/56] to 39%[56/145] after any injection) was the most common solicited systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. None of the subjects in any vaccination groups reported body temperature ≥ 40°C.

The percentages of subjects with any AEs, regardless of their assessment of relatedness, were balanced between the two vaccine groups (55% [80/145] and 51% [71/138] Focetria and 61% [34/56] and 52% [29/56] Fluad, after first and second injection, respectively, for all AE's) and (18% [26/145] and 13% [18/138] Focetria and 14% [8/56] and 18% [10/56] Fluad, after first and second injection, respectively, for at least possibly related AEs)]. No death or AE leading to a subject's withdrawal from the study was reported. Within this age cohort, there was one subject who reported one SAE (hospitalisation due to acute pyelonephritis) but it was assessed as not related to the study vaccines.

Children 3 to <9 years of age:

A total of 136 children were enrolled and randomised in this age cohort, all were vaccinated according to the randomisation list (96 received Focetria and 40 received Fluad). All subjects provided some post-vaccination safety data and were therefore included in at least one safety analysis.

A total of 72% [69/96] of Focetria and 80% [32/40] of Fluad recipients, after first injection and 68% [63/93] of Focetria and 56% [22/39] of Fluad recipients, after second injection, reported at least one solicited local or systemic reaction. Most solicited reactions were mild or moderate, with no more than 5% of each solicited local or systemic reaction classified as severe in either vaccine group, most of them were transient.

Pain (36% [14/39] to 53% [49/93] after any injection) was the most common solicited local reaction, no more than 5% children complained of severe pain after any injection, and headache (9% [8/93] to 23% [9/40] after any injection) was the most common systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. None of the subjects in any vaccine groups reported body temperature ≥ 40°C.

The percentages of subjects with any AEs, regardless of their assessment of relatedness, were similar between the groups [(39% [37/96] and 32% [30/93] Focetria and 30% [12/40] and 36% [14/39] Fluad, after first and second injection, respectively for all AEs) and (15% [14/96] and 16% [15/93] Focetria and 13% [5/39] Fluad, after first and second injection, respectively for at least possibly related AEs)]. No death or AE leading to a subject's withdrawal from the study was reported during the study. One subject reported one SAE, (hospitalisation due to moderate renal injury) was assessed as not related to the study vaccines.

Adolescents 9 to <18 years of age:

A total of 134 adolescents were enrolled and randomised in this age cohort, all were vaccinated according to the randomisation list (93 received Focetria and 41 received Fluad). All subjects provided some post-vaccination safety data and were therefore included in at least one safety analysis.

A total of 91% [85/93] of Focetria and 88% [36/41] of Fluad recipients after first injection and 82% [75/91] of Focetria and 78% [31/40] of Fluad recipients, after second injection, reported at least one solicited local or systemic reaction.

Most solicited reactions were mild or moderate, with no more than 5% of each solicited local or systemic reaction classified as severe in either vaccine group, most of them were transient.

Pain (63% [25/40] to 78% [73/93] after any injection) was the most common local reaction, no more than 5% of adolescents complained of severe pain, and headache (22% [20/91] to 59% [24/41] after any injection) the most common solicited systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. None of the subjects in any vaccine groups reported body temperature ≥ 40°C.

		Number (%) of Subjects With Solicited Reactions					
		Inj.: 1			Inj.: 2		
		Focetria	FLUAD	Total	Focetria	FLUAD	Total
Cohort: Toddlers		N=145	N=56	N=201	N=139	N=56	N=195
	Any	110 (76)	42 (75)	152 (76)	94 (68)	35 (63)	129 (66)
	Local	68 (47)	28 (50)	96 (48)	64 (46)	23 (41)	87 (45)
	Systemic	86 (59)	30 (54)	116 (58)	70 (50)	26 (46)	96 (49)
	Other	25 (17)	13 (23)	38 (19)	22 (16)	11 (20)	33 (17)
Cohort: Children		N=96	N=40	N=136	N=93	N=39	N=132
	Any	69 (72)	32 (80)	101 (74)	63 (68)	22 (56)	85 (64)
	Local	63 (66)	25 (63)	88 (65)	54 (58)	19 (49)	73 (55)
	Systemic	31 (32)	23 (58)	54 (40)	31 (33)	14 (36)	45 (34)
	Other	9 (9)	6 (15)	15 (11)	11 (12)	6 (15)	17 (13)
Cohort: Adolescents		N=93	N=41	N=134	N=91	N=40	N=131
	Any	85 (91)	36 (88)	121 (90)	75 (82)	31 (78)	106 (81)
	Local	75 (81)	29 (71)	104 (78)	64 (70)	26 (65)	90 (69)
	Systemic	64 (69)	33 (80)	97 (72)	47 (52)	20 (50)	67 (51)
	Other	24 (26)	14 (34)	38 (28)	14 (15)	3 (8)	17 (13)

Percentages of subjects with solicited and unsolicited reactions are provided below:

	Injection 1	Injection 2
Toddlers 6 months to < 35 months	**N=145**	**N=138**
Local	47%	46%
Systemic	59%	51%
Fever ≥ 38°C/≥ 39°C/≥ 40° C	7% / 1% / 0%	12% / 3% / 0%
Any other AE	54%	49%
Children 3 years to < 9 years	**N=96**	**N=93**
Local	66%	58%
Systemic	32%	33%
Fever ≥ 38°C/≥ 39°C/≥ 40° C	4% / 1% / 0%	2% / 0% / 0%
Any other AE	36%	31%
Adolescents 9 years to < 18 years	**N=93**	**N=91**
Local	81%	70%
Systemic	69%	52%
Fever ≥ 38°C/≥ 39°C/≥ 40°C	0% / 0% / 0%	1% / 0% / 0%
Any other AE	30%	27%

It can be summarised that two injections of adjuvanted (H5N1) vaccine induced a high proportion of subjects reporting the occurrence of any event following immunisation. Solicited local and systemic reactions after vaccination were mostly mild or moderate in severity. There was no clear and consistent difference in the reactogenicity profile between the two formulations, but a slight increase in the reactogenicity profile with increasing age was noted. The study design was not aimed to identify differences due to the adjuvant presence as both study groups received it. Such issue has been addressed in the study V70P2 whose synopsis has been presented as supporting documentation.

Despite the greater local and general reactogenicity with the adult dose, uptake of the second dose was not affected by withdrawals due to AE onset. In addition the data do not indicate that higher reactogenicity was associated with SAEs.

- Safety related to drug-drug interactions and other interactions

Concomitant administration

Study V101 P1

The MAH presented within the rolling review (RR/04) a Phase II, randomised, placebo-controlled, observer-blind, multi centre study on the safety and immunogenicity of an investigational tetravalent influenza vaccine[10] manufactured by Novartis in adults aged 18 years and above.

A total of 600 study subjects were included in a staggered two-step enrolment.

In this study one group of adults of 199 subjects received one dose of Focetria H5N1 and concomitantly, but in a different arm, one dose of a licensed unadjuvanted seasonal vaccine. This group was compared with two groups receiving either an investigational tetravalent vaccine or Focetria H5N1 alone.

Immunogenicity Objectives

The primary objective was to show that SRH antibody titres against A/H5N1 elicited by the three different immunisation schedules were equivalent at day 43.

Safety Objectives

To evaluate the safety of the administration of one 0.5 mL intramuscular (IM) dose of Focetria given before or after one 0.5 mL intramuscular (IM) dose of a tetravalent vaccine or after a concomitant administration in different sites of Focetria and a licensed seasonal trivalent influenza vaccine.

Results

Across all three vaccine groups the H5N1 strain met all three CHMP criteria as assessed by the SRH assay; for the interpandemic strains (H1N1, H3N2, and B), all three vaccine groups met all three CHMP criteria.

Solicited local and systemic reactions were generally reported most frequently after the tetravalent vaccine, irrespective of vaccine group. Reactogenicity was generally lower with Focetria H5N1, and even lower with the seasonal vaccine.

Data on co-administration of subunit not adjuvanted influenza seasonal and pandemic H5N1 vaccines in adults did not suggest any interference in the immune response to seasonal or to H5N1 antigens or differences in the safety profile between concomitant and non-concomitant administration of the vaccines. The CHMP noted that data on the concomitant use with seasonal flu vaccines in paediatric population are however still lacking.

Data on co-administration of the vaccine (Focetria H5N1) with vaccines other than influenza have so far not been generated.

[10] Vaccine composition: A/ Solomon Islands/3/2006 (H1N1)- like virus; A/ Wisconsin/67/2005 (H3N2)-like virus; B/ Malaysia/2506/2004- like virus, A/Vietnam/1194/2004, (H5N1 Clade 1)

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.

Ancillary analysis on pregnant women

To date, MF59 has been evaluated as an adjuvant for vaccines by Novartis and others against a range of infectious agents, including pandemic and seasonal influenza viruses (e.g., H3N2, H5N1), herpes simplex-2 virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV). An MF59-adjuvanted subunit influenza vaccine (FLUAD) has been licensed for active prophylaxis of seasonal influenza in elderly adults in 12 EU countries with MRP, and several other non-EU countries throughout the world, but not in the USA. To date, there have been no clinical trials designed to evaluate the tolerability and safety of MF59-adjuvanted vaccines in pregnant women.

The MAH analysed the number of pregnancies and relative outcomes occurred in females of childbearing potential included in the safety database of clinical trials with MF59-adjuvanted influenza vaccines.

Overall, 150 pregnancies were reported during clinical trials with MF59-adjuvanted vaccines.
No occurrence of congenital abnormalities was reported.

Data presented are very limited and not allow drawing any conclusion on the safety profile of Focetria administered in pregnant women. These data support the request for a prospective pregnancy registry suggested in the RMP.

- Discussion on clinical safety

The safety analysis was based mainly on the pivotal study with H5N1 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.
Additional information submitted post core-dossier authorisation from a study in 471 children did not raise any new issues for the safety profile of MF-59-adjuvanted vaccine containing the H5N1 strain.

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 has been provided and support the favourable safety profile of Focetria.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan
An updated risk management plan for the A(H1N1)v vaccine was submitted before approval of the strain change variation. This was drafted in accordance with the CHMP core RMP for vaccines intended for use in a declared pandemic situation.

The CHMP, having considered the data submitted in the application of the variation to include the pandemic A(H1N1)v strain was of the opinion that the following activities are appropriate and necessary for the safe and effective use of the medicinal product:

- The MAH will conduct a prospective cohort safety study in at least 9,000 patients, in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed. Interim and final results will be submitted in accordance with the protocol.

- The MAH commits to provide the details of the design and to provide the results of a study in a pregnancy registry. Details are to be submitted within one month of Commission Decision granting the Variation. Results are to be provided in the simplified PSUR.

- The MAH commits to establish mechanisms to promptly investigate issues affecting the benefit-risk balance of the vaccine. The design of additional studies for emerging benefit-risk evaluation is to be agreed with EMEA within 1 month of the Commission Decision granting the Variation.

- The MAH commits to submit the protocol and provide the results of the clinical effectiveness studies carried out in accordance with the study protocols published by ECDC.

- The MAH commits to provide an update of the RMP within one month of Commission Decision granting the Variation.

- The details of the Risk Management plan are in Module 1.8.2. The MAH has committed to update it in line with Annex II.B of the opinion

Summary of the risk management plan

A summary of safety concerns, Pharmacovigilance activities and Risk minimisation activities is presented below.

Identified/Potential safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
None	N/A	• N/A
Important potential risk		
Anaphylaxis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	• Contraindication for history of anaphylactic reaction to any constituent of the vaccine in the proposed labelling • Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components SPC, section 4.8, Post-marketing surveillance: <u>Uncommon</u>*:* *Generalised skin reactions including pruritus, urticaria or non-specific rash.* <u>Rare</u>*:* *Neuralgia, paraesthesia, convulsions, transient thrombocytopenia.* *Allergic reactions, in rare cases leading to shock, have been reported.* <u>Very rare</u>*:* *Vasculitis with transient renal involvement and exudative erythema multiforme.* *Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.* N/A
Bell's palsy	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Convulsion	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Demyelinating disorders	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Encephalitis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Guillain-Barré syndrome	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study • Active surveillance of Guillain-Barré syndrome using data sources supplementing the spontaneous reporting system.	
Neuritis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Vasculitis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Vaccination failure	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Important missing information		
Vaccine effectiveness	Novartis trial V111_05 and collaboration with ECDC effectiveness study	SPC; section 4.2: *There is currently no experience with Focetria (H1N1) in adults, children or adolescents*
Data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy. • Spontaneously reported by patients and HCPs • Enrolled/observed during post-authorisation safety study • Observed during clinical trials • Reported via pregnancy registry in selected countries	SPC, section 4.6: *There are currently no data available on the use of Focetria in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest*

Identified/Potential safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		malformations or foetal or neonatal toxicity. *Animal studies with Focetria do not indicate reproductive toxicity (see section 5.3).* *The use of Focetria may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.* *Focetria may be used in lactating women.*
Data in children	Adverse effects will be followed-up and risk assessed Ongoing and planned clinical trials Prospective cohort safety study	SPC, section 4.2: *There is currently no clinical experience with Focetria (H1N1) in adults, including the elderly, children or adolescents.*
No data in subjects with severe underlying medical conditions and immunocompromised	• Routine pharmacovigilance • Safety monitoring of vaccinated immunocompromised subjects (either due to an underlying disease or due to treatment with immunosuppressants) will be considered; as such patients could be recruited in specialised settings like dialysis or transplant centres.	SPC, section 4.4.:*Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient*
Medication errors/misidentification of vaccine	• Review spontaneous reports of medication errors	• Information provided to Health Care Professionals

2.6 Product Information

Further to the assessment and the scientific discussions held at the CHMP, changes to the SPC/Annex II/labelling/PL were implemented and details of the changes can be found in the final approved product information attached to this report.

2.7 Overall conclusions, risk/benefit assessment and recommendation

Clinical Context

In April 2009, a new strain of human influenza A(H1N1)v was identified and characterised.
On 11 June 2009 the WHO declared Phase 6 of the influenza pandemic. The declaration reflected sustained transmission of the virus from person to person in several WHO regions. WHO and other international agencies are now calling the disease **pandemic (H1N1)v 2009**. For the virus the nomenclature **influenza A(H1N1)v virus** (where v indicates variant) has been chosen.

The attack rate for the A(H1N1)v virus strain is expected to be higher than for recently circulating seasonal strains because of the lower levels of pre-existing immunity in the population. Current estimates for the attack rate associated with the influenza A(H1N1)v virus over the first wave of infection vary from approximately 10-30 % in different geographical areas. As a result, the actual numbers of clinically apparent infections, cases that require hospitalisation and deaths in the pandemic period is expected to be higher than in recent years for seasonal influenza. These estimates may change (upwards or downwards) during the course of the pandemic.

Focetria is a core dossier pandemic 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).
Focetria has been authorised under the core mock-up procedure which foresees the insertion of a pandemic strain A(H1N1)v into the authorised mock-up vaccine. This procedure was performed as a strain variation.

This principle is based on the extrapolation of clinical safety and immunogenicity data obtained with the mock-up vaccine in the Focetria case using the A(H5N1) strain to the same vaccine construct using the current influenza A(H1N1)v pandemic strain.

It is expected that the insertion of the influenza A(H1N1)v strain into the mock-up vaccine construct does not have a substantial effect on safety and immunogenicity compared to the corresponding mock-up vaccine when used in a comparable population (i.e. in terms of naivety, health status and age group). The presence of a comparable effect on immunogenicity will however be verified with the results from the upcoming clinical studies in view of a population that is possibly less naïve towards A(H1N1)v compared to H5N1.

The Focetria SPC summarises the existing clinical data collected with the H5N1 strain and will be updated on an ongoing basis as considered necessary by the CHMP.

Quality

The manufacture of the virus surface inactivated antigen, the formulated drug product bulk and final medicinal product are well defined, appropriately controlled and sufficiently validated. The same manufacturing process was employed for the A(H1N1)v like-strain vaccine as previously established and approved for the mock-up A(H5N1) vaccine. Adequate in-process controls, release and shelf life specifications have been set in line with relevant requirements (e.g. Ph.Eur.). The relevant quality data generated in the mock-up vaccine can be considered supportive for this pandemic strain change. Additional quality data required specifically for the strain change have been provided and satisfactorily demonstrate the quality of the vaccine.

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.

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).

Non-clinical data with Focetria submitted in connection with this variation did not raise concerns in view of reproduction toxicity and gave first information on the effect on immunogenicity of vaccine manufactured with the A(H1N1)v strain.

Clinical

Most of the clinical data at time of the strain variation were generated with vaccine constructs that included an influenza A(H5N1) strain.

It is expected that the insertion of the influenza A(H1N1)v strain into the mock-up vaccine construct does not have a substantial effect on immunogenicity and safety compared to the corresponding mock-up vaccine when used in a comparable population (i.e. in terms of naivety, health status and age group).

Considerations for extrapolation of the clinical data include that the immunogenicity data available for the approved mock-up vaccines were generated using a strain to which the majority of subjects were immunologically naïve based on pre-vaccination testing for neutralising antibody and for antibody that inhibits haemagglutination.

It is assumed that the safety of the H5N1 mock-up vaccine is predictive for the influenza A(H1N1)v strain in the population it has been tested. However rare adverse reactions that might be specific to the influenza A(H1N1)v strain can only be evaluated during very widespread usage.

First clinical data with a vaccine produced in MDCK cell lines containing the influenza A(H1N1)v strain has become available and preliminary results indicate a good immune response after one dose of this different construct, nevertheless containing the same adjuvant (MF59).

Currently there is only limited data with Focetria in children and very limited data in pregnant women, immunocompromised patients and other risk groups or specific populations available. Therefore in populations other than those in which it has been tested, data obtained with a mock-up vaccine would have to be extrapolated from the safety and immunogenicity of a corresponding construct or other age groups containing the A(H1N1)v pandemic strain.

Data from ongoing and planned clinical trials as specified in the agreed pharmacovigilance/risk management plan using the Focetria vaccine construct with the current pandemic influenza A(H1N1)v strain are reviewed on an ongoing basis. These studies will allow obtaining safety, immunogenicity and efficacy data for the influenza A(H1N1)v vaccine.

Efficacy

Clinical trials on protective efficacy for the mock-up vaccine were not possible as the strain causing the current pandemic as well as the subjects with a corresponding infection were not present at that time. Therefore a detailed characterisation of the immunological response has been performed.

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.

A clinical trial submitted post core-dossier authorisation was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) at the dosage of 7.5 µg haemagglutinin [HA]/dose with MF59C.1 adjuvant were administered three weeks apart. 21 days after the second dose the seroprotection and seroconversion rate and for anti-HA antibody antibodies to H5N1 A/Vietnam/1194/2004 in the toddlers aged from 6 to 35 months, 3 to 8 years and 9 to 17 years measured by SRH were all between 98 and 100%. Seroconversion factors varied from 14 and 16 between the 3 age groups. These results indicate a substantiated immune response.

Preliminary data on the single dose in adults receiving H1N1 (MF-59) adjuvanted vaccine have been recently published (Clark TW et al., New England Journal of Medicine, 2009 Sep 10, Epub). However these data have not formally submitted at the time of evaluation. Moreover the antigen used in the polished report has been prepared on the Optaflu platform different form Focetria. However, beside such limitations, the amount of antigen and the amount and production of the adjuvant is the same of Focetria.

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.

All SAEs were considered as not related to vaccination by the investigator. There was one unrelated death across all studies.

There is currently no specific clinical data available on the use of Focetria in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or foetal or neonatal toxicity. Serological studies exploring the immunogenicity suggest that antibody response to seasonal influenza vaccine is similar in pregnant women and non-pregnant women. Therefore it is expected that Focetria will be adequately immunogenic in pregnant women.

In addition the MAH committed to set up a program to monitor pregnancies and related outcomes in women exposed to Focetria during the gestation period as outlined in the Letter of Undertaking and presented in the Risk Management Plan.

Additional information submitted post core-dossier authorisation from a study in 471 children did not raise any new issues for the safety profile of MF-59-adjuvanted vaccine containing the H5N1 strain.

In view of Risk Management, the MAH will submit on a monthly a simplified PSUR on all adverse reactions notified by patients and health care professionals. The Risk Management Plan includes additional Pharmacovigilance activities to address important potential risks and important missing information. This includes the conduct of a study in Italy with at least 9,000 patients across different age groups, recruited at the start of the vaccination campaign, a specific monitoring of special populations such as pregnant women (through pregnancy registry in several EU countries), children and immunocompromised subjects, and the monitoring of adverse events of special interest. Effectiveness studies developed and conducted in accordance with the standard protocols published by the ECDC will be performed.

- User consultation

  The MAH performed readability testing ("user consultation") and a satisfactory report has been provided with the initial MAA.

Risk-benefit assessment

Benefits

The real benefits of Focetria A(H1N1)v can only be assessed by its use during a pandemic. At present the potential benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination with Focetria H5N1.

After two doses Focetria H5N1 administered 21 days apart in adults and elderly the three CHMP criteria as laid down in CPMP/VEG/4717/03 have been fulfilled suggesting that the vaccine is suitably immunogenic.

Based on data in children 6 months - 17 years, it is expected that two full adult doses given three weeks apart will be adequately immunogenic. Ongoing studies with H1N1 with both full and half adult dose will provide further information with regards to the dose for children.

Extrapolation of data collected with (H5N1) and other strains to the influenza A(H1N1)v strain is considered adequate for the population in which the (H5N1) strains have been tested.

Therefore the expected benefit of Focetria is to provide some protection against clinically-apparent infection and/or possibly against development of severe disease in case of an influenza A(H1N1)v 2009 infection.

Risks

Focetria containing a (H5N1) strain 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 the population it has been tested in as described in the SPC.

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 in the population it has been tested. 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 Focetria compared with, for example, seasonal influenza vaccines.

Data generated with Focetria including a H5N1 strain cannot entirely predict the safety profile of Focetria including the influenza A(H1N1)v strain since there remains a possibility of ADRs associated with the antigenicity of a specific influenza strain.

The specific commitments that accompany the strain change variations, including collection of data from the ongoing and planned clinical studies and as specified in the Risk Management Plans, will provide safety and immunogenicity data on a rolling basis.

Balance

Based on all the quality safety and efficacy data that supported approval of the corresponding mock-up vaccine together with quality data specific to the pandemic influenza A(H1N1)v strain it is considered that in the current pandemic situation the benefits outweigh the risks that may be associated with the use of the vaccine in accordance with the SPC.

Recommendation

On the basis of the available data for Focetria A(H1N1)v which is limited primarily to quality data and the data of the initially authorised medicinal product Focetria H5N1, the CHMP considered by consensus that the risk-benefit balance of Focetria H1N1 for the prophylaxis of influenza in an officially declared pandemic situation, in accordance with official guidance, was favourable. Therefore CHMP recommended the variation to the marketing authorisation under exceptional circumstances in accordance with Article 8 of Commission Regulation (EC) No 1085/2003 to the terms of the Marketing Authorisation until specific conditions as defined in Annex II.C (points 1 and 2) are fulfilled.