Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Influenza Virus Haemagglutinin H5N1

Proprietary Product Name: Aflunov/Prepandemic H5N1 adjuvanted Influenza Vaccine

Sponsor: Novartis Vaccines and Diagnostics

July 2011

TGA Health Safety Regulation

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- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New biosimilar medicine similar to other pandemic and seasonal influenza vaccines
Decision:	Approved
Date of Decision:	16 March 2011
Active ingredient(s):	Influenza Virus Haemagglutinin H5N1
Product Name(s):	Aflunov; Prepandemic H5N1 adjuvanted influenza vaccine
Sponsor's Name and Address:	Novartis Vaccines and Diagnostics
	54 Waterloo Rd, North Ryde NSW 2113
Dose form(s):	Solution for Injection
Strength(s):	Potency expressed as ≥7.5 µg Haemagglutinin (HA)/dose
Container(s):	Pre-filled syringe
Pack size(s):	Not specified
Approved Therapeutic use:	Active immunisation against A/Vietnam/1194 2004 (H5N1) like strain (NIBRG-14) subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see Clinical Trials). Aflunov/Prepandemic Influenza Vaccine H5N1 should be used in accordance with official recommendations.
Route(s) of administration:	Intramuscular (IM) or deep subcutaneous (SC)
Dosage:	0.5 mL
ARTG Number (s)	167943 and 167949

Product Background

This submission proposes the registration of a prepandemic influenza vaccine H5N1 (surface antigen, inactivated, adjuvanted) with two trade names; Aflunov; Prepandemic H5N1 adjuvanted influenza vaccine. The vaccine is derived from eggs and is produced using a A/Vietnam/1194 2004 (H5N1) like strain derived through reverse genetics (NIBRG-14[1]). The vaccine is adjuvanted with MF59C.1 (MF59) which is oil-in water emulsion composed mainly of squalene. MF59 is included in the registered trivalent seasonal influenza vaccine (surface antigen, inactivated), Fluad.

The indications proposed are:

> *"Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards*

[1] A reassortant virus produced by reverse genetics containing the internal genes of A/PR/8/34, and hemagglutinin (HA) and neuraminidase (NA) genes from A/Vietnam/1194/04 virus and modified by replacing the polybasic amino acids at the cleavage site to render the virus avirulent.

following administration of two doses of vaccine prepared with H5N1 subtype strains (see Clinical Trials). (Aflunov/Novartis Vaccines and Diagnostics) Prepandemic influenza vaccine H5N1 should be used in accordance with official guidances".

One dose is recommended in adults and elderly (18 years of age and above) at an elected date with a second dose given after an interval of at least three weeks. Prepandemic influenza vaccine H5N1 has been evaluated in adults and elderly following a 1, 22 day schedule. There is limited experience in children between six months and 17 years of age.

The concept behind this vaccine is that it would be available rapidly and in sufficient quantities (with minor antigenic adjustments as necessary) in the event of a pandemic. It can also be used in the inter-pandemic period in the hope of producing some pre-emptive baseline immunity in the community. The design and antigen selection is based on recent global pandemics, as the H5N1 is a likely candidate from which a pandemic influenza strain may evolve.

The rationale for the production of a vaccine against a potential influenza pandemic viral strain during the inter-pandemic period would be that it may:

· Allow early vaccination at the start of a pandemic (World Health Organization [WHO] Phase 6[2]) before the "fast track pandemic" vaccine is not yet available.
· May be used as a primer during prepandemic stages (WHO Phases 3 to 5) to reduce mortality against a closely matched pandemic strain in those countries where infections are occurring.
· Decrease the chance of emergence of a reassortment pandemic strain by vaccinating those (veterinarians, poultry workers, operators involved in the manufacturing of vaccines with pandemic-like strains, laboratory workers) at high risk of both avian and human virus infection.

There is some evidence that even a vaccine of limited efficacy, such a prepandemic vaccine, could mitigate a pandemic. H5N1, which is of avian origin, appears to cause influenza outbreaks in which human transmission is rare, but human infection has a high mortality rate. From the start of the H5N1 outbreaks in mid-2003 until 24 September 2009, 442 individuals were infected with laboratory-confirmed avian H5N1 influenza, 262 of whom died[3].

Regulatory Status

The product was given an EU marketing authorisation dated 29 November 2010 with the indication "Active immunisation against H5N1 subtype of Influenza A virus". Evaluations are ongoing in Switzerland, Singapore and Macau.

Product Information

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

[2] The World Health Organization (WHO) has produced a six-stage classification that describes the process by which a novel influenza virus moves from the first few infections in humans through to a pandemic. Phases 1–3 correlate with preparedness, including capacity development and response planning activities, while phases 4–6 clearly signal the need for response and mitigation efforts.

[3] http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_09_24/en/index.html

II. Quality Findings

Drug Substance

Structure

The drug substance is Influenza Virus Haemagglutinin H5N1 and is similar to other Influenza Virus Haemagglutinins

Manufacture

The drug substance is manufactured by Novartis Vaccines and Diagnostics SrL. The manufacturing process is that approved for Fluad and Agrippal.

Physical and Chemical Properties

Similar to those for other seasonal and pandemic influenza vaccines.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Drug Product

Formulation(s)

The formulation contains H5N1 HA, squalene, polysorbate 80, sorbitan trioleate, sodium citrate, citric acid monohydrate, sodium chloride, potassium chloride, potassium dihydrogen orthophosphate, hydrogen orthophosphate, magnesium chloride, calcium chloride and water for injections.

Manufacture

The product is manufactured by diluting the monovalent bulk to the appropriate HA content and aseptically filling into monodose syringes.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

The proposed shelf life of Aflunov in the syringe presentation is 36 months at 2-8°C.

The MF59 adjuvant when stored either in glass bottles or Polymer flex bags [both with nitrogen overlay] is stable for 36 months at 2-8°C protected from light.

Quality Summary and Conclusions

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

III. Nonclinical Findings

Overall quality and scope of the nonclinical dossier

The nonclinical data for this application comprised four pharmacology studies with Aflunov, several toxicity studies with formulations including MF59 adjuvant and most of the studies previously submitted to support the registration of Fluad (a registered, trivalent seasonal vaccine adjuvanted with the same adjuvant proposed for Aflunov) and/or Agrippal (the registered nonadjuvanted equivalent of Fluad).

Specific toxicity studies with Aflunov have not been submitted but these are not required according to the relevant guideline[4] if the proposed vaccine is to be manufactured and formulated similarly to a licensed seasonal vaccine with the only difference being the strain. Aflunov is the same as Fluad in all aspects except antigen type and content (45 µg HA, compared with 7.5 µg HA in Aflunov). Aflunov and Fluad are also the same as Agrippal in terms of manufacturing and excipient profile, but Agrippal does not contain an adjuvant.

Vaccine identical to that proposed for registration was used in three primary pharmacology studies in ferrets and one in mice and in an embryo-fetal/post-natal development study in rabbits. These address the requirements for non-clinical primary pharmacodynamics and reproductive toxicity studies using the strain intended for the candidate vaccine, as described in the EMEA/CHMP[5]/VWP/263499/2006 guideline.

Taken together, the nonclinical studies for Fluad/Agrippal and Aflunov fulfil the nonclinical requirements set out in the relevant seasonal and pre-pandemic vaccine guidelines[6].

MF59C.1 Adjuvant

The immunological component of MF59 is squalene, a precursor of cholesterol and a natural component found in shark liver, human sebaceous secretions and some fish and vegetable oils, including olive oil. Squalene is found in over 100 oral capsule products and in a small number of topical products registered in Australia but in only two registered parenteral products – Fluad and Pandemrix, a registered pandemic H5N1 vaccine. According to published information, when compared to alum or incomplete Freund's adjuvant, MF59 has been shown in mice, guinea pigs, rabbits and nonhuman primates to augment antigen-specific humoral and T-cell responses to a variety of experimental vaccines. Several published studies provided in the submission (not described in detail in this report) have shown that MF59 (and other adjuvants) enhance various pro-inflammatory elements of the immune system, although the mechanism/s involved in the *in vivo* effect of this and other adjuvants have not yet been determined.

Many of the toxicity studies to support the use of MF59 in Fluad have been re-submitted for this application. In addition, two new acute and eight new repeat-dose toxicity studies have been submitted, which used MF59-adjuvanted vaccines containing antigens from a wide range of viruses. These studies address the potential toxicity of MF59, which is still a relatively new adjuvant and fulfil requirements set out in the relevant guideline[7].

Overall, the non-clinical studies to support this application were of high quality and conformed to required standards in terms of detail of reporting and types of investigations. The scope of the nonclinical studies fulfilled requirements of the relevant guidelines and is considered adequate to support this application.

Pharmacodynamics

Vaccine efficacy studies

The guideline for pre-pandemic vaccines (EMEA/CHMP/VWP/263499/2006) details the importance of non-clinical immunogenicity and proof-of-concept studies to support the

[4] Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context, EMEA/CHMP/VWP/263499/2006

[5] Committee for Medicinal Products for Human Use

[6] Note for guidance on the preclinical pharmacological and toxicological testing of vaccines (CHMP/SWP/465/95) and the Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context (EMEA/CHMP/VWP/263499/2006)

[7] Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004)

efficacy of pre-pandemic vaccines before trialling in humans. These types of studies have been conducted with Aflunov in relevant animal models - mice, rabbits (immunogenicity studies only) and ferrets, the latter of which is the most relevant model of human influenza known currently. All of the elements outlined in the Guideline sections on *Proof-of-concept of protection* and *Nonclinical immunogenicity* were addressed in these studies.

Vaccine-mediated induction of antibodies that detect and/or neutralise the homologous virus strain (A/Vietnam/1194/2004) was demonstrated in mice, rabbits and ferrets; antibody cross-reactivity with a heterologous virus strain (A/turkey/Turkey/1/2005) was shown in two ferret studies. However, on a weight-for-weight basis, doses of 3.75 or 7.5 µg used in the studies with ferrets (about 1 kg) are very high relative to the proposed dose of 7.5 µg in humans (≥ 50 kg).

Immunisation with Aflunov protected against death and clinical disease (symptoms, fever, virus-or disease-associated changes in haematology and clinical chemistry) caused by a highly lethal homologous virus strain (A/Vietnam/1194/2004; in mice and ferrets) and a highly lethal heterologous virus strain (Indonesia/ 5/05 H5N1, in mice). Reductions in viral shedding (mouse and ferret studies) and decreased or absent replication of virus in spleen, lung and brain tissues (in mice) were confirmed in viral challenge studies.

There was adequate evidence that the immunogenic effect of H5N1 vaccine is enhanced by the addition of MF59 adjuvant. It is not possible to comment on whether the efficacy of Aflunov is affected by variations in HA dose or dosing schedule, although it appeared that an earlier immunogenic response was elicited following a two or three dosing schedule than a single dose regime.

The nature of the immunogenic response was investigated only in mice, where it was shown that Aflunov caused proliferation of CD4+ splenocytes that mediated a mainly Th2 immune response (cells produced mainly interleukin-5 (IL-5), tumour necrosis factor (TNFα) and IL-2).

Pharmacology studies re-submitted for this application were conducted with trivalent seasonal influenza vaccine and generally supported the use of the MF59 adjuvant, in particular for enhancing immune responses in the elderly. Some studies included challenge with seasonal influenza virus and these, as well as the challenge studies involving adjuvanted and nonadjuvanted Aflunov (summarised above), are useful for demonstrating that the addition of MF59 did not enhance viral disease, which is a concern arising from past experiences with inactivated adjuvanted vaccines such as those for measles and respiratory syncytial virus vaccines in the 1960s.

Toxicity

As mentioned above, toxicity studies with Aflunov were not submitted but their absence is adequately justified on the basis that the vaccine is identical to a registered vaccine (Fluad) which differs only in terms of antigen strain and content. Fluad contains a higher amount of haemagglutinin (45 µg) compared with Aflunov (7.5 µg). Since, haemagglutinin and neuraminidase antigen toxicity is usually associated with dose rather than subtype, it is reasonable to expect the potential for toxicity would not be greater with Aflunov than with Fluad.

A pivotal toxicity study with Fluad in rabbits was resubmitted for this application, in which it was shown that 0.5 mL vaccine containing 45 µg HA antigens from seasonal influenza viruses caused local but not systemic toxicity when administered twice at two week intervals. Other studies in rabbits or dogs given one or two doses of influenza vaccine at one or two week intervals were also unremarkable except for reversible (over 2 day or 2 week recovery periods) injection site lesions. In all cases, the antigen dose

delivered to animals (in 0.5 mL volumes in a 3 kg rabbit or a 10 kg dog) was *via* the proposed route and was substantially greater than the equivalent HA or adjuvant dose and dose volume in a human.

Adjuvant toxicity studies

Potential for toxicity with MF59 adjuvant has been extensively investigated with a wide variety of vaccines in rabbit and dog studies. Many of these used MF59 with water rather than citrate, but these studies remain valid because water or citrate would not be expected to impact greatly on the activity profile of MF59. In almost all cases, MF59 was administered by the route proposed for humans (IM) in 0.5 mL volumes, either undiluted or diluted 1:1 with buffer or saline: the amount of adjuvant administered to rabbits or dogs in all studies far exceeded the amount of adjuvant to be administered to humans.

The duration of repeat-dose studies with MF59 ranged from 2-10 weeks, with vaccinations given every 2-3 weeks, up to eight months with twelve doses given every two weeks. Recovery periods up to two weeks were included in almost all studies. The eight month study was conducted in rabbits and represented dosing over about 10% of the animals' life span. Another study involved daily vaccinations in rabbits for two weeks. These studies adequately covered the extent of repeat dosing in humans – up to three doses within a six week period for one immunisation.

As with the studies using adjuvanted influenza vaccine, toxicity with MF59 (either by itself or in formulations containing various virus antigens) was limited to injection site lesions that were severe in some cases, but always reversible.

When the safety of MF59 was evaluated for the Fluad application, the nonclinical evaluator noted that the studies raised no significant toxicological concerns, but there were limitations with respect to the extent of data and duration of testing. Local reactions to vaccines incorporating MF59 adjuvant appeared slightly more pronounced than with the corresponding unadjuvanted vaccines in animals, raising the possibility of an increased severity/prevalence of local reactions in humans. While there were no objections to the registration of Fluad for those aged over 65 years, it was suggested that toxicity of the MF59 adjuvant in Fluad vaccine should be reviewed in any subsequent extension of indications to lower age groups.

The concerns of the nonclinical evaluator over data limitations with MF59 have been addressed in the current application, where extensive studies confirmed only local reactions with the adjuvant. These appear to be more severe than nonadjuvanted vaccines, but the lesions were not progressive or cumulative in terms of effects locally or systemically. The sponsor's non-clinical overview also included information providing re-assurance over the lack of safety concerns with any residual dioxins and/or polychlorinated biphenyls (PCBs) present in squalene (main component of the MF59 adjuvant). Given that there are now sufficient data addressing the potential toxicity of the adjuvant, additional data to support its use in various age groups are no longer considered necessary.

Sensitisation potential

No studies were provided with Aflunov but there was no evidence from the pharmacology studies for sensitisation potential with this vaccine. Previously submitted studies of potential for delayed contact hypersensitivity with MF59 adjuvant were unremarkable.

Genotoxicity and carcinogenicity

Carcinogenicity or genotoxicity studies with Aflunov were not conducted or required for this type of product. Bacterial mutation and chromosomal damage studies with MF59 adjuvant (submitted previously) were negative.

Reproductive toxicity

The guideline for pre-pandemic vaccines recommends that a reproductive toxicity study with the vaccine proposed for registration should be conducted before the vaccine is approved if the vaccine is proposed for use in pregnant women, which is the case for Aflunov.

A reproductive toxicity study with Aflunov has been conducted in rabbits (a suitable species), with vaccinations (15 µg HA in 0.5 mL; H5N1 antigens from the strain proposed for the registered formulation) administered five, three and one week prior to mating, on gestation Day 7 (during a key embryofetal development phase) and again in late pregnancy on gestation Day 29. Immune responses to the vaccine in the dams were confirmed by serology studies showing antibodies to the homologous virus strain before mating, throughout gestation and (at lower levels) 29 days after parturition. Antibodies were also found in fetuses on gestation Day 29 (levels similar to those in dams) and in pups on postnatal Day 29 (levels lower than maternal levels).

There was no evidence for adverse effects on female fertility, pregnancy or embryofetal and post-natal development in this study.

The rabbit study fulfilled the requirements for reproductive toxicity testing of pre-pandemic vaccines according to the relevant guideline.

Studies assessing effects on fertility in males were not conducted but there is no plausible reason to expect such effects.

The sponsor also resubmitted two embryofetal development studies addressing the effects of MF59 adjuvant alone or formulated in HIV antigen-containing vaccine. There were no notable findings in these studies (apart from local reactions) except for a significant increase in litter and fetal incidences of incompletely ossified sternebrae, pubes and/or ischia in rats injected with 0.5 mL MF59 alone. This finding is not considered relevant to humans because the equivalent MF59 dose in humans *via* Aflunov would be > 100 times that delivered to the rat. Further, the observed defect is a relatively minor and common variation in rats and its significance in terms of affecting embryonic development is equivocal.

Use in children

The nonclinical data did not include studies that might be used specifically to address the use of Aflunov in children. On the other hand, there were no nonclinical toxicity findings that warrant further investigation before Aflunov is used in particular age groups.

Nonclinical Summary and Conclusions

- The quality and scope of the nonclinical data package adequately supported the current application and comply with relevant EMA/TGA guidelines for pre-pandemic vaccines, vaccines in general and adjuvants.

- Nonclinical pharmacology studies with Aflunov were performed in relevant animal species (challenge and serology studies in mice and ferrets, serology studies in rabbits). They showed vaccine-associated induction of antibodies that recognise and

neutralise a homologous (A/Vietnam/1194/2004) and a heterologous (A/turkey/Turkey/1/2005) virus strain.

- Viral challenge studies in ferrets and mice showed protection against death and disease caused by a highly lethal homologous virus strain and (in mice) a highly lethal heterologous strain, Indonesia/5/05 H5N1. Efficacy was enhanced by the addition of adjuvant; there was no evidence for enhanced viral disease due to the adjuvanted vaccine. The nature of the immune response in mice was predominately of the Th2 type, with most vaccine-stimulated $CD4^+$ T cells producing IL-5 (single positive) > IL-5 and TNF-α and IL-2 (triple positive) > TNF-α and IL-2 (double positive).

- Toxicity studies in rabbits and dogs with MF59 adjuvant alone or formulated with a variety of vaccine antigens showed no systemic toxicity. Local reactions were generally greater with the adjuvant than nonadjuvanted equivalents, but they were reversible and not catastrophic.

- A reproductive toxicity study with Aflunov has been conducted in rabbits immunised three times prior to mating and twice during gestation, in which serology studies confirmed the presence of antigen-specific antibodies in dams, fetuses and pups (on postnatal Day 29). There were no effects on pregnancy, dams or offspring in this study.

- The adjuvant, MF59 was assessed in reproductive toxicity, genotoxicity and sensitisation potential studies, all of which were unremarkable.

The nonclinical development program for Aflunov has adequately addressed nonclinical investigations recommended in regulatory guidelines for pre-pandemic vaccines.

The immunogenicity of the vaccine, its protective efficacy and the capacity of the adjuvant to enhance immune responses have been demonstrated in appropriate species.

The major effect observed in toxicity studies was injection site lesions, which were more severe than the nonadjuvanted equivalent formulations but which were reversible and relatively minor.

Aflunov has been assessed in an appropriate reproductive toxicity study in rabbits and there were no notable findings.

There are no objections on the basis of nonclinical data to the registration of Aflunov H5N1 vaccine containing 7.5 μg HA per dose in adults.

IV. Clinical Findings

Introduction

Type of application and aspects on development

The product in this submission is a prepandemic vaccine, Aflunov (called Fluad-H5N1 throughout this report) for the prophylaxis of avian H5N1 influenza. The data submitted is to be considered in the context of the relevant vaccine guidelines[8] and has been prepared in accordance with European Medicines Agency (EMEA) guidelines for pandemic vaccines[9].

[8] Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context. CHMP/VWP/263499/2006 . http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003872.pdf

[9] Guideline on submission of marketing authorization applications for pandemic influenza vaccines

Most of the studies included in this submission provided information in many areas of the submission – pharmacodynamics, efficacy and safety sections. As real-time disease protection cannot be established, these studies are to support a 'proof of concept' about the efficacy of this vaccine, as well as provide good safety data.

Studies including the V87 series and V101P1 are the main efficacy studies. All these studies were designed to assess safety and immunogenicity in non-elderly adult (18-60 years) subjects (V87P1, V87P2, V87P3, V87P12, V87P13, V101P1). Elderly subjects (> 60 years) were also included in two of these studies (V87P1 and V87P13). The initial studies (V7P37 and its extension V7P37E1) vaccines contained the avian strain H5N3.

The safety data for the 7.5µg Fluad-H5N1 vaccine is based on three datasets:

1) safety analyses on the pooled Fluad-H5N1 safety population of 3011 and 387 adults below and above 60 years (7.5µg and 15µg dosage);

2) the analysis of the safety profile of the MF59-adjuvanted seasonal influenza vaccine, Fluad, which is based on a pooled clinical safety database of 14,586 subjects ≥18 years of age (1383 aged 18-64 years, 12,913 aged >65 years and 290 subjects with underlying disease) from 42 historical clinical trials (and an additional eight extension studies);

3) the Fluad post-marketing surveillance data from over 40 million doses distributed from the initial licensure in September 1997 to April 30, 2008.

Development of the vaccine

Apart from the antigen composition and dose, the candidate vaccine (Fluad-H5N1) against avian H5N1 influenza is identical to the authorized inter-pandemic seasonal influenza vaccine used widely in Europe, Fluad™. These two egg-derived, surface-antigen, inactivated influenza vaccines, adjuvanted with MF59, with identical excipients, are produced with an identical manufacturing process at the same production plant.

Pharmacokinetics

According to the relevant EMEA guideline[10], pharmacokinetic studies are generally not required for injectable vaccines and kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations.

Drug Interactions

No drug interaction studies were submitted.

Pharmacodynamics

The Parent Vaccine, Seasonal Fluad

The parent vaccine of the Fluad-H5N1 was seasonal Fluad which is a well-established vaccine, which was first registered in Italy in May 1997. It is registered for the prophylaxis of seasonal influenza in Europe in 1997 and is currently licensed in 26 countries worldwide (including Australia). The adjuvant choice (and dose), MF59 was based on that used for authorized seasonal Fluad™. MF59 is an oil-in-water emulsion, composed mainly of squalene, an intermediate metabolite in the synthesis of cholesterol. Seasonal Fluad has been shown to confer higher protection against a mismatched seasonal influenza strain than nonadjuvanted subunit and split influenza vaccines. Although Fluad is generally

through the centralized procedure.
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003815.pdf

[10] Guideline for the Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/05).
http://www.tga.gov.au/pdf/euguide/vwp16465305enfin.pdf

targeted at the over-65 age group, epidemiological data on the currently ongoing "swine flu" pandemic caused by a new A/H1N1 strain (A/California/7/2009) also suggests that individuals below 60 years are more vulnerable[11]. The proposed indication for Fluad-H5N1 therefore includes all adults (that is, ≥18 years of age).

Assessment of immune response

Assumptions about the characteristics of the immune response to the vaccine are based on previous experience in the development of potential influenza vaccines[12]. Immunoglobulin (Ig) G, IgA and IgM antibodies appear simultaneously about two weeks after initial influenza infection, more quickly with subsequent infections. Peak antibody response occurs four to seven weeks after infection, IgG is the most reliable[13]. Based on this, 21 days after vaccination was selected as the time point for assessing the immune response (IgG) as is routine for influenza vaccines[14] by hemagglutination inhibition (HI), single radial hemolysis (SRH) and microneutralization (MN) assays.

Seasonal Fluad studies (summary supportive data submitted)

With the exception of antigen amount, the production of the Fluad-H5N1 vaccine is identical to that of the Fluad vaccine. The latter contains influenza strains of subtypes H3N2, H1N1 and B, with MF59 as adjuvant. In one study (V7P17), subjects received two injections four weeks apart. In a few studies, subjects were invited to participate in an extension study one and/or two years later. Regulatory guidelines require that at least one of the CHMP criteria be met for licensure of seasonal influenza vaccines[15]. All trials met at least one of the CHMP criteria for all three strains by HI or SRH assays. Additionally, one or two injections of the seasonal Fluad were safe and well-tolerated in all the studies. Vaccine reactions were generally mild and of short duration. In addition to the seasonal Fluad studies with adults, there are also data for seasonal Fluad in the pediatric population. In the pediatric population studies, all CHMP criteria were met (as defined for adults 18-60 years of age) by subjects who received Fluad.

Surrogates of Protection against Influenza

Overall, three serological assays were performed (HI, SRH and MN) for all studies using vaccines formulated with H5 viral antigens. HI and SRH are standard assays, as recommended by regulatory guidelines, for assessment of antibody titers induced by

[11] Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood FS, Jiain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. *N Engl J Med* 2009 Jun 18;350(25):2605-15

[12] Nicholson KG, Colegate AE, Podda A, Stephenson I, Wood J, Ypma E, et al. Safety and antigenicity of nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a randomised trial of two potential vaccines against H5N1 influenza. *Lancet* 2001 Jun 16 ;357 (9272):1937 -43. Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: Phase I randomised trial. *Lancet* 2006 May 20;367(9523):1657-64.
Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. *N Engl J Med* 2006 Mar 30;354(13):1343-51.

[13] http://www.hhs.gov/pandemicflu/plan/

[14] CPMP/BWP/214/96. Note for Guidance on Harmonization of Requirements for Influenza Vaccines.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf

[15] Note for Guidance on Harmonisation Requirements for Influenza Vaccines (CPMP/BWP/214/96)

influenza vaccines[16]. However it is not know whether these assays and particularly the standard HI assay are appropriate to measure antibodies against avian viruses[17]. SRH has been the preferred assay for demonstrating antibodies to H5N1 viruses in Novartis influenza vaccine trials because it gives more pronounced results: HI titers after exposure to H5 antigens are generally lower. One direct comparison of results from the standard HI using turkey erythrocytes and microneutralization (MN) assays demonstrated that the MN assay was substantially more sensitive in detecting human antibodies to H5N1 virus in infected individuals[18]. In order to improve the sensitivity of the HI assay for pandemic strains, a modified HI using horse erythrocytes[19] was developed and is used in the H5N1 studies. MN assay can sensitively and specifically detect H5N1 antibodies in patients with H5N1 influenza. Although the correlate of protection for infections caused by influenza A/H5N1 viruses is unknown, a serum neutralizing antibody titer of at least 1:40 may be considered protective based on the limited data.

EMEA guidance[8] does not indicate a preference for either one of the two accepted assays (HI or SRH) for the assessment of anti-HA antibody against seasonal influenza vaccines and suggests that neutralizing antibodies (MN) should also be measured, although there are no established clinical correlates of protection for results based on this assay. The EMEA guidance[8] for pandemic vaccines suggests that all criteria currently used during development of seasonal vaccines based on HI or SRH assays should be met since there are no established immunological correlates of pandemic infection. Specifically:

(a) in adult subjects aged 18 to 60 years,

- percentage of seroconversions or significant increases in anti-haemagglutinin (anti-HA) antibody titer/SRH area should be greater than 40%;
- mean geometric increase in HI antibody titers/SRH areas should be greater than 2.5 times baseline;
- percentage of subjects achieving an HI titer >40 or SRH area >25 mm^2 (defined as seroprotection for seasonal influenza vaccines) should be greater than 70%;

(b) in elderly subjects over 60 years,

- percentage of seroconversions or significant increases in anti-HA antibody titer/SRH area should be greater than 30%;

[16] Palmer DF, Dowle WR, Coleman MT, Schild GC. Haemagglutination-inhibition test. In: US Dept Health P.H.S.Atlanta IsNr6, editor. Advanced laboratory technicals for immunological diagnostics. Ed. Welfare ed. 1975. p. 25-62.
Schild GC, Pereira MS, Chakraverty P. Single-radial-hemolysis: a new method for the assay of antibody to influenza haemagglutinin. Applications for diagnosis and seroepidemiologic surveillance of influenza. *Bull World Health Organ* 1975;52(1):43-50.
[17] Nicholson KG, Colegate AE, Podda A, Stephenson I, Wood J, Ypma E, et al. Safety and antigenicity of nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a randomised trial of two potential vaccines against H5N1 influenza. *Lancet* 2001 Jun 16 ;357 (9272):1937 -43 2001;357(9272):1937-43.
Rowe T, Abernathy RA, Hu-Primmer J, Thompson WW, Lu X, Lim W, et al. Detection of antibody to avian influenza A (H5N1) virus in human serum by using a combination of serologic assays. *J Clin Microbiol* 1999 Apr;37(4):937-43.
[18] Rowe T, Abernathy RA, Hu-Primmer J, Thompson WW, Lu X, Lim W, et al. Detection of antibody to avian influenza A (H5N1) virus in human serum by using a combination of serologic assays. *J Clin Microbiol* 1999 Apr;37(4):937-43.
[19] Stephenson I, Wood JM, Nicholson KG, Charlett A, Zambon MC. Detection of anti-H5 responses in human sera by HI using horse erythrocytes following MF59-adjuvanted influenza A/Duck/Singapore/97 vaccine. *Virus Res* 2004 Jul;103(1-2):91-5.

- mean geometric increase in HI antibody titers/SRH areas should be greater than 2.0 times baseline (GMR)
- percentage of subjects achieving an HI titer >40 or SRH area >25 mm^2 (seroprotection for seasonal influenza vaccines) should be greater than 60%.

There are no established correlates of protection for neutralizing antibodies against infections caused by influenza A/H5N1 viruses. MN titers of 20 are thought to be a robust measure of specific antibody detection[20], in particular when baseline titers are low (<5). Others have used at least 4-fold increases above baseline to assess immune responses to H5N1 viruses by MN[21] Antibody titers, measured by MN assay, are a reliable and scientifically accurate method to sensitively and specifically detect H5N1 antibodies in patients with H5N1 influenza and are recommended to further assess immune responses to possible pandemic strains[22]. MN assay results for H5N1 studies are in terms of

(a) percentages of subjects achieving >20, >40 or >80 serum antibody titer cutoff values, which bracket the cutoff values employed or described previously.

(b) percentages of subjects achieving 4-fold increases in MN titers from pre- to post-vaccination.

Dose finding and adjuvant studies

Adjuvant

The adjuvant MF59 was selected for inclusion in the prepandemic vaccine formulation based on substantial previous clinical and post-marketing experience with seasonal Fluad.

Two clinical studies (V7P37 and V7P37E1) were conducted with H5N3 strain to investigate regimen, adjuvant and antigen amount. Initially a vaccine using the H5N1 strain could not be developed, as it was highly pathogenic in chick embryos. Therefore vaccine development began with an apathogenic but antigenically related vaccine (using H5N3) strains. These were used in the initial dose finding and adjuvant studies.

Dosage of hemagglutinin (HA) and schedule

Based on the EMEA-recommended HA content for inter-pandemic seasonal influenza vaccines[14] and the expected initial naïvety of the population against a newly-emerged pandemic strain, early Novartis studies on prepandemic Fluad formulated with H5N3 (Fluad-H5N3) used two vaccinations of 7.5µg, 15µg and 30µg HA (V7P37 and V7P37E1). The immunogenicity data from prepandemic Fluad formulated with H5N3 supported a schedule of two vaccinations of 7.5µg HA H5N1 given three weeks apart (see immunological results).

Summary of Dose finding/adjuvant studies

Study V7P37 evaluated the immune response to two injections of an MF59 adjuvanted vaccine formulated with a H5N3 viral strain in naïve populations and Study V7P37E1 investigated the response following a third (booster) H5N3 dose. Both adjuvanted and

[20] Lin J, Zhang J, Dong X, Fang H, Chen J, Su N, et al. Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (H5N1) vaccine: a Phase I randomized controlled trial. *Lancet* 2006 Sep 16;368(9540):991-7.

[21] Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: Phase I randomised trial. *Lancet* 2006 May 20;367(9523):1657-64.
Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. *N Engl J Med* 2006 Mar 30;354(13):1343-51.

[22] CPMP/VEG/4717/03 Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation applications.

nonadjuvanted vaccine formulations containing 7.5, 15 and 30 µg of H5N3 were evaluated in these studies. A further five studies (V87P1, V87P2, V87P3, V87P12 and V87P13) investigated the immunogenicity and safety of two injections of Fluad-H5N1 vaccine (which in Study V87P3 were given several years after the H5N3 injection in Study V7P3 7E1). In V87P1 and V87P2, the initial studies of the clinical development program for the pandemic H5N1 vaccine, adjuvanted formulations with 7.5 and 15 µg of H5N1 antigen were evaluated while the 7.5µg vaccine was used in all the other studies in the V87 series. In Study V87P1, an additional third injection was administered to a subset of subjects six months after the second dose. Additionally, in Study V87P2 a nonadjuvanted vaccine formulation with 15 µg of H5N1 antigen was studied as a comparator and an additional third injection was administered to all subjects six months after the second dose. In Study V87P3 subjects were given two doses of H5N1 6-8 years after receiving the H5N3 injection in Study V7P37E1. In Study V87P12, subjects received two doses of Fluad-H5N1 one week, two weeks, three weeks, or six weeks apart. In V87P13, two of the four groups of subjects received two doses of Fluad-H5N1 three weeks apart, three weeks after receiving an unadjuvanted trivalent seasonal vaccine (Agrippal™). Finally, Study V101P1 provided data on concomitant administration of Fluad-H5N1 and an inactivated, trivalent seasonal influenza vaccine (Grippeimpfstoff N Hexal™).

Summary of dose finding/adjuvant results

Comparison of all dose finding studies (all strains) found no significant advantage was achieved with the 15 and 30 µg doses when compared with the lower 7.5 µg dose. Geometric mean ratios (GMRs) were similar after two vaccinations with the 7.5 and 15µg doses (Fluad-H5N3 and Fluad-H5N1). The adjuvanted formulations always achieved better immunogenicity results than the nonadjuvanted vaccines, regardless of which serology assay was used. In contrast to nonadjuvanted formulations (assessed by MN) Fluad formulated with H5N3 induced antibodies that cross-reacted against not only the H5N1 outbreak strains but also against the more recent and virulent strains isolated in 2003 and 2004 in Vietnam and Hong Kong. Likewise, both the 7.5µg and 15µg doses of Fluad H5N1 induced antibodies against a heterologous H5N1 strain after the second and third vaccination. Dose and formulation finding studies led to the conclusion that the vaccine containing 7.5 µg of H5N1 antigen (two doses, given 3 weeks apart, of the MF59-adjuvanted formulation) is the most suitable for prepandemic primary immunization.

The nonadjuvanted vaccine had the identical ingredients but no adjuvant (used in V87P2).

In Study V87P4, the reference seasonal vaccine was the inter-pandemic Fluad (2006/7).

In Study V87P13, reference vaccine was adjuvanted seasonal (Fluad), which contained the purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA), including 15 µg of HA of the A/H1N1, A/H3N2 and B antigens recommended for the influenza season 2008/2009 in the Northern Hemisphere, as well as the identical but nonadjuvanted trivalent seasonal influenza vaccine (Agrippal).

Placebo

Placebo consisted of a single 0.5mL IM injection of isotonic saline solution and was administered in the deltoid muscle, preferably of the non-dominant arm.

Results of Individual Studies

H5N3 Studies

For these studies, the recruitment, randomisation, blinding and outcome analyses were similar to those described in the section on Efficacy below. The vaccines used contained 7.5µg, 15 µg or 30 µg of antigen:

Baseline GMT results based on all three assays (HI, SRH and MN) were undetectable for all 18- to 40-year-old subjects who were randomly assigned to receive adjuvanted and nonadjuvanted vaccinations in Study V7P3 7 and the follow-up extension Study V7P37E1, in response to both the H5N1 and H5N3 assay antigens.

V7P37

This was a Phase I, observer-blind, dose-ranging, single center (in the United Kingdom (UK)) pilot study conducted in 1999 to evaluate immunogenicity, tolerability and other safety indicators. Subjects were randomly assigned (1:1) to receive two IM injections, administered three weeks apart of either Fluad-H5N3 or nonadjuvanted formulation, each containing dosages of 7.5, 15 or 30 µg of the H5N3 influenza antigen. A total of 65 healthy young adult subjects aged 18-40 years were vaccinated (10 or 11 subjects per group).

Criteria for immunogenicity evaluation:

All of the following CHMP criteria were evaluated: seroprotection (>70 %), geometric mean ratio (GMRs) (>2.5), seroconversion/significant increase (>40 %) assessed on Day 21 after each vaccination by HI and SRH. In addition, Geometric Mean Titer (GMTs), percentages of subjects with titres >20, >40 and >80 and percentages of subjects with at least 4-fold titer increases from baseline by MN were evaluated. Sera were tested against the vaccine homologous A/Duck/Singapore/645/97 (H5N3) strain but also against the wild heterovariant influenza A/H5N1/HongKong/97 strain (by SRH) to evaluate the immunogenicity of the study vaccines against the virus responsible for the Hong Kong outbreak in 1997.

Immunogenicity results:

Two injections of 7.5µg HA administered three weeks apart induced high post-immunization antibody titers when the MF59 adjuvant was used (GMTs for H5N3 were: 35 by HI; 32 by MN; 92 by SRH; and for H1N1 41 by SRH). Two injections of 7.5 µg Fluad-H5N3 induced the highest seroconversion rates measured by HI (60%) and both SRH tests (100 % for H5N3 and 90 % for H5N1). Two prepandemic Fluad-H5N3 vaccinations at all dose levels met all three CHMP criteria for both H5N3 and H5N1 antigens by SRH assay. By contrast, the nonadjuvanted formulation only met one CHPM criterion with the 15µg dose after two injections.

V7P37E1

Phase I, open-label dose-ranging, single center (UK) extension study conducted in 2000 to evaluate the immunogenicity, tolerability and safety of an H5N3 vaccine booster dose. Subjects who completed Study V7P3 7 were re-vaccinated approximately 17 months after primary vaccination with one IM injection with the same dose of the same vaccine (either Fluad-H5N3 or nonadjuvanted formulation; 7.5, 15, or 30 µg of antigen) given for the primary immunization. A total of 28 healthy young adult subjects aged 18-40 years were vaccinated (two to seven subjects per group).

Criteria for immunogenicity evaluation: as for Study V7P37 above.

Immunogenicity results: Immune responses were significantly higher after the prepandemic Fluad-H5N3 vaccine when compared with the nonadjuvanted vaccine, at all doses. All doses of Fluad-H5N3 met all three CHMP criteria for both H5N3 and H5N1 antigens by the SRH assay but only some by the HI assay. The nonadjuvanted vaccine did not meet any of the CHMP criteria by HI, but the 30µg formulation did meet all three criteria by SRH. Interestingly, MF59-adjuvanted H5N3 vaccine induced antibodies that cross-protected not only against the H5N1 strain from the Hong Kong 1997 outbreak, but

also against A/HongKong/213/03, A/Thailand/16/04 and A/Vietnam/1203/04. The results of these two trials are summarized in Table 1.

Table 1: Selection of the Optimal Dose and Optimal Serology Assay for the H5N3 Adjuvanted and Non-Adjuvanted Formulations: Geometric Mean Titers and Ratios of Change From Baseline

Geometric Mean Titers (GMT) and Ratio (GMR)							
Immunogenicity Parameter	Dosages Tested	Studies V7P37 and V7P37E1 Vaccine Antigen H5N3 Adults 18-40 years, adjuvanted			Studies V7P37 and V7P37E1 Vaccine Antigen H5N3 Adults 18-40 years, non-adjuvanted		
		HI	SRH	MN	HI	SRH	MN
GMT (95% CIs) *total no. subjects* Baseline	7.5 µg	5 (5-5) *10*	4 (4-4) *10*	10 (9.47-11) *10*	5 (5-5) *10*	4 (4-4) *10*	11 (10-11) *10*
	15 µg	5 (5-5) *11*	4 (4-4) *11*	10 (9.49-11) *11*	5 (5-5) *11*	4 (4-4) *11*	10 (9.49-11) *11*
	30 µg	5 (5-5) *11*	4 (4-4) *11*	10 (9.49-11) *11*	5 (5-5) *11*	4 (4-4) *11*	10 (9.49-11) *11*
GMR (95% CIs) *total no. subjects* 21 days after Vaccination 1	7.5 µg	2 (1.23-3.24) *10*	**4.12 (2.4-7.07) *10***	2.14 (1.63-2.83) *10*	1 (0.62-1.62) *10*	1 (0.58-1.72) *10*	1 (0.76-1.32) *10*
	15 µg	2.13 (1.34-3.38) *11*	2.37 (1.42-3.97) *11*	1.46 (1.12-1.9) *11*	1 (0.63-1.59) *11*	1 (0.6-1.67) *11*	1 (0.77-1.3) *11*
	30 µg	1 (0.63-1.59) *11*	1.28 (0.76-2.13) *11*	1.07 (0.82-1.39) *11*	1.13 (0.72-1.8) *11*	1 (0.6-1.67) *11*	1.29 (0.99-1.68) *11*
GMR (95% CIs) *total no. subjects* 21 days after Vaccination 2	7.5 µg	**6.96 (3.6-13) *10***	**23 (15-35) *10***	3.25 (2.32-4.56) *10*	1 (0.52-1.93) *10*	1 (0.65-1.54) *10*	1 (0.71-1.4) *10*
	15 µg	**5.28 (2.73-10) *10***	**19 (13-30) *10***	2.64 (1.88-3.7) *10*	1 (0.53-1.87) *11*	**3.13 (2.07-4.72) *11***	1.13 (0.82-1.57) *11*
	30 µg	2 (1.07-3.75) *11*	**18 (12-27) *11***	2.92 (2.11-4.03) *11*	1.23 (0.64-2.38) *10*	1.96 (1.27-3.01) *10*	1.41 (1.01-1.98) *10*
GMR (95% CIs) *total no. subjects* 21 days after Vaccination 3 Study V7P37E1	7.5 µg	**5.04 (2.62-9.71) *6***	**10 (4.6-22) *6***	**65 (32-134) *6***	1 (0.4-2.53) *3*	**12 (7.27-19) *3***	0.77 (0.28-2.12) *6*
	15 µg	2 (0.79-5.05) *3*	**13 (4.46-31) *3***	**36 (13-100) *3***	1 (0.52-1.93) *6*	**11 (8.03-16) *6***	1.53 (0.75-3.14) *6*
	30 µg	**6.35 (3.3-12) *6***	**3.14 (1.44-6.86) *6***	**40 (20-83) *6***	1 (0.32-3.11) *2*	**17 (9.33-31) *2***	4.69 (1.35-16) *2*

GMR = geometric mean ratio of 21days postvaccination to baseline titer; Bold for HI and SRH = **GMR >2.5** for non-elderly adults 18 – 60 years and CHMP criterion met, or **GMR >2.0** for elderly >60 years.

H5N1 Studies

No advantage for the 30µg dose compared with the 7.5 and 15µg dosages could be seen for Fluad-H5N3 in any of the three assays. Therefore in the dose and schedule finding studies with Fluad-H5N1 (V87P1 and V87P2) it was decided to proceed only with the 7.5 and 15µg dosages. Baseline GMTs and GMRs after first and second vaccination are presented in Table 2. Comparing the GMRs of the two dosages after second vaccination for Fluad-H5N3 and Fluad-H5N1 showed that 7.5µg was not less immunogenic than 15µg. In Study V87P1

it was shown that the immunogenicity following two injections of Fluad-H5N1 vaccine containing 7.5µg of H5N1 influenza antigen was non-inferior to that of two injections of Fluad-H5N1 vaccine containing 15µg of A/H5N1 as evaluated by the HI assay. Therefore, the 7.5µg antigen concentration was selected for the final vaccine and only this dosage was included in the major Phase III study, V87P13.

In studies conducted with H5N1, only a few subjects (18 to 60 years of age) had detectable titers with all three tests at baseline (Table 2). Among elderly subjects in Study V87P1 who received the 7.5 and 15µg vaccine doses some 12% and 11%, respectively, showed seroprotection to H5N1 at baseline based on the HI assay and 11% and 24%, respectively, based on the SRH assay. By comparison, 0% and 3% of non-elderly adult subjects, respectively, were seroprotected against H5N1 at baseline as measured by the HI assay and 5% and 9%, respectively, as measured by the SRH assay. In Study V87P2, across the three vaccine groups, 0% to15% of non-elderly subjects showed seroprotection with both HI and SRH assays. Data on antibody persistence with Fluad-H5N3 is provided by Study V7P3 7E1, 17 months after second vaccination and for Fluad-H5N1, by Study V87P1 six months after second vaccination. Titers against the H5N3 strain had returned to undetectable levels after 17 months as measured by HI and MN assays. The SRH titers bordered on undetectable for recipients of 7.5 and 15µg doses but were higher for recipients of the 30µg dose. For Fluad-H5N1 (V87P1 and V87P2) six months after the second vaccination, decreases were seen in GMA/GMTs for both doses and age groups. However, they were still above baseline as assessed by all three serology assays.

Table 2: Selection of the Optimal Dose and Optimal Serology Assay for H5N1 Adjuvanted and Non-adjuvanted Formulations: Geometric Mean Titers and Ratios of Change from Baseline after First and Second Vaccination

Geometric Mean Titers (GMT/GMA) and Ratios (GMR)											
	Age Group	Dosages Tested	Study V87P1 adjuvanted[a]			Study V87P2 adjuvanted[b]			Study V87P2 non-adjuvanted[b]		
			HI	SRH	MN	HI	SRH	MN	HI	SRH	MN
GMT/GMA (95% CIs) *total no. subjects* Baseline	Adults 18-60 years	7.5 µg	5.12 (4.81-5.44) *151*	4.79 (4.34-5.29) *149*	11 (10-12) *151*	6.47 (4.08-10) *14*	4.37 (3.21-5.96) *14*	14 (9.9-20) *14*	-	-	-
		15 µg	5.52 (5.19-5.87) *147*	5.2 (4.71-5.75) *149*	11 (10-12) *151*	5 (3.13-7.99) *13*	4.81 (3.49-6.63) *13*	12 (8.05-17) *13*	8.07 (5.05-13) *13*	5.59 (4.06-7.7) *13*	15 (11-22) *13*
	Elderly >60 years	7.5 µg	8.13 (6.27-11) *81*	6 (4.9-7.35) *84*	18 (14-22) *84*	-	-	-	-	-	-
		15 µg	8.2 (6.26-11) *74*	7.57 (6.15-9.33) *80*	16 (13-20) *80*	-	-	-	-	-	-
GMR (95% CIs) *total no. subjects* 21 days after Vaccination 1	Adults 18-60 years	7.5 µg	**3.41 (2.59-4.5) *151***	2.38 (2-2.85) *149*	2.41 (2.02-2.89) *151*	2.5 (1.25-4.98) *14*	1.62 (0.98-2.66) *14*	1.76 (0.97-3.19) *14*	-	-	-
		15 µg	**3.75 (2.84-4.97) *147***	**2.84 (2.38-3.39) *149***	3.13 (2.61-3.74) *151*	1.62 (0.79-3.31) *13*	1.58 (0.94-2.64) *13*	1.41 (0.76-2.62) *13*	1.53 (0.75-3.13) *13*	1.43 (0.86-2.4) *13*	1.52 (0.82-2.83) *13*
											continues

Table continued on the next page.

Table 2: continued.

Geometric Mean Titers (GMT/GMA) and Ratios (GMR)												
	Age Group	Dosages Tested	Study V87P1 adjuvanted[a]			Study V87P2 adjuvanted[b]			Study V87P2 non-adjuvanted[b]			
			HI	SRH	MN	HI	SRH	MN	HI	SRH	MN	
	Elderly >60 years	7.5 µg	3.88 (2.64-5.69) *81*	2.85 (2.23-3.65) *84*	2.41 (1.81-3.2) *84*	-	-	-	-	-	-	
		15 µg	4.87 (3.27-7.27) *74*	2.46 (1.91-3.17) *80*	3.17 (2.37-4.25) *80*	-	-	-	-	-	-	
GMR (95% CIs) total no. subjects 21 days after Vaccination 2	Adults 18-60 years	7.5 µg	16 (12-21) *151*	7.74 (6.6-9.07) *149*	11 (8.87-13) *151*	21 (8.41-52) *14*	8.12 (4.61-14) *14*	8.14 (3.78-18) *14*	-	-	-	
		15 µg	15 (12-21) *147*	6.86 (5.85-8.04) *149*	9.2 (7.63-11) *151*	5.77 (2.31-15) *13*	2.27 (1.26-4.09) *13*	5.75 (2.6-13) *13*	2.35 (0.91-6.07) *13*	1.96 (1.09-3.53) *13*	1.62 (0.73-3.58) *13*	
	Elderly >60 years	7.5 µg	9.52 (6.55-14) *81*	4.96 (3.87-6.37) *84*	4.54 (3.44-6.01) *84*	-	-	-	-	-	-	
		15 µg	10 (6.78-15) *74*	4.09 (3.17-5.28) *80*	5.61 (4.22-7.48) *80*	-	-	-	-	-	-	

GMR = geometric mean ratio of 21days postvaccination to baseline titer; Bold for HI and SRH = **GMR >2.5** for non-elderly adults 18–60 years and CHMP criterion met, or **GMR >2.0** for elderly >60 years; a: data from Per Protocol Population; b: data from Full Analysis Set.

Evaluator's overall conclusions on pharmacodynamics

There is sufficient evidence both in the studies using H5N3, H5N1 and the historical data with seasonal Fluad to support the 7.5µg dosage, adjuvanted form and schedule chosen for the current application. There does not appear to be any advantage of using a dose higher than the 7.5µg in its adjuvanted form.

Efficacy

Introduction

The efficacy and safety component of this application contains data from six main trials conducted in a progressive development scheme to produce a prepandemic influenza vaccine. This vaccine strain is thought to be a likely candidate for a pandemic strain, or at least closely related. Initially the H5N1-strain could not be cultured easily, so the studies began with an antigenically similar H5N3 strain (see previous section) and then moved on to use the prepandemic strain, H5N1. There are well established and accepted guidelines for the development and assessment of influenza vaccines (referred to previously). The design and efficacy component of these studies is based around finding the dose, schedule and adjuvant that provides suitable evidence of immunogenicity and safety in accordance with this EMEA regulatory guideline.

Main Clinical Studies

Summary

The V87 series and V101P1 studies were designed to assess safety and immunogenicity in non-elderly adult (18-60 years) subjects (V87P1, V87P2, V87P3, V87P12, V87P13, V101P1). Elderly subjects (> 60 years) were also included in two of these studies (V87P1 and V87P13). The initial studies; (V7P37 and its extension V7P37E1) vaccines contained the avian strain H5N3.

Based on the initial studies using the H5N3 strain, a larger Phase II study (V87P1), conducted in 2006/2007, evaluated the immune response to a prepandemic Fluad

formulation with H5N1. A total of 486 healthy subjects were stratified into non-elderly adult (18-60 years) and elderly (> 60 years) age groups as recommended in the EMEA guideline[23]. Two vaccinations of either 7.5µg or 15µg of adjuvanted vaccine were given three weeks apart. The sample size was chosen to test for non-inferiority of 2 x 7.5µg vaccinations to 2 x 15µg vaccinations with regard to the immune response as measured with HI assay. A booster vaccination was given at Day 202 (six months after the first vaccination) in approximately half of the subjects enrolled in each of the 7.5µg and 15µg groups. Subjects were followed up for a further six months.

A second Phase II study, V87P2, was an immunogenicity and safety study in non-elderly adult subjects. Cell mediated immunity (CMI) was investigated as well as immunogenicity by HI, SRH and MN. A total of 40 non-elderly subjects were enrolled to receive two injections of 7.5 or 15 µg H5N1 MF59-adjuvanted vaccine or 15 µg H5N1 nonadjuvanted vaccine three weeks apart. Six months after the second vaccination, the subjects were given a third vaccination and followed up for a further six months.

V87P3 was a Phase I study carried out to evaluate the strategy of priming a population with a prepandemic vaccine in advance of an emerging pandemic caused by a different strain. Some 58 subjects aged 18 to 65 years who previously participated in studies with the H5N3 prepandemic vaccines (V7P37 and V7P37E1, conducted in 1999-2000) were enrolled to receive 2 x 7.5µg vaccinations of Fluad-H5N1, three weeks apart. Enrolled subjects were stratified in three vaccine groups based on their priming: 1) unprimed subjects, 2) subjects primed with Fluad-H5N3 6 to 8 years before and 3) subjects primed with nonadjuvanted H5N3 vaccines.

Study V87P12 was a Phase III study to evaluate safety and immunogenicity of two injections of Fluad-H5N1 (7.5µg formulation) administered to non-elderly adult subjects (ages 18 to 60 years) using four different vaccination schedules (1, 2, 3 and 6 weeks apart). A total of 240 subjects were randomized at a 1:1:1:1 ratio.

Study V87P13 was a pivotal, large Phase III study conducted to assess safety, tolerability and immunogenicity of two vaccinations of Fluad-H5N1 (7.5µg formulation) in adults and elderly subjects. A total of 3647 subjects were enrolled and randomized within each age group in a 4:1 ratio to receive either the seasonal influenza vaccine (Agrippal) followed by two doses of Fluad-H5N1, or a placebo followed by two doses of the seasonal Fluad vaccine. All vaccinations were administered 3 weeks apart. Immunogenicity was investigated in a subset of the enrolled population. The six month safety follow-up is still ongoing.

In addition to the Fluad-H5N1 studies discussed above that comprise the core development program, a Phase II, randomized, placebo-controlled, observer-blind, study (V101P1) was conducted in adults and elderly subjects to investigate safety and immunogenicity of Fluad-H5N1 (7.5µg formulation) administered before or after a tetravalent influenza vaccine (formulated with three inter-pandemic seasonal influenza strains and the pandemic H5N1 strain) or after a concomitant administration in different injection sites of Fluad-H5N1 and a seasonal trivalent nonadjuvanted influenza vaccine (Agrippal). This study provides the opportunity to assess if concomitant administration of the prepandemic vaccine with a seasonal influenza vaccine has an impact on the immune responses to either H5N1 or influenza seasonal strains (A/H1N1, A/H3N2, and B). Only results for the concomitant administration arm are presented.

There is one other study included in the submitted data, V87P4, but it was not included in any of the pooled efficacy or safety data. It was a Phase III, randomized, controlled, observer-

[23] Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96).

blind, multicenter study to evaluate the immunogenicity, safety and tolerability of two doses of Fluad-H5N1 influenza vaccine in adult and elderly Subjects. It assessed the tolerability of two doses of Fluad-H5N1 vaccine compared to two doses of trivalent, interpandemic Fluad containing the strains recommended by WHO for the 2006/2007 influenza season in the Northern Hemisphere; each dose was administered three weeks apart. In total, 4560 subjects were enrolled but 1042 of these were from sites that were excluded from the analysis. By all serological assessments and criteria for evaluation, the immune response to Fluad-H5N1 formulated with 7.5µg was similar after each of the two injections in both the adult and elderly subjects regardless of baseline titers. Analysis of SRH results showed that all three CHMP criteria were met by the Fluad-H5N1 injection group in the adult and elderly subjects after two injections of Fluad-H5N1 containing 7.5µg A/H5N1 influenza antigen. When using the HI assay, two out of three (the proportion of subjects achieving seroprotection was not met) CHMP criteria (CPMP/BWP/214/96) were met for the adult (18-60 years) Fluad-H5N1 subjects while the elderly subjects (>60 years) also met all three CHMP criteria using the HI assay. Fluad-H5N1 and seasonal Fluad injections were well tolerated. With the exception of a lower percentage of adult Fluad-H5N1 recipients reporting severe local reactions after the first injection, there was no clear and consistent difference in the reactogenicity profile between the two vaccines. It may be that this study has not been referred to because of issues that made the data unsound and the sponsor was asked for confirmation of this.

Methods

The primary objective of each of the studies was to assess safety and immunogenicity of the candidate vaccine Fluad-H5N1 in relation to the EMEA guidelines. Other secondary objectives of each study are detailed below, depending on the design and comparator**.**

Design

Studies V87P1, V87P2, V87P13 and V101P1 were carried out as prospective, randomized observer-blinded studies. V87P13 is the only Phase III study discussed in the submission and is conducted on a large patient base. Study V87P12 was a prospective, randomized, open-label study. Study V87P3 was a prospective, non-randomized, open-label study. In observer-blind studies, both volunteers and investigators responsible for assessing reactogenicity and safety were blinded to the vaccine given, with the exception of a documentation of one unblinded person who gave the vaccine injections and who had no further involvement with the study procedures after vaccination. Two different vaccine dosages (7.5 and15µg) were administered to compare immunogenicity in Studies V87P1 and V87P2. In the other studies, two 7.5 µg Fluad-H5N1 vaccine injections were given. In Study V87P13 the inter-pandemic Fluad vaccine was also administered for the purpose of a safety and tolerability comparison. In V101P1, vaccines were used as follows:

-Subjects were randomly assigned to one of the following 6 vaccination groups using an overall randomization ratio of 17:17:17:3:3:3 for Step 1 (the lead-in phase, 150 subjects) and a 4:4:4:1:1:1 ratio for Step 2 of the study (450 subjects).

1) T/P-A group: On Day 1, one 0.5 mL IM injection of the tetravalent vaccine containing 15 µg of antigen per seasonal strain and 7.5 µg of H5N1 was administered concomitantly, but in different sites, with a placebo (saline). Approximately 3 to 5 weeks later, one 0.5 mL injection of Fluad-H5N1 containing 7.5µg of H5N1 antigen, was administered IM in the deltoid muscle, preferably into the non-dominant arm.

2) A/P-T group: On Day 1, one 0.5 mL injection of Fluad-H5N1 containing 7.5 µg of H5N1 antigen, was administered IM concomitantly, but in different sites, with a placebo (saline). Approximately 3 to 5 weeks later, one 0.5 mL IM injection of the tetravalent vaccine containing 15µg of antigen per seasonal strain and 7.5 µg of H5N1 was administered IM into the deltoid muscle; preferably into the non-dominant arm.

3) A/S-A group: On Day 1, one 0.5 mL IM injection of Fluad-H5N1 containing 7.5µg of H5N1 antigen was administered concomitantly, but in different sites, with a licensed seasonal trivalent vaccine containing 15µg antigen per strain. Approximately 3 to 5 weeks later, one 0.5 mL injection of Fluad-H5N1 containing 7.5µg of H5N1 antigen, was administered IM in the deltoid muscle, preferably into the non-dominant arm.

4) T/P-A group (Cell Mediated Immunity (CMI)): as T/P-A above but with extra blood taken before second vaccination for CMI evaluation.

5) A/P-T group (CMI): as A/P-T above but with extra blood taken before second vaccination for CMI evaluation.

6) A/S-A group (CMI): as A/S-A above but with extra blood taken before second vaccination for CMI evaluation.

The following details applied to all studies:

Inclusion Criteria

Subjects eligible for enrollment into this study were male and female adult volunteers who were:

1. 18 years of age or older, mentally competent, willing and able to give written informed consent prior to study entry;

2. Able to comply with all the study requirements

3. In general good health as determined by:

- Medical history
- Physical examination
- Clinical judgment of the investigator

Informed consent was obtained for all subjects before enrollment in the study.

Exclusion Criteria

Subjects were not to be enrolled into the study if:

1. They had any serious disease such as:

- Cancer (except for benign or localized skin cancer and non metastatic prostate cancer not presently treated with chemotherapy)
- Autoimmune disease (including rheumatoid arthritis)
- Advanced arteriosclerotic disease or complicated diabetes mellitus
- Chronic obstructive pulmonary disease requiring oxygen therapy
- Acute or progressive hepatic disease
- Acute or progressive renal disease
- Congestive heart failure

2. They were hypersensitive to eggs, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin or any other component of the vaccine.

3. They had a history of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine.

4. They had a known or suspected (or have a high risk of developing) impairment/ alteration of immune function (excluding that normally associated with advanced age) resulting, for example, from:

- Receipt of immunosuppressive therapy (any parenteral or oral corticosteroid or cancer chemotherapy/radiotherapy) within the past 60 days and for the full length of the study

- Receipt of immunostimulants
- Receipt of parenteral immunoglobulin preparation, blood products and/or plasma derivates within the past 3 months
- Suspected or known human immunodeficiency virus (HIV) infection or HIV related disease

5. Women who were pregnant or women able to bear children but not willing to practice acceptable contraception for the duration of the trial.

6. Within the past four weeks they had received:

- Another vaccine
- Any investigational agent

7. Within the past seven days, they had experienced:

- Any acute disease
- Infections requiring systemic antibiotic or antiviral therapy (chronic antibiotic therapy for urinary tract prophylaxis is acceptable)

8. Within the past three days, they had experienced:

- Fever (axillary temperature > 38°C)

9. They were taking part in another clinical study

10. They had surgery planned during the study period

11. They had any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objective.

Removal of Subjects from Therapy or Assessment

The subject, or the subject's legally acceptable representative(s), could withdraw consent for participation in the study at any time without prejudice. The investigator could withdraw a subject if, in his or her clinical judgment, it was in the best interest of the subject or if the subject could not comply with the protocol. In addition, a subject was not eligible for subsequent vaccination or was discontinued from the study following occurrence of:

- A febrile convulsion and neurological disturbances after vaccination
- Hypersensitivity to the investigational vaccine
- Other suspected side effects that could compromise the subject's well being.

Any subject who, despite the requirement for adequate contraception, became pregnant during the trial would not receive further vaccination. The site would have to maintain contact with the pregnant subject, complete a "Pregnancy Report" case report form (CRF) and obtain pregnancy outcome information.

Withdrawn subjects were not replaced.

Prior and Concomitant Therapy

Medication prescribed to subjects prior to the start of the study was not collected. All prescription medication, including non-study vaccines, being taken by the subjects on entry to the study and all prescription medication given in addition to the study vaccine during this clinical trial were to be regarded as concomitant medication and were documented. The following concomitant treatments were discouraged and, if used, might have lead to a major protocol violation according to the medical judgment of the Novartis physician (see exclusion criteria):

- Systemic steroids
- Other immunosuppressive agents
- Blood or plasma derivates, including immunoglobulin

- Non-study vaccines (with the exception of post-exposure vaccinations in a medical emergency such as hepatitis, rabies or tetanus).
- Inter-pandemic influenza vaccines

Immunogenicity testing

The primary analysis in these studies was based on the A/H5N1/Vietnam/1194/04 strain. In some studies heterologous strains were also tested (mainly the A/H5N1/turkey/Turkey/05 strain). Immunogenicity was summarized by the GMT of anti-HA antibodies after each vaccination and for HI and SRH assays as the proportions of subjects with seroconversion or significant increase, (seroprotection) and mean geometric increase (GMR) according to the CHMP criteria for inter-pandemic seasonal influenza vaccines. In Studies V87P2, V87P3, V87P12 and V87P13 the full analysis set (FAS) was used for the analysis of immunogenicity. For Study V87P1 the per-protocol (PP) population was chosen as the most conservative population since non-inferiority of the 7.5µg to the 15µg dosage was assessed.

Serum samples for antibody titrations were obtained immediately before each prepandemic vaccine injection and 21 days after each vaccination (V87P1, V87P2, V87P3, V87P12 and V87P13). A booster dose of prepandemic vaccine was administered in Studies V87P1 (to a subset of the subjects) and V87P2 180 days after the second vaccination. In these studies additional serum samples were taken before booster and 21 and 180 days after the booster vaccination. Immunogenicity was assessed by using SRH, HI and MN assays in all studies.

FAS and PP populations were defined in the same way across all studies. The FAS includes all subjects in the enrolled population who actually received a study vaccination and provided at least one evaluable serum sample before and after baseline. The PP set includes all subjects in the FAS who correctly received the study vaccine, provided evaluable serum samples at the relevant time points and had no major protocol violations. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines, with approval from the Ethics Committee or Institutional Review Board prior to study start (as far as can be determined from the data set supplied).

Assessment of Efficacy

The CHMP criteria for inter-pandemic influenza vaccines are based on a population exhibiting some degree of immunity. However, the majority of the target population is expected to be naive against the pandemic strain. As there are currently no established correlates of protection for pandemic vaccines, the serological results, were analyzed using the CHMP criteria for the annual registration of inter-pandemic vaccines. There are three criteria to be fulfilled for the pandemic influenza vaccine registration in the European Union and these are summarized in Table 3.

Table 3: Serological Criteria to Meet CPMP/BWP/214/96 Requirements by Age Group

	HI Assay	SRH Assay	Non-elderly Adults (18-60 years)	Elderly (> 60 years)
Geometric mean ratio	Pre- to post-vaccination ratio	pre- to post-vaccination ratio	> 2.5	> 2.0
Seroprotection	titer ≥ 40	area ≥ 25 mm^2	> 70% of subjects	> 60% of subjects
Seroconversion or significant increase	Negative (< 10) at pre-vacc. AND post-vacc. titer ≥ 40 **or** at least 4-fold titer increase	Negative (≤ 4 mm^2) at pre-vacc. AND post-vacc. area ≥ 25 mm^2 **or** at least 50% area increase	> 40% of subjects	> 30% of subjects

HI = hemagglutination inhibition; SRH = single radial hemolysis; vacc. = vaccination

As mentioned previously, the guideline specifies that neutralizing antibodies should also be measured using the MN assay. However, there are no established correlates of protection even for seasonal influenza strains and there is no inter-laboratory standardization for this test. For this reason and in line with other H5 vaccines, a 4-fold increase in neutralizing antibody titers above baseline was used as an indication of protection against H5 strains. The main immunogenicity analyses use HI, SRH and MN assessments of the Fluad-H5N1 formulations after one and two vaccinations and after a booster. Details of individual Main Studies using the prepandemic strain vaccine are tabulated below (Table 4).

Table 4: Summary of Immunogenicity Results

Study ID	Study Objectives	Study Design: Randomization, Control, Blinding	Test Products: Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Type of Subjects (age)	CHMP Criteria	MN: % with 4-fold titer increases
V87P1	Immunogenicity, persistence of immune response and safety of 2 or 3 injections of 7.5 15 µg HA Fluad-H5N1. Non-inferiority of 7.5 to15 µg HA.	Phase 2. Randomized (1:1). Controlled. Observer-blind	Fluad-H5N1: 7.5 µg Fluad-H5N1: 15 µg IM	486 subjects: 313 aged 18-60 years: (156-157 group) 173 aged > 60 years (86-87 group)	Healthy 18-60 and > 60 year olds	**Non-elderly adults:** HI: 3 3 (7.5 µg & 15 µg): SRH: 3 3 (7.5 µg & 15 µg) **Elderly:** HI: 3 3 (7.5 µg & 15 µg): SRH: 3 3 (7.5 µg &15 µg)	**Non-elderly adults:** 83% (7.5 µg). 77% (15 µg). **Elderly:** 58% (7.5 µg). 61% (15 µg)
V87P2	Immunogenicity, CMI and safety of 2 injections and booster of 7.5 15 µg HA H5N1compared with nonadj vaccine.	Phase 2. Randomized (1:1:1). Controlled. Observer-blind	Fluad-H5N1: 7.5 µg Fluad-H5N1: 15 µg Nonadj.: 15 µg IM	40 subjects: 27 in Fluad-H5N1 (13-14 vaccine group) 13 in Nonadj.	Healthy 18-60 year olds	HI: 3 3 (7.5 µg): 2 3 (15 µg): 0 3 (15 µg nonadj): SRH: 3 3 (7.5 µg): 0 3 (15 µg): 0 3 (15 µg nonadj)	86% (7.5 µg). 54% (15 µg). 23% (15 µg nonadj)
V87P3	Immunogenicity and safety of 2 injections of Fluad-H5N1 influenza vaccine in adults unprimed and primed with MF59-adjuvanted or nonadj H5N3 vaccines	Phase 1. Controlled. Open-label	Fluad-H5N1: 7.5 µg IM	58 subjects: 12 primed to H5 by H5N3– 12 primed to H5 by H5N3- 30 naïve to H5 4 unclear priming	Healthy 18-65 year olds[a]	HI: 3 3 (primed –adj) 2 3 (primed nonadj. SP not met) 2 3 (unprimed): SRH: 3 3 (primed –adj) 3 3 (primed nonadj) 3 3 (unprimed. SP and SC not met)	100% (primed –adj). 83% (primed nonadj). 55% (unprimed)
V87P12	Immunogenicity and safety of 2 injections of 7.5µg Fluad-H5N1 administered using four different vaccination schedules (1, 2, 5, and 6 weeks apart)	Phase 3. Randomized (1:1:1:1). Open-label	Fluad-H5N1: 7.5 µg IM	240 subjects: Day 1–8: 60 Day 1–15: 60 Day 1–22: 60 Day 1–43: 60	Healthy 18-60 year olds	HI: 2 3 Day 1–8 (SP not met) 3 3 in other 3 groups SRH: 3 3 in all groups	Day 1–15: 75% Day 1–22: 73% Day 1–43: 90%
V87P13	Immunogenicity and safety of 2 injections of 7.5µg HA H5N1 after one injection of Agrippal compared with 2 injections of seasonal Fluad after one of placebo.	Phase 3. Randomized (4:1). Controlled. Observer-blind	Fluad-H5N1: 7.5 µg IM	3647 subjects: Fluad-H5N1[b]: –2693 (adults) –219 (elderly) PL_Fluad: –679 (adults) –56 (elderly)	Healthy 18-60 and > 60 year olds	Fluad-H5N1[b]: HI: 2/3 in both groups (SP not met) SRH: 2/3 in both groups (SP not met)	Fluad-H5N1[b]: 65% (adults) 55% (elderly)
V101P1	Immunogenicity and safety of concomitant use of 7.5µg HA H5N1 with seasonal influenza vaccine	Phase 2. Randomized. Placebo-controlled. Observer-blind	Fluad-H5N1: 7.5 µg IM	601 subjects: T/P-A[c]: 199 A/P-T[d]: 203 A/S-A[e]: 199	Healthy 18-60 and > 60 year olds[a]	HI: 2/3 (T/P-A: SP not met) 2/3 (A/P-T: SP not met) 3/3 (A/S-A) SRH: 3/3 (all 3 groups)	T/P-A: 90% A/P-T: 86% A/S-A: 89%

a No elderly subjects (>60 years of age) were enrolled; b AGR_H5N1 arm (2 doses of Fluad-H5N1 administered after one doses of Agrippal); c T/P-A: Tetravalent/ Placebo+Fluad-H5N1: 7.5 µg; d A/P-T: Fluad-H5N1: 7.5 µg/placebo+Tetravalent; e A/S-A :Fluad-H5N1: 7.5 µg/seasonal+ Fluad-H5N1: 7.5 µg; SP = seroprotection; SC = seroconversion or significant increase; adj = adjuvanted; nonadj = nonadjuvanted; CSR = clinical study report.

V87P1

This was a Phase II, observer-blind, dose-ranging, multicenter (Italy) study conducted in 2006-2007 to evaluate safety and immunogenicity. Subjects were randomly assigned (1:1) to receive two IM injections administered 3 weeks apart of Fluad-H5N1 containing either 7.5 or 15 µg of the H5N1 (A/H5N1/Vietnam/1194/04) influenza antigen followed by a booster injection of the same vaccine in a subset (approximately half) of subjects six months later (booster subset). A total of 485 healthy subjects were vaccinated: 312 non-elderly adults aged 18-60 years (156 received the 7.5 µg formulation and 156 received the 15 µg formulations) and 173 elderly adults aged over 60 years (87 and 86 received the 7.5 and 15 µg formulations, respectively).

Criteria for immunogenicity evaluation: All CHMP criteria listed in Table 3 were assessed 21 days after each vaccination by HI and SRH. In addition, assessment by MN of GMTs, GMRs, percentages of subjects with titers > 20, > 40 and >80 and percentages of subjects with at least 4-fold titer increases from baseline were conducted. Non-inferiority of the Fluad-H5N1 7.5 µg compared to Fluad-H5N1 15 µg required that the lower limit of the two-sided 95% confidence interval (CI) for the ratio of the Fluad 7.5 µg over the Fluad 15 µg Day 43 HI GMT be > 0.5 for the total population (pooled adult and elderly subjects).

Immunogenicity results: Demography and baseline characteristics of the 486 enrolled subjects were balanced between the 7.5 µg and 15 µg Fluad-H5N1 groups within both the non-elderly adult and elderly age stratifications. Most subjects did not have detectable baseline titers as assessed by HI, SRH or MN assays. After the primary vaccination cycle (first and second dose) all three CHMP criteria were met for both antigen dose levels in both age strata, by both HI and SRH assays. A high percentage of subjects achieved MN-titers >40 in both the non-elderly adult (85% and 81% in the 7.5 and 15 µg groups, respectively) and elderly groups (79% and 76% in the 7.5 and 15 µg groups, respectively). Similar results were obtained when the analyses were repeated on the baseline seronegative subset of subjects, although responses were generally higher, in particular the GMRs. Similar trends were observed when persistence was assessed by the SRH, HI and MN assays.

After a booster was administered six months after the primary vaccination, GMTs (assessed by HI and SRH) increased significantly above pre-booster levels across age groups. In both assays the respective CHMP criterion for GMR was met for both non-elderly adult and elderly populations. In the analysis of cross-reactivity, the immune response to influenza A/H5N1/turkey/Turkey/05 (NIBRG23) Clade 2.2 was lower than to the homologous strain (A/H5N1/Vietnam/1194/04) across vaccine and age groups, as measured by HI, SRH and MN and by HI and MN (SRH not performed) for the A/H5N1/Indonesia strain (Clade 2.1). The immune response to two 7.5 µg A/H5N1 injections was non-inferior to that of two 15 µg A/H5N1 injections in the overall per protocol study population.

V87P2

Subjects were randomly assigned (1:1:1) to receive two IM injections, administered three weeks apart, followed by a booster injection of the same vaccine six months later. The vaccines tested were Fluad-H5N1 containing either 7.5 or 15µg of the H5N1 (A/H5N1/Vietnam/1194/04) influenza antigen or nonadjuvanted vaccine containing 15µg of the H5N1 influenza antigen. A total of 40 healthy subjects were vaccinated: 14, 13 and 13 subjects received the 7.5µg, 15 µg MF59-adjuvanted formulation, or 15 µg nonadjuvanted formulation, respectively.

Criteria for immunogenicity evaluation: same as for Study V87P1 above.

Immunogenicity results: For both HI and SRH all three CHMP criteria were met after two 7.5µg doses of Fluad-H5N1 but not after two doses of 15µg adjuvanted or 15µg nonadjuvanted formulations, regardless of baseline titer. The immune responses, as assessed by the HI, SRH and MN assays, were generally higher for recipients of the MF59-adjuvanted formulation than for the nonadjuvanted formulations. After two injections the adjuvanted formulation containing 7.5 µg H5N1 influenza antigen was at least as immunogenic as the 15µg adjuvanted formulation. CD4 T-cell response to H5 occurred after the first vaccination and was dominated by a population of memory CD4 T-cells producing the cytokine interleukin-2 (IL-2) but not interferon-gamma (IFN-γ). HI antibody titers decreased to a similar extent in both Fluad-H5N1 formulation groups six months after primary vaccination (Day 202/Day 43 GMR range across vaccine groups, 0.12 –0.19). Similar trends were observed when persistence was assessed by SRH and MN. After a booster administered six months after the primary vaccination, GMRs increased significantly by HI (10 and 13 in the 7.5 and 15 µg MF59-adjuvanted groups, respectively) and SRH (2.49 and 6.21 in the 7.5 and 15 µg MF59-adjuvanted groups, respectively) above pre-booster levels. The CHMP criterion for GMR was met by both groups by HI but only in the 15 µg group by SRH. High titer increases (Day 223/Day 202) were observed by MN assay in both groups (8.5 and 11 in the 7.5 and 15 µg MF59-adjuvanted groups, respectively). Based on the results of this study an MF59-adjuvanted vaccine containing 7.5µg of the A/ H5N1/Vietnam/1194/04 influenza antigen provides a memory response in addition to a high antibody response in adult subjects. Based on the results of this study and of V87P1, the 7.5 µg formulation was selected for further testing in Phase III.

V87P3

This was a Phase II, open-label, single-center (UK) study conducted in 2007/08 to evaluate safety, tolerability and immunogenicity. Subjects aged 18-65 years primed 6-8 years previously by vaccination with either MF59-adjuvanted or nonadjuvanted H5N3 vaccine (A/duck/Singapore/97 (H5N3 Clade 0)) or unprimed were administered two IM injections, 3 weeks apart of Fluad-H5N1 containing 7.5 µg of the H5N1 A/H5N1/Vietnam/1194/04 influenza antigen. A total of 58 healthy subjects were vaccinated, 12 previously primed with the MF59-adjuvanted vaccine, 12 previously primed with the nonadjuvanted vaccine, 30 previously unprimed and 4 with unclear priming status. Blood was taken on Days 1, 8, 15, 22, 43 and 202 for the evaluation of immunogenicity.

Criteria for immunogenicity evaluation: All CHMP criteria listed in Table 3 were assessed 21 days after each vaccination using HI and SRH assays. In addition, assessment by MN of GMTs, GMRs, percentages of subjects with titers >20, >40 and >80 and percentages of subjects with at least 4-fold titer increases from baseline were made. Cell-mediated immunity was measured in this study (H5N1 specific CD4 T-cells and memory B-cells).

Immunogenicity results: Demography and baseline characteristics were balanced between all subjects despite the small sample size in each group. At baseline, none of the subjects in the three priming groups was seroprotected against H5N1.

- All CHMP criteria were met by Fluad-H5N1 vaccine after the first (Day 22) and second vaccinations (Day 43) in the group primed by MF59-adjuvanted H5N3, by both HI and SRH assays.
- In the group primed by nonadjuvanted H5N3, two out of three CHMP criteria were met when serology was assessed by HI assay and all three criteria were met when assessed by SRH after the first injection. After the second vaccination, two out of

the three or all three criteria were met when serology was assessed by HI and SRH, respectively.

- In the unprimed group, after the first vaccination none of the CHMP criteria were met when serology was assessed by HI assay and 2/3 when assessed by SRH. After the second vaccination, two out the three or all three criteria were met when serology was assessed by HI and SRH, respectively. For the MN assay, all subjects in the MF59-adjuvanted H5N3 group exhibited ≥ 4-fold increase in MN titer after the primary course of vaccination (3 weeks after the second vaccination), compared to 83% in the nonadjuvanted H5N3 group and 55% in the unprimed group.
- H5-specific and H5N1-specific CD4 T-cells increased substantially over baseline in all the groups after any vaccination. The frequency of H5N1-IgG memory B-cells increased above baseline in all the groups after any vaccination and a more pronounced increase was seen in the MF59-adjuvanted H5N3 primed group than the nonadjuvanted H5N3 primed and unprimed groups

This study found that an MF59-adjuvanted vaccine containing 7.5 µg of the A/ H5N1/Vietnam/1194/04 influenza antigen can be safely used to provide a high immune response in adult subjects. Moreover, subjects primed several years previously with an MF59-adjuvanted vaccine were rapidly protected after one booster dose, even when the pandemic strain was different from the priming strain.

V87P12

This was a Phase III, randomized, open-label, single-center (Czech Republic) study conducted in 2008-2009 to evaluate safety and immunogenicity of two IM injections of Fluad-H5N1 (7.5µg formulation) administered to non-elderly adult subjects (ages 18 to 60 years) using four different vaccination schedules (1, 2, 3 and 6 weeks apart). A total of 240 subjects were enrolled and randomized at a 1:1:1:1 ratio. The safety follow-up period was evaluated for six months.

Criteria for immunogenicity evaluation: Same as for Study V87P1.

Immunogenicity results: Results show that all three CHMP criteria were met in all four vaccination schedules groups by HI and SRH assays except the seroprotection or significant increase criterion for HI for the Day 1+8 group. This indicates that two doses of Fluad-H5N1 can be administered at 2, 3, or 6 weeks apart interchangeably. In the analysis of cross-reactivity, the immune response to influenza A/H5N1/turkey/Turkey/05 (NIBRG23) Clade 2.2 was lower than to the homologous strain (A/H5N1/Vietnam/1194/04) across vaccine groups.

Conclusion: Based on the results of this study an MF59-adjuvanted vaccine containing 7.5 µg of the A/ H5N1/Vietnam/1194/04 influenza antigen can be safely used to provide a high immune response in adult subjects. Additionally, two doses of Fluad-H5N1 can be administered at 2, 3, or 6 weeks apart interchangeably.

V87P13

This was large and the pivotal Phase III, observer-blind, controlled, randomized, multicenter (Germany, Finland) study conducted in 2008-2009 which evaluated the safety, tolerability and immunogenicity of this vaccine. A total of 3647 subjects were enrolled and were randomly assigned (4:1) to receive a single IM injection of Agrippal followed by two IM injections, administered 3 weeks apart of Fluad-H5N1 containing 7.5µg of H5N1, or a placebo followed by two IM injections of seasonal Fluad containing 15 µg each of A/H1N1, A/H3N2 and B antigens administered three weeks apart. Whereas the primary safety and immunogenicity (Day 43) is complete, the six month follow-up period of the study is ongoing.

Criteria for immunogenicity evaluation: Same as for Study V87P1.

Immunogenicity results: Demography and baseline characteristics of the 504 subjects of the immunogenicity subset were balanced between the group that received Agrippal followed by H5N1 (AGR_H5N1) and the group that received a placebo followed by seasonal Fluad (PL_Fluad) within both the non-elderly adult and elderly age stratifications. When assessed by HI, those in the AGR_H5N1 group met two out of three of the CHMP criteria after the second vaccination (Day 64) in both the adult (N=195) and elderly (N=203) groups. When assessed by SRH, all criteria (3/3) were met in both age groups. For the MN assay, 65% of non-elderly adults and 55% of elderly adults in the AGR_H5N1 group exhibited at least a 4-fold increase from baseline in MN titers after two doses of Fluad-H5N1 compared to 0% (non-elderly) and 10% (elderly) in the PL Fluad group. In the analysis of cross-reactivity, the immune response to influenza A/H5N1/turkey/Turkey/05 (NIBRG23) Clade 2.2 was lower than to the homologous strain (A/H5N1/Vietnam/1194/04) across vaccine groups.

Based on the results of this study, Fluad-H5N1 influenza vaccine containing 7.5 µg of H5N1 Vietnam antigen showed good tolerability and safety, both in adult and elderly subjects, and was immunogenic against the vaccine strain, A/Vietnam/1194/2004.

V101P1

This was a Phase II, observer-blind, randomized, multicenter (Germany), placebo-controlled study conducted in 2007-2008 to evaluate safety, tolerability and immunogenicity of Fluad-H5N1 given before or after one 0.5 mL intramuscular (IM) dose of a tetravalent seasonal TIV + H5N1) vaccine or after a concomitant administration (in different sites) of prepandemic Fluad-H5N1 containing 7.5 µg of the H5N1 (A/H5N1/Vietnam/1194/04) influenza strain and a licensed seasonal trivalent influenza vaccine (Agrippal). A total of 601 subjects were enrolled and randomly assigned (1:1:1) to receive injections of a tetravalent influenza vaccine and a placebo on Day 1 and Fluad-H5N1 3 weeks later (the T/P-A group; N=199), Fluad-H5N1 and a placebo on Day 1 and a tetravalent vaccine three weeks later (the A/P-T group; N=203), or Fluad-H5N1 and a licensed seasonal vaccine on Day 1 and Fluad-H5N1 three weeks later (the A/S-A group; N=199). The population was divided by age into 18-60 and > 60 years. A total of 559 subjects were included in the immunogenicity analysis and all the subjects were in the 18-60 years age group.

Criteria for immunogenicity evaluation: Same as for Study V87P1.

Immunogenicity results: The primary immunogenicity objective was to show that SRH antibody titers against the A/Vietnam/1194/2004 (H5N1 Clade 1) elicited by the three different immunization schedules were equivalent at Visit 3. Equivalence was statistically confirmed by inspections of the CIs of all three pairwise ratios of the GMAs (using the SRH assay). Equivalence between all groups was also confirmed by the MN assay results. In all three vaccine groups the H5N1 strain met all the three defined CHMP criteria as assessed by the SRH assay. The H5N1 strain met two of the three CHMP criteria in the T/P-A and A/P-T groups and all three CHMP criteria in the A/S-A group as assessed by the HI assay. When the serological criteria as assessed by HI assay for the inter-pandemic strains (H1N1, H3N2 and B) were analyzed, all three vaccine groups met all three CHMP criteria. Based on the results of this study there is no impact on the immune response to the H5N1 strain or the seasonal strains when a seasonal influenza vaccine is administered with the Fluad-H5N1 vaccine.

Pooled results

Demographic and Baseline Characteristics

An overview of the demography and other baseline characteristics for the enrolled populations of Studies V87P1, V87P2, V87P3, V87P12 and V87P13 receiving prepandemic Fluad formulated with the H5N1 strain is shown in Table 5 (non-elderly adults) and 6 (elderly). In Studies V87P2, V87P3, V87P12 and V87P13 the full analysis set (FAS) was used for the analysis of immunogenicity. For Study V87P1 the PP population was chosen as the most conservative population since non-inferiority of the 7.5 µg to the 15µg dosage was assessed. Within each study, demographic characteristics were balanced between the dosage groups and in Studies V87P1 and V87P13, both for the non-elderly adult and for the elderly subjects. The gender ratio was generally balanced within each group and subjects were mostly of Caucasian origin. Among non-elderly adults, 0-52% of the subjects of the Fluad-H5N1 groups had previously received seasonal influenza vaccination whereas, as expected, a higher percentage of elderly subjects (43-89%) had been vaccinated against seasonal influenza in the previous years.

Table 5: Demography and Other Baseline Characteristics, Non-Elderly Adults (18-60 years), Enrolled Population

	V87P1		V87P2[a]		V87P3[b]			V87P12	V87P13[c]	
	7.5 µg	15 µg	7.5 µg	15 µg	Fluad-H5N1 primed 7.5 µg	Non-adjuvanted primed 7.5 µg	Unprimed 7.5 µg	7.5 µg, Day 1+22 arm	Agrippal followed by Fluad-H5N1 7.5 µg	Placebo followed by Fluad
	N=157	N=156	N=14	N=13	N=12	N=12	N=30	N=60	N=2692	N=679
Mean age (years)	43.4	42.3	34.7	33.8	35.1	36.8	38.2	32.3	40.7	40.5
Male/female (%)	45/55	45/55	57/43	62/38	42/58	25/75	43/57	52/48	44/56	43/57
Ethnic Origin (%):										
Caucasian	99	97	100	100	92	100	67	100	99	99
Asian	0	1	0	0	8	0	33	0	< 1	< 1
African	0	0	0	0	0	0	0	0	< 1	< 1
Hispanic	0	1	0	0	0	0	0	0	< 1	< 1
Other	< 1	0	0	0	0	0	0	0	< 1	0
Mean Weight (kg)	70.93	70.46	67.9	64.1	76.6	78.1	74.2	75.0	74.5	74.7
Mean Height (cm)	169.7	169.2	173.1	171.2	167.8	168.2	168.6	174.5	172.0	172.1
Previous seasonal flu vaccination (%)	52	56	36	8	42	25	40	0	36	34
Study criteria fulfilled (%)	100	100	64	92	100	100	97	100	100	100

[a] Non-adjuvanted arm is not shown here; [b] An additional group of 4 subjects with unclear priming is not shown here. c 504 subjects (246 adults and 258 elderly) were included in the immunogenicity subset.

Table 6: Demography and Other Baseline Characteristics, Elderly (> 60 years)

	V87P1[a]		V87P13[b,c]	
	7.5 µg	15 µg	Agrippal followed by Fluad-H5N1 7.5 µg	Placebo followed by Fluad
	N=87	N=86	N=219	N=56
Mean age (years)	71.0	70.1	61.9	62.1
Male/female (%)	60/40	56/44	50/50	50/50
Ethnic Origin (%):				
Caucasian	100	100	100	100
Mean Weight (kg)	71.90	73.51	77.3	77.9
Mean Height (cm)	166.0	167.5	170.8	171.4
Previous vaccination (%)	89	85	43	46
Study criteria fulfilled (%)	100	100	100	100

[a] All randomized population; [b] Safety set; [c] 504 subjects (246 adults and 258 elderly) were included in the FAS (immunogenicity subset).

In studies conducted with H5N1 only a few subjects were seropositive in all three tests at baseline (see Table 7). Percentages of seroprotection at baseline were generally low and balanced between the non-elderly groups. In Study V87P1, a range from 11% to 24% of elderly subjects (depending on dosage and assay) showed seroprotection to H5N1 at baseline. This range was 8% to 25% in Study V87P13.

Table 7: Prepandemic Baseline Immune Status

	(95% CIs)	Non-elderly adults (18-60 years)									Elderly (> 60 years)		
		V87P1		V87P2			V87P3[a]	V87P12[b]	V87P13[c]	V101P1[d]	V87P1		V87P13[b]
		Fluad-H5N1 7.5 µg	Fluad-H5N1 15 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 15 µg	Non-adj 15 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 7.5 µg	Fluad-H5N1 15 µg	Fluad-H5N1 7.5 µg
HI Assay	No. subjects	N=151	N=147	N=14	N=13	N=13	N=30	N=60	N=196	N=193	N=81	N=74	N=205
	% SP	0 (0-2)	3 (1-7)	7 (0-34)	0 (0-25)	15 (2-45)	0 (0-12)	3 (0-12)	6 (3-10)	2 (0-4)	12 (6-22)	11 (5-20)	8 (5-12)
	Baseline GMT	5.12 (4.81-5.44)	5.52 (5.19-5.87)	6.4 (4.08-10)	5 (3.13-7.99)	8.07 (5.05-13)	4.00 (4.00-4.00)	5.74 (4.88-6.75)	6.17 (5.58-6.83)	5.85 (5.42-6.32)	8.13 (6.27-11)	8.2 (6.26-11)	6.98 (6.21-7.85)
SRH Assay	No. subjects	N=149	N=149	N=14	N=13	N=13	N=30	N=58	N=197	N=198	N=84	N=80	N=210
	% SP	5 (2-10)	9 (5-14)	0 (0-23)	0 (0-25)	15 (2-45)	3 (0.084-17)	24 (14-37)	19 (14-26)	4 (2-8)	11 (5-19)	24 (15-35)	25 (20-32)
	Baseline GMA	4.79 (4.34-5.3)	5.20 (4.71-5.75)	4.37 (3.21-5.96)	4.81 (3.49-6.63)	5.59 (4.06-7.7)	4.69 (3.93-5.59)	11 (8.76-14)	11 (9.45-12)	4.61 (4.14-5.13)	6 (4.9-7.35)	7.57 (6.15-9.33)	13 (11-14)
MN Assay	No. subjects	N=151	N=151	N=14	N=13	N=13	N=30	N=60	N=197	N=198	N=84	N=80	N=209
	% with MN-titer ≥ 40	3 (1-7)	3 (1-7)	21 (5-51)	8 (0-36)	15 (2-45)	0 (0-12)	0 (0-6)	1 (0-4)	3 (1-6)	18 (10-28)	15 (8-25)	1 (0-3)
	Baseline GMT	11 (10-12)	11 (10-12)	14 (9.9-20)	12 (8.05-17)	15 (11-22)	10 (10-10)	10 (9.31-11)	11 (10-11)	10 (9.55-11)	18 (14-22)	16 (13-20)	10 (9.97-11)

a V87P3 unprimed arm; b Day 1+22 arm; c Day 22 values; d A/S-A arm. Nonadjuv = nonadjuvanted; SP = seroprotection; GMT = geometric mean titer; GMA = geometric mean area. Study V87P1 based on PP population; Studies V87P2, V87P3, V87P12 and V87P13 based on FAS.

Immunogenicity results

Results relating to the CHMP immunogenicity criteria are summarised in Table 8. The HI, GMR and seroconversion criteria were met in all groups. The seroprotection criterion was met in six of the ten study groups across the two age groups, the seroprotection rates for two of the groups that did not meet the criterion were close to meeting the criterion (61% and 57% in non-elderly and elderly adults, respectively) in Study V87P3. As measured by

SRH all criteria were met for all groups with the exception of the 15 µg group in Study V87P2.

Table 8: Assessment of CHMP Criteria after Two Injections of the Prepandemic Fluad-H5N1 in Non-Elderly and Elderly Adults, by HI and SRH

		Non-elderly adults (18-60 years)							Elderly (> 60 years)		
		V87P1		V87P2		V87P3	V87P12	V87P13	V87P1		V87P13
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	15 µg	7.5 µg
HI		N=150	N=150	N=14	N=13	N=29	N=60	N=196	N=84	N=79	N=205
	% SP	+	+	+	-	-	+	-	+	+	-
	GMR	+	+	+	+	+	+	+	+	+	+
	% SC	+	+	+	+	+	+	+	+	+	+
SRH		N=148	N=148	N=14	N=13	N=29	N=58	N=197	N=84	N=79	N=210
	% SP	+	+	+	-	+	+	+	+	+	+
	GMR	+	+	+	-	+	+	+	+	+	+
	% SC	+	+	+	-	+	+	+	+	+	+

+ = criterion met; - = criterion not met. V87P3 unprimed arm; V87P12 Day 1+22 arm; V87P13 previously with Agrippal. SP = seroprotection; GMR = geometric mean ratio Day 43/Day 1 in V87P1, V87P2 and V87P3 and day 64/Day 22 in V87P13; SC = seroconversion or significant increase. Study V87P1 based on PP population; Studies V87P2, V87P3, V87P12 and V87P13 based on FAS

The detailed results after second vaccination for GMRs, seroprotection and seroconversion are presented in Table 9. The HI results for seroprotection and seroconversion were lower in all studies across all groups than the results measured by SRH. GMRs were high in most groups.

Table 9: Summary of Immune Response after Two Injections of prepandemic Fluad-H5N1 in Non-Elderly and Elderly Adults

		Non-elderly adults (18-60 years)							Elderly (> 60 years)		
		V87P1		V87P2		V87P3	V87P12	V87P13	V87P1		V87P13
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	15 µg	7.5 µg
HI		N=151	N=147	N=14	N=13	N=29	N=60	N=196	N=81	N=74	N=205
	% SP (95% CI)	**73 (65-80)**	**72 (64-79)**	**86 (57-98)**	46 (19-75)	52 (33-71)	**74 (61-85)**	61 (53-67)	**75 (64-84)**	**76 (64-85)**	57 (50-64)
	GMR (95% CI)	**16 (12-21)**	**15 (12-21)**	**21 (8.41-52)**	**5.97 (2.31-15)**	**6.62 (3.76-12)**	**22 (13-37)**	**7.1 (5.52-9.14)**	**9.52 (6.55-14)**	**10 (6.78-15)**	**5.15 (4.15-6.4)**
	% SC (95% CI)	**73 (65-80)**	**69 (61-77)**	**79 (49-95%)**	**46 (19-75%)**	**52 (33-71)**	**74 (61-85) N=58**	**56 (49-63) N=195**	**67 (55-77)**	**70 (59-80)**	**50 (43-57)**
SRH		N=149	N=149	N=14	N=13	N=29	N=58	N=197	N=84	N=80	N=210
	% SP (95% CI)	**85 (79-91)**	**85 (79-91)**	**86 (57-98)**	38 (14-68)	**93 (77-99)**	**88 (77-95)**	**91 (87-95)**	**80 (70-88)**	**81 (71-89)**	**82 (76-87)**
	GMR (95% CI)	**7.74 (6.6-9.07)**	**6.86 (5.85-8.04)**	**8.12 (4.61-14)**	2.27 (1.26-4.09)	**9.69 (7.54-12)**	**3.82 (3-4.88)**	**4.03 (3.54-4.59)**	**4.96 (3.87-6.37)**	**4.09 (3.17-5.28)**	**2.9 (2.53-3.31) N=209**
	% SC (95% CI)	**85 (78-90)**	**80 (73-86)**	**86 (57-98)**	38 (14-68)	**90 (73-98)**	**71 (57-82)**	**78 (72-84)**	**70 (59-80)**	**69 (57-79)**	**63 (56-69)**

V87P3 unprimed arm; V87P12 Day 1+22 arm; V87P13 previously vaccinated with Agrippal. SP = seroprotection; SC = seroconversion or significant increase; GMR = geometric mean ratio Day 43/Day 1 in V87P1, V87P2 and V87P3 and day 64/Day 22 in V87P13 Note: For HI and SRH figures are in bold when the CHMP criteria are met. Study V87P1 based on PP population; Studies V87P2, V87P3, V87P12 and V87P13 based on FAS

Assessment of immunogenicity by MN

The percentage of subjects achieving MN titers >40 and 4-fold increase of titers were generally high. For elderly subjects in Studies V87P1 and V87P2 and for both groups in Study V87P13, the results are lower than for the other tests. Detailed results for all groups are presented in Table 10.

Table 10; Microneutralization Response after Two Injections of the Prepandemic Fluad-H5N1 in Non-Elderly and Elderly
Adults

	Non-elderly adults (18-60 years)							Elderly (> 60 years)		
	V87P1		V87P2		V87P3	V87P12	V87P13	V87P1		V87P13
	7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	15 µg	7.5 µg
	N=151	N=151	N=14	N=13	N=29	N=60	N=197	N=84	N=80	N=209
MN ≥ 20	91 (86-95)	88 (82-93)	ND	ND	59 (39-76)	83 (71-92)	79 (73-85)	89 (81-95)	83 (72-90)	72 (65-78)[a]
MN ≥ 40	85 (78-90)	81 (74-87)	93 (66-100)	54 (25-81)	55 (36-74)	73 (60-84)	67 (60-74)	79 (68-87)	76 (65-85)	57 (50-64)[a]
MN ≥ 80	66 (58-74)	64 (56-72)	ND	ND	17 (6-36)	45 (32-58)	50 (43-57)	54 (42-65)	59 (47-70)	33 (26-40)[a]
MN 4-fold	83 (77-89)	77 (70-84)	86 (57-98)	54 (25-81)	55 (36-74)	73 (60-84)	65 (58-72)	58 (47-69)	61 (50-72)	55 (48-62)[a]

a N=208. V87P3 unprimed arm; V87P13 previously vaccinated with Agrippal MN = microneutralization; ND = not determined, Study V87P1 based on PP population; Studies V87P2, V87P3, V87P12 and V87P13 based on FAS

Immunogenicity versus Heterologous Strains

Cross-reactivity of pathogenic avian influenza H5N1 viruses

Immunogenicity analyses were carried out for heterologous strains in Studies V87P1, V87P3, V87P12 and V87P13. In each of these studies, immunogenicity against the A/H5N1/turkey/Turkey/05 (NIBRG23; Clade 2.2) strain was tested by all three assays allowing for comparisons to be made across studies. Additional heterologous strains were tested in Studies V87P1 and V87P3 and the results are shown in the tables.

For the A/H5N1/turkey/Turkey (NIBRG23; Clade 2.2) strain at least one CHMP criterion was met in all four studies when measured by SRH. In Study V87P1 the CHMP criterion for seroprotection was met by both the 7.5 and 15µg non-elderly groups (Table 11) and in the 15 µg group in the elderly (Table 12). The criterion was nearly met in the 7.5µg elderly group as 57% of subjects presented titers >40. In Study V87P1, GMR and seroconversion could not be calculated because baseline values were not obtained. In Study V87P3, all three CHMP criteria were met versus the heterologous Turkey strain. In Study V87P12 (non-elderly subjects) both the criteria for GMR and seroconversion were met and seroprotection was nearly met as 65% of subjects had titers >40 (Table 11). In Study V87P13, only the seroconversion criterion was met although the results for GMR (2.37) were close to the CHMP threshold. For the Turkey strain, the percentage of subjects with titers >40 as measured by MN ranged from 10 in Study V87P3 to 39 in Study V87P13 (Tables 11 and 12). In addition to the Turkey strain, the heterologous A/H5N1/Indonesia (Clade 2.1) was tested by HI and MN in Studies V87P1 and V87P3. The criterion for seroprotection was not met in any of the 7.5 or 15µg groups (in either age group). None of the CHMP criteria were met for the Indonesia strain as measured by HI in Study V87P3. The percentage of subjects with MN titers >40 ranged from 2 to 17 (Table 11). The heterologous H5N1Anhui/1/05 strain (Clade 2.3.4) was tested by HI and MN but not by SRH in Study V87P3. None of the CHMP criteria were met for the Anhui strain as measured by HI in this study. The percentage of subjects with MN titers >40 was 45.

Table 11: Immunogenicity to Heterologous Strains 21 Days After 2 Vaccinations, Adults (18-60 Years)

		V87P1[a]				V87P3[b]			V87P12	V87P13
		A/H5N1/turkey/Turkey/05[c]		H5N1 Clade C2.1 A/Indonesia		A/H5N1/turkey/Turkey/05[c]	H5N1 Indonesia/5/05 strain (Clade2.1.3)	H5N1Anhui/1/05 strain (Clade2.3.4)	H5N1 turkey/Turkey/2005	A/H5N1/turkey/Turkey/05[c]
		7.5 µg	15 µg	7.5µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5µg	7.5 µg
HI	No. of subjects	N=70	N=79	N=70	N=80	N=30	N=30	N=29	N=60	N=197
	GMT (95% CI)	18 (13-24)	14 (10-19)	12 (9.45-16)	10 (7.81-13)	7.93 (5.13-12)	5.2 (3.41-7.93)	6 (3.85-9.35)	11 (8.29-16)	12 (9.77-14)
	GMR (95% CI)	ND*	ND*	ND*	ND*	1.98 (1.22-3.21)	1.3 (0.85-1.98)	1.5 (0.96-2.34)	2.3 (1.67-3.16)	1.92 (1.64-2.25)
	% SP (95% CI)	36 (25-49)9	28 (19-40)	21 (13-33)	18 (10-28)	24 (10-44)	21 (8-40)	21 (8-40)	28 (17-41)	23 (18-30)
	% SC (95% CI)	ND*	ND*	ND*	ND*	21 (8-40)	10 (2-27)	17 (6-36)	28 (17-41)	19 (14-25)
SRH	No. of subjects	N=70	N=81	-	-	N=29	-	-	N=60	N=197
	GMA (95% CI)	23 (19-28)	24 (20-28)	ND	ND	34 (28-40)	ND	ND		23 (21-26)
	GMR (95% CI)	ND*	ND*	ND	ND	**7.67 (6.09-9.67)**	ND	ND	**4.51 (3.63-5.61)**	2.37 (2.1-2.67)
	% SP (95% CI)	**71(58-80)**	**71(59-80)**	ND	ND	**90 (73-98)**	ND	ND	65 (52-77)	59 (52-66)
	% SC (95% CI)	ND*	ND*	ND	ND	**86 (68-96)**	ND	ND	**65 (52-77)**	**49 (42-56)**
MN	No. of subjects	N=70	N=81	N=70	N=81	N=29	N=29	N=29	N=60	N=197
	GMT (95% CI)	19 (15-24)	19 (15-24)	15 (13-17)	11 (9.41-12)	16 (11-23)	18 (13-24)	36 (26-50)	29 (23-38)	30 (26-35)
	GMR (95% CI)	ND*	ND*	ND*	ND*	1.59 (1.12-2.26)	1.76 (1.26-2.46)	3 (2.17-4.15)	2.95 (2.3-3.77)	2.77 (2.4-3.2)
	% ≥ 1: 40 (95% CI)	27 (17-39)	21 (13-31)	13 (6-23)	2 (0-9)	10 (2-27)	17 (6-36)	45 (26-64)	31 (19-44)	39 (32-46)
	4-fold increase	ND*	ND*	ND*	ND*	10 (2-27)	31 (15-51)	34 (18-54)	31 (19-44)	36 (29-43)

a Baseline not tested; b unprimed subjects. c NIBRG23; Clade 2.2. GMT = geometric mean titer; SP = seroprotection; vac = vaccination; ND = not determined Study V87P1 based on PP population; Studies V87P3, V87P12 and V87P13 based on FAS**.** Note: HI and SRH figures are in bold when the CHMP criteria are met.

Table 12: Immunogenicity to Heterologous Strains 21 Days After Two Vaccinations, Elderly (> 60 Years)

		V87P1				V87P13
		A/H5N1/turkey/Turkey/05 (NIBRG23; Clade 2.2)		H5N1 Clade C2.1 A/Indonesia		A/H5N1/turkey/Turkey/05 (NIBRG23; Clade 2.2)
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg
HI	No. of subjects	N=36	N=26	N=36	N=22	N=208
	GMT (95% CI)	14 (8.4-22)	13 (7.74-23)	7.39 (4.9-11)	10 (6.64-16)	12 (10-14) N=207
	GMR (95% CI)	ND*	ND*	ND*	ND*	1.79 (1.56-2.06) N=207
	% SP (95% CI)	36 (21-54)	35 (16-57)	14 (5-29)	22 (7-44)	25 (19-32) N=207
	% SC (95% CI)	ND*	ND*	ND*	ND*	19 (14-25) N=207
SRH	No. of subjects	N=37	N=26	-	-	N=210
	GMA (95% CI)	15 (9.91-22)	24 (16-36)	ND	ND	20 (18-23) N=209
	GMR (95% CI)	ND*	ND*	ND	ND	1.74 (1.57-1.94) N=209
	% SP (95% CI)	57 (39-73)	**77 (56-91)**	ND	ND	48 (41-55) N=209
	% SC (95% CI)	ND*	ND*	ND	ND	**32 (26-39) N=209**
MN	No. of subjects	N=37	N=26	N=37	N=26	N=210
	GMT (95% CI)	12 (9.4-16)	17 (13-23)	11 (9.16-14)	11 (9.3-14)	23 (20-26) N=208
	GMR (95% CI)	ND*	ND*	ND	ND	2.01 (1.78-2.26) N=208
	% ≥ 1: 40 (95% CI)	11 (3-25)	31 (14-52)	5 (1-18)	4 (0.097-20)	30 (24-37) N=208
	4-fold increase	ND*	ND*	ND*	ND*	25 (19-31) N=208

a Baseline not tested ; GMT = geometric mean titer; SP = seroprotection; vac = vaccination; ND = not determined. Study V87P1 based on PP population; Study V87P13 based on FAS**.** Note: HI and SRH figures are in bold when the CHMP criteria are met.

Cross-reactivity to Heterologous Strains Following Homologous Booster

The immune response to heterologous strains following a "booster" vaccination six months after primary vaccination was analyzed in Study V87P1 (Tables 13 and 14).

A/H5N1/turkey/Turkey/05 NIBRG23

In Study V87P1 a subset of subjects were given a third dose of Fluad-H5N1 (homologous booster) six months after receiving a second vaccination. The heterologous A/H5N1/turkey/Turkey/05 NIBRG23; Clade 2.2 strain was assessed by HI, SRH and MN. Only the CHMP criterion of seroprotection could be evaluated since baseline values were not obtained. As measured by HI, the seroprotection criterion was close but not met in either the 7.5 or 15µg non-elderly groups. In the elderly, the CHMP criterion for seroprotection was met by both the 7.5 and 15 µg groups. As measured by SRH, the seroprotection criterion was met by both the 7.5 and 15 µg groups in both age groups.

A/H5N1/Indonesia (Clade 2.1)

The heterologous A/H5N1/Indonesia (Clade 2.1) strain was also assessed in V87P1 by HI and MN but not by SRH. The criterion of seroprotection was not met in any group as measured by HI (Tables 13 and 14).

Cross-reactivity to Heterologous Strains Following Heterologous Booster

Most of the immunogenicity data examined the responses after two vaccinations from the unprimed arm of Study V87P3. The other two arms consisted of subjects who were primed 6-8 years previously by either an MF59-adjuvanted H5N3 vaccine or a nonadjuvanted H5N3 vaccine. They then received two vaccinations of Fluad-H5N1, the first of which can be considered a "heterologous booster". In Table 13, data for the two groups in Study V87P3 primed with H5N3 are presented for the A/Vietnam/1194/04NIBRG-14 (Clade1) and other two strains at 21 days after the first vaccination with H5N1.

A/Vietnam/1194/04NIBRG-14 (Clade1)

Immunogenicity analyses were conducted by HI, SRH and MN for the homologous A/Vietnam/1194/04NIBRG-14 (Clade 1 strain). Already after the first injection, all three CHMP criteria were met by both HI and SRH and the MN results were consistent. This response is similar to what would be expected from a booster dose, even though the strain used for priming 6-8 years previously differed from strain given here (H5N3 versus H5N1/Vietnam).

A/H5N1/turkey/Turkey/05 NIBRG23

Immunogenicity analyses were conducted by HI, SRH and MN for the heterologous A/H5N1/turkey/Turkey/05 NIBRG23; Clade 2.2 strain. All three CHMP criteria were met by both HI and SRH in both the MF59-adjuvanted and nonadjuvanted groups three weeks after the first injection. The immune response of those in the MF59-adjuvanted group was particularly high.

H5N1 Indonesia/5/05 (Clade 2.1.3)

Immunogenicity analyses were also conducted by HI and MN for the heterologous H5N1 Indonesia/5/05 (Clade 2.1.3) strain. As assessed by HI, all three CHMP criteria were met in the MF59-adjuvanted group and 2/3 criteria were met in the nonadjuvanted group. Although the seroprotection criterion was not met it was 67%. The immune response in the MF59-adjuvanted group was greater than that in the nonadjuvanted group.

H5N1Anhui/1/05 (Clade 2.3.4)

Immunogenicity analyses were also conducted by HI and MN for the heterologous H5N1Anhui/1/05 (Clade 2.3.4) strain. As assessed by HI, all three CHMP criteria were met in the MF59-adjuvanted group and two of the criteria were met in the nonadjuvanted group. The seroprotection criterion was not met but was at 67% (Table 14). The immune response in the MF59-adjuvanted group was greater than that in the nonadjuvanted group. The GMR for the adjuvanted group was 88 which can be compared to 21 for the nonadjuvanted group.

Table 13: Immunogenicity to Heterologous Strains (Booster Response), Adults (18-60 Years)

		Homologous Booster (3rd dose)				Heterologous Booster (21 days after 1 booster dose)							
		V87P1[a]				V87P3[c] H5N3 primed with adjuvant				V87P3[c] H5N3 primed with non-adjuvant			
		A/H5N1/turkey/ Turkey/05[b]		H5N1 Clade C2.1 A/Indonesia		A/Vietnam/1194/ 04NIBRG-14 (Clade1)	A/H5N1/ turkey/Turkey/05[b]	H5N1 Indonesia/5/05 strain (Clade 2.1.3)	H5N1 Anhui/1/05 strain (Clade 2.3.4)	A/Vietnam/1194/ 04NIBRG-14 (Clade1)	A/H5N1/ turkey/Turkey/05[b]	H5N1 Indonesia/5/05 strain (Clade 2.1.3)	H5N1 Anhui/1/05 strain (Clade 2.3.4)
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg
HI	No. of subjects	N=70	N=79	N=70	N=80	N=12	N=12	N=12	N=12	N=12	N=12	N=12	N=12
	GMT (95%CI)	58 (39-86)	46 (31-67)	41 (27-60)	28 (19-41)	287(129-641)	279(152-513)	148 (80-274)	352(192-644)	52 (23-117)	99 (54-181)	51 (28-94)	83 (45-152)
	GMR (95%CI)	ND*	ND*	ND*	ND*	**72 (32-160)**	**52 (26-104)**	**37 (20-69)**	**88 (48-161)**	**13 (5.86-29)**	**25 (12-49)**	**13 (6.88-24)**	**21 (11-38)**
	% SP (95% CI)	70 (58-80)	59 (48-70)	60 (48-72)	48 (36-59)	**100 (74-100)**	**100 (74-100)**	**92 (62-100)**	**100 (74-100)**	58 (28-85)	**83 (52-98)**	67 (35-90)	67 (35-90)
	% SC (95%CI)	ND*	ND*	ND*	ND*	**100 (74-100)**	**92 (62-100)**	**92 (62-100)**	**100 (74-100)**	**58 (28-85)**	**83 (52-98)**	**67 (35-90)**	**67 (35-90)**
SRH	No. of subjects	N=70	N=81	-	-	N=12	N=12	-	-	N=12	N=12	-	-
	GMA (95%CI)	30 (26-36)	34 (29-39)	ND	ND	70 (44-111)	68 (45-101)	ND	ND	55 (34-87)	52 (35-78)	ND	ND
	GMR (95%CI)	ND*	ND*	ND	ND	**18 (10-30)**	**17 (10-27)**	ND	ND	**11 (6.66-20)**	**11 (6.85-18)**	ND	ND
	% SP (95% CI)	**83 (72-91)**	**88 (78-94)**	ND	ND	**100 (74-100)**	**100 (74-100)**	ND	ND	**92 (62-100)**	**92 (62-100)**	ND	ND
	% SC (95%CI)	ND*	ND*	ND	ND	**100 (74-100)**	**100 (74-100)**	ND	ND	**83 (52-98)**	**83 (52-98)**	ND	ND

		Homologous Booster (3rd dose)				Heterologous Booster (21 days after 1 booster dose)							
		V87P1[a]				V87P3[c] H5N3 primed with adjuvant				V87P3[c] H5N3 primed with non-adjuvant			
		A/H5N1/turkey/ Turkey/05[b]		H5N1 Clade C2.1 A/Indonesia		A/Vietnam/1194/ 04NIBRG-14 (Clade1)	A/H5N1/ turkey/Turkey/05[b]	H5N1 Indonesia/5/05 strain (Clade 2.1.3)	H5N1 Anhui/1/05 strain (Clade 2.3.4)	A/Vietnam/1194/ 04NIBRG-14 (Clade1)	A/H5N1/ turkey/Turkey/05[b]	H5N1 Indonesia/5/05 strain (Clade 2.1.3)	H5N1 Anhui/1/05 strain (Clade 2.3.4)
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg	7.5 µg
MN	No. of subjects	N=70	N=81	N=70	N=81	N=12	N=12	N=12	N=12	N=12	N=12	N=12	N=12
	GMT (95%CI)	77 (60-100)	93 (74-118)	45 (34-59)	37 (29-47)	1067 (574-1986)	1372 (818-2300)	359 (215-601)	987 (635-1536)	324 (174-603)	409 (244-686)	134 (80-225)	418 (269-651)
	GMR (95%CI)	ND*	ND*	ND*	ND*	107 (57-199)	133 (80-222)	36 (21-61)	47 (32-70)	32 (17-60)	41 (25-68)	13 (7.46-22)	37 (25-55)
	% ≥ 1: 40 (95% CI)	73 (61-83)	79 (69-87)	57 (45-69)	53 (42-64)	100 (74-100)	100 (74-100)	92 (62-100)	100 (74-100)	92 (62-100)	92 (62-100)	92 (62-100)	100 (74-100)
	% 4-fold increase (95% CI)	ND*	ND*	ND*	ND*	100 (74-100)	100 (74-100)	92 (62-100)	100 (74-100)	92 (62-100)	92 (62-100)	82 (48-98) N=11	100 (74-100)

a Baseline not tested; b NIBRG23; Clade 2.2; c two doses were given in V87P3 but only results after one doses are shown as they mimic the real world, that is a prepandemic priming + single heterologous booster dose. GMT = geometric mean titer; SP = seroprotection; vac = vaccination; ND = not determined Study V87P1 based on PP population; Study V87P3 based on FAS. Note: HI and SRH figures are in bold when the CHMP criteria are met.

Table 14: Immunogenicity to Heterologous Strains (Booster Response), Elderly (> 60 Years)

		V87P1[a]			
		A/H5N1/turkey/Turkey/05 (NIBRG23;Clade 2.2)		H5N1 Clade C2.1 A/Indonesia	
		7.5 µg	15 µg	7.5 µg	15 µg
HI	No. of subjects	N=36	N=26	N=36	N=22
	GMT[b] (95%CI)	36 (19-68)	49 (25-97)	18 (9.15-34)	33 (17-66)
	GMR (95%CI)	ND[a]	ND[a]	ND[a]	ND[a]
	% SP (95% CI)	**67 (49-81)**	**66 (44-83)**	47 (30-65)	50 (30-70)
	% SC (95%CI)	ND[a]	ND[a]	ND[a]	ND[a]
SRH	No. of subjects	N=37	N=26	-	-
	GMA (95%CI)	24 (17-34)	33 (23-48)	ND	ND
	GMR (95%CI)	ND[a]	ND[a]	ND	ND
	% SP (95% CI)	**78 (62-90)**	**88 (70-98)**	ND	ND
	% SC (95%CI)	ND[a]	ND[a]	ND	ND
MN	No. of subjects	N=37	N=26	N=37	N=26
	GMT (95%CI)	44 (29-67)	61 (39-95)	21 (13-33)	34 (20-57)
	4-fold increase	ND[a]	ND[a]	ND[a]	ND[a]
	% ≥ 1: 40 (95%CI)	62 (45-78)	66 (44-83)	30 (16-47)	46 (27-67)

a Baseline not tested; b Day 223. GMT = geometric mean titer; SP = seroprotection; ND = not determined. Study V87P1 based on PP population. Note: HI and SRH figures are in bold when the CHMP criteria are met.

Clinical studies in special populations

Comparison of Results in Sub-populations

In compliance with the relevant guidelines, non-elderly adult and elderly populations have been analyzed separately. As measured by HI and SRH, the immune response of the elderly was similar to adults. A general difference can only be seen for the GMRs measured by HI and SRH. When assessed using MN, the immune response of the elderly is always slightly lower than non-elderly adults, especially for the percentages of subjects with a 4-fold increase of MN-titers. Nevertheless, the CHMP criterion for GMR was met in all elderly vaccination groups. Furthermore, the subgroup of seronegative (with a HI titer <10, SRH area <4mm^2, or MN titer < 20) subjects prior to vaccination was investigated in the initial Studies V87P1 and V87P2. This subgroup of subjects was of particular interest as unprimed subjects are at the highest risk in a pandemic and the immune responses in this group can give the best indication of vaccine effectiveness. For non-elderly adults, the seronegative population is nearly identical to that of the total population. Consequently the results by all three assays differed only marginally, if at all, between seronegative subjects and the total population (Table 12). In Study V87P1 all CHMP criteria were met by both the 7.5 and 15µg groups in both age groups and the same is true for those who were seronegative at the start of the study. In Study V87P2, when assessed by HI, all CHMP criteria were met in the 7.5µg group and the seronegative subset, while two criteria were met by both these groups in the 15µg group. As measured by SRH, all criteria were met by those in the 7.5µg group and the seronegative subset, while none were met in the 15µg group and its seronegative subset (Table 15). For the elderly, seropositive titers were seen in about 20% of the population at baseline.

Table 15: Summary of Immune Response after Two Injections of Prepandemic Fluad in Seronegative Subjects Compared with All Subjects

		Non-elderly adults (18-60 years)								Elderly (> 60 years)			
		V87P1				V87P2				V87P1			
		7.5 µg		15 µg		7.5 µg		15 µg		7.5 µg		15 µg	
		all	Seroneg	all	Seroneg	all	Seroneg	all	Seroneg	all	Seroneg	all	Seroneg
HI	No. of subjects	N=151	N=148	N=147	N=141	N=14	N=13	N=13	N=13	N=81	N=64	N=74	N=56
	% SP (95% CI)	**73 (65-80)**	**72 (64-79)**	**72 (64-79)**	**71 (63-78)**	**86 (57-98)**	**85 (55-98)**	46 (19-75)	46 (19-75)	**75 (64-84)**	**72 (59-82)**	**76 (64-85)**	**70 (56-81)**
	GMR (95% CI)	**16 (12-21)**	**16 (12-22)**	**15 (12-21)**	**17 (12-23)**	**21 (8.41-52)**	**25 (9.58-66)**	**5.97 (2.31-15)**	**5.97 (2.27-16)**	**9.52 (6.55-14)**	**12 (7.9-19)**	**10 (6.78-15)**	**12 (7.37-19)**
	% SC (95% CI)	**73 (65-80)**	**74 (66-81)**	**69 (61-77)**	**74 (66-81)**	**79 (49-95)**	**85 (55-98)**	**46 (19-75)**	**46 (19-75)**	**67 (55-77)**	**75 (63-85)**	**70 (59-80)**	**73 (60-84)**
SRH	No. of subjects	N=149	N=133	N=149	N=129	N=14	N=13	N=13	N=11	N=84	N=66	N=80	N=54
	% SP (95% CI)	**85 (79-91)**	**83 (76-89)**	**85 (79-91)**	**84 (76-90)**	**86 (57-98)**	**92 64-100**	38 (14-68)	27 6-61	**80 (70-88)**	**76 (64-85)**	**81 (71-89)**	**74 (60-85)**
	GMR (95 % CI)	**7.74 (6.6-9.07)**	**8.79 (7.52-10)**	**6.86 (5.85-8.04)**	**8.62 (7.36-10)**	**8.12 (4.61-14)**	**9.54 5.33-17**	2.27 (1.26-4.09)	2.07 1.1-3.91	**4.96 (3.87-6.37)**	**6.56 (4.98-8.64)**	**4.09 (3.17-5.28)**	**6.3 (4.64-8.54)**
	% SC (95% CI)	**85 (78-90)**	**85 (78-91)**	**80 (73-86)**	**84 (76-90)**	**86 (57-98)**	**92 64-100**	38 (14-68)	27 6-61	**70 (59-80)**	**77 (65-87)**	**69 (57-79)**	**74 (60-85)**
MN	No. of subjects	N=151	N=141	N=151	N=140	N=14	N=11	N=13	N=12	N=84	N=59	N=80	N=61
	% ≥ 40 (95% CI)	85 (78-90)	84 (77-89)	81 (74-87)	81 (73-87)	93 (66-100)	100 (72-100)	54 (25-81)	58 (28-85)	79 (68-87)	69 (56-81)	76 (65-85)	72 (59-83)
	GMR (95% CI)	11 (8.87-13)	11 (9.44-14)	9.2 (7.63-11)	10 (8.57-13)	8.14 (3.78-18)	12 (6.18-25)	5.75 (2.6-13)	7.8 (4.01-15)	4.54 (3.44-6.01)	5.83 (4.22-8.05)	5.61 (4.22-7.48)	7.71 (5.62-11)
	% 4-fold increase (95% CI)	83 (77-89)	84 (77-89)	77 (70-84)	81 (73-87)	86 (57-98)	100 (72-100)	54 (25-81)	58 (28-85)	58 (47-69)	69 (56-81)	61 (49-72)	72 (59-83)

Seroneg = seronegative; SP = seroprotection; GMR = geometric mean ratio Day 43/Day 1; SC = seroconversion or significant increase. Note: HI and SRH figures are in bold when the CHMP criteria are met. Study V87P1 based on PP population; Study V87P2 based on FAS.

Cell-mediated Immunity (CMI)

Cell mediated immunity was evaluated in Studies V87P2 and V87P3 (Table 15). In both studies the frequency and functionality of circulating H5-specific CD4 T-cells was assessed by intracellular staining and fluorescent activated cell sorting (FACS) analysis of IL-2, IFN-γ, TNF-α and IL-13 production following stimulation of peripheral blood mononuclear cells (PBMC) with H5 influenza viral antigens *in vitro.* The frequency of H5N1-IgG memory B-cells was assessed by an enzyme-linked immunosorbent assay (ELISA)-coupled limiting dilution assay after polyclonal activation of PBMC *in vitro*.

CMI Results of the Homologous Prime-boost Study V87P2

H5-specific CD4 T-cells

Low numbers of H5-specific CD4 T-cells were detected in all subjects at baseline irrespective of the vaccine group. In the nonadjuvanted vaccine group, mean numbers of H5-specific CD4 T-cells increased modestly in response to primary vaccination, as well as to the third booster dose and returned to baseline levels six months after booster. Conversely, in both groups primed with the MF59-adjuvanted vaccines H5-specific CD4 T-cells had increased substantially over baseline even after the first dose (Day 22). Six months later (Day 202) were still higher than at baseline. Following the booster vaccination (Day 223), H5-CD4+ T-cells increased to values well above the numbers observed after primary vaccination and remained above baseline six months later (Day 382) in both the MF59 vaccination groups. H5-specific CD4 T-cells expanded only modestly following primary or booster vaccination with nonadjuvanted H5N1. Conversely, high numbers of H5-specific CD4 T-cells were observed after a single dose of MF59-adjuvanted vaccine (containing either 7.5 or 15 µg of H5N1). These CD4 T-cells displayed a Th1[24] effector-memory functional profile and had expanded to even higher levels after administration of a booster dose (Table 16).

[24] After activation, naive $CD4^+$ T cells can differentiate into functional subsets termed T_H1 or T_H2 cells. T_H1 responses are required to mediate protection against a variety of intracellular infections.

Table 16: Mean Frequency (± SD) of Total H5-Specific CD4 T-cells and Specific T-Cell Populations, V87P2 (FAS)

		Baseline (day 1)	Post 1st inj (day 22)	Post 2nd inj (day 43)	6 months after primary vacc (day 202)	Post- booster inj (day 223)	6 months after booster inj (day 382)
Total H5 CD4 T-Cells	Fluad-H5N1 7.5 µg N=14	188 (±146)	536 (±450)	592 (±476)	372 (±249)	845 (±781)	507 (±503)
	Fluad-H5N1 15 µg N=13	122 (±75)	477 (±406)	384 (±328)	355 (±283)	962 (±514)	328 (±2236)
	Non-adjuvanted 15 µg N=13	179 (±98)	250 (±215)	232 (±233)	224 (±158)	316 (±195)	169 (±121)
IL-13+	Fluad-H5N1 7.5 µg ,N=14	55 (±52)	25 (±23)	33 (±37)	22 (±28)	30 (±42)	17 (±38)
	Fluad-H5N1 15 µg, N=13	47 (±48)	28 (±33)	23 (±27)	50 (±155)	40 (±42)	19 (±33)
	Non-adjuvanted 15 µg, N=13	63 (±45)	30 (±41)	14 (±17)	17 (±24)	12 (±26)	3.14 (±5.53)
IL-2+/IFN-γ-	Fluad-H5N1 7.5 µg ,N=14	71 (±74)	368 (±366)	420 (±387)	208 (±174)	567 (±562)	303 (±338)
	Fluad-H5N1 15 µg, N=13	53 (±44)	342 (±321)	259 (±248)	225 (±188)	647 (±380)	223 (±181)
	Non-adjuvanted 15 µg, N=13	61 (±63)	116 (±127)	124 (±139)	123 (±98)	165 (±138)	99 (±85)
IL-2+/IFN-γ+	Fluad-H5N1 7.5 µg ,N=14	51 (±60)	99 (±95)	107 (±97)	127 (±106)	205 (±208)	161 (±168)
	Fluad-H5N1 15 µg, N=13	18 (±19)	99 (±94)	96 (±92)	96 (±67)	250 (±181)	92 (±63)
	Non-adjuvanted 15 µg, N=13	28 (±24)	62 (±53)	70 (±82)	70 (±59)	114 (±80)	61 (±45)
IL-2+/IFN-γ+	Fluad-H5N1 7.5 µg ,N=14	38 (±32)	57 (±58)	51 (±50)	36 (±48)	60 (±52)	42 (±33)
	Fluad-H5N1 15 µg, N=13	27 (±23)	33 (±26)	24 (±20)	15 (±14)	50 (±33)	10 (±8.31)
	Non-adjuvanted 15 µg, N=13	44 (±35)	67 (±159	34 (±27)	27 (±23)	29 (±25)	7.91 (±12)

inj = injection.

H5-specific memory B cells

At baseline the mean frequency of H5N1-IgG memory B-cells (as a percentage of the total IgG memory B-cells) was similar in all three vaccine groups (0.41% and 1.05% in the Fluad-H5N1 7.5 and Fluad-H5N1 15 groups, respectively, versus 0.36% in the nonadjuvanted vaccine group, Table 17). After two doses of either MF59- adjuvanted H5N1 formulation H5N1-IgG memory B-cells increased substantially. In comparison, these cells had only increased slightly in the nonadjuvanted group (mean frequency on Day 43: 5.24% and 3.08% in the Fluad-H5N1 7.5 and Fluad-H5N1 15 groups, respectively, compared to 1.06% in the nonadjuvanted group). The booster vaccination led to a pronounced increase in H5N1-IgG memory B-cells in both MF59-adjuvanted groups. A lower increase was observed in the nonadjuvanted vaccine group (mean frequency of 11% for both the Fluad-H5N1 7.5 and Fluad-H5N1 15 groups compared to 3.37% in the nonadjuvanted vaccine group).

Such responses consist of populations of cells that secrete IFN-γ, TNF or IL-2 in various combinations. Differences in the types of cytokines produced by individual cells have implications for their capacity to mediate effector function, be sustained as memory cells or both.

Table 17: Frequency of H5N1-IgG Memory B-Cells (as Percentages Total IgG Memory B-Cells) - Study V87P2 (FAS) Mean (± SD) Fluad-H5N1 7.5µg Fluad-H5N1 15 µg Non-adjuvanted 15 µg

	Mean (± SD)		
	Fluad-H5N1 7.5µg	Fluad-H5N1 15 µg	Non-adjuvanted 15 µg
Baseline (day 1)	1.05 (±2.04) N=14	0.41 (±0.83) N=13	0.36 (±0.31) N=13
Post- 1st injection (day 22)	2.99 (±2.68) N=14	1.97 (±2.08) N=13	0.78 (±0.75) N=11
Post- 2nd injection (day 43)	5.24 (±5.12) N=11	3.08 (±1.68) N=12	1.06 (±0.75) N=11
6 months after 2nd injection (day 202)	5.8 (±7.66) N=8	4.74 (±7.25) N=9	1.59 (±1.75) N=8
Post- booster injection (day 223)	11 (±8.12) N=12	11 ±10) N=12	3.37 (±8.56) N=11
6 months after booster injection (day 382)	11 (±15) N=12	9.59 (±11) N=10	1.22 (±1.16) N=11

CMI of the Heterologous Boost Study V87P3

In Study V87P3 Fluad-H5N1 was administered to subjects who had (6-8 years) previously received primary vaccination with two doses of either MF59-adjuvanted or nonadjuvanted H5N3 vaccines. A group of unprimed subjects was also enrolled as comparator.

H5-specific CD4 T-cells

Low frequencies of H5-specific CD4 T-cells were detected in all subjects at baseline irrespective of the priming group, with the lowest frequency observed in the adjuvanted-H5N3 primed group. After the first booster dose (the first heterologous dose with the H5 Vietnam strain on Day 22), H5-specific CD4 T-cells had increased over baseline and the most pronounced increase was seen in the unprimed group, with no further increase after the second dose in all groups. Six months later (Day 202), H5 specific T-cells contracted to levels indistinguishable from baseline in all the groups (Table 18).

Table 18: Total Cytokine-positive H5-Specific CD4 T-cells (cells/1.000.000 Total CD4 T-cells) – Study V87P3 (FAS)

	Mean (± SD)		
	MF59-Adjuvanted H5N3 primed	Non-Adjuvanted H5N3 primed	Unprimed
Baseline (day 1)	216 (±186) N=11	430 (±304) N=10	335 (±233) N=21
Post- 1st injection (day 22)	329 (80) N=11	625 (±337) N=10	668 (±543) N=20
Post-2nd injection (day 43)	264 (±129) N=9	657 (±360) N=8	690 (±824) N=19
6 months after 2nd injection (day 202)	116 (±60) N=11	275 (±214) N=7	181 (±94) N=8

H5-specific memory B cells

At baseline, the frequency of H5N1-IgG memory B-cells was similar in all groups irrespectively of the priming status (Table 19). After the first booster dose (the first heterologous dose with the H5 Vietnam strain on Day 22) of MF59-H5N1, the frequency of H5N1-IgG MBC was substantially higher in the adjuvanted H5N3-primed group (12%) than in the nonadjuvanted H5N3-primed (3.55%) and unprimed groups (2.44%) and it remained unchanged after the second booster dose (Day 43). Six months later (Day 202)

the frequency of H5N1-IgG MBC remained above baseline levels in all groups and was highest in the group primed with the MF59-adjuvanted H5N3. In conclusion, although limited by the low number of subjects per priming group, the results from these analyses suggest that vaccination strategies involving distant priming with MF59-adjuvanted vaccines can be employed to induce long-lasting immune memory that can react to novel pandemic influenza antigens. This was demonstrated by the H5-specific B cell response.

Table 19: Frequency of H5N1-IgG Memory B-Cells (as Percentage of Total IgG Memory B-Cells) - Study V87P3 (FAS)

	Mean (± SD)		
	MF59-Adjuvanted H5N3 primed	Non-Adjuvanted H5N3 primed	Unprimed
Baseline (day 1)	1.20 (±1.39) N=11	0.75 (±0.61) N=6	0.69 (±0.59) N=22
Post- 1st injection (day 22)	12 (±8.74) N=7	3.55 (±2.52) N=7	2.44 (±1.74) N=17
Post-2nd injection (day 43)	9.23 (±7.49) N=8	3.62 (±2.34) N=7	3.59 (±3.04) N=17
6 months after 2nd injection (day 202)	4.07 (±3.19) N=10	2.91 (±2.09) N=7	3.04 (±2.47) N=11

Concomitant Administration of Fluad-H5N1 and Inter-pandemic Influenza Vaccines

Study V101P1 was conducted to evaluate the effect of three different immunization schedules on the immune response to the H5N1 A/Vietnam/1194/2004 strain (Clade 1). A total of 601 subjects were enrolled and randomized: 199 received a pre-formulated tetravalent influenza vaccine (three seasonal influenza strains + Fluad-H5N1 + MF59-adjuvant) and concomitantly a placebo on Day 1, then three weeks later a dose of Fluad-H5N1 (T/P-A group); 203 received a dose of Fluad-H5N1 and concomitantly a placebo on Day 1, then three weeks later a dose of the tetravalent vaccine (A/P-T group); and 199 received one dose of Fluad-H5N1 and concomitantly one dose of a seasonal trivalent vaccine for the 2007/08 influenza season (Agrippal) on Day 1, then three weeks later received a second dose of Fluad-H5N1 (A/S-A group) .

The primary immunogenicity objective was to show that SRH antibody titers against A/H5N1 elicited by the three different immunization schedules were equivalent at Visit 3 planned for Day 43, 1 to 3 weeks after the second vaccination time point. Equivalence between the three vaccination schedules was demonstrated with regards to the analysis of GMTs at Day 43 as the vaccine group ratios were completely within the equivalence range [0.5, 2.0] as assessed by SRH assay. All three CHMP criteria for the H5N1 strain [A/Vietnam/1194/2004 (H5N1 Clade 1)] were met by all three vaccine groups as assessed by SRH assay (Table 20) after two doses of H5N1 vaccine. When assessed by HI assay, two CHMP criteria for the H5N1 strain were met by the T/P-A group and the A/P-T group, whereas all three CHMP criteria were met by the A/S-A group. For the current submission, the results of one study arm (A/S-A group) are shown in Table 20. At three weeks post seasonal vaccination (Day 22), all three vaccine groups met all three CHMP criteria for the inter-pandemic strains (H1N1, H3N2 and B) as assessed by HI assay (Table 20). In conclusion, immune response to the H5N1 strain was not affected when Fluad-H5N1 and a conventional seasonal influenza vaccine were administered concomitantly (for the H5N1 strain all three CHMP criteria were met after two injections of Fluad-H5N1 by both HI and SRH assays). Similarly, immune responses to the seasonal strains as assessed by HI assay, were not affected (all three CHMP criteria were met for all three seasonal strains three weeks after receiving one dose of seasonal vaccine).

Table 20: Immune Responses to the H5N1 Strain and to the Seasonal Strains, A/S-A group (StudyV101P1, PP Population)

		Prepandemic Strain	Seasonal Strains (influenza season 2007/2008)		
		A/H5N1	A/H1N1	A/H3N2	B
		N=199	N=189	N=189	N=189
HI	% SP (95%CI)	**74 (67-80) N=186**	**99 (96-100)**	**98 (95-100)**	**89 (84-93)**
	GMR (95%CI)	**8.78 (5.73-13) N=184**	**9.87 (6.39-15)**	**6.13 (4.34-8.66)**	**8.02 (5.94-11)**
	% SC (95%CI)	**75 (68-81) N=184**	**72 (65-78)**	**71 (64-78)**	**78 (71-83)**
SRH	% SP (95%CI)	**89 (84-93) N=189**	ND	ND	ND
	GMR (95%CI)	**8.30 (7.02-9.80) N=189**	ND	ND	ND
	% SC (95%CI)	**86 (80-91) N=189**	ND	ND	ND
MN	MN ≥ 40 (95%CI)	**89% (84-93) N=189**	ND	ND	ND
	GMR (95%CI)	**13 (10-16) N=189**	ND	ND	ND
	4-Fold Increase (95%CI)	**89% (84-93)**	ND	ND	ND

a Fluad-H5N1/Seasonal influenza vaccine, followed by second dose of Fluad-H5N1 SP = seroprotection; GMR = geometric mean ratio; SC = seroconversion or significant increase. ND = Not determined. Note: HI and SRH figures are in bold when the CHMP criteria are met.

Different Vaccination Schedules

A comparison of different administration schedules for the two vaccinations of Fluad-H5N1 in Study V87P12 showed that a one week separation between the first and second vaccination may be insufficient. However, there was no meaningful difference noted when separating the administration of the second vaccination by two, three or six weeks. Based on HI assay results, all three CHMP criteria were met after the second injection with the exception of the one week schedule for which the seroprotection criterion was not achieved (Table 21). As assessed with the SRH assay, all three CHMP criteria were met after the second injection regardless of the vaccine schedule. MN results also confirmed that similar results were obtained with the two, three and six week schedules. However, lower immune responses were observed with the one week-apart schedule.

Table 21: Immunogenicity Results 21 Days After second Vaccination, Study V87P12, FAS

		DAY1+8	DAY1+15	DAY1+22	DAY1+43
		N=60	N=60	N=60	N=60
HI	% SP (95%CI)	55% (42-68)	76% (63-86) N=59	74% (61-85) N=58	79% (67-89) N=58
	GMR (95%CI)	7.73 (4.64-13)	21 (13-35) N=59	22 (13-37) N=58	36 (22-61) N=58
	% SC (95%CI)	53 (40-66)	76 (63-86) N=59	74 (61-85) N=58	79 (67-89) N=58
SRH	% SP (95%CI)	86 (75-94) N=59	98 (91-100) N=59	88 (77-95) N=58	97 (88-100) N=58
	GMR (95%CI)	2.92 (2.29-3.72) N=59	3.26 (2.56-4.15) N=59	3.82 (3-4.88) N=58	4.57 (3.58-5.84) N=58
	% SC (95%CI)	64 (51-76) N=59	75 (62-85) N=59	71 (57-82) N=58	90 (79-96) N=58
MN	MN ≥ 40 (95%CI)	38 (26-52)	76 (63-86) N=59	73 (60-84)	90 (79-96) N=59
	GMR (95%CI)	2.22 (1.67-2.96)	6.78 (5.07-9.06) N=59	7.49 (5.62-9.98)	17 (13-23) N=59
	4-Fold Increase (95%CI)	35 (23-48)	75 (62-85) N=59	73 (60-84)	90 (79-96) N=59

Immunogenicity was also compared to a heterologous strain (H5N1 turkey/Turkey/2005) for the Day 1+15 and Day 1+22 groups with similar results.

Persistence of Efficacy and/or Tolerance Effects and Antibody Response to a Booster Dose of Fluad-H5N1

Data on antibody persistence six months after primary vaccination for Fluad-H5N1 are provided by Studies V87P1, V87P2 and V87P3 and for a further six months after a third dose in Study V87P1. Across all studies, and in both adults and elderly subjects, antibody titers (as assessed by HI, SRH and MN) six months after primary vaccination schedule (Dose 2) had decreased when compared with the primary vaccination. GMRs had decreased to approximately 1/1.5 - 1/8 of the titers achieved on Day 43, approximately three weeks after the end of the primary vaccination schedule (range 0.12-0.41; Table 22) although they were still above baseline (Day 1). The decrease in GMTs was similar for the 7.5 and 15 µg Fluad-H5N1 groups (Studies V87P1 and V87P2). A third (booster) vaccination of Fluad-H5N1 was administered six months after the primary vaccination. A noteworthy increase in titers was seen after this booster vaccination in both age groups. CHMP criteria for GMRs and for seroprotection were met in nearly all study groups using SRH and HI. In the small sample size Study V87P2 in adults, seroprotection was not met in the 15µg Fluad-H5N1 group by HI, and GMR was not met by SHR in the 7.5µg Fluad-H5N1 group; seroconversion/significant increase CHMP criterion was always achieved (Table 23). The GMRs as measured by MN were generally comparable with the GMRs with the other two assays. A high percentage of subjects (92-100% across Fluad-H5N1 groups and age groups) achieved MN-titers >40 (Table 23).

Similar to the pattern observed six months after primary vaccination, in Studies V87P1 andV87P2 in both adults and elderly subjects, antibody titers obtained six months after booster vaccination as assessed by HI, SRH and MN decreased compared to titers obtained approximately 3 weeks after booster: GMTs decreased to approximately 1/1.5 -1/7 of that three weeks after the booster dose; Table 24) although they were still above baseline (Day 1). The decrease in GMTs was similar for the 7.5 and 15µg Fluad-H5N1 groups (Studies V87P1 and V87P2). Overall these results show that although antibody titers decreased over six months, they quickly increased to high levels after a booster shot. This suggests that there was immunological memory.

Table 22 Antibody Persistence 6 Months After Primary Vaccination with H5N1

		Non-elderly adults (18-60 years)					Elderly (> 60 years)	
		V87P1		V87P2		V87P3	V87P1	
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	7.5 µg	15 µg
HI		N=116	N=122	N=13	N=12	N=26	N=66	N=51
	GMT day 202 pre-booster	12 (9.63-16)	17 (13-21)	16 (7.26-34)	6.67 (2.99-15)	7.28 (4.63-11)	23 (15-37)	31 (19-51)
	GMR day 202/day 43	0.15 (0.11-0.2)	0.22 (0.16-0.28)	0.12 (0.047-0.3)	0.19 (0.073-0.51)	0.30 (0.20-0.44)	0.33 (0.24-0.46)	0.41 (0.29-0.6)
	% SP day 202 pre-booster	27 (17-39)*	34 (24-45)*	31 (9-61)	8 (0-38)	8 (1-25)	54 (37-71)*	62 (41-80)*
SRH		N=116	N=122	N=13	N=12	N=26	N=66	N=55
	GMA day 202 pre-booster	8.06 (6.67-9.75)	9.11 (7.56-11)	15 (8.92-27)	8.45 (4.77-15)	17 (13-23)	6.96 (5.26-9.2)	11 (8.04-15)
	GMR day 202/day 43	0.22 (0.18-0.26)	0.26 (0.21-0.31)	0.45 (0.3-0.67)	0.71 (0.47-1.08)	0.40 (0.32-0.51)	0.24 (0.18-0.32)	0.36 (0.26-0.48)
	% SP day 202 pre-booster	18 (10-29)*	25 (16-36)*	31 (9-61)	25 (5-57)	54 (33-73)	21 (10-37)*	62 (41-80)*
MN		N=116	N=122	N=13	N=12	N=26	N=66	N=55
	GMT day 202 pre-booster	35 (29-42)	45 (37-55)	30 (16-54)	31 (17-58)	21 (14-30)	33 (24-46)	47 (33-67)
	GMR day 202/day 43	0.29 (0.23-0.35)	0.47 (0.38-0.58)	0.26 (0.17-0.39)	0.4 (0.26-0.62)	0.68 (0.52-0.89)	0.43 (0.33-0.56)	0.53 (0.4-0.71)
	% ≥ 1:40 day 202 pre-booster	41 (29-53)*	53 (42-64)*	31 (9-61)	50 (21-79)	12 (2-30)	42 (26-59)*	69 (48-86)*

Table 23 Booster Immune Response After Third Vaccination Non-elderly adults (18-60 years) Elderly (> 60 years)

		Non-elderly adults (18-60 years)				Elderly (> 60 years)	
		V87P1		V87P2		V87P1	
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	15 µg
HI	No. of subjects	N=71	N=82	N=13	N=12	N=37	N=26
	% SP (95% CI) day 223 post booster	**83 (72-91)**	**76 (65-84)**	**85 (55-98)**	67 (35-90)	**92 (78-98)**	**96 (80-100)**
	GMR (95% CI) (day 223 post booster /day 202 pre-booster)	**11 (7.59-16)**	**6.54 (4.61-9.27)**	**10 (3.74-28)**	**13 (4.75-38)**	**5.02 (2.8-8.98)**	**5.07 (2.67-9.63)**
	% SC (95%CI) day 223	**73 (61-83)**	**62 (51-73)**	**77 (46-95)**	**58 (28-85)**	**51 (34-68)**	**54 (33-73)**
SRH	No. of subjects	N=71	N=83	N=13	N=12	N=38	N=26
	% SP (95% CI) day 223	**89 (79-95)**	**92 (83-97)**	**85 (55-98)**	**100 (74-100)**	**84 (69-94)**	**88 (70-98)**
	GMR (95% CI) (day 223/day 202)	**5.96 (4.72-7.53)**	**5.22 (4.2-6.49)**	2.49 (1.56-3.98)	**6.21 (3.81-10)**	**5.15 (3.46-7.66)**	**2.69 (1.73-4.18)**
	% SC (95%CI) day 223	**83 (72-91)**	**81 (71-89)**	**69 (39-91)**	**100 (74-100)**	**63 (46-78)**	**65 (44-83)**
MN	No. of subjects	N=71	N=83	N=13	N=12	N=38	N=26
	% ≥ 1:40 (95% CI) day 223	94 (86-98)	96 (90-99)	92 (64-100)	100 (74-100)	97 (86-100)	96 (80-100)
	GMR (95% CI) (day 223/day 202)	6.44 5.03-8.26	4.99 3.96-6.28	8.5 (4.86-15)	11 (6.15-20)	4.99 3.17-7.88	3.59 2.16-5.95
	MN ≥ 4-fold increase	68 (55-78)	55 (44-66)	69 (39-91)	75 (43-95)	55 (38-71)	46 (27-67)

SP = seroprotection; GMR = geometric mean ratio; SC = seroconversion or significant increase Note: HI and SRH figures are in bold when the CHMP criteria are met. Study V87P1 based on PP population; Study V87P2 based on FAS.

Table 24: Persistence 6 Months After third (Booster) Vaccination

		Non-elderly adults (18-60 years)				Elderly (> 60 years)	
		V87P1		V87P2		V87P1	
		7.5 µg	15 µg	7.5 µg	15 µg	7.5 µg	15 µg
HI	No. of subjects	N=69	N=76	N=12	N=10	N=35	N=22
	% SP (95% CI) day 382	52 (40-64)	46 (35-58)	58 (28-85)	60 (26-88)	57 (39-74)	**77 (55-92)**
	GMT (95%CI) day 382	27 (18-41)	29 (20-42)	44 (15-126)	41 (13-133) N=10	36 (20-68)	71 (34-145)
	GMR (95% CI) (day 382/day 223)	0.22 (0.16-0.31)	0.27 (0.19-0.38)	0.29 0.15-0.57	0.62 0.29-1.31	0.3 (0.19-0.49) N=34	0.35 (0.2-0.6)
SRH	No. of subjects	N=69	N=76	N=12	N=10	N=35	**N=22**
	% SP (95% CI) day 382	55 (43-67)	55 (43-67)	67 (35-90)	**70 (35-93)**	43 (26-61)	**77 (55-92)**
	GMA (95%CI) day 382	17 (13-21)	17 (14-21)	28 (16-49)	22 (12-42)	13 (8.42-19)	25 (16-39)
	GMR (95% CI) (day 382/day 223)	0.41 (0.33-0.5)	0.41 (0.34-0.51)	0.73 0.5-1.07	0.45 0.29-0.68	0.38 (0.27-0.52)	0.56 (0.39-0.81)
MN	No. of subjects	N=69	N=76	N=12	N=10	N=35	N=22
	% ≥ 1: 40 (95% CI) day 382	41 (29-53)	46 (35-58)	75 (43-95)	70 (35-93)	37 (21-55)	64 (41-83)
	GMT (95%CI) day 382	34 (26-44)	35 (27-44)	83 (41-168)	70 (32-153)	25 (17-39)	46 (28-75)
	GMR (95% CI) (day 382/day 223)	0.16 (0.14-0.19)	0.16 (0.14-0.19)	0.33 0.21-0.53	0.25 0.15-0.42	0.17 (0.13-0.21)	0.22 (0.17-0.29)

SP = seroprotection; GMT = geometric mean titer; GMR = geometric mean ratio. Note: HI and SRH figures are in bold when the CHMP criteria are met. Study V87P1 based on PP population; Study V87P2 based on FAS

Evaluator's overall conclusions on clinical efficacy

The discussion of these clinical trials needs to be considered in the context of the EMEA guidelines that Australia has adopted for the evaluation of influenza vaccines. These guidelines specifically detail the requirements for the development and testing of 'mock up' vaccines such as the prepandemic influenza vaccine, Fluad-H5N1. The development and testing of the proposed vaccine has been done in accordance with these guidelines. The dose studies and adjuvant studies all support marketing of the 7.5mg adjuvant-combined dose as adequate and appropriate in terms of efficacy against H5N1. The criteria for seroconversion and seroprotection have been adhered to in terms of assessing efficacy, although with MN, there is no definitive standard for what level of antibody production represents community protection from disease. The groups studied have included both a general adult group (above 18 years of age) and in some of the studies, also an elderly group. The strain selected is a good candidate to assess (that is, likely to be closely related to a pandemic strain) but there is never any certainty about exactly what strain may cause the next pandemic. A number of the studies have also examined heterologous protection and this does not meet all the criteria. However, there are some data supporting heterologous protection against other strains.

Summary:

- Two vaccinations of Fluad-H5N1 containing A/H5N1/Vietnam/1194/04 (NIBRG14; Clade 1) strain, each with an antigen dosage of 7.5µg was used for most of these studies. This was found to produce an increase of titers against the homologous H5N1 strain as measured with HI, SRH and MN assays in both non-elderly (18-60 years) and elderly (> 60 years) adults. As assessed by SRH, all

CHMP criteria (seroprotection, geometric mean ratio and seroconversion) were met after 2 vaccinations. As assessed by HI, all CHMP criteria were also met in most study groups. The exception was seroprotection in some groups. MN titers >40 or a 4-fold increase of titers were comparable or only slightly lower than the SRH rates for seroprotection and seroconversion, respectively.

- In general, results in the elderly population are similar to those in the non-elderly population. However, GMRs and percentages of subjects with a 4-fold increase of MN-titers were generally lower.
- Cell mediated immunity (CMI) was investigated in Studies V87P2 and V87P3. One injection of Fluad-H5N1 induced an increase in the frequency of H5-specific CD4 T-cells with a memory TH0/TH1 phenotype, with high survival potential *in vivo* and the ability to expand and differentiate into effector cells upon infection. Two vaccinations were needed to expand long lasting H5N1-specific memory B-cells which further expanded upon boosting, either with a vaccine formulated with the same pandemic strain or with a novel pandemic antigen.
- Concomitant administration of Fluad-H5N1 and a seasonal trivalent influenza vaccine (TIV) did not have negative impact on immunogenicity of either vaccine.
- The immune response to the H5N1 strain was not affected when Fluad-H5N1 and a conventional seasonal influenza vaccine were administered concomitantly. Similarly, immune responses to the seasonal strains, as assessed by HI assay, were not affected.
- A comparison of different administration schedules showed that separating the two administrations by one week may be insufficient, but that there was no significant difference in separating the administration of the second vaccination by two, three or six weeks.
- The effect of the vaccinations persisted beyond the initial vaccination schedule. Antibody titers decreased but were still above baseline six months after the second vaccination as measured by HI, SRH and MN assays. A booster vaccination (third dose) of Fluad-H5N1 7.5µg administered six months after the second dose induced a noteworthy increase of titers, indicating that the first two vaccinations were sufficient to induce immunological memory. A second booster vaccination administered six months after the first booster again induced an increase of titers.

Safety

Patient exposure

The overall safety profile of the Fluad-H5N1 (7.5µg formulation) vaccine in the adult population is based on data from the same six studies used for the efficacy data conducted from 2006 to present. A total of 3001 and 387 adults below and above 60 years, respectively, received at least one vaccination with either the 7.5µg or the 15µg Fluad-H5N1formulation. Of these, 2842 and 301 adults below and above 60 years, respectively, received 7.5µg Fluad-H5N1. The pooled safety database includes subjects from Studies V87P1, V87P2, V87P3 (all subjects exposed to Fluad-H5N1 in Study V87P3 were included in the pooled safety analyses regardless of the priming status). The pivotal safety Study V87P13 was specifically designed to make a direct comparison between the safety profile of Fluad-H5N1 and of the MF59-adjuvanted seasonal vaccine (Fluad) and contributed most of the data for the pooled Fluad-H5N1 analysis. The study sample size was calculated so that the size of the overall Fluad-H5N1 safety database from the clinical trials would be sufficient to detect rare (at ≤0.1% frequency) adverse events (AEs) in adults below 60 years and uncommon (at ≤1% frequency) AEs in adults above 60 years.

Safety data providing insight regarding the influence of both antigen amount and MF59-adjuvant on the prepandemic vaccine is provided by early studies with the H5N3 vaccine

(V7P37 and V7P37E1) and by the first studies with the H5N1 strain (V87P1 and V87P2). In the H5N3 studies, safety of vaccines formulated with three different HA antigen amounts, 7.5µg, 15µg and 30µg, with and without adjuvant was evaluated. Although limited by the small number of subjects in each group (2 to 11 subjects) no major differences in the safety profile were observed across the groups regardless of antigen amount. However, a trend for a higher local reactogenicity was observed for the adjuvanted versus nonadjuvanted vaccines. These results were confirmed by the initial studies with the H5N1 strain in which safety of 7.5µg and 15 µg H5N1 adjuvanted (Studies V87P1 and V87P2) and 15µg nonadjuvanted (Study V87P2) H5N1 vaccines were assessed.

The extensive analysis of the historical clinical safety database of seasonal Fluad may present a worst-case estimate of incidence rates of possible adverse reactions since the antigen content of 7.5µg Fluad-H5N1 is 6-fold less than that for licensed seasonal Fluad while adjuvant content is the same. The established safety profile of the licensed Fluad is based on extensive clinical experience in over 40 clinical trials on approximately 15,000 subjects in addition to post-marketing surveillance from more than 40 million doses distributed. According to the submission, there is a greater than 99.9% probability that the clinical and post-marketing surveillance databases would detect adverse drug reactions with frequencies of 1/1000 and 1/100,000, respectively.

All enrolled subjects who received at least one vaccination of Fluad-H5N1 and provided post-vaccination safety data (that is, the safety population) were included in the safety analyses.

In all Fluad-H5N1 studies there were no notable differences between the enrolled, exposed and safety populations, which only differed by approximately 2% of subjects. In all Fluad-H5N1 studies safety was monitored by AEs reporting with a consistent method. Unsolicited AEs, such as local reactions, systemic reactions and other indicators of reactogenicity [indicated by the use of analgesics/antipyretics] collected for seven days post-vaccination, were solicited from the subjects using a diary card. All unsolicited AEs were collected up to three weeks after each vaccination. Serious AEs, AEs leading to withdrawal or necessitating a physician's visit were collected throughout the entire study duration. Additionally, clinical laboratory data (serum chemistry and hematology) were collected in a subset of 150 subjects from Study V101P1 prevaccination (Day 1) and three weeks after second vaccination (Day 43). Overall, no medically significant changes in these laboratory parameters were observed.

There is great variability in the safety collection method across the historical Fluad studies as well as in the duration of the monitoring periods used in the seasonal Fluad studies and Fluad-H5N1 studies. The Day 1-4 reactogenicity profile of the historical Fluad pooled safety database still provides useful information about safety of the prepandemic vaccine as most of the solicited reactions reported in the Fluad-H5N1 studies occurred within four days of vaccination.

Solicited Adverse Events (tables 29-31)

Influence of Antigen Amount and Adjuvant on Reactogenicity

The early studies on Fluad-H5N3 (V7P37 and V7P37E1; N=65: 18-40 year olds) showed that MF59-adjuvanted vaccines had a higher rate of mild solicited reactions than nonadjuvanted formulations, as previously documented[25]. This tendency was also

[25] Minutello M, Senatore F, Cecchinelli G, Bianchi M, Andreani T, Podda A, Crovari P. Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly subjects, immunized for three consecutive influenza seasons. *Vaccine* 1999; Jan;17(2):99-104.

observed in V87P2 (Table 27) in which a nonadjuvanted comparator was used; 50% to 93% of subjects receiving either 7.5µg or 15µg Fluad-H5N1 versus 0 to 46% of subjects receiving the nonadjuvanted vaccine reporting any solicited reactions within seven days of vaccination. The differences between adjuvanted and nonadjuvanted vaccines were accounted for by mild and moderate local reactions of short duration, mostly pain at the injection site. There were no major differences related to antigen amount in the reactogenicity profiles of the adjuvanted vaccines used in studies V7P37 and V7P37E1.

Reactogenicity following primary and booster vaccination with 7.5µg and 15µg HA Fluad-H5N1 administered to naïve populations was assessed in Studies V87P1 and V87P2. In both studies, no clear and consistent trend for age affecting reactogenicity was observed following administration of the higher (15µg) HA antigen dose (Study V87P1 in which adults below and above 60 years were enrolled).

Severity and Duration

In the four Fluad-H5N1 studies which contributed the majority of the data to support the proposed indication, most of the local reactions reported by the elderly subjects were mild to moderate in severity and transient in duration.

Table 25: Percentages of Non-Elderly Adults Ages 18 to 60 Years Reporting Local Reactions after First, Second and Third Vaccinations with 7.5µg Fluad-H5N1 or Comparator, by Study (Days 1-7)

	V87P1			V87P13			
	Fluad-H5N1			Fluad-H5N1		Seasonal Fluad	
Vaccination / Reaction	1st N=87	2nd N=86	3rd N=38	1st N=214	2nd N=212	1st N=54	2nd N=53
Ecchymosis	2%	1%	0	6%	5%	4%	11%
Erythema	5%	2%	3%	15%	10%	19%	13%
Induration	3%	3%	5%	9%	2%	7%	15%
Pain	17%	9%	8%	30%	22%	24%	30%
Swelling	2%	3%	3%	7%	3%	9%	2%

In all studies, second vaccination was administered 3 weeks after the first; when a third vaccination was administered (V87P1 and V87P2), it was a booster vaccine administered six months after the second primary course vaccination.

Table 26: Percentages of Elderly Subjects Ages >60 Years Reporting Local Reactions after First, Second and Third Vaccination with 7.5µg Fluad-H5N1 or Comparator, by Study (Days 1-7)

	Non-elderly adults 18-60 years									Elderly >60 years		
	V87P1			V87P2						V87P1		
	Fluad-H5N1			Fluad-H5N1			Non-adjuvanted			Fluad-H5N1		
Vaccination / Reaction	1st N=156	2nd N=153	3rd N=83	1st N=13	2nd N=13	3rd N=12	1st N=13	2nd N=13	3rd N=11	1st N=86	2nd N=80	3rd N=28
Ecchymosis	4%	3%	2%	8%	0	0	8%	0	0	1%	0	4%
Erythema	7%	7%	6%	8%	8%	8%	8%	8%	0	5%	3%	0
Induration	17%	9%	12%	8%	8%	8%	0	0	0	10%	5%	4%
Pain	60%	43%	37%	38%	31%	25%	23%	15%	0	21%	19%	7%
Swelling	10%	8%	12%	8%	8%	8%	0	0	0	3%	3%	0

In both studies, second vaccination was administered 3 weeks after the first; third vaccination in Study V87P1 was a booster vaccine administered six months after the second primary course vaccination.

Table 27: Percentages of Subjects Reporting Local Reactions after First, Second and Third Vaccination with 15µg Fluad-H5N1 or Comparator (Days 1 – 7)

	Non-elderly adults 18-60 years									Elderly >60 years		
	V87P1			V87P2						V87P1		
	Fluad-H5N1			Fluad-H5N1			Non-adjuvanted			Fluad-H5N1		
Vaccination / Reaction	1st N=156	2nd N=153	3rd N=83	1st N=13	2nd N=13	3rd N=12	1st N=13	2nd N=13	3rd N=11	1st N=86	2nd N=80	3rd N=28
Ecchymosis	4%	3%	2%	8%	0	0	8%	0	0	1%	0	4%
Erythema	7%	7%	6%	8%	8%	8%	8%	8%	0	5%	3%	0
Induration	17%	9%	12%	8%	8%	8%	0	0	0	10%	5%	4%
Pain	60%	43%	37%	38%	31%	25%	23%	15%	0	21%	19%	7%
Swelling	10%	8%	12%	8%	8%	8%	0	0	0	3%	3%	0

In both studies, second vaccination was administered 3 weeks after the first while third vaccination was a booster vaccine administered six months after the second primary course vaccination.

In Study V87P13, the safety profile of 7.5 µg Fluad-H5N1 was similar to that of seasonal Fluad. For both adults below and above 60 years each local or systemic reaction within 7 days of vaccination was reported by a similar or lower percentage of subjects in the Fluad-H5N1 group than in the seasonal Fluad group (Table 25). The results from this pivotal safety study were consistent with the reactogenicity profile observed in the pooled Fluad clinical safety database of 42 historical studies and eight extension studies

Solicited AEs for Fluad-H5N1 – Pooled data

As previously observed in influenza vaccine studies[26] within both age groups the incidence rates of both local and systemic solicited reactions after the first vaccination with Fluad-H5N1 were higher than after the second or third (booster) vaccination (Tables 28). As antigen amount did not influence AE report rates, the results for the two formulations of Fluad-H5N1 (7.5 and 15µg) in this submission have been pooled. The percentages of

[26] Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: Phase I randomised trial. *Lancet* 2006 May 20;367(9523):1657-64.
Frey S, Poland G, Percell S, Podda A. Comparison of the safety, tolerability and immunogenicity of a MF59-adjuvanted influenza vaccine and a nonadjuvanted influenza vaccine in non-elderly adults. *Vaccine* 2003 Oct 1;21(27-28):4234-7.
Squarcione S, Sgricia S, Biasio LR, Perinetti E. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. *Vaccine* 2003 Mar 7;21(11-12):1268-74.

subjects reporting solicited reactions were higher for adults below 60 years than for adults above 60 years.

Across all studies using 7.5µg Fluad-H5N1, the most frequently reported solicited local reactions in the 7-day observation period after each vaccination in both age groups were local pain (range across vaccinations for the pooled 7.5µg Fluad-H5N1 safety database: 38%-51% for adults below 60 years, and 8%-27% for adults above 60 years), induration and erythema (both with lower rates than pain; Table 28). Most of these reactions had an onset close to the time of vaccination, were mild- moderate in severity and mostly transient in duration.

The most frequently reported solicited systemic reactions across studies in the 7-day period after each vaccination in both age groups were myalgia, headache and fatigue (observation range across vaccinations for the pooled 7.5µg Fluad-H5N1 safety database: myalgia 18%-27% for adults below 60 years, and 8%-17% for adults above 60 years; headache 11%-18% for adults below 60 years, 0-11% for adults above 60 years; fatigue 11%-17% for adults below 60 years, and 0-7% for adults above 60 years; Table 29). Fever was rarely reported and no more than 1% of subjects in the pooled 7.5µg Fluad-H5N1 database reported this reaction in any vaccine group across vaccinations. Most of the systemic reactions were mild or moderate in severity, had onsets close to the time of vaccination and were mostly transient in duration.

Table 28: Percentages of Subjects Reporting Solicited Local Severe/>50mm) Reactions Within 7 days of Each Vaccination

	Non-elderly Adults (18-60 years)							Elderly (>60 years)						
	Pooled 7.5 µg Fluad-H5N1 [a]			V87P13				Pooled 7.5 µg Fluad-H5N1 [a]			V87P13			
				Fluad-H5N1		Fluad					Fluad-H5N1		Fluad	
Reaction	1st N=2841	2nd N=2784	3rd N=87	1st N=2605	2nd N=2554	1st N=655	2nd N=638	1st N=301	2nd N=298	3rd N=38	1st N=214	2nd N=212	1st N=54	2nd N=53
Ecchymosis (>50mm)	6% (0)	4% (<1%)	1% (0)	6% (0)	4% (<1%)	8% (0)	6% (<1%)	5% (0)	4% (0)	0	6% (0)	5% (0)	4% (0)	11% (0)
Erythema (>50mm)	16% (<1%)	16% (<1%)	9% (0)	17% (<1%)	17% (<1%)	23% (1%)	20% (1%)	12% (0)	8% (0)	3% (0)	15% (0)	10% (0)	19% (0)	13% (2%)
Induration (>50mm)	15% (<1%)	13% (<1%)	14% (0)	14% (<1%)	13% (<1%)	21% (2%)	16% (1%)	7% (<1%)	3% (0)	5% (0)	9% (<1%)	2% (0)	7% (0)	15% (2%)
Pain	51% (1%)	38% (1%)	43% (5%)	51% (1%)	38% (<1%)	61% (2%)	45% (0)	27% (0)	18% (<1%)	8% (0)	30% (0)	22% (<1%)	24% (0)	30% (0)
Swelling (>50mm)	10% (<1%)	9% (<1%)	7% (0)	11% (<1%)	9% (<1%)	18% (1%)	15% (2%)	6% (<1%)	3% (0)	3% (0)	7% (<1%)	3% (0)	9% (0)	2% (0)

Studies V87P1, V87P2, V87P3, V87P13: the second vaccination was administered three weeks after the first; when third vaccination was administered (V87P1 and V87P2) it was a booster vaccine administered six months after the second primary course vaccination.

Table 29: Percentages of Subjects Reporting Solicited Systemic (Severe) Reactions Within 7 days of Each Vaccination

	Non-elderly adults (18-60 years)							Elderly (>60 years)						
	Pooled 7.5 µg Fluad-H5N1[a]			V87P13				Pooled 7.5 µg Fluad-H5N1[a]			V87P13			
				Fluad-H5N1		Fluad					Fluad-H5N1		Fluad	
Reaction	1st N=2841	2nd N=2783	3rd N=87	1st N=2606	2nd N=2555	1st N=656	2nd N=639	1st N=301	2nd N=298	3rd N=38	1st N=214	2nd N=212	1st N=54	2nd N=53
Arthralgia	5% (<1%)	4% (<1%)	10% (3%)	4% (<1%)	4% (<1%)	9% (<1%)	5% (0)	4% (<1%)	4% (<1%)	3% (0)	3% (0)	5% (<1%)	4% (0)	6% (0)
Chills	8% (<1%)	7% (<1%)	9% (2%)	8% (<1%)	7% (<1%)	14% (1%)	8% (<1%)	8% (<1%)	6% (<1%)	3% (0)	9% (0)	8% (<1%)	11% (0)	9% (0)
Fatigue	17% (<1%)	13% (1%)	11% (2%)	17% (1%)	14% (1%)	24% (2%)	13% (1%)	7% (1%)	6% (<1%)	0	8% (<1%)	8% (<1%)	9% (0)	8% (2%)
Fever[b]	N=2840 1% (0)	N=2780 <1%(0)	0	1% (0)	<1% (0)	2% (<1%)	<1% (0)	0	<1% (0)	0	0	<1% (0)	0	2% (0)
Headache	18% (1%)	14% (1%)	11% (0)	18% (1%)	14% (1%)	23% (2%)	12% (<1%)	11% (1%)	8% (0)	0	12% (1%)	10% (0)	13% (0)	6% (0)
Malaise	9% (<1%)	7% (<1%)	6% (2%)	9% (1%)	6% (1%)	17% (1%)	7% (<1%)	6% (<1%)	5% (<1%)	0	7% (0)	6% (<1%)	6% (0)	6% (2%)
Myalgia	27% (<1%)	18% (1%)	22% (5%)	26% (<1%)	19% (<1%)	37% (2%)	21% (0)	17% (0)	11% (<1%)	8% (0)	20% (0%)	13% (<1%)	17% (0)	19% (0)
Nausea	5% (<1%)	3% (<1%)	5% (0)	5% (<1%)	3% (<1%)	8% (<1%)	4% (<1%)	4% (0)	2% (0)	0	4% (0)	3% (0)	4% (0)	2% (2%)
Sweating	6% (<1%)	4% (<1%)	7% (0)	6% (<1%)	4% (<1%)	8% (1%)	3% (<1%)	3% (<1%)	2% (0)	0	3% (0)	2% (0)	2% (0)	2% (0)

[a]Studies V87P1, V87P2, V87P3, V87P13: the second vaccination was administered 3 weeks after the 1st; when third vaccination was administered (V87P1 and V87P2) it was a booster vaccine administered six months after the second primary course vaccination; [b]Fever: temperature ≥38°C, severe fever: >40°C.

Unsolicited adverse events

In all studies with Fluad-H5N1, all unsolicited AEs were collected for three weeks after each vaccination. Additionally, SAEs and AEs leading to withdrawal or necessitating a physician visit were collected throughout the entire study duration. The six months safety follow up for Study V87P13 is still ongoing.

For both adults below and above 60 years, the percentages of subjects reporting both all and possibly/probably related AEs in the three weeks following each vaccination decreased with the number of vaccinations, with no possibly or probably related AE after the third vaccination. Most AEs were unrelated to the vaccine and were common illnesses expected within these populations. Most possibly or probably related AEs reported in the three weeks following vaccination were known side effects of influenza vaccination or solicited reactions continuing past the 7-day observation period. In both age groups, each of the most commonly reported possibly/probably related AEs was reported by no more than 1% of subjects in the pooled Fluad-H5N1 database (Table 30). Across vaccinations no more than 1% of subjects of either age group reported severe possibly/probably related AEs as these were mostly mild or moderate in severity. As expected, only very few AEs were reported in the follow up period, since only AEs necessitating a physician's visit or leading to premature withdrawal or SAEs were recorded.

In Study V87P13, after both primary course vaccinations the percentages of subjects with any AEs regardless of vaccine relatedness were similar (adults below 60 years) or lower (adults above 60 years) for Fluad-H5N1 compared with seasonal Fluad. For possibly or probably related AEs there was a general tendency in both age groups for slightly lower frequencies in the Fluad-H5N1 group than in the seasonal Fluad group (Table 30). Most possibly or probably related AEs were known side effects of influenza vaccination or solicited reactions continuing past the 7-day observation period. Each of the most commonly reported possibly/probably related AE by preferred term was reported by no more than 1% of subjects in each vaccine group for adults below 60 years and by no more than 1% of Fluad-H5N1 and by 2%-4% of seasonal Fluad subjects for adults above 60

years (Table 30). The percentages of subjects reporting AEs in the pooled seasonal Fluad database were consistent with those observed in the V87P13 study. The most commonly reported possibly/probably related AEs in the pooled seasonal Fluad database were overall similar to those observed in adults below and above 60 years receiving Fluad in Study V87P13 and were mostly known vaccine reactions continuing past the observation period.

Table 30: Most Frequently Reported At Least Possibly Related Unsolicited AE by Preferred Term Within 3 Weeks of Vaccination

Non-elderly Adults (18-60 years)					
Pooled 7.5µg Fluad-H5N1[b]		V87P13			
		Fluad-H5N1		Fluad	
1st N=3011	2nd N=2953	1st N=2607	2nd N=2559	1st N=657	2nd N=639
Nasopharyngitis, 1% Oropharyngeal pain, 1% Upper respiratory tract infection, 1% Headache, 1% Inj. site haemorrhage, 1% Rhinitis, 1% Fatigue, 1%	Oropharyngeal pain, 1% Fatigue, 1% Upper respiratory tract infection, 1%	Fatigue 1% Inj. site haemorrhage, 1% Nasopharyngitis, 1% Rhinitis, 1% Upper respiratory tract infection, 1% Headache, 1% Oropharyngeal pain, 1%	Fatigue, 1% Nasopharyngitis, 1% Upper respiratory tract infection, 1% Oropharyngeal pain, 1%	Lymphadenopathy, 1% Fatigue, 1% Inj. site haemorrhage, 1% Nasopharyngitis, 2% Arthralgia, 1% Oropharyngeal pain, 1%	Inj. site haemorrhage, 1% Rhinitis, 1%
Elderly (>60 years)					
Pooled 7.5µg Fluad-H5N1[d]		V87P13			
		[d,e]Fluad-H5N1		Fluad	
1st N=387	2nd N=378	1st N=214	2nd N=212	1st N=54	2nd N=53
Myalgia, 1% Arthralgia, 1% Ecchymosis, 1% Inj. site haemorrhage, 1% Oropharyngeal pain, 1% Upper respiratory tract infection, 1%	Inj. site haemorrhage, 1% Cough, 1% Oropharyngeal pain, 1%	Inj. site haemorrhage, 1% Upper respiratory tract infection, 1% Oropharyngeal pain, 1% Ecchymosis, 1%	Inj. site haemorrhage, 1% Oropharyngeal pain, 1%	Abdominal pain upper, 2% Diarrhea, 2% Dyspepsia, 2% Inj. site erythema, 2% Inj. site haemorrhage, 2% Rhinitis, 2% Upper respiratory tract infection, 4% Headache, 2% Oropharyngeal pain, 2% Rhinorrea, 2% Urticaria, 2%	Diarrhea 2% Pneumonia, 2% Headache, 2% Tremor, 2% Insomnia, 2% Bronchial hyperreactivity, 2% Cough, 2% Ecchymosis, 2%

a.e., experienced by ≥1% of subjects; b:none reported for third vaccination, N=182; d:none reported for third vaccination, N=66; Inj. =injection

Safety Profile of Different Immunization Schedules (Study V87P12)

The impact of the time interval between the two primary course vaccinations on the safety profile of Fluad-H5N1 was evaluated in the Phase III Study V87P12 in which the two 7.5µg Fluad-H5N1 vaccinations were given to adults below 60 years of age either 1, 2, 3, or 6 weeks apart. The Fluad-H5N1 safety profile was not affected by the time interval between the two primary course vaccinations. As reported for all studies and in the pooled 7.5µg Fluad-H5N1 safety database, the most frequently reported solicited reactions regardless of the vaccine schedule were pain, fatigue, headache, myalgia and malaise. All reactions were mostly mild or moderate in severity and transient. The range for unsolicited AEs reported across the different vaccine schedule groups was consistent with that of the pooled Fluad-H5N1 safety database. Very few of these were judged as possibly related to vaccine administration. Overall, the safety profile of Fluad-H5N1 did not change when the two primary vaccinations were administered as close as one week apart.

Concomitant Administration of Fluad-H5N1 and Seasonal Influenza Vaccine (Study V101P1)

Fluad-H5N1 was administered either before or after Agrippal, or concomitantly with a subunit seasonal influenza vaccine as first vaccination followed by a second Fluad-H5N1 administration. Regardless of the timing of administration, reactogenicity of Fluad-H5N1 was consistent with that observed for the other studies and for the pooled safety database. When Fluad-H5N1 was administered concomitantly with Agrippal, overall reporting of solicited reactions did not increase. Solicited local reactions were more frequently reported for Fluad-H5N1 than for Agrippal (70% versus 41%). This difference was mostly

due to higher percentages of subjects reporting injection site pain (66% versus 41% section). Injection site pain was the only local reaction reported more frequently when Fluad-H5N1 and Agrippal were administered concomitantly but in different arms. Fatigue, headache and myalgia were the most frequently reported solicited systemic reactions after Fluad-H5N1 administration and similar percentages were observed in both groups.

Serious adverse events (SAEs), pregnancies and deaths

SAE

No SAEs or deaths were reported in the early studies with H5N3 strain. Overall, in the six studies with Fluad H5N1 in the adult population, 45 SAEs were reported in 35 adults below 60 years and 8 SAEs in 6 adults above 60 years of age. All SAEs were judged by the investigator as unrelated to the study vaccine except for two events in two adults below 60 years of age and three events in two adults above 60 years of age in the still ongoing Study V87P13. These were assessed as possibly or probably related to vaccination. One of these five SAEs, reported by an adult below 60 years of age, was experienced following vaccination with Fluad-H5N1 and consisted of an anaphylactic reaction minutes after vaccination. It was thought to be probably related to study vaccine.

In the historical Fluad safety database of approximately 14,000 subjects, between 1% and 7% of subjects reported SAEs after each vaccination. Only two of these SAEs (pancreatitis and cholangitis) reported by a 70 year old man were assessed as at least possibly related to vaccination by the investigator. Most of the SAEs were experienced by subjects aged ≥65 years and were accounted for by the underlying diseases in the ≥65 years of age population of Study V7P3 5 (safety population, N=9204).

Death

Only one subject died (a 77 year old man in Study V87P1) following an acute myocardial infarction during the six months follow up period after the booster vaccination. The death was considered unrelated to the study vaccination. Overall, 146 deaths, all non-related to vaccine administration, occurred in the historical population of ≥65 years of approximately 13,000 subjects. This number is consistent with a population of this age and of individuals with underlying chronic diseases. Of these deaths, only 13 were possibly caused by influenza or its complications.

Pregnancies

A total of 13 pregnancies were reported after administration of Fluad-H5N1in Studies V87P1, V87P12, V87P13 and V101P1. For nine of these the pregnancy outcome is unknown. However, one was live born delivery and another woman had a therapeutic abortion. Two women (in Studies V87P13 and V101P1) had spontaneous abortions.

Laboratory findings

No laboratory evaluations were assessed for the evaluation of safety in the Fluad-H5N1 Studies V87P1, V87P2, V87P3, V87P12 and V87P13. Only in Study V101P1 were laboratory data regarding safety evaluated (vaccine groups: T/P-A = tetravalent vaccine and placebo on Day 1 and Fluad-H5N1 on Day 22; A/P-T = Fluad-H5N1 and placebo on Day 1 and tetravalent on Day 22; A/S-A = Fluad-H5N1 and nonadjuvanted seasonal influenza vaccine on Day 1 and Fluad-H5N1 on Day 22). Blood was collected for the first 150 subjects immediately prior to vaccination on Day 1 and on Day 43 for serum chemistry and hematology clinical laboratory testing.

In the analysis of serum chemistry at baseline, a total of 10 subjects demonstrated lab values in the upper level of normal range. Elevated alanine transaminase (ALT) was reported in four subjects (two subjects in T/P-A group, one subject each in A/P-T and A/S-

A groups). Elevated aspartate aminotransferase (AST) was reported in three subjects (two in the T/P-A group and one in the A/S-A group). Fewer than 4% of subjects demonstrated elevated levels in the rest of the parameters. A total of 23 subjects demonstrated lab values in the upper level of normal range in the analysis of the final blood draw. Elevated ALT was reported in five subjects (three in the A/P-T group and two in the A/S-A group). Elevated potassium was reported by five subjects (three in the A/S-A group and one each in the T/P-A and A/P-T groups). Elevated sodium was reported by nine subjects (one in the T/P-A group, five in the A/S-A group and three in the A/P-T group). In the analysis of hematology at baseline, a total of seven subjects demonstrated values in the upper level of normal range. Five subjects demonstrated values in the upper level of normal range at the final analysis.

Immunological events

The data on these are documented under section 'Adverse events of special interest'.

Safety related to drug-drug interactions and other interactions

Concomitant administration with seasonal-Fluad and Agrippal is discussed above as per Study V87P13 and V101P1.

Discontinuation due to adverse events

Very few enrolled subjects did not complete the study. Withdrawals were equally distributed among recipients of the different dosages. The most common reason for discontinuation was consent withdrawal. Across all vaccination groups, the frequency of AEs leading to withdrawal was below 1%.

Post-marketing experience (Tables 31 and 32)

There is no post-marketing information for Fluad-H5N1. There is however a large amount of post-marketing data for the MF59 adjuvanted, trivalent subunit inactivated influenza vaccine, Fluad, which were submitted to provide information regarding the use of theMF59 adjuvant and a similar vaccine composition. This analysis includes all safety reports that were received from 1997 (launch) until April 30 2008. The case reports for products which are licensed and distributed by other partners including Chiromas, Gripguard, Influpozzi Adjuvato, Adiugrip, Addigrip and Prodigrip were also included in this analysis. Overall, there have been 574 safety reports. Since market launch in 1997 approximately 40 million doses of Fluad have been sold, thus approximately 1.4 cases per 100,000 sold doses were reported. The majority of these are in the elderly.

Table 31: Summary of most frequently affected System Organ Class (reporting ratio>10% in any group)

	Fluad		Agrippal
SOC	All cases	Italian cases	Italian cases
	N=574	N=211	N=214
Gastrointestinal disorder	62 (11%)	29 (14%)	25 (12%)
General Disorders & Administration Site Conditions	376 (66%)	120 (57%)	111 (52%)
Musculo., Connective Tissue & Bone Disorders	111 (19%)	40 (19%)	36 (17%)
Nervous System Disorders	136 (24%)	56 (27%)	53 (25%)
Respiratory, Thoracic & Mediastinal Disorders	64 (11%)	22 (10%)	23 (11%)
Skin & Subcutaneous Tissue Disorders	84 (15%)	33 (16%)	56 (26%)
Surgical & Medical Procedures	167 (29%)	60 (28%)	-

N: total number of cases

Table 32: Summary of most frequently reported adverse experiences by MedDRA preferred term (reporting ratio>=4% in any group)

	Fluad		Agrippal
MedDRA Preferred Term	**All cases**	**Italian cases**	**Italian cases**
	N=574	**N=211**	**N=214**
Off Label Use	166 (29%)	60 (28%)	-
Injection Site Erythema	113 (20%)	29 (14%)	18 (8%)
Pyrexia	99 (17%)	31 (15%)	27 (13%)
Injection Site Swelling	89 (16%)	5 (2%)	12 (6%)
Injection Site Pain	58 (10%)	19 (9%)	19 (9%)
Injection Site Pruritus	51 (9%)	1 (<1%)	5 (2%)
Fatigue	34 (6%)	3 (1%)	3 (1%)
Hyperpyrexia	34 (6%)	28 (13%)	12 (6%)
Pain in Extremity	34 (6%)	3 (1%)	6 (3%)
Asthenia	33 (6%)	10 (5%)	12 (6%)
Headache	33 (6%)	9 (4%)	6 (3%)
Chills	32 (6%)	5 (2%)	4 (2%)
Arthralgia	30 (5%)	17 (8%)	16 (7%)
Myalgia	29 (5%)	16 (8%)	9 (4%)
Malaise	28 (5%)	7 (3%)	9 (4%)
Dyspnea	24 (4%)	10 (5%)	6 (3%)
Injection Site Reaction	23 (4%)	10 (5%)	5 (2%)
Nausea	21 (4%)	7 (3%)	8 (4%)
Injection Site Edema	16 (3%)	15 (7%)	14 (7%)
Urticaria	20 (3%)	10 (5%)	21 (10%)
Hypotension	10 (2%)	8 (4%)	6 (3%)
Paresthesia	14 (2%)	8 (4%)	16 (7%)
Vomiting	14 (2%)	8 (4%)	5 (2%)
Pruritus	11 (2%)	2 (1%)	12 (6%)

N: total number of cases

Adverse experiences of special interest

Fatal cases, life-threatening cases, cases leading to permanent disability and pregnancy cases were considered AEs of special interest. Frequencies of the other cases of special interest are provided in Table 33. About 30% of the cases were considered serious. Fluad and Agrippal (Italian cases) showed comparable reporting ratios for the AEs of special interest.

Table 33: Summary of AEs of special interest

	Fluad		Agrippal
AEs of special interest	**All cases**	**Italian cases**	**Italian cases**
	N=574	**N=211**	**N=214**
Serious, n (%)	172 (30%)	68 (32%)	72 (34%)
Fatal, n (%)	23 (4%)	6 (3%)	4 (2%)
Life-threatening, n (%)	29 (5%)	3 (1%)	5 (2%)
Disabling, n (%)	10 (2%)	4 (2%)	4 (2%)

N: number of cases

Seasonal influenza vaccination is a prophylactic measure in high-risk groups with underlying chronic diseases. Hence it is not surprising that deaths/life-threatening events or events with outcome "permanent disability" occur in close temporal association with vaccination against influenza. At present there is no evidence for a specific vaccine-related effect in the case reports presented in the tables below. No clusters have been reported.

Autoimmune disease

Aggregate analysis

Both the Fluad and the Agrippal adverse reaction cases were screened for potential autoimmune disease (Table 34). The overall reporting ratios for autoimmune diseases did not differ relevantly between the vaccine groups.

Table 34: Summary of cases with suspected autoimmune disease Fluad Agrippal

		Fluad		Agrippal
	Suspected autoimmune disease	All cases	Italian cases	Italian cases
<18 years		N=7	N=5	N=31
	Any autoimmune disease, n (%)	-	-	1(3%)
	GBS, n (%)	-	-	-
Adults 18 – 64		N=166	N=64	N=64
	Any autoimmune disease, n (%)	12 (7%)	5 (8%)	4 (6%)
	GBS, n (%)	6 (4%)	3 (5%)	3 (5%)
Adults ≥65		N=336	N=135	N=116
	Any autoimmune disease, n (%)	21 (6%)	10 (7%)	14 (12%)
	GBS, n (%)	10 (3%)	5 (4%)	5 (4%)
Unknown		N=65	N=7	N=3
	Any autoimmune disease, n (%)	2 (3%)	-	-
	GBS, n (%)	1 (2%)	-	-
Total		N=574	N=211	N=214
	Any autoimmune disease, n (%)	35 (6%)	15 (7%)	19 (9%)
	GBS, n (%)	17 (3%)	8 (4%)	8 (4%)

N: total number of cases

Review of case reports after the use of Fluad (worldwide cases) revealed 17 possible case reports. When Novartis reviewed the clinical signs and treatments to apply the Brighton Collaboration draft case definitions on Guillain-Barré-Syndrome (GBS), occurring within 5-6 weeks of vaccination, three cases are consistent with the draft case definition[27]. In three cases, the available information is inconsistent with diagnosis of GBS. In all other cases information available is insufficient to assess cases. This analysis had the incidence of GBS at 0.025 per 100,000 doses, much less than the spontaneous incidence of GBS, which is approximately 0.4 to 4 cases per 100,000 persons per year[28]. Similarly, the reporting rate of GBS cases following immunization with Agrippal is lower than the spontaneous incidence rate of GBS (Table 35). The analysis consisted of calculation of

[27] GBS Brighton Collaboration Case Definition (Level 1):-Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs with or without involvement of respiratory or cranial nerve-innervated muscles. -Decreased or absent deep tendon reflexes at least in affected limbs. -Monophasic illness pattern, with weakness nadir reached between 12 hours and 28 days, followed by clinical plateau and subsequent improvement, or death. -Cerebrospinal fluid (CSF) with a total white cell count <50 cells/mm^3 (with or without CSF protein elevation above laboratory normal value). -Electrophysiologic (NCS/EMG) findings consistent with GBS.

[28] Hughes RAC, Rees JH. Clinical and Epidemiologic Features of Guillain-Barre´ Syndrome. *The Journal of Infectious Diseases* 1997;176(Suppl 2):S92–8.
Magira EE, Papaioakim M, Nachamkin I, Asbury AK, Li CY, Ho TW, Griffin JW, McKhan GM, Monos DS. Differential Distribution of HLADQ beta/DR beta Epitopes in the Two Forms of Guillain-Barre´ Syndrome, Acute Motor Axonal Neuropathy and Acute Inflammatory Demyelinating Polyneuropathy (AIDP): Identification of DQ beta Epitopes Associated with Susceptibility to and Protection from AIDP1. *J Immunol* 2003, 170: 3074–3080.

overall and event specific reporting ratios, of comparison of reporting ratios for Fluad to the ones for a nonadjuvanted influenza vaccine and in depth analyses of cases of special interest with adjudication of key cases performed by internal experts. The cumulative safety analysis demonstrates that the current safety profile of an MF59-containing influenza vaccine is comparable with that of the nonadjuvanted conventional subunit influenza vaccine containing the same antigens. Analysis of key events such as GBS or autoimmune diseases did not reveal a signal or risk above that of a conventional subunit influenza vaccine.

Table 35: Signal detection for autoimmune diseases - Fluad vs. Agrippal – Italian cases only

	Disease	Fluad (N=211)	Agrippal (N=214)	Proportional reporting ratio (FLUAD vs. Agrippal)	Continuity corrected Chi Square	Signal according to screened proportional ratio method
Primary analysis (confirmed cases)	Any autoimmune disease	2	6	0.338	1.10388	No
	GBS	-	2	-	0.48830	No
Sensitivity analysis #1	Any autoimmune disease	8	10	0.811	0.04421	No
	GBS	4	5	0.811	0.00000	No
Sensitivity analysis #2 (all cases)	Any autoimmune disease	15	19	0.801	0.24354	No
	GBS	8	8	1.014	0.00000	No

Confirmed cases: confirmed cases with onset between Day 5 and Day 42 p.v.; sensitivity analysis #1: confirmed cases or cases with insufficient data with onset between Day 5 and Day 42 p.v.

The screened proportional reporting ratio method[29] was applied to detect signals of disproportionate reporting of any autoimmune disease and especially GBS cases comparing the Italian cases of Fluad (N=13.2 million doses) with Agrippal (N=14.9 million doses; Table 36). Different sensitivity analyses were performed based on the certainty of diagnosis (confirmed, not confirmed, insufficient data) and on temporal relationship (onset of symptoms within/not within 5 to 42 days post-vaccination). In all analyses, proportional reporting ratios for Fluad to Agrippal were close to or below 1 and the continuity-corrected Chi-square statistic was far below 4; thus no evidence for an increased risk of autoimmune diseases (especially GBS) following Fluad vaccination was observed when compared with Agrippal.

[29] Banks D, Woo EJ, Burwen DR, Perucci P, Braun MM and Ball R. Comparing data mining methods on the VAERS database. *Pharmacoepidemiol Drug Saf.* 2005 Sep;14(9):601-9.

Table 36: Signal Detection for Autoimmune Diseases. Seasonal Fluad versus Agrippal. Italian Cases Only

Disease (Confirmed Cases)	Fluad (N=211)	Agrippal (N=214)	Proportional reporting ratio (Fluad vs. Agrippal)	Continuity corrected Chi Square	Signal according to screened proportional ratio method
Any autoimmune disease	2	6	0.338	1.10388	No
GBS	-	2	-	0.48830	No

The cumulative safety analysis confirms that the current safety profile of the MF59-containing influenza vaccine (Fluad) is comparable with that of the nonadjuvanted influenza vaccine (Agrippal) containing the same amount of antigens. Analysis of key events, such as GBS, did not reveal a signal or risk above those following exposure to a conventional subunit influenza vaccine.

Product information (PI) with respect to safety

The product information is thorough and reflects the safety findings from the clinical trials accurately, including the different rates of all the relevant adverse events.

Under section *'Special warnings and precautions for use'* it should also list, as a special precaution, previous allergic reaction or hypersensitivity to any influenza vaccine. In this case, consultation with a doctor should be obtained before administering.

Evaluator's overall conclusions on clinical safety

The adverse effects related to this vaccine are similar to those associated with the currently licensed influenza vaccines. The AEs (solicited and non-solicited, local and systemic and serious) all appear to have similar incidence in the pivotal Study V87P13, the pooled analysis and the historical comparison to the collected data for Fluad.

In the relevant EMEA guideline it recommends that safety in the target group be examined and this has been done (adults both younger and older than 65). It also recommends that a cohort of at least 1000, preferably 3000 be vaccinated with the vaccine. In Study V87P13 alone, the vaccine was given to 2826 assessable subjects, so this has also been done adequately. This in conjunction with the rest of the studies and the historical database based on Fluad is a very good basis for assumptions about the safety issues with this vaccine.

Essentially no new or unexpected adverse reactions, either closely linked or long term were detected in the Fluad H5N1 studies, nor have they been detected in the post-marketing data associated with the parent vaccine, Fluad. Other specific safety conclusions in the presented data are:

- The incidence and type of both local and systemic reactions following vaccination with Fluad-H5N1 were similar to those found in association with administration with Fluad, the licensed parent vaccine.
- There were fewer reactions to Fluad-H5N1 and seasonal Fluad after the second vaccination compared with the first. A third booster could also be safety administered six months or more after primary course vaccination.
- The safety profile was not impacted by the (shorter) time interval between the two primary vaccinations (Study V87P12).

- The safety profile of Fluad-H5N1 was maintained when concomitantly administered with a seasonal subunit influenza vaccine (Study V101P1).

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "List of Questions" to the sponsor is generated.

On 13 June 2008, Novartis Vaccines and Diagnostics notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application for a marketing authorisation for Aflunov for the prophylaxis of H5N1 avian influenza in adults and the elderly, because of concerns the CHMP had about the way the main clinical study was carried out. An inspection of some of the study sites showed that the study had not been conducted in compliance with 'good clinical practice' (GCP). Which study did this concern relate to?

Study V87P4 is included in the submitted data and one table, but is not referred to in the clinical summary or overview or included in the list of the six main efficacy and safety trials, or the pooled data for efficacy or safety. What is the reason for this? Is it excluded because of the issues referred to in the question above?

Clinical Summary and Conclusions

Protective efficacy of the vaccine cannot be established in clinical trials. Hence the submission relies on satisfying the CHMP immunogenicity criteria, which it does, particularly in the large pivotal Phase III immunogenicity study - V87P13. Cross-protection of the vaccine against other related strains is probable, but immunogenicity does not meet the CHMP criteria as consistently. Concern that influenza vaccines could induce disease enhancement (as reported with inactivated adjuvanted measles and respiratory syncytial virus vaccines in the 1960's) has not been investigated but has not been detected in any of the safety data from either this vaccine, or the historical post-marketing safety data from Fluad. Although with typical influenza the elderly are at most risk, all ages can be affected by pandemic strains and the studies have looked at adults as well as the elderly (with a number of paediatric studies ongoing) and found good efficacy in all groups, with an acceptable safety profile. The seroprotection and seroconversional criterion used are in accordance with the relevant EMEA guideline and appear adequate. Some additional markers of immunological function and memory (CMI and production of pro-inflammatory cytokines) have also been investigated and look favourable. The dose finding studies and adjuvant/no adjuvant studies support the use of the 7.5µg dose of Fluad-H5N1 with adjuvant. Although the adjuvanted form has a slightly increased rate of local side effects, the increased efficacy still favours its use.

Benefit risk assessment

Benefits

- This vaccine appears to have good efficacy and an acceptable safety profile, similar to its parent vaccine, seasonal Fluad.
- It complies with the EMEA requirements for an acceptable influenza vaccine.
- It may well provide inter-pandemic immunity which, in the event of a pandemic, would translate into a pre-existing immune, or partially immune, population.

Risks

The major immediate risks are those associated with side effects, as detailed below. There is also the risk that this strain of influenza is not the next pandemic strain and that this vaccine does not provide appropriate protection.

Safety specification

There are side effects associated with the administration of this vaccine. Most are local and minor. Serious adverse events are rare, but do occur (such as anaphylaxis).

Balance

The development strategy for this vaccine makes sense. Firstly a good, or a likely, pandemic candidate strain was identified. Secondly, the aim of vaccination was protective immunity in the community, with some strain heterogeneity and also longevity and memory. There is however no guarantee that this strategy will work to protect a community from pandemic influenza. The flaws may lie in the strain picked or that there is no gold standard for measuring a protective immune response, as well as no definitive knowledge about longevity and immunity of this response.

Benefits and Risks Conclusions

It is not possible to determine the likelihood of an H5N1 pandemic. Therefore the benefit of a prepandemic vaccine is not easy to predict. Current thoughts, based on modeling, suggest a huge benefit in having low antigen, adjuvanted vaccines such as this on hand for a future pandemic.

Vaccination is expected to be the most important component of an effective and efficient strategy to prevent an outbreak of pandemic influenza or to mitigate the worst consequences of pandemic disease. In preparing for this, the production of a vaccine against a potential influenza pandemic viral strain may be useful at three stages:

• during the inter-pandemic period to reduce the chance of an emergence of a reassortant pandemic strain by vaccinating those at high risk of both avian and human virus infection,

• priming during prepandemic stages (WHO Phases 3 to 5) to reduce mortality against a closely matched pandemic strain,

• to permit early vaccination at the start of a pandemic (WHO Phase 6) when the pandemic vaccine is not yet available.

Along with the recently identified A/H1N1 strain of "swine influenza", the A/H5N1 avian strain is currently considered a most likely source of a new pandemic strain.

Conclusions

The MF59 adjuvanted 7.5µg Fluad-H5N1 vaccine schedule presented in this application fulfills the characteristic features for a prepandemic influenza vaccine:

- It is able to induce satisfactory antibody responses in healthy adults below and above 60 years of age, with low HA antigen quantities thus allowing for "antigen sparing",
- Is able to induce H5-specific CD4 T-cell memory already after the first and memory B-cells after the second primary course vaccinations.
- Subjects primed with an MF59 adjuvanted vaccine containing the heterologous strain A/H5N3 were successfully boosted 6-8 years later with an antigenically distinct avian strain (A/H5N1) supporting a "prime-heterologous booster" strategy.
- Antibody responses are boosted by subsequent vaccinations, thus confirming that primary vaccination with prepandemic formulated vaccines with an H5 viral strain primes naïve populations.
- Priming with a prepandemic vaccine may increase the immune response to a vaccine mismatched strain.

- In adults below and above 60 years of age, an overall reactogenicity profile similar to that of authorized seasonal Fluad was noted, which is considered to be safe and comparable to conventional, nonadjuvanted inter-pandemic influenza vaccines based on the over 40 million doses already administered[13].
- Most of the reactions are mild, of short duration and qualitatively similar to those induced by conventional influenza vaccines. The adjuvant is associated with a slightly higher frequency of local reactions (mostly mild pain) compared with conventional, nonadjuvanted influenza vaccines
- Prepandemic Fluad-H5N1 has a safety profile consistent with that of other H5N1 adjuvant[30], subvirion[31], or whole virion adjuvanted[32] vaccines.
- It can be safely administered concomitantly with a seasonal influenza vaccine without affecting either vaccine's immunogenicity.
- It can be safely administered according to different vaccination schedules without reducing immunogenicity. This flexible schedule allows for a greater adaptability to different pandemics scenarios.

Conditions for registration

Although the clinical evaluator supported the registration of this product on the basis of the efficacy and safety data as provided in the current Australian submission and assuming the above questions are adequately addressed, this is not strategy for determining how this vaccine should be used in Australia. A utilisation strategy will depend on many factors well beyond the scope of this report, including modelling and financial considerations. Similarly in Europe, this vaccine is currently being recommended for registration, but to date the clinical evaluator did not know of a plan as to how it will be used.

In accordance with the EMEA guideline, it is imperative Novartis makes a number of post-approval commitments such as the following:

- Plans should be in place to assess antibody persistence, cross-reactivity to new circulating strains and responses to booster doses in cohorts of vaccinees from each age and risk group for which an indication has been granted.
- There should be plans to assess exposure of any vaccinees to circulating avian influenza strains so that breakthrough cases can be identified and studied. This will enable some 'real time' assessment of efficacy.
- Whenever possible, further information should be collected from observational studies to expand the safety and the immunogenicity database.
- In the event of a declared pandemic, attempts should be made to estimate the effectiveness of prior vaccination.

It also needs to submit a Risk Management Plan (RMP) to provide safety information for each major population group that has not been studied or has only been studied to a limited degree in the pre-authorisation phase.

[30] Bresson JL, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: Phase I randomised trial. *Lancet* 2006 May 20;367(9523):1657-64.
[31] Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. *N Engl J Med* 2006 Mar 30;354(13):1343-51.
[32] Lin J, Zhang J, Dong X, Fang H, Chen J, Su N, et al. Safety and immunogenicity of an inactivated adjuvanted whole-virion influenza A (H5N1) vaccine: a Phase I randomized controlled trial. *Lancet* 2006 Sep 16;368(9540):991-7.

As for seasonal influenza vaccines, it might be necessary to change the influenza strain included in the avian influenza vaccine, especially if antibodies raised against the vaccine strain show no or negligible cross reactivity against circulating viruses. In order to incorporate a new strain into the avian influenza vaccine, the marketing authorisation holder will have to submit all manufacturing and quality data related to the new strain. A clinical study should be conducted to demonstrate that immune responses to the new strain in the vaccine are at least as good as were those to the initial strain in the licensed product.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

The RMP submitted by the sponsor is dated 17 November 2009. The RMP has not been produced in accordance with the relevant guideline[33] which provides recommendations on how routine and additional pharmacovigilance activities should be conducted during the pandemic period, as well as the preparatory activities to be undertaken in the pre-pandemic period to achieve a high level of preparedness. The content of the pharmacovigilance plan should be updated to incorporate the recommended activities. The absence of this information in the RMP made it difficult to assess. A summary of the RMP submitted by the sponsor is shown in Table 37.

[33] "CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine" (EMEA/359381/2009)

Table 37: RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks: • None	• Not applicable	None
Important potential risks: • Neuritis • Convulsion • Anaphylaxis • Encephalitis • Vasculitis • Guillain-Barré Syndrome • Demyelination • Bell's palsy • Vaccination failure • Interaction with regular childhood vaccines • Medication errors	Enhanced pharmacovigilance Evaluated at weekly, cross-functional Medical case review meetings	SPC, section 4.8, Post-marketing surveillance: No post-marketing surveillance data are available following Aflunov administration. From Post-marketing surveillance with seasonal trivalent vaccines in all age groups and with the MF59adjuvanted seasonal trivalent vaccines with the similar composition of Aflunov (surface antigen, inactivated, adjuvanted with MF59C.1), licensed for use in elderly subjects above 65 years of age, the following adverse events have been reported: Uncommon: Generalised skin reactions including pruritus, urticaria or non-specific rash. Rare: Neuralgia, paraesthesia, convulsions, transient thrombocytopenia. Allergic reactions, in rare cases leading to shock, have been reported. Very rare: Vasculitis with transient renal involvement and exudative erythema multiforme. Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome
Important missing	All pregnancies will be	SPC, section 4.6:

Table 37 continued on next page.

information: • Safety during pregnancy or lactation	followed-up and risk to mother and child assessed	No data have been generated in pregnant women with Aflunov or with any other vaccine that contains the MF59C.1 adjuvant. In animals, there were no adverse effects on female fertility, pregnancy, embryofetal development, parturition or post-natal development (see section 5.3). Healthcare providers need to assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendation. There are no data regarding the use of Aflunov during lactation. The potential benefits to the mother and risks to the infant should be considered before administering Aflunov during lactation..
• Use in children (limited data from clinical trials available)	Adverse effects will be followed-up and risk assessed Ongoing and planned clinical trials	SPC, section 4.2: There is limited experience in children between 6 months and 17 years of age (see section 4.8 and 5.1).
• Vaccination effectiveness	Not applicable	SPC; section 4.2: Aflunov has been evaluated in adults aged 18-60 years and elderly over 60 years following a 0, 21 day schedule. There is limited experience in children between 6 months and 17 years of age.
• Safety in subjects with underlying diseases or immunocompromised patients	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 specialized settings like dialysis or	SPC, section 4.4.: Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient

Routine pharmacovigilance practices involve the following activities:

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

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

The following are specific Office of Product Review recommendations relating to the current RMP:

- The sponsor is required to incorporate the *CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine* into the pharmacovigilance plan. Specifically, the sponsor should:
    - describe specific activities performed during a pandemic in relation to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions;
    - describe the format and content of the simplified Periodic Safety Update Report (PSUR);
    - describe specific activities performed for signal detection;
    - undertake the post-authorisation safety study; the protocol of the prospective cohort study should be presented in Annex 5 of the Risk Management Plan
    - undertake additional activities related to the:
        - detection of cases of Guillain-Barré syndrome
        - the monitoring of immunocompromised subjects exposed to the vaccine
        - the monitoring of pregnant women exposed to the vaccine.
- The sponsor should include the details of Studies V87P14 and V87P18 being undertaken as part of the Paediatric Investigational Plan in the RMP.
- The sponsor should provide comment on the post authorisation experience with other seasonal trivalent vaccines and with M59-adjuvanted seasonal vaccines with similar composition to Aflunov.
- The sponsor should update Section 1.5.2 of the RMP to include the details of the important potential risks. Specifically, for each important identified potential risk the following information should be provided: identified risk, seriousness/outcomes, severity and nature of risk, frequency (with 95% CI), background incidence/prevalence, risk groups or risk factors, potential mechanisms, preventability, potential public health impact of safety concern, evidence source and regulatory action taken.
- The discussion of the epidemiology of potential risks should be extended to include all important potential risks.
- The draft Product Information and Consumer Medicine Information documents should be revised, having regard to comments made in this evaluation report.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

Prepandemic Influenza Vaccine H5N1 is essentially manufactured using the same antigen manufacturing process and with the same adjuvant as Fluad seasonal influenza vaccine. The seed virus (NIBRG-14) is prepared via reverse genetics because H5N1 is pathogenic in chick embryos. Quality data are considered acceptable.

Nonclinical

Nonclinical pharmacology studies with Aflunov were performed in relevant animal species (challenge and serology studies in mice and ferrets, serology studies in rabbits). They

showed vaccine-associated induction of antibodies that recognise and neutralise a homologous (A/Vietnam/1194/2004) and a heterologous (A/turkey/Turkey/1/2005) virus strain.

Viral challenge studies in ferrets and mice showed protection against death and disease caused by a highly lethal homologous virus strain and (in mice) and a highly lethal heterologous strain, Indonesia/5/05 H5N1. Efficacy was enhanced by the addition of adjuvant; there was no evidence for enhanced viral disease due to the adjuvanted vaccine. The nature of the immune response in mice was predominately of the Th2 type, with most vaccine-stimulated CD4+ T cells producing IL-5 (single positive) > IL-5 and TNF-α and IL-2 (triple positive) > TNF-α and IL-2 (double positive).

Toxicity studies in rabbits and dogs with MF59 adjuvant alone or formulated with a variety of vaccine antigens showed no systemic toxicity. Local reactions were generally greater with the adjuvant than nonadjuvanted equivalents, but they were reversible and not catastrophic.

A reproductive toxicity study with Aflunov has been conducted in rabbits immunised three times prior to mating and twice during gestation, in which serology studies confirmed the presence of antigen-specific antibodies in dams, fetuses and pups (on postnatal day 29). There were no effects on pregnancy, dams or offspring in this study.

The adjuvant MF59 was assessed in reproductive toxicity, genotoxicity and sensitisation potential studies, all of which were unremarkable.

The nonclinical development program for Aflunov has adequately addressed nonclinical investigations recommended in regulatory guidelines for pre-pandemic vaccines. There are no objections on the basis of nonclinical data to the registration of Aflunov H5N1 vaccine containing 7.5 µg HA per dose in adults.

Clinical

Clinical development of this prepandemic influenza vaccine H5N1 has been based on the relevant EMEA guideline[34] and TGA has adopted this guideline.

Six clinical studies with egg derived, inactivated, surface antigen H5N1 (A/Vietnam/1194 2004 like strain) influenza vaccine adjuvanted with MF59 and two earlier studies of a H5N3 vaccine were conducted.

Overall, three serological assays were performed (HI, SRH and MN) for all studies using vaccines formulated with H5 viral antigens. HI and SRH are standard assays. SRH has been the preferred assay for demonstrating antibodies to H5N1 viruses in Novartis influenza vaccine studies because it gives more pronounced results. One direct comparison of results from the standard HI using turkey erythrocytes and MN assays demonstrated that the MN assay was substantially more sensitive in detecting human antibodies to H5N1 virus in infected individuals. In order to improve the sensitivity of the HI assay for pandemic strains, a modified HI using horse erythrocytes was developed and is used in the H5N1 studies. MN assay can sensitively and specifically detect H5N1 antibodies in patients with H5N1 influenza.

EMEA guidance, given there are no established immunological correlates of protection for pandemic infections, recommends that all criteria currently used during development of

[34] Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (CHMP/VWP/263499/2008) http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003872.pdf.

seasonal vaccines should be met, based on HI or SRH assays as stated in CPMP/BWP/214/96.

There are no established correlates of protection for neutralizing antibodies against infections caused by influenza A/H5N1 viruses. MN assay results for H5N1 studies are reported in terms of percentages of subjects achieving >20, >40 or >80 serum antibody titer cutoff values and percentages of subjects achieving 4-fold increases in MN titers from pre- to post-vaccination.

Immunogenicity analyses were carried out for heterologous strain A/H5N1/Turkey//05 (Clade 2.2) and A/H5N1Indonesia/05 (Clade 2.1) in addition to A/H5N1/Vietnam /1194/04 strain (Clade 1), in several studies.

Two clinical studies were conducted with H5N3 strain (V7P37 & V7P37E1) to investigate antigen dose, regimen and adjuvant. Both adjuvanted and nonadjuvanted vaccine formulations containing 7.5, 15 and 30 µg of H5N3 were evaluated in these studies.

A further six studies (V87P1, V87P2, V87P3, V87P12, V87P13, V101P1) investigated the immunogenicity and safety of two injections of MF59-adjuvanted H5N1 vaccine (A/Vietnam/1194 2004 like strain). V87P1 and V87P2 were Phase II clinical studies which evaluated MF59 adjuvanted formulations with 7.5 and 15 µg of H5N1 antigen. V87P1 involved a total of 486 subjects stratified for age 18-60 years and greater than 60 years. Demographic and baseline characteristics were balanced between treatment groups and low proportions of subjects had detectable baseline titres assessed by HI, SRH or MN assays. Comparison of dose finding studies (H5N3 & H1N1) found no significant advantage was achieved with the 15 and 30 µg adjuvanted doses when compared with 7.5 µg adjuvanted. Geometric mean ratios (GMRs) were similar after two vaccinations with the 7.5 and 15µg doses (Fluad-H5N3 and Fluad-H5N1). The adjuvanted formulations always achieved better immunogenicity results than the nonadjuvanted vaccines. The 7.5µg MF59 adjuvanted vaccine was selected for further clinical study.

V87P3 is intended to evaluate priming with a prepandemic vaccine in advance of a pandemic caused by a different strain. A total of 58 adult subjects were enrolled, 12 of whom had received MF59-adjuvanted H5N3 vaccine and 12 of whom had received nonadjuvanted H5N3 vaccine (in Studies V7P37 & V7P37E1) 6 to 8 years previously. Two injections of 7.5 µg H5N1 MF59 adjuvanted vaccine were given three weeks apart.

All CHMP criteria were met by H5N1 adjuvanted vaccine three weeks after first injection (Day 22) and second injection (Day 43) in the group primed with MF59-adjuvanted H5N3 vaccine. In the group primed with H5N3 nonadjuvanted vaccine, after the first injection (Day 22) two CHMP criteria were met by HI assay and all three criteria were met by SRH assay. After the second injection (Day 43) two criteria were met by HI assay and all three criteria were met by SRH assay. In the unprimed group after the first injection (Day 22) no criteria were met by HI assay and two criteria were met by SRH assay. After the second injection (Day 43) two criteria were met by HI assay and all three criteria were met by SRH assay.

For MN assay, $\geq$ 4 fold increase in MN titre three weeks after second injection (Day 43) was reported for all subjects in the group primed with MF59-adjuvanted H5N3 vaccine, compared to 83% in the group primed with H5N3 nonadjuvanted vaccine and 55% in the unprimed group.

V87P12 was a Phase III, open label study to evaluate two injections of 7.5 µg H5N1 MF59-adjuvanted vaccine using four vaccination schedules (1, 2, 3 and 6 weeks apart) in a total of 240 adult subjects 18-60 years of age. All three CPMP criteria were met by HI and SRH assays for all four schedules except for seroprotection by HI in the Day 1 and 8 group. In

the analysis of cross-reactivity, the immune response to influenza A/H5N1/turkey/Turkey/05 (NIBRG23) Clade 2.2 was lower than to the homologous strain The study concluded MF59-adjuvanted vaccine containing 7.5 µg of the A/ H5N1/Vietnam/1194/04 influenza antigen provides high immune response in adult subjects and two doses can be administered at 2, 3, or 6 weeks apart interchangeably.

V87P13, the pivotal Phase III study is a randomized, observer blinded, controlled study conducted in Germany and Finland in 2008/2009. A total of 3647 adults were enrolled stratified for ages 18-60 years and > 60 years. Study treatment was a single injection of unadjuvanted, inactivated, trivalent seasonal influenza vaccine (Agrippal) followed by two injections of MF59-adjuvanted vaccine containing 7.5 µg of the A/ H5N1/Vietnam/1194/04 influenza antigen administered three weeks apart, or placebo followed by two injections of MF59-adjuvanted, trivalent, seasonal influenza vaccine (Fluad) containing 15 µg of A/H1N1; A/H3N2 and B antigens administered 3 weeks apart. Demographics and baseline characteristics were balanced between treatment groups within both age stratifications. When assessed by HI, those in the Agrippal H5N1 group met two out of three of the CHMP criteria after the second vaccination (Day 64) in both the adult (N=195) and elderly (N=203) groups. When assessed by SRH, all criteria (3/3) were met in both age groups. For the MN assay, 65% of non-elderly adults and 55% of elderly adults in the Agrippal_H5N1 group exhibited at least a 4-fold increase from baseline in MN titers after two doses of MF59-adjuvantedH5N1 compared to 0% (non-elderly) and 10% (elderly) in the Placebo Fluad group. In the analysis of cross-reactivity, the immune response to influenza A/H5N1/Turkey/Turkey/05 (NIBRG23) Clade 2.2 was lower than to the homologous strain (A/H5N1/Vietnam/1194/04) across vaccine groups.

V101P1 is a Phase II study which assessed 7.5 µg H5N1 MF59-adjuvanted vaccine given before or after a dose of tetravalent MF59 adjuvanted seasonal TIV+H5N1 vaccine, or concomitant administration of 7.5 µg H5N1 MF59-adjuvanted vaccine and nonadjuvanted seasonal TIV vaccine. A total of 601 subjects were enrolled and divided into age groups 18-60 years and > 60 years. The primary immunogenicity objective was to show that SRH antibody titers against the A/Vietnam/1194/2004 (H5N1) elicited by the three different immunization schedules were equivalent at Visit 3. Equivalence was statistically confirmed by inspections of the CIs of all three pairwise ratios of the GMAs (SRH assay).

In all three vaccine groups the H5N1 strain met all the three defined CHMP criteria as assessed by the SRH assay. The H5N1 strain met two of the three CHMP criteria in the T/P-A and A/P-T groups and all three CHMP criteria in the A/S-A group as assessed by the HI assay. When the serological criteria as assessed by HI assay for the inter-pandemic strains (H1N1, H3N2 and B) were analyzed, all three vaccine groups met all CHMP criteria. The study concluded that there is no impact on the immune response to the H5N1 strain or the seasonal strains when a seasonal influenza vaccine is administered with the MF59-adjuvanted-H5N1 vaccine.

Percentages of seroprotection at baseline were generally low and balanced between the groups in non-elderly adults. For non-elderly adults, the seronegative population is nearly identical with the total population and the results by all three assays differed only marginally, if at all, between seronegative subjects and the total population. For the elderly, seropositive titers were seen in about 20% of the populations at baseline. In Study V87P1 all CHMP criteria were met by SRH in the elderly seronegative group.

The seroprotection criterion measured by HI was met in six of the ten study groups across the two age groups. As measured by SRH, all criteria were met for all groups with the exception of the 15 µg group (n=13) in Study V87P2. The percentage of subjects achieving MN titers >40 and 4-fold increase of titers were generally high. For elderly subjects in Studies V87P1 and V87P13, the MN results were lower than for the other tests.

Immunogenicity to Heterologous strains.

Cross-reactivity of pathogenic avian influenza H5N1 viruses

Immunogenicity analyses were carried out for heterologous strains in Studies V87P1, V87P3, V87P12 and V87P13. In each of these studies, immunogenicity against the A/H5N1/turkey/Turkey/05 (NIBRG23; Clade 2.2) strain was tested by all three assays.

For the A/H5N1/turkey/Turkey (NIBRG23; Clade 2.2) strain at least one CHMP criterion was met in all four studies when measured by SRH. In Study V87P1 the CHMP criterion for seroprotection by SRH was met by both the 7.5 and 15µg groups in the non-elderly population and in the 15 µg group of elderly subjects. In Study V87P3 all three CHMP criteria by SRH were met versus the heterologous Turkey strain. In Study V87P12 (non-elderly subjects) both the criteria for GMR and seroconversion were met in the SRH analysis and seroprotection was nearly met (at 65%). In Study V87P13 only the seroconversion criterion by SRH was met. For the Turkey strain, the percentage of subjects with titers >40 as measured by MN ranged from 10% in Study V87P3 to 39% in Study V87P13.

Cross-reactivity to Heterologous Strains Following Homologous Booster

In Study V87P1, a subset of subjects were given a third dose of MF59-H5N1 (homologous booster) six months after receiving a second vaccination and assessed for immune response to heterologous A/H5N1/turkey/Turkey/05 NIBRG23; Clade 2.2 strain by HI, SRH and MN. Only the CHMP criterion of seroprotection could be evaluated because baseline values were not obtained. As measured by HI, the seroprotection criterion was close but not met in either the 7.5 or 15µg groups in the non-elderly population. In the elderly population, the CHMP criterion for seroprotection was met by both the 7.5 and 15 µg groups. As measured by SRH, the seroprotection criterion was met by both the 7.5 and 15 µg groups in both age groups.

The heterologous A/H5N1/Indonesia (Clade 2.1) strain was also assessed in V87P1 by HI and MN, though not by SRH. The criterion of seroprotection was not met in any group as measured by HI

Cross-reactivity to Heterologous Strains Following Heterologous Booster

Cell mediated immunity (CMI) was investigated in Studies V87P2 and V87P3. One injection of MF59 adjuvanted H5N1 induced an increase in the frequency of H5-specific CD4 T-cells with a memory TH0/TH1 phenotype, with high survival potential *in vivo* and the ability to expand and differentiate into effector cells upon infection. Two vaccinations were needed to expand long lasting H5N1-specific memory B-cells that further expanded upon boosting either with a vaccine formulated with the same pandemic strain or with a novel pandemic antigen

Persistence of Efficacy and/or Tolerance Effects and Antibody Response to a Booster Dose of MF5 adjuvanted-H5N1

Data on antibody persistence six months after primary vaccination for Fluad-H5N1 are provided by Studies V87P1, V87P2 and V87P3 and for further six months after a third dose in Study V87P1. Across all studies, and in both adults and elderly subjects, antibody titers six months after a two dose primary vaccination as assessed by HI, SRH and MN, decreased substantially compared although above baseline titers. GMRs Day 202 /Day 42 were generally in the range 0.15 to 0.4 by HI or SRH. The decrease in GMTs was similar for the 7.5 and 15 µg MF59-H5N1 groups in Studies V87P1 and V87P2.

A third (booster) vaccination of MF59-H5N1 was administered six months after the primary vaccination in Studies V87P1 and V87P2. Increase of titers was seen after this

booster vaccination in both age groups. CHMP criteria for GMRs and for seroprotection were met in nearly all study groups with SRH and HI. A high percentage of subjects (92-100% across Fluad-H5N1 groups and age groups) achieved MN-titers >40.

Similar to the pattern observed six months after primary vaccination, in Studies V87P1 and V87P2 in both adults and elderly subjects, antibody titers obtained six months after booster vaccination as assessed by HI, SRH and MN decreased compared to titers obtained approximately three weeks after booster. Overall these results show that although antibody titers decreased over six months, they quickly increased to high levels after a booster shot suggesting there was immunological memory.

Clinical Safety

The safety population for MF59-adjuvanted vaccine containing 7.5 µg or 15 µg of the A/ H5N1/Vietnam/1194/04 influenza antigen was a total of 3001 adults 60 years and below and 387 adults above 60 years, of whom 2842 adults and 301 elderly received the 7.5 µg dose.

In all studies safety was monitored by dairy cards for seven days after vaccination. Unsolicited AE were collected up to three weeks after each vaccination. Serious AE, AE lading to withdrawal or necessitating physician visit were collected through the duration of studies. Laboratory data were collected in a subset of 150 subjects from Study V101P1. The pivotal safety Study V87P13 was designed to allow comparison between MF59 adjuvanted H5N1 and MF59 adjuvanted seasonal vaccine.

Solicited adverse event experience in early studies showed that MF59 –H5N3 and MF59-H5N1 had a higher rate of mild solicited local reactions than nonadjuvanted formulations. Local reactions reported in V87P13 were similar or lower in the MF59-H5N1 group compared to seasonal–Fluad. Across all studies using 7.5µg Fluad-H5N1, the most frequently reported solicited local reaction in the 7-day observation period after each vaccination for in both age groups was local pain (range across vaccinations for the pooled 7.5µg Fluad-H5N1 safety database: 38%-51% for adults below 60 years, 8%-27% for adults above 60 years), induration and erythema (both with lower rates than pain). Most of these reactions were mild- moderate in severity, with onset close to the time of vaccination and were mostly transient and with severe systemic reactions terms reported in 1% or less in pooled analysis..

The most frequently reported solicited systemic reactions across studies in the 7-day period after each vaccination in both age groups were myalgia, headache and fatigue (observation range across vaccinations for the pooled 7.5µg Fluad-H5N1 safety database: myalgia 18%-27% for adults below 60 years, 8%-17% for adults above 60 years; headache 11%-18% for adults below 60 years, 0-11% for adults above 60 years; fatigue 11%-17% for adults below 60 years, 0-7% for adults above 60 years). Fever was rarely reported and no more than 1% of subjects in the pooled 7.5µg MF59-H5N1 database reported this reaction in any vaccine group across vaccinations. The frequency of solicited systemic reactions was lower in the MF59-H5N1 group compared to seasonal–Fluad, especially after first dose (Study V87P13). Most of the systemic reactions were mild or moderate in severity, had onsets close to the time of vaccination and were mostly transient and with severe systemic reactions terms reported in 1% or less in pooled analysis.

For both adults below and above 60 years, the percentages of subjects reporting both all and possibly/probably related AEs in the three weeks following each vaccination were low and decreased with the number of vaccinations. Most possibly or probably related AEs reported in the three weeks following vaccination were known side effects of influenza vaccination or solicited reactions continuing past the 7-day observation period. In both

age groups, each of the most commonly reported possibly/probably related AEs was reported by no more than 1% of subjects in the pooled MF59-H5N1 group.

Very few AEs were reported in the follow up period, since only AEs necessitating a physician's visit or leading to premature withdrawal or SAEs were recorded. Across all vaccination groups, the frequency of AEs leading to withdrawal was below 1%.

Overall, in the six studies with Fluad H5N1 in the adult population, 45 SAEs were reported in 35 adults below 60 years and 8 SAEs in 6 adults above 60 years. All SAEs were judged by the investigator as unrelated to the study vaccine except two in two adults below 60 years and three in two adults above 60 years in the still ongoing Study V87P13 which were assessed as possibly or probably related to vaccination. One of these five SAEs, consisted of an anaphylactic reaction minutes after vaccination with MF59-H5N1, thought to be probably related to study vaccine. A total of 13 pregnancies were reported after MF59-H5N1. The pregnancy outcome is unknown for nine of these but one woman had a normal delivery, one had a therapeutic abortion and two had spontaneous abortions. One subject died, a 77 year old man in Study V87P1, following an acute myocardial infarction six months into follow up period, after the booster vaccination. The death was considered unrelated to the study vaccination.

The impact of the time interval between the two primary course vaccinations on the safety profile of Fluad-H5N1 assessed in V87P12 and administration of MF59-H5N1 concomitantly with seasonal influenza vaccine in V101P1, were concluded not to change the safety profile. Data are also presented on administration of booster dose which supported safety of a third dose administered six months after the primary series.

The clinical evaluation report (CER) has considered the safety profile of clinical studies of MF59 adjuvanted seasonal influenza vaccine (Fluad), with a pooled safety database of approximately 14,000 adults for whom SAE were reported in between 1% and 7% of subjects after vaccination. Only 2 SAE were assessed as possibly related to vaccination. Post-marketing experience of Fluad is based on more than 40 million doses distributed from 1997 to 2008 with 574 safety reports. Of these, 30% were serious and 4% fatal. The sponsor comments that there is no evidence of a specific vaccine related adverse effect in case reports and no clusters have been reported. Screened proportional reporting did not suggest a signal for autoimmune disease or GBS comparing post-marketing case reports from Italy for Fluad (n=13.2 million doses) and Agrippal (n=14.9 million doses).

CER Summary and Benefit and Risk Conclusion

The MF59 adjuvanted 7.5µg H5N1 (A/Vietnam/1194/2004 like strain) vaccine schedule presented in this application fulfills the characteristic features for a prepandemic influenza vaccine (summarised under *Benefits and Risk Conclusions* above).

Risk Management Plan (RMP)

The sponsor has provided a RMP updated in August 2010 which put into place measures undertaken with Focetria during the 2009 H1N1 pandemic[35]. The RMP evaluator requests submission of planned clinical studies in children. The RMP evaluation recommends further amendment to Section 1.5.2 of the RMP to provide further details on important potential risks.

[35] Focetria: Influenza A(H1N1) monovalent vaccine formulated with MF59 adjuvant marketed by Novartis.

Risk-Benefit Analysis

Delegate's Considerations

The rationale for the production of a vaccine against a potential influenza pandemic viral strain during the inter-pandemic period put forward by the sponsor is that it may:

Permit early vaccination at the start of a pandemic (World Health Organization [WHO] phase 6) when the pandemic vaccine is not yet available;

Be used to prime during prepandemic stages (WHO Phases 3 to 5) to reduce mortality against a closely matched pandemic strain;

Reduce the chance of emergence of a reassortment pandemic strain by vaccinating those (veterinarians, poultry workers, operators involved in the manufacturing of vaccines with pandemic-like strains, laboratory workers) at high risk of both avian and human virus infection.

The CER supports registration of this product as a prepandemic vaccine, but also comments that a utilisation strategy would depend on factors outside the scope of this report.

The relationship of the vaccine A/Vietnam/1194 2004 (H5N1) like strain to any H5N1 pandemic strain is uncertain. Cross protection to H5N1 Clade 2.1 and Clade 2.2 viruses was assessed but antibody responses to heterologous virus were lower and comprehensive assays were not undertaken.

All three serological assays to homologous virus show a significant increase in antibody titers after two injections administered three weeks apart and all CHMP immunogenicity criteria are met when using the SRH assay (with the exception of the 15 μg group [n=13] in Study V87P2). The closer agreement of GMR, seroprotection and seroconversion rates between SRH and MN than between HI and SRH or MN, support reports of others that HI assay is not sensitive in measurement of antibodies to H5 pandemic strains. The percentage of subjects achieving MN titers >40 and 4-fold increase of titers were generally high. The weighting of the CER to results based on SRH and MN assays is accepted by the Delegate. The nonclinical viral challenge studies also support efficacy of this vaccine in appropriate animal models against disease caused by lethal homologous virus and heterologous virus strains.

The CER has noted that Novartis withdrew a marketing authorization application to EMA for Aflunov in June 2008, because of GCP concerns regarding the main study site. The 2008 withdrawal assessment report identifies that GCP concerns related to Study V87P4 which was not included in the listed efficacy and safety studies supporting the application to TGA.

The submitted draft product information refers to a clinical trial conducted with a H5N1 vaccine combined with MF59 adjuvant in children from six months to 17 years of age. This study was not included in the CER or RMP evaluation. The Sponsor in the Pre Advisory Committee for Prescription Medicines (ACPM) response should identify whether the vaccine studied corresponds to that proposed for registration and if so the availability of a clinical study report.

Safety of this vaccine in the adult and elderly populations studied appeared acceptable compared to the registered MF59 adjuvanted seasonal influenza vaccine, Fluad. Safety data are incomplete for the six months follow-up in Study V87P13 and the sponsor should comment in the Pre-ACPM response on the availability of a subsequent study report or addendum. The clinical trial and post-marketing experience with MF59 adjuvanted Fluad also support safety.

The Delegate considered that this application provided adequate support for registration of this vaccine in line with EMA guideline[36]. TGA has not previously registered a prepandemic influenza vaccine.

Delegate's Proposed Action

The Delegate proposed to register Prepandemic Influenza Vaccine , H5N1 (surface antigen, inactivated, adjuvanted) with trade names Aflunov Prepandemic Influenza Vaccine H5N1(surface antigen, inactivated, adjuvanted) 0.5 mL pre-filled syringe and Prepandemic Influenza vaccine, H5N1(surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 0.5 mL pre-filled syringe, which contains 7.5 µg influenza virus haemagglutinin of A/Vietnam/1194/2004 (H5N1) like strain per 0.5 mL dose. The indications are for

> *" Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine containing A/Vietnam/1194/2004 (H5N1) like strain (see Clinical Trials). (Aflunov/Novartis Vaccines and Diagnostics). Prepandemic influenza vaccine H5N1 should be used in accordance with official guidances".*

The advice of ACPM is requested.

Response from Sponsor

Nonclinical Evaluation:

Novartis accepts the evaluator's recommendation for approval of the product. The amendments requested by the toxicological evaluator to the Product Information (PI) document have been accepted and an updated PI is included in this submission.

Clinical Evaluation:

Novartis accepts the evaluator's conclusion that there is sufficient evidence in the data presented in the dossier to support the dosage, adjuvanted form of 7.5 µg and schedule chosen for this application.

Novartis accepts the evaluator's conclusion that the development and testing of Aflunov has been conducted in accordance with the relevant EMA (European Medicine Agency) guidelines and in turn supports efficacy against H5N1.

Novartis also accepts the evaluator's conclusion that the adverse effect profile for Aflunov is similar to currently licensed influenza vaccines and no new or unexpected adverse reactions, either closely linked or long-term were detected in the clinical studies, nor have they been detected in the post-marketing data associated with the parent vaccine – Fluad.

Risk Management Plan (RMP):

a. The clinical evaluator had requested submission of planned clinical studies in children.

In the initial Australian submission, Novartis had provided the report for clinical Study V87P6, which was conducted in children (A Phase II, Randomized, Controlled, Observer-blind, Single-center Study to Evaluate the Immunogenicity, Safety and Tolerability of Two Doses of Fluad-H5N1 Influenza Vaccine in Subjects aged six months to 17 years). Data from this study is reflected in the updated PI and are in turn aligned with the EU SmPC.

[36] "Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (CHMP/VWP/263499/2008) http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003872.pdf

Novartis also provided details of proposed the clinical studies in children. Novartis would like to highlight that the timeline for the paediatric plan is under discussion with the EMA Paediatric Committee (PDCO) as Novartis had suggested postponement of studies due to issues with recruitment following the 2009 H1NI pandemic.

b. The clinical evaluator recommends further amendment to section 1.5.2 of the RMP to provide further details on important potential risks. Novartis had updated this section of the RMP in August 2010 and wit as in turn submitted based on EU recommendations including etiological adjudication using Brighton Collaboration, when available. Novartis are in the process of updating this section of the RMP and is expecting to release the next version at the end January 2011. In the interim, Novartis provided a line listing of important identified and potential risks (including newly identified) with full narrative.

Delegate's Overview:

Novartis accept the Delegate's recommendation for approval of Aflunov for the nominated indications. The Delegate's recommendations for amendments to the PI have been considered and appropriate amendments have been made.

Question (a). The submitted draft PI refers to a clinical trial conducted with a H5N1 vaccine combined with MF59 adjuvant in children from six months to 17 years of age. This study was not included in the CER or RMP evaluation. The sponsor in pre-ACPM response should identify whether the vaccine studied corresponds to that proposed registration and if so the availability of the clinical study report.

(Answer) Novartis confirmed that Study V87P6 was included in the original dossier (Section 5.3.5.4 of Module 5) and cited in the RMP. Relevant data from this study is reflected in the draft PI and wording in turn is aligned with the approved EU SmPC. Further copies of this report are available upon request.

Question (b). Safety data are incomplete for the six months follow-up in Study V87P13 and the sponsor should comment in the Pre-ACPM response on availability of the subsequent study report or addendum.

(Answer) The V87P13 addendum report, dated 20 April 2010, was provided to the TGA on 16 June 2010. The updated PI reflects this report.

Product Information (PI):

Novartis have considered changes recommended to the PI by the non-clinical and clinical evaluators and the Delegate and made corresponding amendments.

Changes relating to updates to the RMP and non-clinical reports (August and September 2010 respectively) have also been included, with particular reference to non-clinical data, pregnant women and children.

Conclusion (Delegate's proposed action):

Novartis have accepted the recommendations for approval of each of the quality, nonclinical and clinical evaluators and provided responses to specific questions raised by the clinical evaluator and the Delegate.

A minor amendment to the nominated indications is proposed with reference to official recommendations instead of official guidances. The nominated indications now read:

> *"Active immunisation against A/Vietnam/1194 2004 (H5N1) like strain (NIBRG-14) subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strain (see Clinical Trials). Aflunov should be used in accordance with official recommendations."*

Advisory Committee Considerations

ACPM recommends approval of the submission from Novartis Vaccines and Diagnostics Pty Ltd to register a new chemical entity, prepandemic influenza vaccine, H5N1 (surface antigen, inactivated, adjuvanted) [Aflunov and Novartis Vaccines and Diagnostics prepandemic influenza vaccine, H5N1 (surface antigen, inactivated, adjuvanted)] injections 7.5 µg per 0.5 mL for the indication:

Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see Clinical Trials). (Aflunov and Novartis Vaccines and Diagnostics prepandemic influenza vaccine, H5N1 (surface antigen, inactivated, adjuvanted) prepandemic influenza vaccine H5N1 should be used in accordance with official guidelines.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) included in the pre-ACPM advice were considered acceptable.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of approve the registration of Aflunov(r) Prepandemic Influenza Vaccine, H5N1 (surface antigen, inactivated, adjuvanted) 0.5mL pre-filled syringe and Prepandemic Influenza Vaccine H5N1 (surface antigen, inactivated, adjuvanted) Novartis Vaccines and Diagnostics 0.5mL pre-filled syringe, indicated for:

> *Active immunisation against A/Vietnam/1194 2004 (H5N1) like strain (NIBRG-14) subtype of Influenza A virus.*
>
> *This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see Clinical Trials).*
>
> *Aflunov/Prepandemic Influenza Vaccine H5N1 should be used in accordance with official recommendations*.

The following special conditions of registration apply to this product:

1. For each batch of vaccine imported into Australia the sponsor should supply the following documentation:
    i. Complete protocols for the manufacture of final product including all steps in production.
    ii. Number of doses to be released in Australia with accompanying expiry dates for vaccine and diluent.
    iii. Evidence of product stability at release including results of the accelerated thermostability testing.
    iv. Evidence of maintenance of satisfactory transport conditions to Australia.
    v. Twenty doses of product (including diluent) with the Australian approved labels, PI and packaging for initial shipment, 3 doses for subsequent shipments of the same batch.
    vi. Any other reagents required to undertake testing as specified by the Office of Laboratories and Scientific Services (OLSS).

Distribution of each batch is conditional upon fulfilment of these conditions and approval of release by the OLSS.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION
Aflunov® Prepandemic influenza vaccine, H5N1

NAME OF THE MEDICINE

Aflunov® suspension for injection in pre-filled syringe.
Prepandemic influenza vaccine, H5N1 (surface antigen, inactivated, adjuvanted).

Pharmacotherapeutic group: Influenza vaccines, ATC code: JO7BB02.

DESCRIPTION

Aflunov® is a prepandemic influenza vaccine, monovalent H5N1, surface antigen, inactivated, adjuvanted with MF59C.1. Aflunov® contains 7.5 micrograms (expressed in microgram haemagglutinin) per 0.5 ml dose of A/Vietnam/1194/2004 (H5N1) - like strain used (NIBRG-14).
The vaccine is propagated in eggs

Each 0.5 ml of the adjuvant MF59C.1 contains:

squalene	9.75 milligrams
polysorbate 80	1.175 milligrams
sorbitan trioleate	1.175 milligrams

A complete list of excipients is provided in Presentation and Storage Conditions.The pharmaceutical form is a suspension (milky-white liquid) for injection in pre-filled syringe.

CLINICAL TRIALS

The clinical experience with Aflunov® following a two-dose administration is described below.

A clinical trial was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 486 healthy adult volunteers. Two doses of vaccine containing H5N1 (A/Vietnam/1194/2004) (7.5 µg haemagglutinin [HA]/dose) with MF59C.1 adjuvant were administered three weeks apart.

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in the adults measured by SRH were as follows:

Anti-HA antibody	**21 days after 1st dose**	**21 days after 2nd dose**
Seroprotection rate	41% (95% CI: 33-49)	86% (95% CI: 79-91)
Seroconversion rate	39% (95% CI: 31-47)	85% (95% CI: 79-91)
Seroconversion factor	2.42 (2.02-2.89)	7.85 (6.7-9.2)

* measured by SRH assay ≥ 25 mm^2

** geometric mean ratios of SRH

The seroprotection rate*, seroconversion rate* and the seroconversion factor** for anti-HA antibody to H5N1 A/Vietnam/1194/2004 in subjects aged over 60 measured by SRH were as follows:

Anti-HA antibody	**21 days after 1st dose**	**21 days after 2nd dose**
Seroprotection rate	53% (95% CI: 42-64)	81% (95% CI: 71-89)
Seroconversion rate	45% (95% CI: 34-56)	71% (95% CI: 60-81)
Seroconversion factor	2.85 (2.22-3.66)	5.02 (3.91-6.45)

* measured by SRH assay ≥ 25 mm^2
** geometric mean ratios of SRH

Limited data on the persistence of antibodies in elderly immunised with Aflunov® showed that up to 50% of the subjects were seroprotected at six months.

Cross-reactivity of highly pathogenic variants of A/Vietnam/1194/2004 (H5N1) in subjects 18 years and above.
Immunogenicity analyses were carried out for influenza A/H5N1/turkey/Turkey/05 (NIBRG23; clade 2.2) with HI, SRH, and MN and for influenza A/H5N1/Indonesia (clade 2.1) with HI and MN, on sera collected 3 weeks after the second vaccination (day 43) and 3 weeks after the booster vaccination (day 223).

In the adult and elderly age groups, responses to the heterologous strains increased after booster vaccination with Aflunov® by these assays, although antibody responses were lower than those observed to homologous strains.

Supportive Studies
Study on different vaccination schedules:
A prospective, randomized, open-label phase II study evaluated in 240 subjects aged 18 to 60 years 4 different vaccination schedules, with the second dose given after 1, 2, 3 and 6 weeks after the first immunization.

After 3 weeks from the 2nd vaccination all the vaccine schedule groups achieved the SRH CHMP criteria for seasonal vaccines. The magnitude of immune response was lower in the group who received the 2nd dose 1 week later and higher in the groups with longer interval schedules.

Studies in children
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. Two doses of Aflunov® were administered three weeks apart and a third dose 12 months following the first dose. .

After 3 weeks from the 2nd vaccination all the different age groups (6-35 month, 3-8 years and 9-17 years) achieved all the three CHMP criteria measured with SRH and HI assays. In this trial no vaccine related SAEs were observed. Results are provided in the table below. In the absence of CHMP immunogenicity criteria for use of pandemic influenza vaccines in children, the CHMP immunogenicity criteria used to evaluate seasonal influenza vaccines in adults were applied to the serological data obtained after vaccination of children.

Serological results from the Paediatric Clinical Trial

		Toddlers (6-<36 months)	Children (3-<9 years)	Adolescents (9-<18 years)
		N=134	**N=91**	**N=89**
HI	% SP (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
	GMR Day 43 to Day 1	129 (109-151)	117 (97-142)	67 (51-88)
	% SC (95% CI) Day 43	97% (92-99)	97% (91-99)	89% (80-94)
SRH		**N=133**	**N=91**	**N=90**
	% SP (95% CI) Day 43	100% (97-100)	100% (96-100)	100% (96-100)
	GMR (95% CI) Day 43 to Day 1	16 (14-18)	15 (13-17)	14 (12-16)
	% SC (95% CI) Day 43	98% (95-100)	100% (96-100)	99% (94-100)

Microneutralisation (MN) results against a A/Vietnam/1194/2004 indicate a seroprotection rate of 99% (95%CI: 94-100), a seroconversion rate ranging from 97% (95%CI: 91-99) to 99% (95%CI: 96-100) and a GMR ranging from 29 (95%CI: 25-35) to 50 (95%CI: 44-58).

INDICATIONS

Active immunisation against A/Vietnam/1194 2004 (H5N1) like strain (NIBRG-14) subtype of Influenza A virus.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strain (see Clinical Trials).

Aflunov® should be used in accordance with official recommendations.

CONTRAINDICATIONS

Anaphylactic hypersensitivity to the active substance, to any of the constituents and to eggs, chicken proteins, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB).

However, in a pandemic situation caused by the strain included in this vaccine, it may be appropriate to give this vaccine to individuals with a history of anaphylaxis as defined above, provided that facilities for resuscitation are immediately available in case of need.

PRECAUTIONS

Caution is needed when administrating this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues (eggs and chicken proteins, ovalbumin, kanamycin and neomycin sulphate, formaldehyde and cetyltrimethylammonium bromide (CTAB)).

Very limited data in subjects with co-morbidities, including immunocompromised subjects are available for this H5N1 vaccine.

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

Immunization shall be postponed in patients with febrile illness or acute infection.

The vaccine should under no circumstances be administered intravascularly or intradermally.

There are no data with Aflunov®using the subcutaneous route. Therefore, healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleedings.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

A protective immune response may not be elicited in all vaccinees (see Clinical Trials).

Some cross-protection was observed against related H5N1 virus variants in clinical trials (see Clinical Trials).

Since a second dose is recommended, it should be noted that there are no safety, immunogenicity or efficacy data to support interchangeability of Aflunov® with other H5N1 monovalent vaccines.

Paediatric Populations
Refer Clinical Trials.

Use in Pregnancy (Category B2)
In an embryofoetal and postnatal development study in which rabbits were intramuscularly injected with Aflunov® (15 μg HA antigen, ie twice the clinical dose)) 35, 21 and 7 days prior to mating and on gestation days 7 and 20, there were no significant toxicological effects in the dams, or their fetuses or kits. Anti-HA antibodies were detected in vaccine-treated females, their litters and pups.

Limited data was obtained during the course of clinical trials from pregnant women who received Aflunov® and H1N1v vaccines adjuvanted with MF59C.1.
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It is estimated that more than 90,000 women have been vaccinated during pregnancy with H1N1v vaccine Focetria which contains the same amount of adjuvant MF59C.1 as Aflunov®. However information on outcomes from these pregnancies is currently limited. Preliminary data from spontaneously reported events and ongoing post-marketing studies (pregnancy registry and prospective interventional study) do not suggest direct or indirect harmful effects on influenza vaccines adjuvanted with MF59 with respect to pregnancy, fertility, embryonic/foetal development, parturition, or post natal development.

Since Aflunov® is expected not to be used in an emergency situation, its administration during pregnancy might be deferred as a precautionary approach.

Healthcare providers need to assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations.

Use in Lactation
There are no data regarding the use of Aflunov® during lactation. The potential benefits to the mother and risks to the infant should be considered before administering Aflunov® during lactation.

In an embryofoetal and postnatal development study in rabbits, maternal treatment with Aflunov® prior to mating and during gestation had no effects on kit development, assessed to lactation day 29 (see also Use in Pregnancy).

Effects on Fertility
There were no effects on the mating performance or fertility of female rabbits in an embryofoetal and postnatal development study in which rabbits were intramuscularly injected with Aflunov® (15 μg HA antigen, 0.5 ml) 35, 21 and 7 days prior to mating and on gestation days 7 and 20 (see also Use in Pregnancy).

Carcinogenicity
No carcinogenicity studies have been conducted with Aflunov®.

Genotoxicity

No genotoxity studies have been conducted with Aflunov®. In standard genotoxicity tests. MF59 adjuvant was not mutagenic in *Salmonella typhimurium* or *E.coli* WP2*uvr*A, nor did it induce micronuclei in mouse bone marrow erythrocytes *in vivo.*

Interaction with other medicines

Data from a phase II, randomized, placebo-controlled, observer-blind, and multi-centre study in adults showed that combination of seasonal and pandemic antigens did not lead to any interference neither for seasonal strains nor for H5N1 strains. SRH antibody response against an homologous H5N1 Vietnam strain at day 43 reached all CHMP criteria for all 3 strains.

Co-administration was not associated with higher rates of local or systemic reactions compared to administration of Aflunov® alone.

Therefore the data indicate that Aflunov® may be co-administered with non-adjuvanted seasonal influenza vaccines.

There are no data on co-administration of Aflunov® with vaccines other than seasonal influenza vaccines.
If co-administration with another vaccine is considered, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

The immunological response may be diminished if the patient is undergoing immunosuppressant treatment.

Following influenza vaccination, false positive serology test results may be obtained by the ELISA method for antibody to human immunodeficiency virus-1 (HIV-1), hepatitis C virus and, especially, HTLV-1. In such cases, the Western Blot method is negative. These transitory false positive results may be due to IgM production in response to the vaccine.

Non-clinical data obtained with Aflunov® and with seasonal influenza vaccine containing MF59C.1 adjuvant reveal no special hazard for humans based on conventional studies of efficacy, repeated dose toxicity, and reproductive and developmental toxicity.

ADVERSE EFFECTS

Some of the undesirable effects mentioned in this section may affect the ability to drive or operate machinery.

Adverse reactions from clinical trials in 18 years old and above.

The incidence of adverse reactions has been evaluated in approximately six clinical trial with approximately 4,000 adults and elderly who have received formulations containing at least 7.5 microgram HA/MF59. There were 3678 subjects 18-60 years of age, 264 subjects 61-70 years of age, and 41 subjects greater than 70 years of age.

Consistent with the data observed by study for solicited reactions, there was a general trend towards decreased reports of local reactions after the second and booster vaccination compared with the first injection.

Irrespective of antigen dose, almost all systemic reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following.

The adverse reaction rates reported are listed according to the following frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

<u>*Nervous system disorders*</u>
Very common: headache
Rare: convulsions

<u>*Skin and subcutaneous tissue disorders*</u>
Common: sweating
Uncommon: urticaria
Rare: eye swelling

<u>*Musculoskeletal and Connective Tissue disorders*</u>
Very common: myalgia
Common: arthralgia

<u>*General disorders*</u>
Common: nausea

<u>General disorders and administration site conditions</u>
Very common: injection site swelling, injection site pain, injection site induration, injection site redness, fatigue
Common:injection site ecchymosis, fever, malaise, shivering
Uncommon: influenza like illness

Rare: anaphylaxis

The side effects usually disappeared within 1-2 days without treatment.

A comparative table is presented below showing adverse events for Aflunov and seasonal Fluad to an incidence of 1% based on study V87P13.

Summary of All Unsolicited Serious AEs by System Organ Class, Primary Period, Adults (18 ≤ age ≤ 60)

System Organ Class	Number (%) of Subjects with Adverse Events	
	All	
	TIV-Aflunov®	Adjuvanted Placebo Comparator
	N=2683	N=678
Any Serious Adverse Event	16(1)	4(1)
Cardiac Disorders	1(<1)	0
Ear & Labyrinth Disorders	1(<1)	0
Gastrointestinal Disorders	2(<1)	1(<1)
Hepato-Biliary Disorders	2(<1)	0
Immune System Disorders	1(<1)	0
Infections & Infestations	4(<1)	0
Neoplasm: Benign/Malignant(Including Cysts and Polyps)	2(<1)	0
Nervous System Disorders	1(<1)	2(<1)
Pregnancy: Puerperium & Perinatal Conditions	1(<1)	0
Psychiatric Disorders	2(<1)	0
Respiratory, Thoracic & Mediastinal Disorders	1(<1)	1(<1)

Summary of All Unsolicited Serious AEs by System Organ Class, Primary Period, Elderly (age > 60)

System Organ Class	Number (%) of Subjects with Adverse Events	
	All	
	TIV-Aflunov®	Adjuvanted Placebo Comparator
	N=219	N=56
Any Serious Adverse Event	2(1)	2(4)

Infections & Infestations	0	1(2)
Injury & Poisoning	0	1(2)
Renal & Urinary Disorders	1(<1)	0
Respiratory Thoracic & Mediastinal Disorders	0	1(2)
Surgical & Medical Procedures	1(<1)	0

Adverse reactions reported from other clinical studies list by organ class".

Percentage of Non-Elderly Adults Reporting All Unsolicited AEs by System Organ Class: Aflunov® and Historical Fluad® Pooled Data after First, and Second, Vaccination[ab]

	Primary Period[c]			
	Aflunov® (18-60 yrs)		Historical Fluad® (18-64yrs)	
Vaccinations	**1st**	**2nd**	**1st**	**2nd**
System Organ Class	**N=3011**	**N=2953**	**N=1351**	**N=155**
Any	**725 (24%)**	**573 (19%)**	**284 (21%)**	**36 (23%)**
Blood & Lymphatic System Disorders	5 (<1%)	1 (<1%)	9 (1%)	2 (<1%)
Cardiac Disorders	6 (<1%)	9 (<1%)	0	1 (1%)
Ear & Labyrinth Disorders	17 (1%)	12 (<1%)	3 (<1%)	0
Endocrine Disorders	1 (<1%)	1 (<1%)	0	0
Eye Disorders	14 (<1%)	12 (<1%)	5 (<1%)	1 (1%)
Gastrointestinal Disorders	89 (3%)	52 (2%)	35 (3%)	3 (2%)
General Disorders & Admin Site Conditions	110 (4%)	77 (3%)	62 (5%)	7 (5%)
Hepato-biliary Disorders	2 (<1%)	0	1 (<1%)	0
Immune System Disorders	5 (<1%)	3 (<1%)	0	0
Infections & Infestations	361 (12%)	278 (9%)	98 (7%)	20 (13%)
Injury & Poisoning	26 (1%)	26 (1%)	3 (<1%)	1 (1%)
Investigations	1 (<1%)	2 (<1%)	0	0
Metabolism & nutrition Disoders	1 (<1%)	1 (<1%)	0	0
Musculoskeletal and Connective Tissue disorders	88 (3%)	85 (3%)	33 (2%)	1 (1%)
Neoplasm: benign and malignant (including cysts and polyps)	3 (<1%)	2 (<1%)	0	0
Nervous System Disorders	100 (3%)	78 (3%)	48 (4%)	6 (4%)
Pregnancy, puerpeium & perinatal conditions	1 (<1%)	0	0	0
Psychiatric Disorders	16 (1%)	2 (<1%)	7 (1%)	0
Renal & Urinar Disorders	0	3 (<1%)	0	0
Reproductive System &Breast Disorders	13 (<1%)	11 (<1%)	3 (<1%)	1 (1%)
Respiratory Thoracic & Mediastinal Disorders	102 (3%)	68 (2%)	39 (3%)	8 (5%)
Skin & Subcutaneous Tissue Disorders	35 (1%)	34 (1%)	18 (1%)	1 (1%)
Social circumstances	0	1 (<1%)	0	0
Surgical & medical producers	4 (<1%)	2 (<1%)	0	0
Vascular Disorders	3 (<1%)	5 (<1%)	7 (1%)	0

[a]In all Aflunov® studies, 2nd vaccination was administered 3 weeks after the 1st;

[b]In the historical Fluad® pooled analysis, a total of 155 non-elderly adults received 2nd vaccination as follows: 4 weeks apart (32 subjects), 3 weeks apart (16 subjects), 12 months apart (107 subjects);

[c]For Aflunov®: 21 days after each injections, for historical Fluad®: study-specific, range: 3-28 days after each injection (onset between days 1 and 29 post-injection)

Percentage of Elderly Subjects Reporting All Unsolicited AEs by System Order Class: Aflunov® and Historical Fluad® Pooled Data after First, and Second Vaccination[ab]

	Primary Period[c]			
	Aflunov® (>60yrs)		Seasonal Fluad® (≥65 yrs)	
Vaccination	1st	2nd	1st	2nd
System Organ Class	N=387	N=378	N=3741	N=632
Any	**64 (17%)**	**43 (11%)**	**439 (12%)**	**125 (20%)**
Blood & Lymphatic System Disorders	0	0	2 (<1%)	2 (1%)
Cardiac Disorders	0	0	15 (<1%)	5 (1%)
Ear & Labyrinth Disorders	2 (1%)	3 (1%)	4 (<1%)	3 (<1%)
Eye Disorders	4 (1%)	1 (<1%)	10 (<1%)	5 (1%)
Gastrointestinal Disorders	4 (1%)	0	61 (2%)	9 (1%)
General Disorders & Administration Site Conditions	8 (2%)	10 (3%)	121 (3%)	43 (7%)
Hepato-biliary Disorders	0	0	1 (<1%)	1 (<1%)
Immune System Disorders	0	1 (<1%)	1 (<1%)	1 (<1%)
Infections & Infestations	19 (5%)	18 (5%)	90 (2%)	31 (5%)
Injury & Poisoning	1 (<1%)	0	24 (1%)	4 (1%)
Investigations	0	0	3 (<1%)	0
Metabolism & Nutrition Disorders	0	0	8 (<1%)	1 (<1%)
Musculoskeletal and Connective Tissue disorders	9 (2%)	7 (2%)	63 (2%)	13 (2%)
Neoplasm : benign./malignant (including cysts and polyps)	1 (<1%)	0	4 (<1%)	1 (<1%)
Nervous System Disorders	9 (2%)	5 (1%)	50 (1%)	11 (2%)
Psychiatric Disorders	0	0	8 (<1%)	2 (<1%)
Renal & Urinary Disorders	1 (<1%)	0	3 (<1%)	1 (<1%)
Reproductive System &Breast Disorders	1 (<1%)	0	2 (<1%)	0
Respiratory Thoracic & Mediastinal Disorders	12 (3%)	7 (2%)	47 (1%)	7 (1%)
Skin & Subcutaneous Tissue Disorders	8 (2%)	3 (1%)	31 (1%)	9 (1%)
Surgical & medical porcedures	0	1 (<1%)	0	0
Vascular Disorders	1 (<1%)	0	9 (<1%)	17 (3%)

[a]In all Aflunov® studies, 2nd vaccination was administered 3 weeks after the 1st;

[b]In the historical Fluad® pooled analysis, a total of 632 elderly adults received 2nd vaccination as follows: 4 weeks apart (145 subjects), 12 months apart (487 subjects);

[c]For Aflunov®: 21 days after each injections, for historical Fluad®: study-specific, range: 3-28 days after each injection (onset between days 1 and 29 post-injection);

Percentage of Elderly Adults Reporting SAEs by System Organ Class: Aflunov® and Historical Fluad® Pooled Data

System Organ Class	Aflunov® (18-60 yrs)	Historical Fluad® (18-64yrs)	
	N=3011	N=1383[a]	N=155[b]
Any	**17 (1%)**	**7 (1%)**	**4 (3%)**
Ear & Labyrinth Disoders	1 (<1%)	0	0
Gastrointestinal Disorders	3 (<1%)	0	2 (1%)
Hepato-biliary Disorders	3 (<1%)	0	0
Immune System Disorder	1 (<1%)	0	0
Infections & Infestations	4 (<1%)	2 (<1%)	1 (1%)
Injury & Poisoning	1 (<1%)	1 (<1%)	0
Musculoskeletal and Connective Tissue disorders	0	1 (<1%)	1 (1%)
Neoplasm benign/malignant (including cysts and polyps)	1 (<1%)	1 (<1%)	0
Nervous System Disorders	2 (<1%)	0	0
Pregnancy, puerpeium & perinatal conditions	1 (<1%)	0	0
Psychiatric Disorders	1 (<1%)	0	0
Reproductive System &Breast Disorders	0	1 (<1%)	0
Skin & Subcutaneous Tissue Disorders	0	1 (<1%)	0
Surgical & medical producers	1 (<1%)	0	0

[a]1st vaccination;

[b]2nd vaccination; in the historical Fluad® pooled analysis, a total of 155 non-elderly adults received 2nd vaccination as follows: 4 weeks apart (32 subjects), 3 weeks apart (16 subjects), 12 months apart (107 subjects);

Adverse reactions from clinical trial in children aged 6 months to 17 years (Study V87P6).

Regardless of age, reactogencity was higher after the first dose than after the second vaccination. Reactogenicity after a third dose, administered 12 months following the first dose, was higher than after both first and second dose. The percentages of subjects reporting local reactions were higher in the older age groups, mainly due to the higher reports for pain. In toddlers erythema and tenderness were the most commonly reported solicited local reactions; irritability and unusual crying were the most commonly reported solicited systemic reactions. In children and adolescents pain was the most frequently reported solicited local reaction, and fatigue and headache were the most commonly reported solicited systemic reactions. Across all ages, low percentages of subjects reported fever. The general adverse event profile observed in the paediatric study is provided below:

General adverse event profile observed in the paediatric clinical study.

	Injection 1	Injection 2	Injection 3
	Aflunov	**Aflunov**	**Aflunov**
Toddlers (6-<36 months)	**N=145**	**N=138**	**N=124**
Any	76%	68%	80%
Local	47%	46%	60%
Systemic	59%	51%	54%
Fever ≥ 38°C (≥ 40°C)	7% (0%)	12% (0%)	14 % (0%)
Any Other Adverse Event	54%	49%	35%
Children (3-<9 years)	**N=96**	**N=93**	**N=85**
Any	72%	68%	79%
Local	66%	58%	74%
Systemic	32%	33%	45%
Fever ≥ 38°C (≥ 40°C)	4% (0%)	2% (0%)	6% (1%)
Any Other Adverse Event	36%	31%	19%
Adolescents(9-<18 years)	**N=93**	**N=91**	**N=83**
Any	91%	82%	89%
Local	81%	70%	81%
Systemic	69%	52%	69%
Fever ≥ 38°C (≥ 40°C)	0% (0%)	1% (0%)	2% (0%)
Any Other Adverse Event	30%	27%	22%

- Post-marketing surveillance

No post-marketing surveillance data are available following Aflunov® administration.

The following additional adverse events were reported from post-marketing surveillance with Focetria H1N1v (licensed for use from 6 months of age and with a composition that is similar to Aflunov®, differing only in the nature of the influenza antigen):

Blood and lymphatic system disorders

Lymphadenopathy.

Cardiac disorders
Palpitation, tachycardia.

General disorders and administration site conditions
Asthenia.

Muscoskeletal and connective tissue disorders
Muscular weakness, pain in extremities.

Respiratory disorders
Cough.

Skin and subcutaneous tissue disorders
Generalised skin reactions including pruritus, urticaria or non-specific rash; angioedema.

Gastrointestinal disorders
Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhoea.

Nervous system disorders
Headache, dizziness, somnolence, syncope. Neurological disorders, such as neuralgia, paraesthesia, convulsions and neuritis.

Immune system disorders
Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

The following additional adverse events were reported from post-marketing surveillance with seasonal non-adjuvanted trivalent vaccines in all age groups and an MF59 seasonal adjuvanted trivalent vaccine with a composition similar to Aflunov® (surface antigen, inactivated, adjuvanted with MF59C.1) that is licensed for use in elderly subjects 65 years of age and older:

Blood and lymphatic system disorders
Transient thrombocytopenia.

Immune system disorders

Vasculitis with transient renal involvement and exudative erythema multiforme.

Nervous system disorders
Neurological disorders, such as encephalomyelitis, and Guillain Barré syndrome.

DOSAGE AND ADMINISTRATION

Adults and elderly (18 years of age and above):

One dose of 0.5 ml at an elected date.

A second dose of vaccine should be given after an interval of at least 3 weeks.

Aflunov® was evaluated in adults aged 18-60 years of age and in elderly over 60 years of age.

There is limited experience in children between 6 months and 17 years of age and in elderly over 70 years of age.

A complete vaccination course with Aflunov® consists of two doses. However, in the event of an officially declared influenza pandemic, persons previously vaccinated with one or two doses of Aflunov® that contained HA antigen derived from a different clade of the same influenza subtype as the pandemic influenza strain may receive a single dose of Aflunov® instead of two doses that are required in previously unvaccinated individuals.

Method of administration
Immunisation should be carried out by intramuscular injection into the deltoid muscle.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

No case of overdose has been reported.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for general advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Aflunov® is presented as a 0.5 ml pre-filled Type I glass syringe with a bromo-butyl rubber plunger-stopper in packs of 1 or 10.

List of excipients
Sodium chloride,
Potassium chloride,
Potassium phosphate - monobasic,
Disodium phosphate dihydrate,
Magnesium chloride,
Calcium chloride,
Sodium citrate,
Citric acid,
Water for injections.

Shelf life and Storage Conditions
3 years.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.

The vaccine should be allowed to reach room temperature before use. Gently shake before use.

Any unused vaccine and waste material should be disposed of in compliance with local requirements.

NAME AND ADDRESS OF THE SPONSOR
Novartis Vaccines and Diagnostics Pty. Ltd
54 Waterloo Road
North Ryde
NSW 2113

POISON SCHEDULE OF THE MEDICINE
All states and ACT Schedule 4 (Prescription-Only Medicine)

AFLUNOV® prepandemic influenza vaccine H5N1 (surface antigen, inactivated, adjuvanted) (AUST R 167943)

DATE OF APPROVAL

Date of TGA Approval: 16 March 2011

® Registered Trademark of Novartis Vaccines and Diagnostics S.r.l., Italy.

Product Information (PI) and Consumer Medicine Information (CMI) documents are regularly updated.

Please also refer to the TGA web site (http://www.tga.gov.au/meds/picmi.htm) for the most up to date PI and CMI.

For medical enquiries please contact 1800 671 203 (phone) or medinfo.phauno@novartis.com (email).

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Issue 1

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #