Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for trivalent seasonal influenza vaccine, inactivated, MF59C.1 adjuvanted

Proprietary Product Name: Fluad Paediatric

Sponsor: Novartis Vaccines and Diagnostics Pty Ltd

October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- 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 Biological Entity
Decision:	Withdrawn
Date of Decision:	13 February 2012
Active ingredient(s):	Influenza virus haemagglutinin (HA), influenza virus neuraminidase
Product Name(s):	Trivalent seasonal influenza vaccine, inactivated, MF59C.1 adjuvanted
Label Name(s):	Fluad Paediatric influenza vaccine
Sponsor's Name and Address:	Novartis Vaccines and Diagnostics Pty Ltd PO Box 101 North Ryde NSW 1670
Dose form(s):	0.25 mL/0.5 mL suspension for intramuscular injection in an milky white emulsion in prefilled syringe
Strength(s):	7.5 µg HA/dose H1N1; 7.5 µg HA/dose H3N2; 7.5 µg HA/dose B. 15.0 µg HA/dose H1N1; 15.0 µg HA/dose H3N2; 15.0 µg HA/dose B
Container(s):	Clear, Type 1 glass, prefilled syringe with needle attached. Clear, Type 1 glass, prefilled syringe needle free.
Pack size(s):	1 x 0.25 mL; 10 x 0.25 mL 1 x 0.50 mL; 10 x 0.50 mL
Route(s) of administration:	Intramuscular (IM)
Dosage:	Infants and children from 6 to less than 36 months: · who are receiving their first seasonal influenza vaccination ('naive'): two 0.25 mL doses, 4 weeks apart · who have previously received seasonal influenza vaccination ('primed'): a single 0.25 mL dose. Children from 3 years to less than 9 years: · who are receiving their first seasonal influenza vaccination ('naive'): two 0.5 mL doses, 4 weeks apart · who have previously received seasonal influenza vaccination ('primed'): a single 0.5 mL dose.

Product background

This AusPAR describes an application by the sponsor, Novartis Vaccines and Diagnostics Pty Ltd, to register a major variation for Fluad. This drug product has been on the Australian Register of Therapeutic Goods (ARTG) since 2002: 0.5 mL dose containing 15.0 µg haemagglutinin (HA) of each of the two influenza virus Type A and one Type B surface antigens. This is an adjuvanted vaccine with oil (squalene) in water adjuvant MF59C.1 and is approved for active immunisation against influenza in elderly (> 65 years of age)

especially for those with an increased risk of associated complications, that is, patients affected by underlying chronic diseases including diabetes, cardiovascular and respiratory diseases.

The current submission seeks to extend the indications for this product to active immunisation against influenza in infants and children from 6 months to less than 9 years of age.

In doing thus the product will be marketed under the tradename Fluad Paediatric and will include 0.5 mL (45 µg total antigen) and 0.25 mL (22.5 µg total antigen) presentations.

The vaccine product will contain strains recommended for the 2012 season (no change from 2011 season).

Regulatory status

Fluad was first registered in Italy in 1997 for use in the elderly 65 years of age or above. It has since been approved in 17 European countries, 12 of which approved through a Mutual Recognition Procedure. Since its first registration, the vaccine has obtained approval for use in the elderly in 30 countries worldwide; Fluad is also licensed for use in the paediatric population (6 to 36 months of age) in Mexico. Since 1997, more than 50 million doses of Fluad have been distributed worldwide.

II. Quality findings

Formulation

The maximum batch size of the final bulk is 360 L. The final product is formulated by addition of calculated amounts of citrate buffer, WFI (water for injection) and adjuvant to the trivalent bulk. Calculations are based on the required HA content at release to cover expected drop in potency over the expiry period.

Manufacture

All components used to generate the final bulk are sterile filtered. The final bulk is then prepared by sequential addition of citrate buffer, adjuvant and monovalent bulks into a sterile tank. The final bulk vaccine is subdivided by aliquoting for fill and finish. A test for HA identity for each strain is performed on a sample of the finished packed product.

MF59C.1 is an oil in water emulsion composed of squalene as the oil phase, stabilised with the surfactants Polysorbate 80 and sorbitan trioleate in citrate buffer.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, are attached. Appropriate validation data have been submitted in support of the test procedures.

Stability

No real time stability data for the 0.25 mL presentation was supplied. Accelerated stability data for the product stored at 25°C and 37°C indicates the potency of the vaccines is

maintained above the lower fiducial limit of >6 µg HA per dose for 1 week and 3 days respectively. The sponsor will be requested to supply real time stability data prior to the supply of the product. The proposed shelf life based on the stability of the 0.5 mL dosage form is 1 year when stored at 2-8°C. However, the reduced volume dosage may affect the stability of the product in terms of potency measured via HA content. The product should be stored in original packaging to product from light. The product should not be frozen due to the presence of the adjuvant.

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

Introduction

Nonclinical data have been previously evaluated in registration applications for the trivalent influenza vaccine (TIV) Fluad and the related vaccines Agrippal S1 (Agriflu, "Biocine"), a TIV with the same composition as Fluad, but is unadjuvanted, and Aflunov, a monovalent H5N1 vaccine with the same quantity of MF59C.1 adjuvant, and the same antigen manufacturing process as Fluad.

The nonclinical data for Fluad included immunogenicity, challenge, repeat dose toxicity, local tolerance and sensitisation studies. The data for MF59C.1 adjuvant include repeat dose toxicity, local tolerance, sensitisation, embryofetal development and genotoxicity studies. The nonclinical studies were consistent with regulatory guidelines for vaccines[1] and adjuvants,[2] and the toxicity studies were compliant with Good Laboratory Practice (GLP) guidelines.

This assessment focuses on new studies, and previously evaluated studies directly relevant to the paediatric extension of indications.

Immunogenicity

Immune responses to inactivated seasonal influenza vaccines are generally poorer in young (6-36 months) children and the elderly, and the incorporation of MF59C adjuvant in Fluad aims to improve the antibody response, which is correlated with protection in adults. A significant proportion of young children are immunologically naive to influenza virus, and two Fluad doses, separated by ≥4 weeks, are proposed in naive children to increase the antibody response.

MF59C.1 is an oil in water emulsion composed of squalene as the oil phase, stabilised with the surfactants Polysorbate 80 and sorbitan trioleate in citrate buffer. The mechanisms of

[1] European Medicines Agency, "Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines", 17 December 1997, Web, accessed 18 June 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004004.pdf>.

[2] European Medicines Agency, "Guideline on Adjuvants in Vaccines for Human Use", 20 January 2005, Web, accessed 18 June 2012 <http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf>

action of MF59 adjuvant are not fully understood. The actions of MF59 do not require direct association between the adjuvant and antigen, that is, as a depot, but may involve local induction of chemokines required for antigen presenting cell (APC) recruitment,[3] and pro inflammatory cytokines involved in antigen presentation, APC differentiation, and cell migration to the draining lymph node.[4]

Previous immunogenicity studies in young (3 month old) seronegative mice showed that the addition of MF59 adjuvant to a TIV increased antibody titers, and spleen lymphoproliferative responses after two subcutaneous doses. In addition to increasing antibody titers, there is evidence in that MF59 adjuvant also broadens the human antibody response to influenza virus.[5]

Safely pharmacology

No specific safety pharmacology studies have been conducted with Fluad, however the safety pharmacology parameters of rectal temperature, and heart and respiration rates were measured 2 h post dose in Fluad toxicity studies in rabbits, and were unaffected by treatment.

Pharmacokinetics

No pharmacokinetic studies were conducted with Fluad, and they were not required.

The distribution and clearance of MF59 adjuvant was previously studied in mice and rabbits.

Toxicology

Acute toxicity

No single dose toxicity studies were performed with Fluad, but toxicological assessments were conducted after a single dose in the repeat dose toxicity studies.

[3] Calabro S, et al. Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. *Vaccine* 29: 1812-1823 (2011).

[4] O'Hagan DT. MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection. *Expert Rev. Vaccines* 6: 699-710 (2007).

[5] Khurana S, et al. Vaccines with MF59 adjuvant expand the antibody repertoire to target protective sites of pandemic avian H5N1 influenza virus. *Science Translational Medicine* 2: 15ra5 (2010).

Repeat dose toxicity

Fluad

Three new GLP compliant repeat dose toxicity studies in rabbits with Fluad were evaluated in the current submission, and a fourth (940292) with the Fluad equivalent (Agrippal + MF59 adjuvant) was previously evaluated. Two of the four studies (486688, 6560-106) were non pivotal, their aim was to test the effects of novel adjuvants on Fluad, and neither had a saline control group. In all four toxicity studies, two or three consecutive human doses of Fluad were administered, equal to or exceeding the maximum of two doses of Fluad to be administered to children in a season. The studies had a two week recovery period. Vaccine immunogenicity was assessed by HA assay in three of the four studies. On the basis of bodyweight, a single vaccine dose of 0.5 mL in a 3 kg rabbit is ~3.8x a 0.25 mL dose administered to a six month old female infant weighing 5.7 kg (conservative value), and the cumulative total of three doses in rabbits was ~5.7x the total of two 0.25 mL doses administered to an infant.

Most of the Fluad toxicity studies showed slight increases in fibrinogen, and slight decreases in the prothrombin time (PT) and activated partial thromboplastin time (APTT), which had returned to normal after two weeks recovery. These reflect a transient inflammatory response to the adjuvanted vaccine. Slight increases in globulin and protein levels, decreases in the albumin/globulin ratio, and enlargement of the draining lymph nodes reflected the immune response. An antigen specific immune response after the first dose was confirmed in all rabbits assessed by HI.

As noted above (Safety Pharmacology), the Fluad toxicity studies incorporated measurements of rectal temperature, and heart and respiration rates, which showed no treatment related effects. Local tolerance was investigated in all toxicity studies.

MF59C.1 adjuvant

Repeat dose toxicity studies in adult rats (1303-002) and rabbits (90-6081, 2670-100, 00-2673) with MF59 adjuvant have been evaluated previously. The dose of MF59 in these studies was 0.25 or 0.5 mL (1-2 times human dose). The sponsor provided conservative estimates of exposure multiples to MF59, based on bodyweight and body surface area, for a six month old female with a bodyweight of 5.7 kg, and the lowest dose of MF59 per rat or rabbit per study (Table 1).

Table 1: MF59 adjuvant dose multiples (animal/infant) in repeat dose toxicity studies based on bodyweight and body surface area.

MF59 per dose	Basis for comparison	Multiple based on single dose	Multiple based on cumulative dose
0.25 mL	Bodyweight	1.5 to 25x	9 to 75x
	Body surface area	1.3 to 11x	8 to 35x
0.125 mL	Bodyweight	3 to 50x	18 to 150x
	Body surface area	2.6 to 22x	16 to 70x

Mean female infant bodyweight of 5.7 kg from 2000 CDC Growth charts for the United States, with 3rd and 97th percentiles.

Mean female infant BSA = 0.32 m^2. Infant body surface area (BSA) = (Weight+4)/30 from J.D. Current: A Linear Equation for Estimating the Body Surface Area in Infants and Children. *The Internet Journal of Anesthesiology* vol. 2 no. 2 (1998).

Rabbit BSA = KW2/3 where K = 10.0 from MJ Derelenko: *Toxicologist's Pocket Handbook*. CRC Press LLC (2000).

On the basis of these conservative estimates, exposure multiples in the toxicity studies were adequate, in terms of the proposed paediatric age group.

Genotoxicity

No genotoxicity studies were conducted with Fluad, and they are not required.

Previous genotoxicity studies (bacterial reverse mutation assay, mouse micronucleus assay) with MF59 adjuvant (water and citrate formulations) were negative.

Carcinogenicity

No carcinogenicity studies have been conducted with Fluad, and they are not required.

Reproductive toxicity

No reproductive toxicity studies have been conducted with Fluad, as the vaccine is not proposed for use in women of childbearing potential.

Embryofetal development studies with MF59 adjuvant in rats and rabbits have been evaluated previously. A previous combined reproductive and developmental toxicity study with Aflunov showed no adverse effects.

Local tolerance

Local tolerance of Fluad was investigated by gross and microscopic examination in all repeat dose toxicity studies in adult rabbits. Slight inflammatory changes (erythema and/or oedema, mixed inflammatory infiltrate) were observed at the Fluad injection sites, which were slightly more marked in comparison with the unadjuvanted vaccine, and partially/fully resolved within two weeks. Local tolerance was acceptable.

Fluad and MF59C adjuvant were not sensitisers in previous Magnusson-Kligman Maximisation tests in guinea pigs.

Use in children

No toxicity studies were conducted with Fluad in young animals. In the absence of a specific guideline for vaccines, the sponsor consulted the European guidelines.[6] The sponsor justified the lack of toxicity studies in young animals as follows: "The safety of Fluad has been demonstrated clinically in children, and administration of the vaccine results in the same pharmacological effect (elicitation of antibodies) in children and adults. Because the nonclinical and clinical programs have not identified any findings that require additional investigation, it was concluded that studies in juvenile animals are not justified. In the Fluad toxicity studies, the full human dose was administered to adult rabbits of ~3 kg body weight, and exposure multiples were adequate in terms of a conservative estimate of 5.7 kg body weight for a six month old human infant.

A safety concern regarding TIV use in children arose in Australia in April 2010, when an apparent increase in incidences of severe febrile reactions, some with febrile seizures, led to suspension of the national influenza vaccination program for children aged 5 years and under. Following an extensive investigation by the TGA, which concluded that the febrile convulsions were associated with one of the three vaccines used, the program resumed in July 2010 with the two alternative vaccines available.

Febrile convulsions (seizures) are the most common form of childhood seizure, affecting 2-5% of children between about 3 months and 5 years of age, with a peak at about 1 year of age. They are provoked by fever (body temperature ≥38°C), and are usually a

[6] European Medicines Agency, "Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications", 24 January 2008, Web, accessed 18 June 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003305.pdf>.

consequence of respiratory or gastrointestinal infection. Simple seizures generally have no long lasting effects.[7]

Despite extensive investigation the cause of the increases in severe febrile reactions and febrile convulsions has not been determined. It has been postulated that the increases may have been caused by a viral like pyrogenic cytokine response, based on significantly elevated plasma levels of some cytokines (interferon gamma induced protein 10 (IP-10, CXCL10), macrophage inflammatory protein, MIP-1α), and a trend towards increased plasma levels of the pyrogenic cytokines IFN-α, IL-1β and IL-6 in samples from a small number of children shortly after vaccine-related febrile convulsions. Cultured peripheral blood mononuclear cells (PBMCs) from healthy young donors showed significant increases in inflammatory cytokines (IFN-α, IL-1β, IL-6, IL-10, IP-10, MIP-1α) when incubated for 6 h with undiluted Fluvax, in comparison with Influvac or Vaxigrip.[8] IL-6 and IFN-α levels are closely correlated with peak symptoms including fever in influenza virus A infection.[9] Fluvax (2010) also showed a greater likelihood of local reactions in adults, compared with Influvac.[10]

Although Fluad Paediatric contains MF59 adjuvant, the amount of HA antigen (7.5 or 15 µg) has not been reduced in comparison with other unadjuvanted vaccines registered for use in the same age group. Improvements in vaccine immunogenicity must be balanced against the potential for greater reactogenicity. Nonclinical toxicity studies in relatively small numbers of adult rabbits showed no effects of Fluad on rectal temperatures. Injection site reactions were within acceptable limits, although slightly more severe in comparison with the unadjuvanted vaccine. Slight increases in fibrinogen and decreases in PT and APTT probably reflected a transient inflammatory response to the vaccine. Transient increases in inflammatory proteins (C-reactive protein, TNF-α) have also been documented in humans administered unadjuvanted TIV.[11] The potential risk of increased severe febrile reactions or convulsions with Fluad can be best addressed in clinical studies with adequate numbers of subjects.

Excipients

The toxicity of squalene, polysorbate 80 and sorbitan trioleate have been evaluated previously, and would not present a toxicological hazard at the levels proposed in Fluad Paediatric.

Nonclinical summary and conclusions

Summary

1. Fluad (0.5 mL injection syringe) is a trivalent, inactivated, MF59C.1 adjuvanted vaccine registered for use in adults 65 years and older. The sponsor has proposed to extend the indications to infants and children from 6 months to less than 9 years of

[7] Fetveit A. Assessment of febrile seizures in children. *Eur. J. Pediatr.* 167: 17-27 (2008).

[8] Blyth CC, et al. Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. *Vaccine* 29: 5107-5113 (2011).

[9] Hayden FG, et al. Local and systemic cytokine responses during experimental influenza A virus infection. Relation to symptom formation and host defence. *J. Clin. Invest.* 101: 643-649 (1998).

[10] Leeb A, et al. Reactogenicity of two 2010 trivalent inactivated influenza vaccine formulations in adults. *Vaccine* 29: 7920-7924 (2011).

[11] Christian LM, et al. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. *Vaccine* 29: 8982-8987 (2011).

age (Fluad Paediatric, 0.25 and 0.5 mL, containing 7.5 and 15 µg HA, respectively). The proposed dose schedule is shown in Table 2.

Table 2: Proposed dose regimen for Fluad Paediatric influenza vaccine.

Age range	Naive	Primed
6 months to <36 months	Two 0.25 mL doses, 4 weeks apart	A single 0.25 mL dose
3 years to <9 years	Two 0.50 mL doses, 4 weeks apart	A single 0.50 mL dose

2. Nonclinical registration data for Fluad and the related vaccines Agrippal and Aflunov have been evaluated previously.
3. The current submission provided three new GLP compliant repeat dose toxicity studies, in which adult rabbits were administered two or three consecutive human doses of Fluad IM, followed by two weeks recovery. Injection sites showed low level inflammatory responses, which were slightly more marked in comparison with the unadjuvanted vaccine, and partially/fully resolved after two weeks. Rectal temperature, heart and respiration rate were unaffected. Slightly increased fibrinogen, and slightly decreased prothrombin time and activated partial thromboplastin time probably reflected a transient inflammatory response to the adjuvanted vaccine. Slightly increased globulin and protein levels and enlargement of lymph nodes proximal to injection sites were a consequence of the immune response. An antigen specific antibody response was confirmed by HI after the first dose in all rabbits. Vaccine and MF59 exposure multiples, based on a conservative bodyweight of 5.7 kg for a 6 month infant, were adequate.
4. Toxicity studies were not performed with Fluad in young animals.

Summary

Toxicity studies in adult rabbits showed acceptable local tolerance, although slightly more severe in comparison with the unadjuvanted vaccine. Significant changes in some haematological parameters probably reflected a transient inflammatory response, but rectal temperatures and heart and respiration rates were unaffected. Vaccine and adjuvant exposure multiples in toxicity studies, in terms of a six month old human infant, were adequate.

Although Fluad Paediatric contains an adjuvant, the amount of HA antigen (7.5 or 15 µg) has not been reduced in comparison with registered unadjuvanted vaccines. The potential risk for increased severe febrile reactions or convulsions with Fluad can be addressed in clinical studies with adequate numbers of subjects.

The nonclinical studies raise no objections to the proposed extension of indications for Fluad to infants and children aged 6 months to less than 9 years.

IV. Clinical findings

Pharmacokinetics

Fluad is a trivalent influenza virus vaccine, presented as a suspension for injection in a prefilled syringe, containing the surface antigens of influenza viruses type A (two strains) and B. The product complies with the European Pharmacopoeia monograph for influenza vaccines, surface antigen, inactivated and includes MF59C.1 as an adjuvant. Fluad contains purified HA and neuraminidase (NA) antigens from the surface of each of the three influenza virus strains, types A and B, recommended annually for immunisation by the World Health Organisation (WHO) and TGA for the southern hemisphere. The influenza virus strains are individually grown in embryonated chicken eggs and inactivated by

formaldehyde treatment before purification of the surface antigens and formulation with the MF59C.1 adjuvant into a sterile suspension. The MF59C.1 adjuvant contained in Fluad is an oil in water emulsion composed of squalene as the oil phase, with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer. The potency of the vaccine is expressed as the amount of the HA protein per dose. The strains contained in the Study vaccines are shown in Table 3. In the paediatric clinical Fluad studies, the vaccine was administered with a similar dosing regimen to other vaccines that are licensed for administration in the paediatric population:

- In children <36 months of age, the paediatric dose was half the adult dose (that is, 0.25 mL) and was administered to immunologically naïve children as a two dose regimen, with the doses approximately one month apart.
- Children 3 years to <9 years of age received the adult dose, which is administered in immunologically naïve children as a two dose regimen, with the doses approximately one month apart.
- Children 9 years to <18 years of age receive adult dose vaccination.

Table 3: Vaccine virus strain composition.

Study Season	Vaccine Antigen	Assay	Vaccine strains (homologous)
V70P5 2007/2008	A/H1N1	HI SRH MN	A/Solomon Island/3/2006-like (A/Solomon Island/3/2006, Reass. IVR-145)
	A/H3N2		A/Wisconsin/67/2005-like (A/Wisconsin/67/2005, NYMC X161B)
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]
V70P5 2008/2009	A/H1N1	HI SRH MN	A/Brisbane/59/2007-like (A/ Brisbane/59/2007, Reass. IVR-148)
	A/H3N2		A/Brisbane/10/2007-like (A/Uruguay/716/2007, Reass. NYMC X-175C)
	B		B/Florida/4/2006-like (B/Florida/4/2006)[c]
V70P5 2009/2010	A/H1N1	HI SRH MN	A/Brisbane/59/2007-like (A/ Brisbane/59/2007, Reass. IVR-148)
	A/H3N2		A/Brisbane/10/2007-like (A/Uruguay/716/2007, Reass. NYMC X-175C)
	B		B/Brisbane/60/2008-like (B/Brisbane/60/2008)[b]
V70P2, 2006/2007	A/H1N1	HI	A/New Caledonia/20/99 (H1N1)-like (A/New Caledonia/20/99, Reass. IVR-148)
	A/H3N2		A/Wisconsin/67/2005-like (A/Wisconsin/67/2005, Reass. IVR-142)
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]
V70P6, 2007/2008	A/H1N1	HI	A/Solomon Islands/3/2006 (H1N1)-like (A/Solomon Island/3/2006, Reass. IVR-145)
	A/H3N2		A/Wisconsin/67/2005-like (A/Wisconsin/67/2005, Reass. NYMC X161B)
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]
V70P2E1, 2007/2008	A/H1N1	HI	A/Solomon Islands/3/2006-like (A/Solomon Island/3/2006, Reass. IVR-145)
	A/H3N2		A/Wisconsin/67/2005-like (A/Wisconsin/67/2005, NYMC X161B)
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]
V7P29 1996/1997	A/H1N1	HI	A/Singapore/6/86-like (X113 reassortant of A/Texas/36/91)
	A/H3N2		A/Wuhan/359/95-like (RESVIR 9 reass. of A/Nanchang/933/95)
	B		B/Beijing/184/93-like (B/Harbin/7/94)[b]
V87P6 2007/2008	A/H1N1	HI SRH MN[a]	A/Solomon Island/3/2006-like (A/Solomon Island/3/2006, Reass. IVR-145)
	A/H3N2		A/Wisconsin/67/2005-like (A/Wisconsin/67/2005, NYMC X161B)
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]
V104P2 2008/2009	A/H1N1	HI	A/Brisbane/59/2007-like (A/ Brisbane/59/2007, Reass. IVR-148)
	A/H3N2		A/Brisbane/10/2007-like (A/Uruguay/716/2007, Reass. NYMC X-175C)
	B		B/Florida/4/2006-like (B/Florida/4/2006)[c]
	B		B/Malaysia/2506/2004-like (B Malaysia/2506/2004)[b]

HI = hemagglutination inhibition; SRH = single radial hemolysis; MN = microneutralisation

a, Immunogenicity in this study was not evaluated for Fluad, only for the H5N1 pandemic vaccine

b,Yamagata lineage

c, Victoria lineage

The selection of dose, dose schedule, and formulation of the final product were based on the following considerations:

1. Immunogenicity and assessment against European Union CHMP (Committee for Medicinal and Products for Human Use) criteria. Results from Studies V70P2, V70P6 and V70P5 showed that one vaccination with Fluad was not sufficient to meet all CHMP criteria for the B strain in unprimed children 6 months to <36 months and 36 months to <72 months of age. In addition to CHMP criteria, Fluad immunogenicity was significantly better than immunogenicity of non adjuvanted influenza vaccines. Importantly, in Study V70P5, superiority for all three strains via immunogenicity was only clearly met after two doses. This was particularly evident for the B strain responses.
2. Demonstration of efficacy using the proposed posology: The absolute vaccine efficacy as compared with a non influenza control was 81.36% (95% CI [Confidence Interval]: 49.24- 93.16%) in 6 to <36 month olds and 95.5% (95% CI: 80.92-98.94%) in 36 to <72 month olds with an acceptable safety profile in both age groups. The efficacy was significantly higher relative to non adjuvanted influenza vaccine control. These results strongly supported the chosen posology, similar to vaccination dosing and schedules already in current paediatric practice.
3. A dose finding clinical study: Study V104P2 in children 6 to <36 months of age was conducted to compare the immunogenicity and safety of different formulations of a tetravalent MF59 adjuvanted influenza vaccine (the vaccine contains an additional B strain, that is, two A strains and two B strains) with different formulations of trivalent MF59 adjuvanted Influenza Vaccine. Groups receiving non adjuvanted TIV with different HA content were also included.
    a. This study demonstrated the ability of adjuvanted formulations to meet all CHMP criteria against influenza A strains after a single dose of vaccine. However, two doses of adjuvanted formulation were needed to meet all three CHMP criteria for the B strains. None of the non adjuvanted formulations met all three criteria even after the second vaccination.
    b. The addition of adjuvant resulted in a clear increase in Geometric Mean Titers (GMTs) and further small increases in GMT with increasing MF59 dose. Data from the V70P5 efficacy study suggest that HI titers much greater than 1:40 (that is, HI titers of 1:110) correlated with a 50% clinical protection rate against influenza illness. Further, higher titers correlated with higher levels of protection (HI titers of 1:215, 1:330, and 1:629 correlated with clinical protection rates of 70%, 80%, and 90%, respective.

Efficacy

Introduction

The dossier contained the following clinical studies:

- one pivotal Phase 3 study (Study V70P5)
- four Phase 2 studies (Studies V70P2, V70P2E1, V70P6 and V7P29)

The pivotal Phase 3 Study V70P5 was designed to assess the efficacy, immunogenicity and safety of two doses given 4 weeks apart in children 6 to <72 months of age. The study was conducted over three consecutive seasons (2007/2008, 2008/2009 and 2009/2010) in order to reach the planned sample size and to obtain the number of influenza cases needed to evaluate the study objectives regarding efficacy.

The two Phase 2 studies V70P2 and V70P6 were designed to assess immunogenicity and safety in a two dose schedule given 4 weeks apart in children 6 months to <36 months of age and 36 months to <60 months of age (only Study V70P6). The extension Study V70P2E1 investigated the immunogenicity and safety of a third dose in children 6 to<36 and ≥36 months given 1 year after the first two doses in Study V70P2.

The supportive Fluad Study V7P29 was designed to investigate the immunogenicity and safety of 1 dose of Fluad in children 9 to <18 years of age.

The supportive Study V87P6 was conducted for the development of the H5N1 pandemic vaccine. Fluad was given as comparator vaccine only for safety assessment. All children 6 months to < 18 years of age received two vaccine doses separated only by 3 weeks.

Main clinical studies – methods

A total of 5854 children 6 months to <18 years of age were enrolled. Of these, 2498 were enrolled to receive Fluad and 3356 to receive control vaccine (either licensed influenza vaccine [2317 subjects] or non influenza control [1039 subjects]).

Studies V70P5 and V70P2 enrolled children who had not been vaccinated against influenza in a previous season; Study V70P6 enrolled subjects who had never received two doses of influenza vaccine before the study, either in two consecutive influenza seasons or in one influenza season. Children in these three studies received two doses of vaccine one month apart. Children 36 months of age and above received two adult doses, each of which contained 15 µg of HA from the H1N1, H3N2 and B strains and 100% MF59 (squalene content of 9.75 mg per dose) in a total volume of 0.50 mL. Children 6 to <36 months of age received two paediatric doses (that is, half the adult dose), each dose containing 7.5 µg of HA from each strain and one half the quantity of MF59, in a total volume of 0.25 mL. In Study V7P29, previously unvaccinated older children and adolescents 9 to <18 years of age received one adult dose. Study V70P2E1 was designed to evaluate revaccination of children who had previously been vaccinated with Fluad. In this study, children <36 months of age received one paediatric (0.25 mL) dose whereas children ≥36 months of age received one adult (0.5 mL) dose. Fluad vaccine strains were selected based on the yearly recommendation by WHO; the influenza strains used in each study are listed in Table 3. The vaccine was formulated in compliance with European Pharmacopoeia requirements. Apart from Study V7P29, all studies focused on younger children from 6 months to either <36 months, <60 months or <72 months.

All studies enrolled children in general good health, as determined by medical history and physical examination at study entry. Children with a serious disease (for example, cancer, autoimmune disease), severe acute infectious disease (including severe acute respiratory disease requiring antibiotic or antiviral treatment) or with known or suspected alteration of immune function were not enrolled. The studies also excluded children for whom vaccination against influenza would be contraindicated (that is, children with an allergy to eggs, egg proteins or other components of the vaccines) and children with a history of anaphylaxis. Children were not to have been administered licensed vaccines within a four week period prior to enrollment; this was shortened to 14 days for licensed inactivated vaccines in studies V70P5 and V70P6.

All studies were randomised and controlled. Parallel groups in each study received commercially available non adjuvanted influenza vaccines [either whole virion vaccine (Fluogen, Parke Davis; Study V7P29), split virion vaccine (Flushield, Wyeth-Ayerst; Vaxigrip, Sanofi-Pasteur, Fluzone, Sanofi-Pasteur or Influsplit SSW, GlaxoSmithKline; all studies), or subunit vaccine (Agrippal, Novartis Vaccines; Study V70P5)]. One group in Study V70P5 (identified as the non flu vaccine control group) did not receive influenza vaccine; children 6 to <12 months in this group received Menjugate (*N. menigitidis* serogroup C conjugate vaccine, Novartis Vaccines) whereas children 12 to <72 months of

age received Encepur Children (tick borne encephalitis vaccine, Novartis Vaccines). To protect blinding, control vaccines were administered on schedules which were identical to those used for Fluad.

All studies were run under observer blind conditions. During the study, designated nurses or physicians unblinded to the randomisation scheme were responsible for administering the study vaccines to the subjects and for keeping daily and final accountability records of the vaccine supplies. The identity of the study vaccines were not revealed to the subject's parents/legal guardians or to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the study, except in an emergency. The designated unblinded individuals had no access to any subject's case report form (CRF) data and had no contact with the subjects except during the administration of the study vaccine.

Assessment of immunogenicity

A correlate of protection has not been defined in children, but it is widely established that protection against influenza can be conferred by serum antibodies. Serological surrogates are generally used to assess the immune responses to influenza vaccines. In the studies included in the current submission, the HI assay is the principal assay which was used to assess vaccine immunogenicity. In Study V70P5, vaccine immunogenicity was also assessed by Single Radial Hemolysis (SRH) and microneutralisation (MN), as exploratory tests, in order to better characterise the immune response to vaccination.

In studies where two doses of vaccine were administered (Studies V70P2, V70P5 and V70P6), blood sampling for the analysis of immunogenicity was performed prior to vaccination (Day 1), at the time of the second dose (Day 29) and approximately 3 weeks after completion of the vaccination course (Day 50). Only results obtained after the second dose are presented in the data submitted. In studies where one dose of vaccine was administered, blood sampling was performed prior to vaccination and approximately 3 weeks (Day 22; Study V70P2E1) or 4 weeks (Day 28; Study V7P29) after vaccination. In some studies blood was collected at day 180 to assess persistence of HI antibody following vaccination. In Study V70P5, serology was assessed using SRH and MN.

With the exception of Study V70P5, blood sampling was planned for all subjects. In Study V70P5, vaccine immunogenicity was evaluated on samples from a subset, which included all subjects in specific study centres in Germany (Season 2008/09), Finland (Seasons 2008/09 and 2009/10) and Italy (Season 2009/10) for whom parents gave consent for blood to be taken. The subset was intended to include approximately 20% of the population enrolled in each of the three influenza seasons. Due to the delayed start of the study during Season 2007/08, the number of subjects from whom serum samples were obtained was low. Immunogenicity data during Season 2009/10 was also compromised by the H1N1 pandemic; a large proportion of the children were withdrawn prior to administration of the second dose of study vaccine in order to receive pandemic influenza vaccine. As a result of the above, the analysis of immunogenicity has been restricted to Season 2008/09. Testing by SRH and MN, done exclusively in Study V70P5, was performed on a randomly selected sub cohort of all subjects in the subset.

The data of the immunogenicity subset were used to evaluate the relationship between antibody level and clinical protection from influenza. As almost all influenza cases were caused by A/H3N2 strains the analysis was confined to antibodies against A/H3N2.

The acceptability of a serological surrogate as a measure of efficacy of influenza vaccines is well established.[12] The criteria set forth by the CHMP as providing satisfactory evidence of

[12] European Medicines Agency, "Note for Guidance on Harmonisation of Requirements for Influenza Vaccines", 12 March 1997, Web, accessed 18 June 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf>.

immunogenicity following vaccination against influenza in adults and the elderly are shown in Table 4. There are no standard CHMP criteria for assessing immunogenicity in persons below 18 years of age. By convention, the immunogenicity of the influenza vaccines used in the studies conducted in children is assessed based on the CHMP criteria for adults 18-60 years of age. These criteria have therefore been used to assess the immunogenicity of Fluad in the studies submitted in this application.

Table 4: CHMP criteria for evaluation of influenza vaccines.

CHMP Criteria	Children and Adolescents <18 years	Adults 18–60 Years	Adults ≥61 Years
Seroprotection (SP)[a]	Not defined	>70%	>60%
Geometric Mean Ratio (GMR)[b]	Not defined	>2.5	>2.0
Seroconversion/ significant increase (SC)[c]	Not defined	>40%	>30%

a: Seroprotection = the percentage of subjects achieving a HI antibody titer ≥40 or the percentage of subjects achieving a SRH area ≥25 mm^2

b: GMR = geometric mean of postvaccination/prevaccination ratio of individual titers

c: For HI: Seroconversion = the percentage of subjects with a prevaccination (baseline) HI titer <10 and postvaccination HI titer ≥40; Significant increase = the percentage of subjects with a prevaccination HI titer ≥10 and a ≥4-fold increase in postvaccination HI antibody titer compared to baseline.

Seroprotection (SP), defined as the percentage of subjects with antibody titers ≥40 by HI or an area of ≥25 mm^2 by SRH, was evaluated at each time point that samples were taken. Vaccine immunogenicity was also summarised by means of GMT. GMTs were calculated using the logarithmically (base 10) transformed titer values, with values for titers below the limit of detection being set to one half the limit for the purposes of analysis. In addition, the proportions of subjects with seroconversion or significant increase (indicated as "SC" in the tables), and geometric mean ratio (GMR; also referred to as mean geometric increase) were calculated according to the CHMP guidance. No serological surrogate as a measure of efficacy of influenza vaccines has been defined for neutralisation titers evaluated by MN assay. In the present summary, MN assay results are presented in terms of:

- percentages of subjects achieving an antibody titer of at least 80,
- percentages of subjects achieving 4 fold increases in MN titers from pre to post vaccination,
- GMTs and GMR in MN titers from pre to post vaccination.

Subjects excluded from the efficacy and immunogenicity analyses

In Study V70P5, the analysis of efficacy was performed on the Efficacy FAS (Full Analysis Set). The Efficacy FAS included >98%, by group and by season, of all subjects enrolled in Seasons 2007/08 and 2008/09. The Efficacy FAS excluded only those subjects who were not vaccinated. The analysis of immunogenicity in this study was performed on the Immunogenicity FAS, which was derived from a cohort of approximately 20% of all subjects enrolled during Season 2008/09. All subjects who were not vaccinated and all subjects who did not provide at least one evaluable sample pre and post vaccination were excluded from this analysis set.

In the Phase 2 studies, the analysis of immunogenicity was based on the per protocol (PP) population. The main reasons for exclusion of subjects from the PP population were unavailability of a post second dose blood sample, blood sampling performed outside of the protocol defined window or incomplete vaccination (that is, second dose not administered). In most groups, the PP population included >70% of the vaccinated

subjects. The exception to this was Study V70P6, where the PP population in subjects >36 months of age represented ~40% of the vaccinated subjects.

The induction of strong cross reactive responses is an important side issue and is clinically important in years when the vaccine strains are a poor match to circulating strains. The ability of Fluad to elicit a cross reactive HI response in children has also been assessed in all studies except for Study V7P29. The heterologous influenza strains used for this evaluation are described in Table 3. In all studies with the exception of Study V70P2, a B strain from a different lineage was used for testing. Consistent with WHO recommendations, A strains from another season were used to evaluate the presence of cross reacting antibodies.

The analysis of immunogenicity was performed on the Immunogenicity FAS in Study V70P5 and on the PP population in the other studies. The exclusion of subjects from the analysis set was defined prior to unblinding of the studies. Two sided 95% CIs were determined for all immunogenicity parameters. For GMT and GMR values, 95% CIs were determined using analysis of variance; factors considered were vaccine group, season and centre, as applicable.

Pivotal phase 3 study V70P5

Methods

Study V70P5 dates:

- Part I (2007/08 influenza season) 2 November 2007 to 22 July 2008
- Part II (2008/09 influenza season) 29 September 2008 to 27 February 2010
- Part III (2009/10 influenza season) 30 September 2009 to 5 August 2010

This was a Phase 3, randomised, observer blind, controlled, multicentre study conducted over three consecutive seasons in Germany, Finland and Italy. Part I (2007/08 influenza season) and Part II (2008/09 influenza season) enrolled healthy children aged 6 to <72 months (stratified into two age groups: 6 to <36 months and 36 to <72 months); Part III (2009/10 influenza season) enrolled healthy children aged 6 to <36 months. Subjects enrolled during Parts I and III were followed-up for a period of 6 months; follow up in Part II was extended to 1 year for a longer term evaluation of safety. Children with a previous history of vaccination against influenza were excluded from the study.

Subjects received Fluad or one of two different control vaccines – an influenza ("flu") control vaccine or a non influenza ("non flu") control. During Part I, a non adjuvanted subunit influenza vaccine, Agrippal, was used as the flu control vaccine, following a 2:1:1 randomization scheme. A split virion influenza vaccine (Influsplit SSW) was used during Parts II and II in order to confirm results observed in the Phase 2 studies V70P2 and V70P2E1; to evaluate a potential difference in vaccine efficacy between Fluad and split influenza vaccine (as a secondary objective), randomisation was amended to follow a 2:2:1 scheme. The non flu control group received Menjugate (children 6 to <12 months of age) or Encepur Children (children ≥12 months of age). All subjects received two doses of vaccine at an interval of approximately 4 weeks. In the Fluad and flu control groups, children 6 to <36 months of age received two 0.25 mL doses, children ≥36 months of age received two 0.5 mL doses. In accordance with the Summary of Product Characteristics, subjects who received two doses of Encepur Children received a third dose after study unblinding.

The study enrolled a total of 4902 subjects: 2019 were enrolled into the Fluad group, 1849 into the flu control (Agrippal or Influsplit SSW) group and 1034 into the non flu control (Menjugate/Encepur Children) group.

The study aimed to evaluate vaccine efficacy over three seasons However, the advent of the swine influenza pandemic during study Part III (2009/10 season) resulted in an amendment to the protocol to permit the administration of pandemic influenza vaccine to all participants (as per National recommendations); evaluation of efficacy of Fluad was therefore performed only on data from the 2007/08 and the 2008/09 seasons. The evaluation of the immune responses to vaccination was restricted to study Part II (2008/09 season).

Assessment of efficacy

Efficacy against virus confirmed influenza was evaluated in this study. The study was planned to be conducted over three consecutive influenza seasons, defined as the period starting from 01 December to the end of the influenza surveillance period (approximately determined by the surveillance organizations of the countries where the trial was conducted) for the respective season. In practice, efficacy could only be validly estimated over the first two years (Seasons 2007/08 and 2008/09) of the planned three year surveillance. The evaluation of efficacy against seasonal strains was stopped early during the third year (Season 2009/10) due to the occurrence of the H1N1 pandemic. Children enrolled during this season were offered vaccination against the pandemic strain.

During each of the first two influenza seasons in which the study was conducted, parents/legal guardians of all children who received two doses of vaccine and who presented symptoms of influenza like illness (ILI, based on the definition set forth by the US Centres for Disease Control and Prevention) were asked to bring their child to the study site to be evaluated for influenza infection. If the child could not be brought to the study site, reasonable effort was made to visit the child at home and/or to obtain results from hospital, when available. Nasopharyngeal specimens were to be collected within 24 hours of the onset of symptoms – a window of up to 3 days or 7 days was allowed during Season 2007/08 and Season 2008/09, respectively. Samples were sent for testing and evaluation of subtype (A/H1N1, A/H3N2 and B) by PCR to a single reference laboratory in Germany. Efficacy was calculated on PCR confirmed cases.

Criteria for efficacy and immunogenicity evaluation

Absolute efficacy (efficacy in comparison with the non flu control) and relative efficacy (efficacy in comparison with the flu control) against PCR confirmed community acquired influenza were calculated

- Against strains matching those contained in the vaccine, and
- Against any strain.

Results

Table 5 shows the number of children available for evaluation.

Table 5: Inclusion of Subjects in the Efficacy and Immunogenicity Analyses – Study V70P5.

Age range	6 to <36 months[a]			36 to <60 months[a]		
Vaccine group	Fluad	Influsplit SSW	Menjugate/ Encepur	Fluad	Influsplit SSW	Encepur
Efficacy Analysis (Season 2007/08 and Season 2008/09)						
Total enrolled and randomized	1105[b]	996[c]	566	836[d]	777	427[e]
Efficacy FAS (%)	1103 (100)	995 (100)	566 (100)	834 (100)	777 (100)	427 (100)
Season 2007/08						
Total enrolled and randomized	188[b]	94	97	137	71	67[e]
Efficacy FAS (%)	187 (99)	93 (99)	97 (100)	136 (99)	71 (100)	67 (100)
Season 2008/09						
Total enrolled and randomized	917[b]	902[c]	469	699[d]	706	360[e]
Efficacy FAS (%)	916 (100)	902 (100)	469 (100)	698 (100)	706 (100)	360 (100)
Immunogenicity Analysis (Season 2008/09 only)						
Immunogenicity FAS (%)	166 (18)	165 (18)	83 (18)	153 (22)	151 (21)	75 (21)

a, age groups as randomised

b, two children≥36 months of age were incorrectly randomized into the 6 to <36 month cohort (one in Season 2007/08, and one in Season 2008/09); they received the 0.25 mL dose of Fluad

c, one child≥36 months of age was incorrectly randomised into the 6 to <36 month cohort; they received the 0.25 mL dose of Influsplit SSW

d, one child <36 months of age was incorrectly randomised into the 36 to <72 month cohort; they received the 0.5 mL dose of Fluad

e, three children <36 months of age were incorrectly randomised into the 36 to <72 month cohort (one in Season 2007/08, and two in Season 2008/09); all received Encepur Children

Demographics were evenly balanced between all the groups.

Efficacy results

In the 6 to <36 months age group, the overall incidence of influenza (any strain) for the two seasons was 0.82% in the Fluad group, 2.51% in the flu control (Agrippal/Influsplit SSW) group and 3.89% in the non flu (Menjugate/Encepur) group. In the overall population 6 <72 months of age, the overall incidences were, respectively, 0.67%, 2.82% and 4.73%. Most of the influenza cases reported were due to matched strains.

Absolute efficacy

The primary objective called for evaluation of the efficacy of Fluad vs. a non-flu control against influenza caused by strains matching those in the vaccine among 6 to <36 month old infants. The absolute efficacy of Fluad in the 6 to <36 months age group was estimated to be 81.36% (97.66% CI of 49.24-93.16) against matched strains. The primary objective of the study was achieved as the lower limit of the 97.66% CI was over the pre specified threshold of 40%. The absolute efficacy of Fluad against influenza due to any strain in this age group was 79.18% (95% CI of 54.78-90.42). The absolute vaccine efficacy of Fluad in the 6 to <72 months age group (secondary study objective) was 89.07% (95% CI of 77.55-94.68) to matched strains and 86.17% (95% CI of 74.48-92.51) to any strain.

Relative efficacy

Secondary objectives of the study also included evaluating the relative efficacy of Fluad as compared with a non adjuvanted flu vaccine against influenza caused by strains matching those in the vaccine and any strain among children 6 to <36 months and 6 to <72 months

of age. The relative efficacy of Fluad in the 6 to <36 months age group was estimated as 68.42% (95% CI of 26.59-86.41) for matched strains and 64.16%; 95% CI of 23.21-83.28) for any strain. The relative efficacy of Fluad in the 6 to <72 months age group was estimated as 80.17% (95% CI of 59.44-90.31) for antigenically matching strains and 75.49% (95% CI of 54.97-86.66) for any strain.

Baseline seroprotection (that is, percentage of subjects with an antibody titer ≥ 40 as determined by the HI assay) were similar between the Fluad and the comparator group for all vaccine antigens for each age cohort. The GMTs on the day of the first vaccination in each age cohort were balanced between vaccination groups. As could be expected, both seroprotection rates and GMTs tended to be higher in subjects above 36 months of age in comparison to younger subjects.

Comparison of efficacy results across all time periods in Study V70P5

Vaccine efficacy was evaluated across two influenza seasons (2007/08 and 2008/09) in children 6 to <72 months of age.

Demonstration of efficacy against vaccine matched strains

Ninety-four cases of PCR confirmed influenza due to vaccine matched strains were identified in children aged 6 to <72 months during Seasons 2007/08 and 2008/09. Nine cases were identified in children who had received Fluad, with 44 cases and 41 cases identified in the flu control and non flu control groups, respectively.

The attack rate for matched strains was 0.46% for Fluad recipients; this is lower than the attack rates of 2.48% and 4.13% observed for the flu control and non flu control groups, respectively.

The point estimate of the absolute efficacy of Fluad vaccine (that is, versus the non flu control vaccine) against matched strains was 89.07%. The point estimate of the relative efficacy (that is, versus the flu control vaccine) was calculated as 80.17%. The lower limits of the two sided CIs for both the absolute and the relative efficacy were well above zero (0), showing that the efficacy of Fluad against vaccine matched strains was statistically significantly higher with respect to both non flu and flu control vaccines.

Vaccine efficacy against vaccine matched strains in the cohort 6 to <36 months of age

Vaccine efficacy against vaccine matched strains in children 6 to <36 months of age was the primary efficacy objective of Study V70P5. For efficacy to be concluded, the lower limit of the two sided 97.66% CI around the estimated efficacy was to be at least 40%.The attack rate for vaccine matched strains in children aged 6 to <36 months was 0.63% for the Fluad group. This contrasts with markedly higher rates of 2.21% and 3.41%, respectively, for the flu control and non flu control groups. The absolute efficacy of Fluad against vaccine matched strains in this cohort was calculated to be 81.36%. The lower limit of the CI was 49.24%, thus showing that the primary objective was achieved. The relative efficacy against matched strains in this age cohort was estimated to be 68.42%.

Vaccine efficacy against vaccine matched strains in the children 36 to <72 months of age

Similarly to what was observed for children in the 6 to <36 months cohort, the attack rates in children 36 to <72 months of age were much lower for subjects in the Fluad group than for the flu control and non flu control groups. The absolute efficacy and relative efficacy of Fluad against matched strains in the older age cohort were both >90% (96% and 91%, respectively), that is, higher than what was observed in the younger children.

Demonstration of efficacy against any strain

A total of 110 PCR confirmed cases of influenza due to any strain (matched and mismatched) were reported in children aged 6 to <72 months over the two influenza seasons; 94 of these were matched H3N2 strains (described above). Of the 16 remaining

cases, 8 were due to mismatched B strains (3 in Season 2007/08 and 5 in Season 2008/09), 4 were B type viruses (lineage unknown; 2 in Season 2007/08 and 2 in Season 2008/09), and 4 were due to A strains (subtype unknown; Season 2008/09). As shown in Table 6, of the 110 total cases, 13 occurred in the Fluad group. Fifty and 47 confirmed cases occurred in the flu control and non flu control groups, respectively. The attack rate for confirmed influenza was therefore 0.67% in the Fluad group. The attack rates were markedly higher in the flu control (2.82%) and non flu control (4.73%).The point estimate of the absolute efficacy of Fluad against confirmed influenza due to any strain, that is, regardless of the antigenic match with the strains, was 86.17%, with the lower limit of the two sided CI above 40% for children 6 to <72 months of age. The point estimate of the relative efficacy of Fluad against confirmed influenza due to any strain was 75.49%.

Table 6: Efficacy of Fluad in children in Phase 3 Study V70P5 - Subjects with PCR-confirmed influenza (Efficacy FAS).

	6 to <36 months			36 to <72 months			6 to <72 months		
	Number of confirmed influenza cases	Number of subjects in efficacy population[a]	Attack Rate	Number of confirmed influenza cases	Number of subjects in efficacy population[a]	Attack Rate	Number of confirmed influenza cases	Number of subjects in efficacy population[a]	Attack Rate
Matched Strains (Seasons 2007/08 and 2008/09)									
Fluad	7	1103	0.63%	2	834	0.24%	9	1937	0.46%
Influenza control	22	995	2.21%	22	777	2.83%	44	1772	2.48%
Non-influenza control	19	566	3.41%	22	427	5.15%	41	993	4.13%
Any Strain (Seasons 2007/08 and 2008/09)									
Fluad	9	1105	0.82%	4	834	0.47%	13	1937	0.67%
Influenza control	25	995	2.51%	25	777	3.22%	50	1772	2.82%
Non-influenza control	22	566	3.89%	25	427	5.85%	47	993	4.73%

Vaccine efficacy against any strain in the cohort of children 6 to <36 months of age

The attack rate for influenza due to any strain (vaccine matched and mismatched) in children aged 6 to <36 months was 0.82% for the Fluad group (Table 6). The attack rates were distinctly higher in the flu control and non flu control groups (attack rates of 2.51% and 3.89%, respectively).The absolute efficacy of Fluad against any strain in this cohort was estimated to be 79.18% and the relative efficacy was estimated to be 64.16%.

Vaccine efficacy against any strain in the cohort of children 36 to <72 months of age

The attack rate for influenza due to any strain (matched and mismatched) in children in the 36 to <72 month age cohort was 0.47% for the Fluad group (Table 8). Clearly higher attack rates were seen in the flu control and non flu control groups, where rates of 3.22% and 5.85% were observed. The absolute efficacy of Fluad against any strain in this age cohort was estimated to be 92.1% and the relative efficacy was estimated to be 85.66 % (Table 7).

Table 7: Absolute and relative efficacy of Fluad in children in Study V70P5 (Efficacy FAS).

	6 to <36 months	36 to <72 months	6 to <72 months
Absolute Vaccine Efficacy - Fluad versus non-influenza control			
VE against matched strains (% CI[a])	**81.36 (49.24-93.16)**	95.5 (80.92-98.94)	89.07 (77.55-94.68)
VE against any strain (95% CI)	79.18 (54.78-90.42)	92.1 (77.35-97.24)	86.17 (74.48-92.51)
Relative Vaccine Efficacy - Fluad versus influenza control			
VE against matched strains (95% CI)	68.42 (26.59-86.41)	91.36 (63.35-97.96)	80.17 (59.44-90.31)
VE against any strain (95% CI)	64.16 (23.21-83.28)	85.66 (58.95-94.99)	75.49 (54.97-86.66)

VE against any strain (95% CI) a 97.66% CI for primary study endpoint (absolute efficacy against vaccine matched strains in subjects 6 to <36 months); 95% CI for absolute efficacy against vaccine matched strains in subjects 36 to <72 months and in subjects 6 to <72 months; VE = vaccine efficacy; bold = primary study objective

Antibody titer as correlated with protection

To evaluate whether the protective effect of a vaccine can be explained by the day 50 antibody titer linear logistic regression models were fit with log titer and vaccine group included as independent predictors and onset of influenza as dependent variable. The titers are highly inversely (p=0.0071) related to infection incidence indicating that the higher the titer the lower the risk of acquiring an infection. The effect of the vaccine group however changed from significant (p=0.03) to non significant (p=0.1349) after controlling for antibody titer, indicating that the antibody titer mediates most of the vaccine effect on incidence of infection. Thus, according to the Prentice criterion,[13] antibody titer can be considered as correlate of protection. The probability between occurrence of influenza and H3N2 antibody titer level was evaluated using a model[14] that accommodates both antibody titers and factors independent of antibody titers. Results suggest that the conventional use of the adult correlate of protection (threshold titer of 40 to predict a clinical protection rate of 50%) may not be appropriate in children, and that a higher threshold (estimated as a titer of 110) may be a more accurate predictor. Titer cut off of 215, 330 and 629 may be used to predict more desirable protection rates of 70%, 80% and 90%, respectively.

Immunogenicity in children 6 to <36 months of age

Study V70P5 was designed to enroll only children who had not been vaccinated in a previous influenza season; all children were therefore administered two doses of vaccine. No changes in antibody levels the non flu (Menjugate/Encepur) control group were observed following vaccination in this group. HI antibody titers approximately three weeks after receipt of the second vaccine dose in children enrolled in this season is shown by age group in Table 8. Vaccination with Fluad induced a robust immune response in children 6 to <36 months of age as shown by the increase in HI antibody levels post vaccination (Table 9). The GMR across strains ranged between 14 and 86 for Fluad and between 2.05 and 5.57 for the influenza vaccine control (Influsplit SSW) in 6 to <36 month old children. The higher immunogenicity of Fluad was demonstrated as the lower limit of the two sided 95% CI of the ratio of the post vaccination GMTs (GMT Fluad/GMT flu control) was 5.72 or above at Day 50 for the A and B strains and the lower limit was >1.

[13] Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat. Med.* 8: 431-440 (1989).

[14] Dunning AJ. A model for immunological correlates of protection. *Stat. Med.* 25: 1485-1497 (2006).

Table 8: Immunogenicity of Fluad in children in Study V70P5 (Immunogenicity FAS) – HI assay (homologous strains) at Day 50 (post vaccination 2) – Season 2008/09.

		6 to <36 months			36 to <72 months		
VaccineGroup		Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)	Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)
Number of subjects at Day 50		N=160	N=162		N=150	N=147	
H1N1	GMT (95% CI)	513 (405-652)	35 (27-44)	15 (11-21)	1101 (853-1421)	264 (204-343)	4.16 (2.94-5.89)
	GMR[a] (95% CI)	83 (70-98)	4.55 (3.84-5.39)	18 (14-23)	68 (57-80)	19 (16-22)	3.59 (2.84-4.54)
	% SP[b] (95% CI)	100 (98-100)	38 (31-46)	62 (54-69)	100 (98-100)	82 (75-88)	18 (12-25)
	% SC[c] (95% CI)	100 (98-100)	38 (30-46)	62 (55-69)	100 (98-100)	82 (75-88)	18 (12-25)
H3N2	GMT (95% CI)	510 (426-609)	32 (27-39)	16 (12-20)	1145 (871-1505)	308 (233-407)	3.72 (2.56-5.39)
	GMR[a] (95% CI)	86 (73-102)	5.57 (4.73-6.55)	16 (12-19)	40 (32-51)	12 (9.37-15)	3.39 (2.45-4.68)
	% SP[b] (95% CI)	99 (97-100)	45 (37-53)	54 (47-62)	98 (94-100)	88 (83-93)	10 (5-17)
	% SC[c] (95% CI)	98 (95-100)	44 (36-52)	54 (46-62)	97 (92-99)	84 (77-90)	12 (6-19)
B	GMT (95% CI)	86 (74-100)	12 (11-14)	6.99 (5.72-8.53)	139 (118-163)	41 (35-48)	3.39 (2.71-4.23)
	GMR[a] (95% CI)	14 (13-16)	2.05 (1.81-2.31)	6.97 (5.9-8.24)	20 (18-23)	5.55 (4.83-6.38)	3.69 (3.06-4.45)
	% SP[b] (95% CI)	88 (81-92)	19 (13-25)	69 (60-76)	99 (95-100)	60 (51-68)	39 (31-47)
	% SC[c] (95% CI)	88 (81-92)	19 (13-25)	69 (60-76)	99 (95-100)	59 (50-67)	40 (32-48)

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs

b, SP = seroprotection = HI titer≥ 40

c, cask = seroconversion or significant increase = the percentage of subjects achieving at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (~10) or a rise from < 10 to ~40 in those who were seronegative

d, ratios between groups are presented for GMTs and GMRs; differences between groups are presented for SP and SC

Most subjects (88-100%) who received Fluad had HI antibody titers ≥ 40 against A and B strains three weeks after the second dose. Antibody titers elicited to the B strain were comparatively lower with respect to the A strains. However, titers achieved following vaccination with Fluad for the B strain were approximately 7 fold higher compared to the influenza control. The higher immunogencity of Fluad resulted in more CHMP criteria (those set for adults 18-60 years of age) being met. All three criteria as measured by the HI assay were met for all strains after the two dose course with Fluad, whereas two criteria at most were achieved with the influenza control in the younger children. The major differences between groups were observed for the B strain.

Strong immune responses following vaccination with Fluad were also observed using the SRH test (Table 9). The CHMP criteria for the SRH response as set for adults 18-60 years of age were also met for all strains after the two dose course with Fluad. Similarly to what was observed using the HI test, antibody levels as measured by SRH were higher in Fluad recipients in comparison with Influsplit SSW recipients. Seroprotection rates ≥80% were observed for Fluad recipients for the three vaccine strains; the seroprotection rates in Influspit SSW recipients was no higher than 55% for any strain. The superior immunogenicity of Fluad was further confirmed by the results from the MN test.

Table 9: Immunogenicity of Fluad in children in Study V70P5 (Immunogenicity FAS) – SRH assay (homologous strains) at Day 50 (post vaccination 2) – Season 2008/09.

		6 to <36 months			36 to <72 months		
Vaccine Group		Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)	Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)
Number of subjects at Day 50		N=15	N=22		N=22	N=15	
H1N1	GMT (95% CI)	51 (33-77)	21 (15-29)	2.43 (1.47-4.01)	52 (33-81)	28 (17-46)	1.88 (0.9-3.89)
	GMR[a] (95% CI)	**8.6 (5.54-13)**	**3.3 (2.31-4.69)**	2.61 (1.55-4.39)	**6.11 (3.79-9.85)**	**3.87 (2.25-6.65)**	1.58 (0.73-3.43)
	% SP[b] (95% CI)	**87 (60-98)**	55 (32-76)	32 (2-56)	**90 (70-99)**	60 (32-84)	30 (3-57)
	% SC[c] (95% CI)	**87 (60-98)**	**64 (41-83)**	23 (-7-47)	**90 (70-99)**	**60 (32-84)**	30 (3-57)
H3N2	GMT (95% CI)	45 (30-65)	12 (8.55-16)	3.82 (2.42-6.03)	65 (47-90)	38 (26-54)	1.74 (1.03-2.94)
	GMR[a] (95% CI)	**4.14 (2.72-6.32)**	1.74 (1.24-2.45)	2.38 (1.44-3.92)	**4.21 (2.82-6.3)**	**4.2 (2.66-6.63)**	1 (0.52-1.93)
	% SP[b] (95% CI)	**100 (78-100)**	32 (14-55)	68 (44-84)	**100 (84-100)**	**73 (45-92)**	27 (9-52)
	% SC[c] (95% CI)	**100 (78-100)**	36 (17-59)	64 (40-80)	**100 (84-100)**	**53 (27-79)**	47 (25-70)
B	GMT (95% CI)	29 (18-48)	13 (8.91-20)	2.17 (1.2-3.92)	36 (25-50)	41 (28-60)	0.87 (0.5-1.52)
	GMR[a] (95% CI)	**6.2 (3.91-9.82)**	2 (1.38-2.89)	3.1 (1.5-5.35)	**3.94 (2.58-6.03)**	**6.06 (3.75-9.8)**	0.65 (0.33-1.3)
	% SP[b] (95% CI)	**80 (52-96)**	32 (14-55)	48 (16-71)	**90 (70-99)**	**73 (45-92)**	17 (-8-44)
	% SC[c] (95% CI)	**80 (52-96)**	32 (14-55)	48 (16-71)	**90 (70-99)**	**80 (52-96)**	10 (-13-37)

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs

b, SP = seroprotection = SRH diameter ≥25 mm2

c, SC = seroconversion or significant increase = the percentage of subjects achieving at least a 4-fold increase in SRH diameter from a seropositive pre-vaccination titer (≥25 mm2) or a rise from <25 mm ^{2} to ≥25 mm^2 in those who were seronegative

d, Ratios between groups are presented for GMTs and GMRs; differences between groups are presented for SP and SC. Bold when the respective CHMP criterion for adults 18-60 years of age is achieved

The immune responses measured by HI in the Phase 2 Studies V70P2, V70P6 and V7P29 are shown in Table 10. In each of the studies, vaccination of children 6 to <36 months of age with Fluad induced high levels of HI antibodies; the CHMP criteria for immunogenicity set for adults 18-60 years of age were met for each strain. In each of the studies, Fluad induced a stronger HI response (as assessed either by seroprotection or seroconversion rates or by GMRs) for at least one of the component antigens with respect to the comparator vaccine.

Table 10: Immunogenicity of Fluad in children in pivotal Phase 3 Study V70P5 (Immunogenicity FAS) – MN assay (homologous strains) at Day 50 (post vaccination 2) – Season 2008/09.

		6 to <36 months			36 to <72 months		
Vaccine		Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)	Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)
Number of subjects at Day 50		N=56	N=66		N=48	N=56	
H1N1	GMT (95% CI)	325 (217-486)	22 (15-31)	15 (8.78-26)	781 (451-1352)	223 (135-367)	3.51 (1.72-7.17)
	GMR[a] (95% CI)	58 (43-78)	3.27 (2.5-4.27)	18 (12-26)	59 (43-82)	14 (10-19)	4.18 (2.73-6.4)
	% ≥80[b] (95% CI)	98 (90-100)	27 (17-40)	71 (58-81)	96 (86-99)	64 (50-77)	32 (18-45)
	% ≥4-fold[c] (95% CI)	100 (94-100)	36 (25-49)	64 (52-74)	100 (93-100)	82 (70-91)	18 (10-30)
H3N2	GMT (95% CI)	443 (320-613)	26 (19-35)	17 (11-26)	721 (429-1209)	174 (108-278)	4.15 (2.11-8.15)
	GMR[a] (95% CI)	74 (57-95)	4.44 (3.51-5.61)	17 (12-23)	31 (21-46)	10 (7.17-15)	2.99 (1.77-5.03)
	% ≥80[b] (95% CI)	100 (94-100)	26 (16-38)	74 (63-83)	98 (89-100)	71 (58-83)	26 (14-40)
	% ≥4-fold[c] (95% CI)	100 (94-100)	50 (37-63)	50 (38-62)	94 (83-99)	73 (60-84)	21 (7-34)
B	GMT (95% CI)	407 (282-588)	28 (20-39)	15 (9.04-24)	562 (382-827)	126 (89-179)	4.45 (2.69-7.37)
	GMR[a] (95% CI)	62 (46-83)	4.24 (3.23-5.56)	15 (9.8-22)	83 (59-116)	16 (12-22)	5.15 (3.32-7.99)
	% ≥80[b] (95% CI)	95 (85-99)	30 (20-43)	64 (50-75)	98 (89-100)	68 (54-80)	30 (18-43)
	% ≥4-fold[c] (95% CI)	100 (94-100)	48 (36-61)	52 (40-63)	98 (89-100)	86 (74-94)	12 (2-24)

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs
b, % ≥80 = percentage of subjects with MN titer ≥80 post vaccination 2

c, % ≥4-fold = the percentage of subjects achieving at least a 4 fold increase in MN titer from pre-vaccination
d, Ratios between groups are presented for GMTs and GMRs; differences between groups are presented for SP and SC

Immunogenicity in children 36 months of age and above

Data accrued for the 36 to <72 month age cohort in pivotal Study V70P5 is shown in Table 8. A strong immune response following vaccination with Fluad was also observed in children 36 to <72 months of age. The GMR of HI antibody levels across strains ranged between 20 and 68 for Fluad and between 5.55 and 19 for the influenza vaccine control. Similarly to what was observed in the younger age cohort, the lower limit of the two sided 95% CI of the ratio of the post vaccination GMTs (GMT Fluad/GMT flu control) was ≥2.56 at Day 50 for all strains; as the lower limits were >1, the null hypothesis that Fluad is not more immunogenic than flu control can therefore also be rejected in this age cohort.

Virtually all subjects (≥ 98%) who received Fluad had HI antibody titers ≥ 40 against A and B strains after the second dose. As shown previously for the younger age cohort, antibody titers elicited to the B strain were lower compared to the A strains. All CHMP criteria (as set for adults 18-60 years) of age were met in this age cohort after the two dose course with Fluad and most were met after a two dose course of the influenza vaccine control. Higher HI antibody levels (whether expressed as GMTs, seroprotection or seroconversion rates) were invariably attained following vaccination with Fluad for all vaccine strains.

As shown in Table 9, strong immune responses following vaccination with Fluad were also observed using the SRH test. The CHMP criteria set for adults 18-60 years of age for the SRH response were met for all strains after the two dose course with Fluad in children in the older age cohort. Higher GMTs were obtained after vaccination with Fluad in comparison with the influenza vaccine control for both A strains; higher seroprotection and seroconversion rates were observed after vaccination with Fluad for all three strains. The superior immunogenicity of Fluad was also observed when antibody levels were assessed using MN test (Table 10).

Phase 2 studies

Study V70P2

Study V70P2 dates:

· 14 November 2006 to 24 August 2007

This was a Phase 2, observer blind, randomised, single centre study performed in Finland to evaluate the immunogenicity and safety of Fluad and Vaxigrip in healthy children aged 6 to <36 months. Children were enrolled and randomly assigned (1:1) to receive two 0.25 mL doses of vaccine administered 4 weeks apart. The study subjects were stratified into five age groups (6 to <12 months; 12 to <18 months; 18 to <24 months; 24 to <30 months; 30 to <36 months), each one maintaining the 1:1 randomisation ratio between the two vaccines. A total of 281 subjects were enrolled, 139 to receive Fluad and 142 to receive Vaxigrip.

Criteria for immunogenicity evaluation

Antibody levels against homologous strains were measured by HI on sera collected at baseline (Day 1), after one injection (Day 29) and after two injections (Day 50). Antibody persistence was evaluated at Day 209.

Immunogenicity results

The primary objective of this study was to compare, using the CHMP criteria, the immune response after one Fluad injection to that after two Vaxigrip injections (all age strata combined). After one Fluad injection, two of the three CHMP criteria were met for the A/H1N1 strain, all three criteria were met for the A/H3N2 strain but no criteria were met

for the B strain. After two Vaxigrip injections all three CHMP criteria were met against both of the A strains whereas only one CHMP criterion was met for the B strain. For all three strains and in each of the five age strata, HI titers after one injection of Fluad were lower (as shown by the point estimates of the post vaccination GMTs) than after two injections of Vaxigrip.

After the second injection (Day 50), Fluad fulfilled all three CHMP criteria for the three strains. Higher GMTs were observed in the Fluad group in comparison with the Vaxigrip group for each strain, as shown by the 95% CIs of the GMT ratios (GMT Fluad/GMT Vaxigrip; all age strata combined) which did not include the value one (1.0).

At six months after the second injection, the point estimates of the GMTs, and the point estimates of the GMRs of HI titers relative to baseline, were higher in the Fluad group compared with the Vaxigrip group.

Study V70P2

Study V70P2E1 dates:

· 14 November 2007 to 11 June 2008

This was a Phase 2, observer blind, single centre, extension study performed in Finland to evaluate the immunogenicity and safety of Fluad and Vaxigrip in healthy children who were vaccinated approximately one year earlier in Study V70P2. In this study, children were divided into two age strata: <36 months and ≥36 months. Children who received Fluad in Study V70P2 received a single dose of Fluad in this study; children who received Vaxigrip in Study V70P2 received a single dose of Vaxigrip. Children <36 months of age received a 0.25 mL dose and children ≥36 months received a 0.5 mL dose. A total of 89 children were enrolled, 43 to receive Fluad and 46 to receive Vaxigrip.

Criteria for immunogenicity evaluation

Antibody levels were measured by HI in samples obtained pre vaccination (Day 1 of the extension study) and post vaccination (Day 22). The primary objective was the evaluation of the immune response to homologous vaccine strains, in the overall population and in each age stratum, via the point estimates of post vaccination GMTs. Post vaccination GMTs were compared as a secondary objective, with non inferiority to be concluded if the lower limit of the 95% CI for the ratio of post-vaccination GMTs (GMT Fluad/GMT Vaxigrip) was >0.5 for each strain. The immunogenicity of Fluad and Vaxigrip was also evaluated using the CHMP criteria for subjects 18-60 years old. Immunogenicity was also evaluated to heterologous influenza strains.

Immunogenicity results

At Day 1, the point estimates of the geometric mean HI titers in children vaccinated during the previous influenza season (Study V70P2) with Fluad were higher in comparison with children vaccinated with Vaxigrip, both overall and in each age stratum (<36 months and ≥36 months). Fluad induced higher GMTs compared with Vaxigrip, against all three homologous influenza strains, irrespective of the age stratum. Due to the low number of subjects enrolled, the study did not have enough power to test the null hypothesis associated with the secondary immunogenicity objective. Nevertheless, the 90% CIs of the post vaccination GMT ratios (GMT Fluad/GMT Vaxigrip; both strata combined) excluded 1, suggesting a better response for Fluad than for Vaxigrip. Three weeks after vaccination, Fluad fulfilled all three CHMP criteria against all three strains, while Vaxigrip failed to reach the cut-off for seroprotection against the B strain in children <36 months of age. Both vaccines met all three CHMP criteria against the three strains in children ≥36 months of age. Fluad consistently induced higher HI antibody titers, as shown by the higher point-estimates of the GMTs for the three heterologous strains evaluated compared to Vaxigrip. Seroprotection rates were high (>70%) for both heterologous A strains in Fluad

recipients, but were low (<10%) for the heterologous B strain. This was not unexpected as the B strain in the vaccine was of a different lineage to the strain used for testing.

Study V70P6

Study V70P6 dates:

· 28 January 2008 to 15 October 2008

This was a Phase 2, observer blind, randomised (1:1 ratio), multicentre study performed in Guatemala to evaluate the safety and immunogenicity of Fluad and Fluzone in healthy children aged 6 to <60 months. Children 6 to <36 months of age received two 0.25 mL doses, and children 36 to <60 months of age received two 0.5 mL doses, administered 4 weeks apart. The study subjects were stratified into six age groups (6 to <12 months, 12 to <18 months: 18 to <24 months, 24 to <30 months, 30 to <36 months and 36 to <60 months), each one maintaining the 1:1 randomisation ratio between the two vaccines. A total of 360 children were enrolled, 180 to receive Fluad and 180 to receive Fluzone.

Criteria for immunogenicity evaluation

Antibody levels were measured by HI on sera collected at baseline (Day 1), after one injection (Day 29), and after two injections (Day 50). The immunogenicity objectives of the study were the evaluation of the post second dose immune response to homologous and heterologous strains in children aged 6 to <36 months, 36 to <60 months and overall (6 to <60 months).

Immunogenicity results

Immunogenicity results in children 6 to <36 months of age: After the second vaccine dose (Day 50), all three CHMP criteria, as defined for healthy adults, were met in both Fluad and Fluzone groups for the three vaccine strains. The point estimates of the GMTs and GMRs were consistently higher in the Fluad group compared to the Fluzone group. The seroprotection rate against the B strain was also higher in the Fluad group (95% versus 75% for the Fluzone group). The point estimates for GMTs, SP and SC rates against heterologous strains were higher in the Fluad group compared to the Fluzone group.

Immunogenicity results in children 36 to <60 months of age: After the second vaccine dose (Day 50), all three CHMP criteria, as defined for healthy adults, were met in both Fluad and Fluzone groups for the three vaccine strains. The point estimates of the GMRs were higher in the Fluad group compared to the Fluzone group for all three vaccine strains. Point estimates for GMTs were higher in the Fluad group compared to the Fluzone group against A/H1N1 and B strains, whereas the GMT was higher in the Fluzone group against the A/H3N2 strain. Seroprotection against the B strain after vaccination was higher in the Fluad group (96% versus 80% for the Fluzone group). Fluad induced at least equal GMTs, seroprotection and seroconversion rates in comparison with Fluzone against heterologous vaccine strains.

Immunogenicity results in children 6 to <60 months of age

The data for the overall population were similar to those observed for each age strata, with the most pronounced differences between treatment groups observed for the homologous and heterologous B strains.

Study V70P29

Study V70P29 dates:

· 12 August 1996 to 14 June 1997

This was a Phase 2, randomised, multicentre study performed in the United States to evaluate the safety and immunogenicity of Fluad and Fluogen/Flushield in healthy children and adolescents 9 to 17 years of age. In the pilot phase of the study, 10 children 9

to 12 years of age and 5 children 13 to 17 years of age received one 0.5 mL dose of Fluad. In the observer-blinded phase, 202 children in two stratified age groups (9 to 12 years of age and 13 to 17 years of age) were randomly assigned (1:1) to receive one 0.5 mL dose of either Fluad or Fluogen/Flushield.

Criteria for immunogenicity evaluation

Antibody levels were measured by HI on sera collected at baseline and 28 days after vaccination. The primary immunogenicity objective was to compare antibody responses at 28 days post immunisation in the Fluad group to those of the Fluogen/Flushield group.

Immunogenicity results

At Day 28, no statistically significant differences in GMTs were seen between vaccine groups for any strain in either age stratum. The GMRs for the B strain were higher in the Fluad group than in the Fluogen/Flushield group for both age strata (23 versus 13 in the 9-12 year stratum and 14 versus 8.4 in the 13-17 year stratum); the differences between groups were statistically significant ($p<0.01$). The percentage of subjects with at least a fourfold increase in titer from baseline to postvaccination for the A/H3N1 and the B strains was significantly higher in the Fluad group in the older age stratum (both $p<0.05$).

Analysis performed across trials (pooled analyses and meta analysis)

Study populations

Apart from the 2009/10 season in Study V70P5, the majority of subjects completed the studies. Withdrawals were generally equally distributed among Fluad and control vaccine groups. In Study V70P5, >95% of the subjects, by group, completed the study during seasons 2007/08 and 2008/09. In the 2007/08 season, a slightly higher percentage of premature withdrawals were observed in the Fluad and flu control (Agrippal) group with respect to the Menjugate/Encepur group. Most of the premature withdrawals were due to the subjects being lost to follow up. In the 2009/10 season, more than 50% of the subjects were withdrawn prematurely, mostly due to withdrawal of consent (33-37% across the vaccine groups) and protocol deviations (19-20% across vaccine groups). This was the direct result of the decision to favor vaccination against pandemic strains, rather than seasonal strains, during this season. In Phase 2 studies V7P29 and V70P2, the most common reason for discontinuation was consent withdrawal, whereas in Study V70P6, it was lost to follow up. Across all vaccination groups, the frequency of AEs leading to withdrawal was less than or equal to 1.1%. Withdrawal was due to death for one subject enrolled in Study V70P6 (thought to be unrelated to study drug.

The populations included in the evaluation of efficacy in all studies were mostly balanced for age, gender, and ethnic origin among the groups receiving Fluad and the groups receiving comparator vaccines. Imbalances between groups, when present, were not considered to be of clinical relevance for the evaluation of the immunological profiles of the vaccines.

Phase 2 study results

Baseline immune status

Differences in baseline titers could were most likely to be due to the difference in age and exposure. In Study V7P29, subjects had higher baseline titers for all three strains, in Study V70P6, subjects had higher baseline titers for the H1N1 and H3N2 strains. Baseline titers were however generally similar across treatment groups within the same study. The exception to this was Study V70P2E1, for which the antibody levels of the group previously vaccinated with Fluad were higher than those of the group previously vaccinated with comparator influenza vaccine.

Immunogenicity in children vaccinated in the previous influenza season

Table 11 shows the results obtained Study V70P2E1, where children previously vaccinated in Study V70P2 received a third consecutive dose (at an interval of approximately one year) of either Fluad or comparator vaccine. The CHMP criteria were met for all three strains when either of the two vaccines was administered. Fluad induced higher GMTs against all three vaccine antigens with respect to Vaxigrip. Indeed, in both age strata combined, the 90% CIs of the post vaccination GMT ratios (GMT Fluad/GMT Vaxigrip) always excluded 1. The most marked differences been treatment groups were seen in the 6 to <36 month cohort, where the highest seroconversion rates and GMRs were invariably achieved in Fluad recipients.

Table 11: Immunogenicity of Fluad after a third consecutive dose in children in the Study V70P2E1 (PP population) – HI assay (homologous strains) at Day 22 post vaccination.

Age range		16 to <36 months		≥36 months	
Vaccine group		Fluad	Vaxigrip	Fluad	Vaxigrip
Number of subjects at Day 22		N=23	N=20	N=18	N=20
A/H1N1	GMT (95% CI)	1068 (671-1701)	283 (171-471)	978 (617-1549)	511 (297-879)
	GMR[a] (95% CI)	**122 (77-194)**	**43 (25-75)**	**63 (28-141)**	**64 (34-121)**
	% SP[b] (95% CI)	**100 (85-100)**	**100 (83-100)**	**100 (81-100)**	**100 (83-100)**
	% SC[c] (95% CI)	**100 (85-100)**	**95 (75-100)**	**89 (65-99)**	**95 (75-100)**
A/H3N2[e]	GMT (95% CI)	1401 (1020-1924)	251 (186-338)	1076 (765-1513)	608 (398-926)
	GMR (95% CI)	**17 (11-24)**	**7.86 (5.01-12)**	**18 (9.58-34)**	**19 (9.68-36)**
	% SP (95% CI)	**100 (85-100)**	**100 (83-100)**	**100 (81-100)**	**100 (83-100)**
	% SC (95% CI)	**100 (85-100)**	**85 (62-97)**	**94 (73-100)**	**85 (62-97)**
B[e]	GMT (95% CI)	178 (137-231)	21 (14-32)	187 (130-269)	83 (56-121)
	GMR (95% CI)	**19 (14-27)**	**4.14 (2.7-6.35)**	**17 (11-26)**	**16 (11-24)**
	% SP (95% CI)	**100 (85-100)**	**45 (23-68)**	**100 (81-100)**	**90 (68-99)**
	% SC (95% CI)	**96 (78-100)**	**45 (23-68)**	**100 (81-100)**	**90 (68-99)**

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs

b, SP = seroprotection = HI titer≥ 40

c, SC = seroconversion or significant increase = the percentage of subjects achieving at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (≥10) or a rise from < 10 to≥40 in those who were seronegative

e, The A/H3N2 and B strains in the vaccine were the same as the previous year (Study V70P2)

bold, when the respective criterion for adults 18-60 years of age is achieved

Immunogenicity results against heterologous strains

The antibody response to heterologous strains was examined in all studies with the exception of Study V7P29.

Immunogenicity in children 6 to <36 months of age

Table 12 shows the results for subjects who received either Fluad or comparator vaccine in pivotal Study V70P5. HI antibody levels were higher in the Fluad group with respect to the flu control groups in children 6 to <36 months of age for both of the heterologous A strains. The difference was statistically significant as the lower limit of the two sided 95% CI around the GMT ratio (GMT Fluad/GMT flu control) was 5.33 or above, that is, >1 for the two A strains. The response elicited to the heterologous B strain was weak in both the Fluad and flu control groups with GMTs below or close to 10. These results were not unexpected given the differences in lineages between the vaccine and the test strains. The lower limit of the two sided 95% CI of the GMT ratio (GMT Fluad/GMT flu control) was nevertheless >1, showing a statistically significant difference in response between the Fluad and flu control group.

Table 12: Immunogenicity of Fluad in children in Study V70P5 (PP population) – HI assay (heterologous strains) at Day 50 (post vaccination 2) – Season 2008/09.

Age range		6 to <36 months			36 to <72 months		
Vaccine Group		Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)	Fluad	Influsplit SSW	Differences or ratios[d] between groups (95% CI)
Number of subjects at Day 50		N=160	N=162		N=150	N=147	
H1N1	GMT (95% CI)	122 (94-157)	16 (13-21)	7.54 (5.33-11)	463 (328-653)	120 (85-171)	3.84 (2.4-6.15)
	GMR[a] (95% CI)	18 (16-21)	1.96 (1.7-2.25)	9.32 (7.69-11)	22 (19-25)	6.52 (5.6-7.58)	3.31 (2.71-4.05)
	% SP[b] (95% CI)	95 (90-98)	24 (18-31)	71 (63-78)	98 (94-100)	68 (60-75)	30 (23-38)
	% SC[c] (95% CI)	94 (89-97)	23 (17-30)	71 (63-78)	98 (94-100)	68 (60-75)	30 (23-38)
H3N2	GMT (95% CI)	261 (218-313)	20 (17-24)	13 (10-16)	1044 (758-1437)	272 (197-377)	3.84 (2.48-5.93)
	GMR[a] (95% CI)	43 (37-50)	3.01 (2.59-3.51)	14 (12-17)	26 (22-31)	7.33 (6.09-8.81)	3.57 (2.79-4.57)
	% SP[b] (95% CI)	100 (98-100)	30 (23-37)	70 (63-77)	99 (96-100)	80 (73-86)	19 (13-26)
	% SC[c] (95% CI)	100 (98-100)	27 (20-35)	73 (66-79)	97 (92-99)	72 (64-79)	25 (17-33)
B	GMT (95% CI)	9.64 (8.96-10)	5.55 (5.16-5.97)	1.74 (1.57-1.92)	15 (13-17)	8.23 (7.32-9.26)	1.84 (1.57-2.15)
	GMR[a] (95% CI)	1.94 (1.8-2.08)	1.11 (1.03-1.19)	1.74 (1.58-1.93)	2.98 (2.67-3.32)	1.61 (1.44-1.8)	1.85 (1.59-2.14)
	% SP[b] (95% CI)	5 (2-10)	0 (0-2)	5 (3-10)	15 (10-22)	5 (2-10)	10 (5-17)
	% SC[c] (95% CI)	5 (2-10)	0 (0-2)	5 (3-10)	15 (10-22)	5 (2-10)	10 (5-17)

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs

b, SP = seroprotection = HI titer≥ 40

c, SC = seroconversion or significant increase = the percentage of subjects achieving at least a 4 fold increase in HI titer from a seropositive pre vaccination titer≥(10) or a rise from < 10 to≥ 40 in those who were seronegative

d, Ratios between groups are presented for GMTs and GMRs; differences between groups are presented for SP and SC

Similar results were obtained in the Phase 2 studies (Table 13), where the antibody responses to the heterologous A strains were higher than the responses observed to the heterologous B strains. In all instances, the antibody responses elicited to heterologous strains in children vaccinated with Fluad were more robust than those observed following vaccination with comparator influenza vaccine in that seroconversion rates, seroprotection rates and GMTs were invariably higher in Fluad recipients.

Table 13: Immunogenicity of Fluad in children in Phase 2 Studies V70P2 and V70P6 (PP population) – HI assay (heterologous strains) at Day 50 (post vaccination 2).

Age range		6 to <36 months				≥36 to <60 months	
Study		V70P2		V70P6		V70P6	
Vaccine Group		Fluad	Vaxigrip	Fluad	Fluzone	Fluad	Fluzone
Number of subjects at Day 50		N = 104	N = 118	N=97	N=102	N=23	N=20
H1N1	GMT (95% CI)	35 (41-72)	26 (20-34)	394 (298-522)	279 (213-367)	458 (259-809)	426 (228-793)
	GMR[a] (95% CI)	9.11 (7.57-11)	4 (3.36-4.76)	9.09 (7.06-12)	6.24 (4.88-7.97)	12 (6.7-20)	7.01(3.83-13)
	% SP[b] (95% CI)	71 (61-80)	35 (26-44)	100 (96-100)	98 (93-100)	96 (78-100)	100 (83-100)
	% SC[c] (95% CI)	71 (61-80)	34 (25-43)	87 (78-93)	73 (63-81)	74 (52-90)	80 (56-94)
H3N2	GMT (95% CI)	106 (80- 141)	41 (31- 53)	475 (346-651)	141 (103-192)	629 (363-1091)	1014 (556-1850)
	GMR[a] (95% CI)	13 (11-15)	4.78 (4.1-5.58)	25 (19-33)	8.71 (6.64-11)	16 (8.97-27)	16 (8.59-29)
	% SP[b] (95% CI)	93 (87-97)	53 (43-62)	100 (96-100)	91 (84-96)	100 (85-100)	100 (83-100)
	% SC[c] (95% CI)	92 (85-97)	49 (40-59)	96 (90-99)	79 (70-87)	91 (72-99)	90 (68-99)
B	GMT (95% CI)	11 (9.75 -12)	6.07 (5.42 - 6.8)	55 (47-65)	25 (21-29)	73 (45-119)	80 (47-136)
	GMR[a] (95% CI)	2.12 (1.88-2.38)	1.21 (1.09-1.35)	3.73 (3.06-4.54)	1.77 (1.46-2.15)	4.88 (2.92-7.2)	2.24 (1.37-3.66)
	% SP[b] (95% CI)	9 (4-16)	3 (1-7)	90 (82-95)	56 (46-66)	78 (56-93)	80 (56-94)
	% SC[c] (95% CI)	8 (3-15)	3 (1-7)	55 (44-65)	19 (12-28)	70 (47-87)	45 (23-68)

a, GMR = geometric mean ratio = Ratio of day 50/day 1 GMTs

b, SP = seroprotection = HI titer≥ 40

c, SC = seroconversion or significant increase = the percentage of subjects achieving at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (≥10) or a rise from < 10 to ≥40 in those who were seronegative

Immunogenicity in children 36 months of age and above

In Study V70P5, HI antibody levels to all three heterologous strains were higher in the 36 to <72 month cohort with respect to children below 36 months of age (Table 12). As observed in younger children, the response to the heterologous B strain was the weakest of the responses.

The differences in responses between the Fluad group and the flu control group were statistically significant for both A strains as the GMT ratios (GMT Fluad/GMT flu control) were >1, with a lower limit for the two sided 95% CI ≥2.4. A strong immune response to heterologous strains was also observed in the Phase 2 Study V70P6 (Table 13). The seroprotection rate after two doses of Fluad was at least 96% for the two A strains and was 78% for the B strain. Similar results were obtained for Fluad and the comparator vaccine (Fluzone).

Immunogenicity in children vaccinated in the previous influenza season

The immune response towards heterologous strains in children administered three consecutive dose of Fluad or comparator vaccine (Vaxigrip) in Studies V70P2 and V70P2E1 is shown in Table 14. High seroconversion and seroprotection rates (≥89%) were observed for heterologous A strains after vaccination with Fluad; a less robust response (seroconversion and seroprotection rates of approximately 30%) was observed against the heterologous B strain in both age cohorts. Importantly, for all three heterologous strains, the immune response after vaccination with Fluad was similar to, or higher than, that observed after vaccination with Vaxigrip in both age cohorts.

Table 14: Immunogenicity of Fluad as a third dose in children in Study V70P2E1 (PP population) – HI assay (heterologous strains) at Day 22 post vaccination.

Age range		6 to <36 months		≥36 months	
Vaccine Group		Fluad	Vaxigrip	Fluad	Vaxigrip
Number of subjects at Day 22		N=23	N=20	N=18	N=20
H1N1	GMT (95% CI)	1037 (676-1590)	211 (127-351)	871 (586-1294)	485 (266-885)
	GMR[a] (95% CI)	57 (34-94)	22 (13-36)	37 (18-77)	49 (24-98)
	% SP[b] (95% CI)	100 (85-100)	95 (75-100)	100 (81-100)	95 (75-100)
	% SC[c] (95% CI)	100 (85-100)	90 (68-99)	89 (65-99)	90 (68-99)
H3N2[e]	GMT (95% CI)	378 (244-585)	87 (57-134)	308 (185-514)	181 (109-300)
	GMR[a] (95% CI)	21 (13-32)	10 (6.57-15)	21 (12-37)	16 (8.43-29)
	% SP[b] (95% CI)	100 (85-100)	95 (75-100)	100 (81-100)	95 (75-100)
	% SC[c] (95% CI)	100 (85-100)	85 (62-97)	100 (81-100)	80 (56-94)
B[e]	GMT (95% CI)	24 (17-32)	6.16 (4.97-7.62)	22 (15-31)	10 (7.25-15)
	GMR[a] (95% CI)	4.72 (3.43-6.49)	1.23 (0.99-1.52)	4.16 (2.89-5.98)	2.07 (1.45-2.96)
	% SP[b] (95% CI)	30 (13-53)	0 (0-17)	33 (13-59)	15 (3-38)
	% SC[c] (95% CI)	30 (13-53)	0 (0-17)	33 (13-59)	15 (3-38)

a, GMR = geometric mean ratio = Ratio of day 22/day 1 GMTs

b, SP = seroprotection = HI titer≥ 40

c, SC = seroconversion or significant increase = the percentage of subjects achieving at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (≥10) or a rise from < 10 to ≥ 40 in those who were seronegative

e, The A/H3N2 and B strains in the vaccine were the same as the previous year (Study V70P2)

Clinical studies in special populations

In Study V70P5, subgroup analyses of vaccine efficacy and immunogenicity by baseline HI status against the A/H3N2 strain were performed. Efficacy was also analysed by

stratifying the subgroups of subjects into alternate age cohorts (6 to <24 months and 24 to <72 months).

For the analysis by A/H3N2 antibody status, subjects were classified into two subgroups (seronegative or seropositive) based on baseline HI titers, using a threshold HI value of 10 to determine status. Among these subjects, the incidence of symptomatic PCR confirmed influenza was significantly lower in the Fluad group with respect to the other two treatment groups; Fluad therefore showed high absolute (74%) and relative (79%) efficacy in this subgroup of children.

Both baseline seropositive and baseline seronegative subjects showed a strong immune response following vaccination with Fluad that was significantly higher than the responses of subjects in other control vaccine groups (flu control and non flu control). Fluad induced a robust immune response in both baseline seropositive and seronegative subjects whereas the flu control vaccine did not induce a strong response in subjects seronegative at baseline.

Fluad was found to be highly efficacious in the 6 to <24 month cohort; the absolute and relative VEs were equal to 75%. The absolute and relative VE for the 24 to <72 month cohort were, respectively, 92% and 82%. Immunogenicity analyses in the alternate age subgroups also showed that Fluad induced robust immune responses even after a single dose against the homologous strains and after two doses against the heterologous strains. The responses in terms of seroconversion and seroprotection rates and GMRs were significantly higher in the Fluad group than in the flu control group.

Persistence of efficacy and/or tolerance effects

Study V70P5 examined the persistence of HI antibodies against both homologous and heterologous strains over a period of approximately 6 months. Seroprotection rates and GMTs over the course of the study for antibodies against homologous strains are represented graphically in Figure 1 for subjects aged 6 to <36 months and Figure 2 for subjects >36 months; data for heterologous strains are presented in Figure 3. At baseline, a small percentage of subjects had HI titers ≥1:40 against the three homologous strains. Antibody levels rose markedly after completion of the vaccination course. Three weeks after receiving the second vaccine dose most of the subjects in both age groups who received Fluad had HI titers ≥1:40 against both A and B strains. About 6 months after the second vaccination almost all the subjects in the Fluad groups had HI antibody titers ≥1:40 against the A strains. The persistence of antibodies was not as good for the B strains, although antibody levels remained above baseline at Day 180. The immune response following vaccination with flu control vaccine was weaker with respect to that elicited by Fluad. The levels of antibodies at Day 180 in flu control vaccine recipients are also below those of the Fluad recipients. As expected, there was no considerable difference in the percentage of subjects with HI titer ≥1:40 from baseline in the non flu control group throughout the follow up period, with the exception of a slight increase in antibodies against H3N2 (which was the strain circulating during the follow up period) at Day 180.

Figure 1: Antibody persistence following vaccination in Study V70P5 (PP population; subjects aged 6 to <36 months) – HI assay (homologous strains) – Season 2008/09.

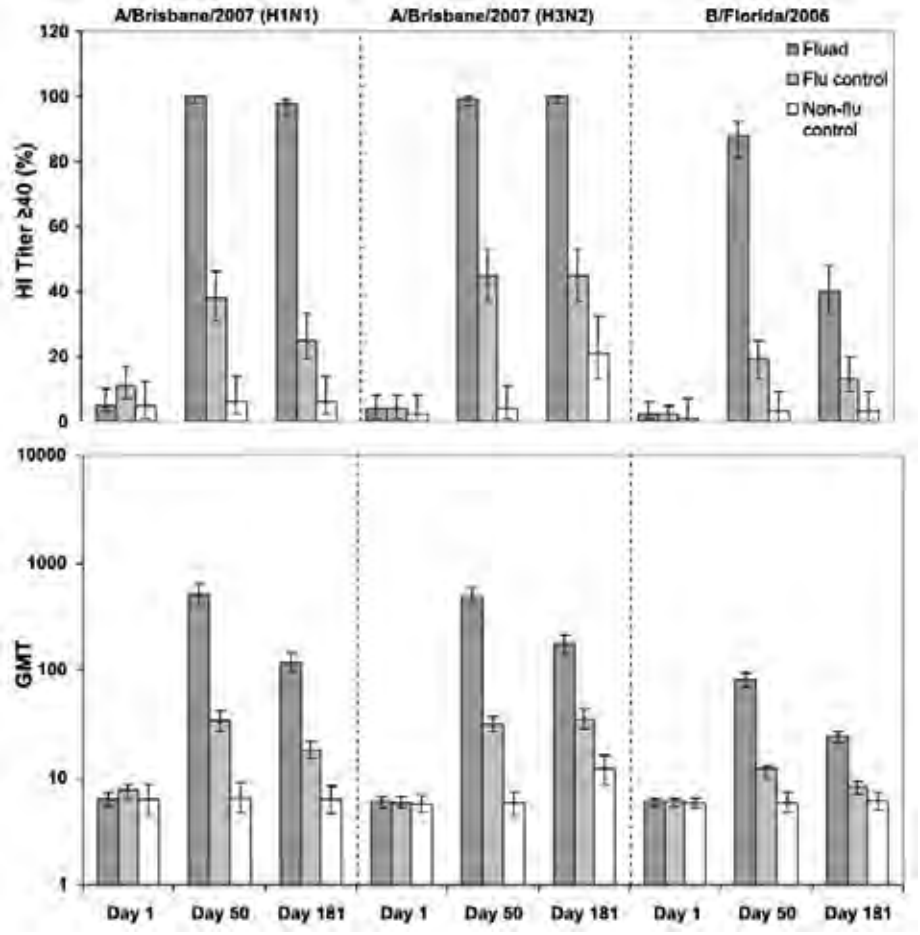


Figure 2: Antibody persistence following vaccination in Study V70P5 (PP population; subjects aged 36 to <72 months).

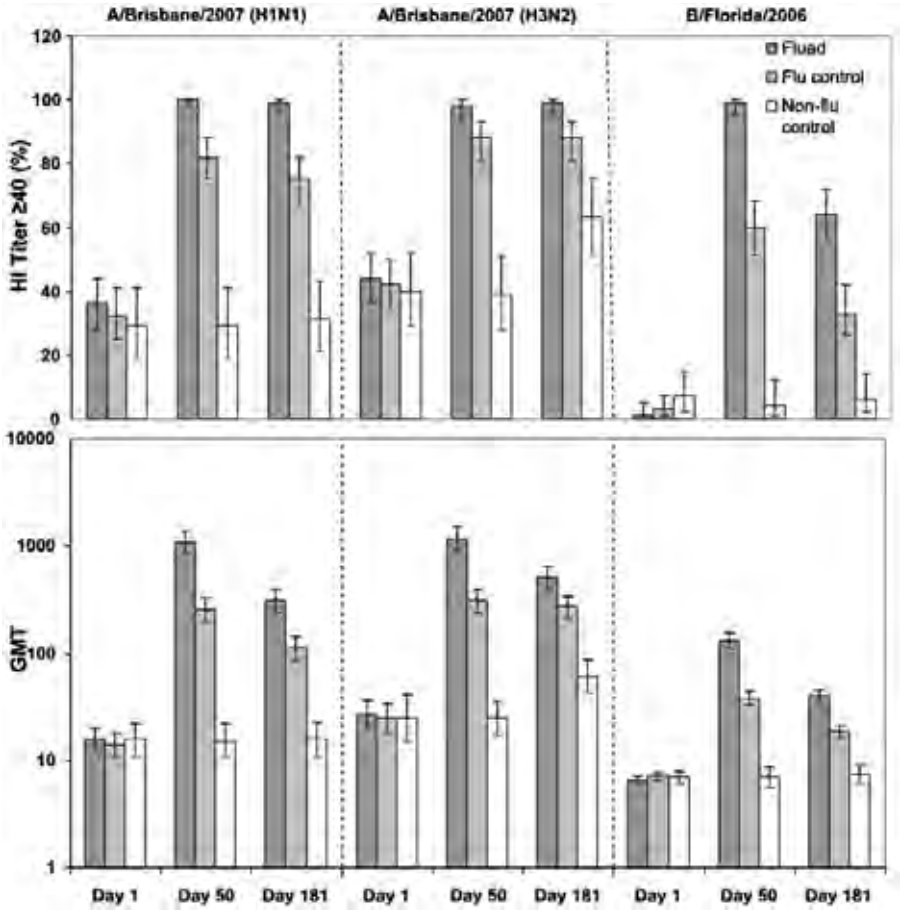
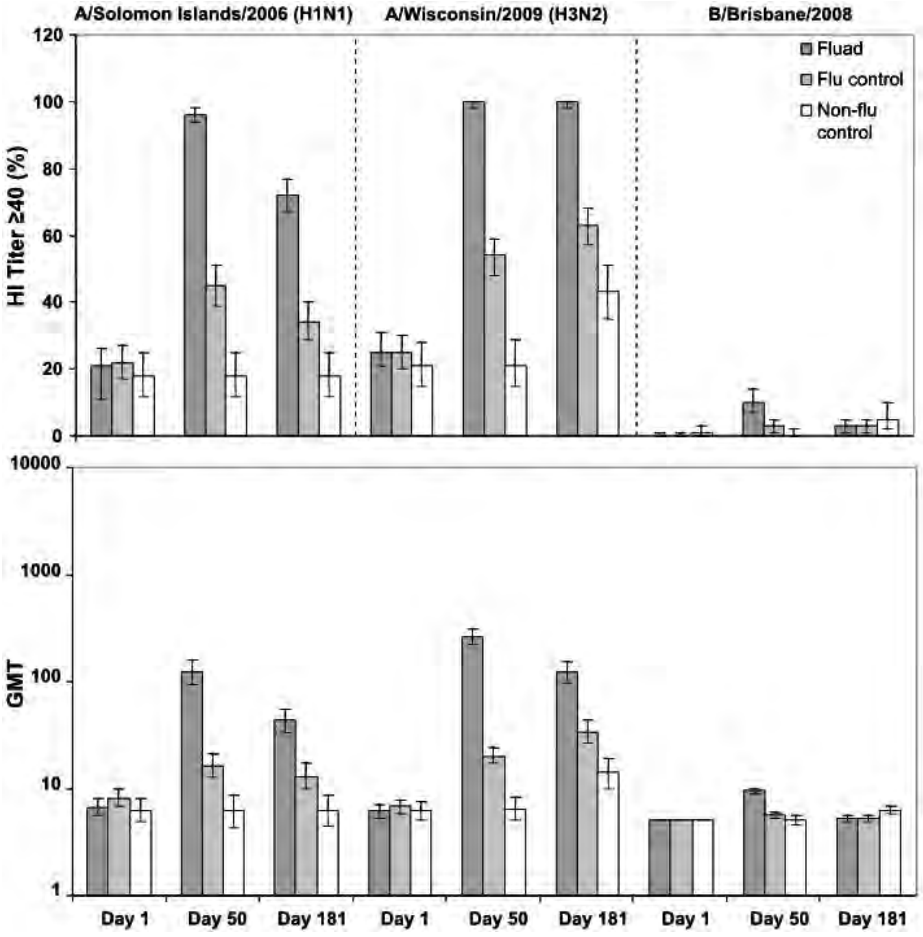


Figure 3: Antibody persistence following vaccination in Study V70P5 (PP population; subjects aged 36 to < 72 months) – HI assay (heterologous strains) – Season 2008/09.



Additional persistence data are provided by Study V70P2, where children were followed up for a total period of approximately 7 months. Data from both age cohorts have been combined. The results from this study are consistent with those obtained in Study V70P5. At Day 209, antibody levels of subjects administered Fluad remained above baseline levels for all three vaccine strains. A trend for higher GMTs was observed in subjects administered Fluad with respect to those administered Vaxigrip.

Evaluator's overall conclusions on clinical efficacy

The data submitted show evidence of the good efficacy of Fluad Paediatric in the age groups studied, particularly under 72 months (where the greatest numbers have been studied). The pivotal trial in particular is large, well constructed and carried out, and shows good evidence of clinical efficacy in preventing influenza diseases, in addition to the immunogenicity data shown by all the trials. There is also very good correlation data between immunogenicity and disease prevention. The pivotal trial in particular, was well designed; it was unfortunate about the data from the third year being compromised by the outbreak of pandemic influenza and the global recommendations for children to be vaccinated against pandemic strain. However, there is still good data from the first two years of the study. The results of Study V70P5 indicate that Fluad was efficacious in preventing symptomatic confirmed influenza caused by both matched strains and also against any circulating influenza virus strain in children 6 to <72 months of age.

Relative efficacy was also shown as Fluad was more effective than the influenza-control vaccines in providing protection against strains matched to those in the vaccine and other

circulating influenza virus strain, as shown by the high point estimate for the relative vaccine efficacy across all age cohorts.

The primary efficacy objective of the main Study V70P5 (which was the evaluation of the absolute efficacy of Fluad against vaccine matched strains in children 6 to <36 months of age across the two influenza seasons) was satisfied. A secondary objective of the study which was to evaluate the superiority of Fluad compared with non adjuvanted flu vaccine as demonstrated by HI GMTs postvaccination in children 6 to <36 months and 6 to <72 months of age was also fulfilled. After receiving two doses of the study vaccines, the Fluad group showed significantly higher GMTs than the flu control group against the homologous A and B strains (lower limit of the two sided 95% CI of the GMT ratios [GMT Fluad/GMT Flu control] >1 at day 50)

In both the 6 to <36 months and the 6 to <72 months age groups, all three CHMP criteria were achieved at day 50 for Fluad but were not for the flu control vaccine. Significantly higher GMTs were observed in the Fluad group with the HI, SRH and MN assays.

Safety

Introduction

Clinical safety data from all the clinical trials is included in this submission. In addition to this, there is already significant clinical experience with the adult formulation of Fluad vaccine in adults, as it has been licensed and used globally for 14 years. There is additional data (not submitted) to support the safety of Fluad in the paediatric population is provided by studies of Fluad in elderly subjects (>65 years) and by ongoing studies of MF59 adjuvanted H1N1 swine flu vaccines in children (6 months to <18 years).

Patient exposure

The safety analysis population consists of 2839 infants, toddlers and children 6 to <36 months of age (Fluad 1500, Flu comparator 1339), 1744 children 3 to <9 years of age (Fluad 918, Flu comparator 826) and 257 children and adolescents 9 to <18 years of age (Fluad 157, Flu comparator 100).

Only a small percentage of early withdrawals were due to adverse events (AEs). Tables 15-17 summarise the total number of AEs, both local and systemic in the different studies and age groups, by vaccination.

Table 15: Overview of subjects with solicited AEs by study, vaccination (7.5 µg) and vaccine group: – 6 to <36 months.

	Number (%) Subjects with Solicited AEs							
Study	V70P2 [1] and V70P2E1 [2]		V70P6 [3]		V70P5		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [7]	Flu-vacc. Control [6]	Fluad	PanH5N1 [5]
1st vaccination	N=130	N=139	N=130	N=130	N=1178	N=1068	N=56	N=145
Any	93 (72%)	86 (62%)	68 (52%)	56 (43%)	819 (70%)	722 (68%)	42 (75%)	110 (76%)
Local	74 (57%)	61 (44%)	42 (32%)	38 (29%)	479 (41%)	367 (34%)	28 (50%)	68 (47%)
Systemic	65 (50%)	58 (42%)	52 (40%)	39 (30%)	638 (54%)	576 (54%)	30 (54%)	86 (59%)
Other [7]	23 (18%)	17 (12%)	28 (22%)	22 (17%)	223 (19%)	201 (19%)	13 (23%)	25 (17%)
2nd vaccination	N=117	N=127	N=124	N=121	N=1147	N=1039	N=56	N=139
Any	72 (62%)	63 (50%)	56 (45%)	42 (35%)	722 (63%)	616 (59%)	35 (63%)	94 (68%)
Local	52 (44%)	43 (34%)	30 (24%)	21 (17%)	438 (38%)	337 (32%)	23 (41%)	64 (46%)
Systemic	48 (41%)	39 (31%)	37 (30%)	34 (28%)	579 (50%)	476 (46%)	25 (45%)	71 (51%)
Other [7]	18 (15%)	17 (13%)	31 (25%)	23 (19%)	209 (18%)	171 (16%)	11 (20%)	22 (16%)
3rd vaccination	N=25	N=23	*No 3rd vaccination as per protocol*					N=124
Any	18 (72%)	13 (57%)						99 (80%)
Local	15 (60%)	10 (43%)						75 (60%)
Systemic	11 (44%)	9 (39%)						67 (54%)
Other	5 (20%)	3 (13%)						23 (19%)

Source: ISS (all subjects 1: Second vaccination given 4 weeks (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1 (MF59-adjuvanted pandemic flu vaccine): Second vaccination given 3 weeks after the first vaccination. 5: Randomisation ratio of Fluad:Flu-vaccination- control:Non-flu-vacc.-control was 2:1:1 for Part I (season 2007-2008) and 2:2:1 for Part II and Part III (seasons 2008-2009 and 2009/2010). 6: Agrippal S1 for Part I, Influsplit SSW for Part II and Part III. 7: additional "Other" for Study V70P6 stayed home due to reaction.

Table 16: Overview of subjects with solicited AEs by study, vaccination (15 µg) and vaccine group – 3 to <9 years.

	Number (%) Subjects with Solicited AEs							
Study	V70P2 [1] and V70P2E1 [2]		V70P6* [3]		V70P5*		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [6]	Flu-vacc. Control [6]	Fluad	PanH5N1 [5]
1st vaccination	N=0	N=0	N=50	N=50	N=833	N=778	N=46	N=96
Any	–	–	34 (68%)	27 (54%)	582 (70%)	464 (60%)	31 (78%)	69 (72%)
Local	–	–	30 (60%)	23 (46%)	469 (56%)	382 (49%)	25 (63%)	63 (66%)
Systemic	–	–	17 (34%)	16 (32%)	408 (49%)	250 (32%)	22 (55%)	28 (29%)
Other [7]	–	–	11 (22%)	7 (14%)	129 (15%)	55 (7%)	6 (15%)	9 (9%)
2nd vaccination	N=0	N=0	N=48	N=47	N=813	N=757	N=39	N=93
Any	–	–	30 (63%)	28 (60%)	560 (69%)	418 (55%)	21 (54%)	62 (67%)
Local	–	–	26 (54%)	21 (45%)	458 (56%)	337 (45%)	19 (49%)	54 (58%)
Systemic	–	–	13 (27%)	14 (30%)	349 (43%)	212 (28%)	13 (33%)	29 (31%)
Other [7]			8 (17%)	9 (19%)	137 (14%)	44 (6%)	6 (15%)	11 (12%)
3rd vaccination	N=18	N=23	*No 3rd vaccination, as per protocol*					N=85
Any	16(89%)	14(61%)						67 (79%)
Local	15(83%)	11(48%)						63 (74%)
Systemic	7(39%)	8(35%)						38 (45%)
Other	4(22%)	1(4%)						12 (14%)

Source: ISS

*: upper age limit lower than "<9 years": in V70P6="<5 years" and in V70P5= "<6 years". 1: Second vaccination given 4 weeks after the first vaccination. 2: 3rd vacc. given 12 months after 2nd vaccination. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1: Second vaccination given 3 weeks after the first vaccination. 5: Randomisation ratio of Fluad:Flu-vaccination-control:Non-flu-vacc.-control was 2:1:1 for Part I (season 2007-2008) and 2:2:1 for Part II and Part III (seasons 2008-2009 and 2009/2010). 6: Agrippal S1 for Part I, Influsplit SSW for Part II and Part III. 7: additional "Other" for Study V70P6 stayed home due to reaction.

Table 17: Overview of subjects with solicited AEs by study, vaccination (15 µg) and vaccine group – 9 to <18 years.

	Number (%) Subjects with Solicited AEs			
Study	V87P6 [1]		V7P29 [2]	
Vaccine group	Fluad	PanH5N1 [3]	Fluad	Flushield or Fluogen
1st vaccination	N=41	N=93	N=116	N=100
Any	36 (88%)	85 (91%)	102 (88%)	67 (67%)
Local	29 (71%)	75 (81%)	101 (87%)	59 (59%)
Systemic	33 (80%)	64 (69%)	50 (43%)	18 (18%)
Other	14 (34%)	24 (26%)	46 (40%)	21 (21%)
2nd vaccination	N=40	N=91	*No 2nd vaccination*	
Any	31 (78%)	74 (81%)		
Local	26 (65%)	64 (70%)		
Systemic	20 (50%)	46 (51%)		
Other	3 (8%)	14 (15%)		
3rd vaccination	No 3rd vacc.	N=83		
Any		74 (89%)		
Local		67 (81%)		
Systemic		57 (69%)		
Other		13 (16%)		

Source: ISS; Section 5.3.5 CSR V87P6. 1: Supportive study with PanH5N1: Second vaccination given 3 weeks after the first vaccination. 2: Control vaccine was a non-adjuvanted, trivalent split virus seasonal flu vaccine manufactured by Wyeth-Ayerst (Flushield®) or by Parke- Davis (Fluogen). 3: Third vaccination of PanH5N1 given 12 months after 2nd vaccination.

Adverse events

Solicited AEs/reactions

Subjects were observed for immediate solicited reactions for approximately 30 minutes after each vaccination. Solicited reactions occurring on the day of, and 6 days after, each vaccination were recorded. Temperature was also recorded daily. Use of any prescription medication taken to treat AEs was recorded throughout the studies. Non study vaccines administered during the studies were also to be reported. Although there were slight variations among the individual studies in the size categories used, the pooled data analysis used the following size categories for measurements of the diameter of local reactions (ecchymosis, erythema, swelling, and induration): none, 1 to ≤10 mm, 11 to ≤25 mm, 26 to ≤50 mm, 51 to ≤100 mm and >100 mm.

Within each study and age group, incidence rates of reactogenicity (any, local, systemic and other) were higher for the Fluad group than for the control vaccine (that is, Flu comparator: non adjuvanted seasonal flu vaccine) (excluding PanH5N1 of V87P6). In general, the proportion of subjects with reactogenicity events was approximately 10% higher in the Fluad group than in the control group (range 0-25% for systemic reactions). In addition, incidence rates of reactogenicity events were higher after the first than after the second vaccination, with the exception of Study V70P5 age group 6 to <36 months (no difference between Fluad and flu vaccine control in the systemic or other reactogenicity rates) (Tables 15-17). Within each study (excluding PanH5N1 of V87P6) and across vaccine and age groups, incidences of local reactions were higher than those of systemic reactions, with the exception of the age group 6 to <36 months in Studies V70P5 and V70P6, after both vaccinations (incidences of systemic reactions were higher than those of local reactions). Of note, for the 9 to <18 years age group, incidence rates of local (Studies V87P6 and V7P29) and systemic reactions (Study V87P6) were higher than for the other two age groups (Tables 15-17). After third vaccination (Study V70P2E1) incidence rates were similar (overall reactogenicity age group 6 to <36 months, systemic reactions age group ≥36 months) or higher (any and local reactions age group ≥36 months) compared to the first vaccination in other studies.

Solicited local reactions

Children 6 to <36 months

The most frequently reported local reaction after 1st vaccination was tenderness (range: Fluad 18-33%, Flu comparator 15-26%) for Studies V70P2, V70P6 and V87P6, and erythema (Fluad 24%, Flu comparator 20%) for Study V70P5, followed by erythema (range: Fluad 15-25%, Flu comparator 11-22%) for Studies V70P2, V70P6 and V87P6 and tenderness (Fluad 19%, Flu comparator 17%) for Study V70P5. The most frequently reported local reaction after the 2nd vaccination was erythema (range: Fluad 15-27%, Flu comparator 7-22%) for Studies V70P6, V70P5 and V87P6, and tenderness for Study V70P2 (Fluad 29%, Flu comparator 22%), followed by tenderness (range: Fluad 11-21%, Flu comparator 9-16%) for Studies V70P6, V70P5 and V87P6, and erythema (Fluad 25%, Flu comparator 17%) for V70P2. Most local reactions across studies, vaccine groups and vaccinations were mild or moderate, with the following exceptions: severe tenderness reported by 1-2% of subjects (1-2 subjects) each in the Fluad groups of V70P2 and V70P6; severe tenderness by ≤1% of subjects (range across vaccinations: Fluad 5-6 subjects, Flu-comparator 1-4 subjects) in both vaccine groups of V70P5; severe erythema by 1% of subjects (1 subject) in the Fluad group of V70P6 after 2nd vaccination; severe erythema by <1% of subjects in the Fluad group after both vaccinations in Study V70P5; severe ecchymosis, induration or swelling by <1% of subjects after the 2nd vaccination in Study V70P5 (Table 18). Similar to the first two vaccinations tenderness was the most commonly reported local reaction (Fluad 32%, Flu comparator 30%) after the third vaccination in Study V70P2E1. Interestingly after third vaccination no difference was seen in incidence rates of local reactions between Fluad and Flu comparator (Table 18).

Table 18: Percentage of subjects with solicited local reactions by study, vaccination (7.5 µg) and vaccine group – 6 to <36 months.

	% Subjects with Solicited Local Reactions (% Subjects with Severe Local Reactions*)							
Study	V70P2 [1] and V70P2E1 [2]		V70P6 [3]		V70P5		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [5]	Flu-vacc. Control [5]	Fluad	PanH5N1 [4]
1st vaccination	N=130	N=139	N=130	N=130	N=1178	N=1068	N=56	N=145
Ecchymosis	8% (0)	9% (0)	8% (0)	13% (0)	7% (0)	6% (0)	9% (0)	10% (0)
Erythema	25% (0)	22% (0)	12% (0)	11% (0)	24% (<1%)	20% (0)	23% (0)	32% (1%)
Induration	8% (0)	9% (0)	5% (0)	2% (0)	10% (0)	7% (0)	5% (0)	11% (0)
Swelling	8% (0)	2% (0)	5% (0)	2% (0)	5% (0)	5% (0)	4% (0)	12% (1%)
Tenderness	33% (2%)	26% (0)	18% (2%)	15% (0)	19% (<1%)	17% (<1%)	29% (0)	26% (1%)
2nd vaccination	N=117	N=127	N=124	N=121	N=1111	N=1000	N=56	N=138
Ecchymosis	8% (0)	6% (0)	9% (0)	7% (0)	7% (<1%)	5% (0)	5% (0)	5% (0)
Erythema	25% (0)	17% (0)	15% (1%)	7% (0)	27% (<1%)	22% (0)	27% (0)	33% (1%)
Induration	10% (0)	9% (0)	8% (0)	2% (0)	13% (<1%)	8% (0)	2% (0)	10% (0)
Swelling	7% (0)	4% (0)	2% (0)	2% (0)	7% (<1%)	6% (0)	4% (0)	6% (1%)
Tenderness	29% (2%)	22% (0)	11% (1%)	9% (0)	19% (1%)	16% (<1%)	21% (0)	24% (1%)
3rd vaccination	N=25	N=23	*No 3rd vaccination as per protocol*					N=124
Ecchymosis	8% (0)	13% (0)						10% (0)
Erythema	32% (0)	30% (0)						44% (1.5%)
Induration	12% (0)	13% (0)						32% (0)
Swelling	12% (0)	17% (0)						27% (8%)
Tenderness	32% (0)	30% (0)						46% (2%)

*: Severe local reactions defined as: ecchymosis, eythema, induration or swelling >50mm or tenderness 1: Second vaccination given 4 weeks after the 1st vacc. 2: 3rd vacc. at 12 months post 2nd vacc. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1: 2nd vacc. at 3 weeks post 1st vacc. 5: Randomisation ratio.

Children 3 to <9 years

Within each study, the incidence rates of local reactions were higher for Fluad than for controls (excluding PanH5N1 in Study V87P6), and incidence rates for most local reactions were similar after both the first and second vaccination. The most frequently reported local reaction after both vaccinations in all studies of this age group was pain at injection site (range across vaccinations: Fluad 36-48%, Flu comparator 27-35%), followed by erythema (range across vaccinations: Fluad 23-36%, Flu comparator 22-28%). Most local

reactions across studies, vaccine groups and vaccinations were mild or moderate, with the following exceptions: severe pain at injection site was reported by 5% of subjects (2 subjects) in the Fluad group of V87P6 and by ≤1% of subjects (range across vaccinations: Fluad 11 subjects, Flu comparator 1-4 subjects) in the Fluad and flu vaccine control groups of V70P5, severe erythema, induration and swelling were reported by 3% of subjects (1 subject) in the Fluad group of V87P6 and by ≤1 to 3% of subjects in the Fluad and flu-vaccine control groups of Study V70P5. Of note, incidence rates of erythema and severe erythema increased after the 2nd vaccination in both vaccine groups of Phase 3 Study V70P5 (Table 19). The higher incidence rate of local reactions after the third vaccination in Study V70P2E1 was mainly due to a higher incidence rate of pain at the injection site (67%) and swelling (17%). Incidences rate of other local reactions were within the range of incidence rates seen in other studies after first and second vaccination (Table 20).

Table 19: Percentage of subjects with solicited local reactions by study, vaccination (15 µg) and vaccine group – 3 to <9 years.

	% Subjects with Solicited Local Reactions (% Subjects with Severe Local Reactions*)							
Study	V70P2 [1] and V70P2E1 [2]		V70P6** [3]		V70P5**		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [5]	Flu-vacc. Control [6]	Fluad	PanH5N1 [4]
1st vaccination	N=0	N=0	N=49	N=49	N=833	N=778	N=40	N=96
Ecchymosis	–	–	18% (0)	10% (0)	8% (0)	7% (0)	10% (0)	5% (0)
Erythema	–	–	27% (0)	22% (0)	23% (<1%)	22% (<1%)	30% (3%)	31% (1%)
Induration	–	–	24% (0)	10% (0)	10% (<1%)	11% (0)	10% (3%)	11% (1%)
Swelling	–	–	12% (0)	4% (0)	9% (<1%)	9% (0)	10% (3%)	9% (1%)
Pain at inj. site	–	–	43% (0)	27% (0)	45% (1%)	35% (<1%)	48% (5%)	51% (1%)
2nd vaccination	N=0	N=0	N=48	N=47	N=813	N=757	N=39	N=93
Ecchymosis	–	–	8% (0)	13% (0)	9% (0)	6% (0)	5% (0)	8% (0)
Erythema	–	–	33% (0)	28% (0)	31% (3%)	25% (2%)	36% (5%)	25% (1%)
Induration	–	–	29% (0)	23% (0)	15% (1%)	14% (1%)	13% (3%)	6% (0)
Swelling	–	–	13% (0)	11% (0)	14% (1%)	13% (1%)	13% (3%)	9% (1%)
Pain at inj. site	–	–	46% (0)	30% (0)	43% (1%)	32% (1%)	36% (5%)	53% (0)
3rd vaccination	N=18	N=23	No 3rd vaccination as per protocol					N=85
Ecchymosis	6% (0)	17% (0)						4% (0)
Erythema	28% (0)	22% (0)						41% (0)
Induration	28% (0)	22% (0)						18% (0)
Swelling	17% (0)	0 (0)						19% (0)
Pain at inj. site	67% (6%)	26% (0)						68% (0)

Source: ISS

–: not applicable (no subjects in this age group). *: Severe local reactions defined as >50mm. **: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)". 1: 2nd vacc. at 4 weeks post 1st vacc. 2: 3rd vacc. at 12 months after 2nd vacc. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1. 6: Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Children 9 to <18 years

In Study V7P29, the most frequently reported local reactions were pain at injection site (Fluad 83%, Flu comparator 53%) and increased temperature at injection site (Fluad 65%, Flu comparator 77%). In this age group, this study compared Fluad with a non adjuvanted influenza comparator. Frequency of all solicited local reactions was lower after vaccination with Fluad. Most local reactions across vaccine groups were mild or moderate with the following exceptions in both vaccine groups: severe increased temperature at injection site (each 2% or two subjects) and severe induration (Fluad 2% or two subjects, Flu comparator 3% or three subjects). Severe pain at injection site (3% or three subjects) and severe erythema (1% or one subject) were both reported by subjects in the Fluad group only (Table 20). In Study V87P6, the most frequently reported local reaction was pain at injection site (range across vaccinations: Fluad 63-71%), followed by erythema (range across vaccinations: Fluad 20-23%), and incidence rates for most local reactions were the same or slightly lower after the second vaccination than after the first vaccination (see percentage ranges below). Most local reactions across vaccinations were

mild or moderate with the exception of severe pain at injection site (5% or two subjects), induration and swelling (each 2% or one subject) in the Fluad group of V87P6 (Table 20).

Table 20: Percentage of subjects with solicited local reactions by study, vaccination (15 µg) and vaccine group - 9 to <18 years.

	% Subjects with Solicited Local Reactions (% Subjects with Severe Local Reactions*)			
Study	**V87P6 [1]**		**V7P29 [2]**	
Vaccine group	**Fluad**	**PanH5N1 [3]**	**Fluad**	**Flushield or Fluogen [4]**
1st vaccination	**N=41**	**N=93**	**N=116**	**N=100**
Ecchymosis	10% (0)	4% (0)	NS	NS
Erythema	20% (0)	16% (1%)	16% (1%)	9% (0)
Induration	7% (2%)	10% (0)	16% (2%)	14% (3%)
Swelling	17% (2%)	11% (1%)	NS	NS
Pain at injection site	71% (5%)	78% (3%)	83% (3%)	53% (0)
Increased Temperature at injection site	NS	NS	65% (2%)	77% (2%)
2nd vaccination	**N=40**	**N=91**	***No 2nd vaccination***	
Ecchymosis	0 (0)	5% (0)		
Erythema	23% (0)	23% (0)		
Induration	3% (0)	18% (1%)		
Swelling	18% (0)	13% (2%)		
Pain at inj. site	63% (0)	65% (2%)		
3rd vaccination	***No 3rd vacc.***	**N=83**		
Ecchymosis		7% (0)		
Erythema		28% (0)		
Induration		25% (1%)		
Swelling		25% (1%)		
Pain at inj. site		80% (0)		

Source: ISS and Studies V87P6, V7P29. NS = not solicited, as per protocol *: Severe local reactions defined as >50mm. 1: Supportive study with PanH5N1: Second vaccination given 3 weeks after the first vaccination. 2: This study was initiated with an open-label part (15 subjects receiving Fluad) for which data are not shown 3: Third vaccination of PanH5N1 given 12 months after 2nd vaccination. 4: Control vaccine was a non-adjuvanted, trivalent split virus seasonal flu vaccine manufactured by Wyeth-Ayerst (Flushield) or by Parke-Davis (Fluogen).

Severity and duration (all age groups)

In all studies, for all vaccinations most of the local reactions reported in any of the age groups were mild to moderate in severity and transient in duration.

Local reactions - pooled analysis

Results from the pooled analyses were consistent with those from the by study analyses (Tables 21-23). Within each age group, incidence rates of reactions were higher for Fluad than for Flu-comparators (excluding PanH5N1 in Study V87P6). In the 6 to <36 months age group, incidence rates for most local reactions were lower after the 2nd than after the 1st vaccination. In the 3 to <9 years age group, incidence rates were similar after both the 1st and 2nd vaccination. The higher local reactogenicity reported for the 9 to <18 years age group was mainly due to a higher incidence of pain at injection site. Differences between age groups:

- Age group 6 to <36 months – incidence rates of reactogenicity were higher in the Fluad than in control group and slightly higher after 1st than after 2nd vaccination. Systemic reactions were reported at a higher rate than local reactions. Reports of severe events were rare.
- Age group 3 to <9 years – incidence rates of reactogenicity were higher in the Fluad than in control group, and comparable after 1st than after 2nd vaccination. Local

reactions were reported at a higher rate than systemic reactions. However, the differences in incidence rates between the Fluad and control groups were greater for systemic than for local reactions. Reports of severe events were infrequent.

- Age group 9 to <18 years – incidence rates of reactogenicity were higher in the Fluad than in control group and slightly higher after 1st than after 2nd vaccination. Local reactions were reported at a higher rate than systemic reactions. However, the differences in incidence rates between the Fluad and control groups were greater for systemic than for local reactions. Reports of severe events were infrequent. Incidence rates of local, systemic and other reactions were higher in the 9 to <18 years age group compared with the other two age groups.

Table 21: Overview of subjects with solicited reactions in the pooled safety population by vaccination (7.5 µg) and vaccine group – 6 to <36 months.

V70P2, V70P6[1], V70P5, and V87P6	Number (%) Subjects with Solicited AEs			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control[2]	Fluad	Flu-Control[2]
Pooled Safety Population	N=1494[1]	N=1337[1]	N=1444[1]	N=1287[1]
Any	1022 (68%)	864 (65%)	886 (61%)	721 (56%)
Any (severe only)	17 (1%)	5 (<1%)	13 (1%)	11 (1%)
Local	623 (42%)	466 (35%)	543 (38%)	401 (31%)
Local (severe only)	11 (1%)	4 (<1%)	12 (1%)	4 (<1%)
Systemic[3]	785 (53%)	673 (50%)	689 (48%)	549 (43%)
Systemic[3] (severe only)	6 (<1%)	4 (<1%)	1 (<1%)	7 (1%)
Other	287 (19%)	240 (18%)	269 (19%)	211 (16%)

Source: ISS. 1: Study V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomised to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 2: Flu Control vaccines were: Vaxigrip for Study V70P2, Fluzone for Study V70P6, Agrippal S1 for Part I of Study V70P5, Influsplit SSW for Part II and Part III of Study V70P5, and none for Study V87P6. 3: Including fever (defined as≥38°C) and body temperature ≥40°C (severe fever).

Table 22: Overview of subjects with solicited reactions in the pooled safety population by vaccination (15 µg) and vaccine group – 3 to <9 years.

V70P6[1,2], V70P5[1], and V87P6	Number (%) Subjects with Solicited AEs			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control[3]	Fluad	Flu-Control[3]
Pooled Safety Population	N=923[2]	N=828[2]	N=900[2]	N=804[2]
Any	647 (70%)	491 (59%)	611 (68%)	446 (55%)
Any (severe only)	61 (7%)	19 (2%)	63 (7%)	28 (3%)
Local	524 (57%)	405 (49%)	503 (56%)	358 (45%)
Local (severe only)	16 (2%)	2 (<1%)	37 (4%)	16 (2%)
Systemic[4]	447 (48%)	266 (32%)	372 (41%)	226 (28%)
Systemic[4] (severe only)	52 (6%)	17 (2%)	33 (4%)	14 (2%)
Other	146 (16%)	62 (7%)	131 (15%)	53 (7%)

Source: ISS. 1: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)". 2: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 3: Flu- Control vaccines were: Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6. 4: Including fever (defined as≥38°C) and body temperature ≥40°C (severe fever).

Table 23: Overview of subjects with solicited reactions in the pooled safety population by vaccination (15 µg) and vaccine group – 9 to <18 years.

V87P6 and V7P29	Number (%) Subjects with Solicited AEs			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control [1]	Fluad	Flu-Control [1]
Pooled Safety Population	N=157	N=100	N=40	N=0
Any	138 (88%)	67 (67%)	31 (78%)	0
Any (severe only)	13 (8%)	4 (4%)	2 (5%)	0
Local	130 (83%)	59 (59%)	26 (65%)	0
Local (severe only)	10 (6%)	3 (3%)	0	0
Systemic [2]	83 (53%)	18 (18%)	20 (50%)	0
Systemic [2] (severe only)	4 (3%)	1 (1%)	2 (5%)	0
Other	60 (38%)	21 (21%)	3 (8%)	0

Source: ISS (all subjects enrolled). 1: Flu Control vaccines were: None for V87P6, and Fluogen/Flushield for Study V7P29. 2: Including fever (defined as≥38°C) and body temperature ≥40°C (severe fever).

Severe local or systemic reactions (including fever) were reported by a few subjects (≤1%) in both vaccine groups of the 6 to <36 months age group (Table 21). However, for the two higher age groups (3 to <9 years and 9 to <18 years), higher incidence rates of severe local or systemic (including fever) reactions were reported in the Fluad group (range: 2-6%) compared with the Flu comparator group (range: <1-3%) (Tables 22-23). In addition, higher incidence rates of severe local or systemic (including fever) reactions were reported in the two higher age groups (range across vaccine and age groups: <1-6%) compared with the 6 to <36 months age group (range across vaccine groups: <1%).

Children 6 to <36 months

The most frequently reported local reaction after both vaccinations was erythema (range: Fluad 23-26%, Flu comparator 19-20%), followed by tenderness (Fluad 19-21%, Flu comparator 16-18%). Local reactions across vaccine groups and vaccinations were mild or moderate, apart from severe tenderness reported by ≤1% of subjects (range across vaccinations: Fluad 9 subjects, Flu comparator 1-4 subjects), severe erythema in <1% of subjects in the Fluad group after both vaccinations, and severe ecchymosis, induration and swelling, each in <1% of subjects in the Fluad group after the 2nd vaccination.

Children 3 to <9 years

The most frequently reported local reaction after both vaccinations was pain at injection site (range: Fluad 43-45%, Flu comparator 32-35%), followed by erythema (range: Fluad 24-31%, Flu comparator 22-26%). Local reactions across vaccine groups and vaccinations were mild or moderate, with the following exceptions: severe pain at injection site reported by ≤1% of subjects (range: Fluad 13 subjects, Flu comparator 1-4 subjects), severe erythema reported by ≤1 to 2% of subjects (range: Fluad 2-22 subjects, Flu-comparator 1-12 subjects), and severe induration and swelling both reported by ≤1% of subjects (range across vaccinations: Fluad 2-8 subjects, Flu comparator 0-5 subjects).

Children 9 to <18 years

The most frequently reported local reaction after both vaccinations was pain at injection site (range: Fluad 63-80%, Flu comparator 53%), followed by erythema (range: Fluad 17-23%, Flu comparator 9%). Local reactions across vaccine groups and vaccinations were mild or moderate, apart from severe pain at injection site reported by 4% of subjects, severe induration and swelling both reported by 2% of subjects and severe erythema reported by 1% of subjects in the Fluad Group after the 1st vaccination.

Solicited systemic and other reactions - by study analysis

Children 6 to <36 Months

Within each study, the incidence rates of most systemic and other reactions were higher for Fluad than for Flu comparators (excluding PanH5N1 in Study V87P6). Incidence rates for most systemic and other reactions were lower after the 2nd than after the 1st vaccination. The most frequently reported systemic reaction across vaccinations was irritability (range: Fluad 21-32%, Flu comparator 19-26%) for Studies V70P2 and V70P5, and unusual crying (Fluad 15-16%, Flu comparator 12-17%) for Study V70P6 and for Study V87P6 (Fluad 16-30%), followed by change in eating habits (range: Fluad 12-18%, Flu comparator 7-17%) for Study V70P2, unusual crying (Fluad 21-22%, Flu comparator 20- 22%) for Study V70P5, fever (Fluad 18-19%, Flu comparator 12-17%) for Study V70P6 and irritability (Fluad 20-21%) for Study V87P6 (Table 24). Across all studies, 4-24% of subjects reported fever (body temperature ≥38°C) after Fluad vaccination and 7-20% after vaccination with non adjuvanted influenza comparator. Body temperatures of ≥40°C were reported in Study V70P5 only, for ≤1% of subjects (range: Fluad 1-6 subjects, Flu comparator 4-7 subjects) in the Fluad and Flu comparator groups.

Table 24: Percentage of subjects with solicited systemic and other reactions by study, vaccination (7.5 µg) and vaccine group – 6 to <36 months.

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)							
Study	V70P2 [1] and V70P2E1 [2]		V70P6 [3]		V70P5		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [5]	Flu-vacc. Control [6]	Fluad	PanH5N1 [2]
1st vaccination	N=130	N=139	N=130	N=130	N=1178	N=1068	N=56	N=145
Sleepiness	18% (0)	18% (0)	8% (0)	5% (0)	22% (0)	21% (0)	20% (0)	23% (0)
Diarrhea	8% (0)	8% (0)	8% (0)	4% (0)	14% (0)	14% (0)	14% (0)	19% (0)
Vomiting	3% (0)	3% (0)	8% (0)	4% (0)	6% (0)	7% (0)	5% (0)	8% (0)
Irritability	32% (0)	26% (0)	11% (0)	10% (0)	24% (0)	28% (0)	21% (0)	39% (0)
Change in eating habits	18% (0)	17% (0)	12% (0)	12% (0)	18% (0)	16% (0)	16% (0)	19% (0)
Shivering	NS	NS	3% (0)	1% (0)	4% (0)	4% (0)	7% (0)	1% (0)
Unusual Sweating	NS	NS	NS	NS	NS	NS	0 (0)	6% (0)
Unusual Crying	12% (0)	8% (0)	16% (0)	17% (0)	22% (0)	22% (0)	30% (0)	33% (0)
Fever [7] (≥40°C)	12% (0)	7% (0)	18% (0)	12% (0)	21% (1%)	20% (<1%)	4% (0)	7% (0)
Analgesics/Antipyretics	18%	12%	19%	16%	19%	19%	23%	17%
Stayed at home due to reaction	NS	NS	14%	8%	NS	NS	NS	NS
2nd vaccination	N=117	N=127	N=124	N=121	N=1147	N=1039	N=56	N=138
Sleepiness	15% (0)	10 (0)	3% (0)	2% (0)	20% (0)	16% (0)	14% (0)	21% (0)
Diarrhea	8% (0)	6% (0)	6% (0)	4% (0)	12% (0)	10% (0)	16% (0)	15% (0)
Vomiting	4% (0)	4% (0)	2% (0)	2% (0)	6% (0)	6% (0)	4% (0)	2% (0)
Irritability	25% (0)	19% (0)	11% (0)	12% (0)	21% (0)	20% (0)	20% (0)	29% (0)
Change in eating habits	15% (0)	7% (0)	9% (0)	5% (0)	16% (0)	13% (0)	14% (0)	17% (0)
Shivering	NS	NS	2% (0)	1% (0)	3% (0)	3% (0)	4% (0)	1% (0)
Unusual Sweating	NS	NS	NS	NS	NS	NS	2% (0)	1% (0)
Unusual Crying	18% (0)	9% (0)	15% (0)	12% (0)	21% (0)	20% (0)	16% (0)	27% (0)

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)							
Study	V70P2 [1] and V70P2E1 [2]		V70P6 [3]		V70P5		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [5]	Flu-vacc. Control [6]	Fluad	PanH5N1 [2]
2nd vaccination (cont.)	N=117	N=127	N=124	N=121	N=1147	N=1039	N=56	N=138
Fever [7] (≥40°C)	12% (0)	8% (0)	10% (0)	12% (0)	24% (<1%)	19% (1%)	9% (0)	12% (0)
Analgesics/Antipyretics	15%	13%	23%	16%	35%	17%	20%	16%
Stayed home due to reaction	NS	NS	15%	15%	NS	NS	NS	NS
3rd vaccination	N=25	N=23	*No 3rd vaccination as per protocol*					N=124
Sleepiness	4% (0)	17% (0)						20% (0)
Diarrhea	24% (0)	13% (0)						11% (0)
Vomiting	0 (0)	4% (0)						2% (0)
Irritability	36% (0)	22% (0)						27% (0)
Change in eating habits	12% (0)	22% (0)						19% (0)
Shivering	0 (0)	0 (0)						6% (0)
Unusual Sweating	NS	NS						4% (0)
Unusual Crying	8% (0)	17% (0)						23% (0)
Fever [7] (≥40°C)	16% (0)	9% (0)						0 (0)
Analgesics/Antipyretics	20%	13%						19%

Source: ISS (all subjects enrolled) and clinical safety reports from Studies V70P2E1 and V87P6. 1: Second vaccination given 4 weeks after the 1st vacc. 2: 3rd vacc. at 12 months post 2nd vacc. 3: Study V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age; "stayed home due to reaction" collected as solicited other reaction in all age groups. 4: Supportive study with PanH5N1: 2nd vacc. at 3 weeks post 1st vacc. 5:

Randomization ratio: Agrippal S1 for Part I, Influsplit SSW for Part II and Part III. 7: fever defined as body temperature ≥38°C, and (% subjects with severe reaction/fever) = (body temperature ≥40°C)

Children 3 to <9 years

Within each study, the incidence rates of most systemic and other reactions were higher for Fluad than for Flu comparators (excluding PanH5N1 in V87P6). Incidence rates for most systemic and other reactions were lower after the 2nd than after the 1st vaccination. The most frequently reported systemic reaction after first vaccination was malaise (range: Fluad and Flu comparator 16%) for Study V70P6 and fatigue (Fluad 21-33%, Flu comparator 17-20%) for Studies V70P5 and V87P6, followed by headache in all studies (range: Fluad 12-23%, Flu comparator 7-18%). After second vaccination incidences of systemic reactions across studies were unevenly distributed, the most commonly reported systemic reactions were malaise and fever in Study V70P6, fatigue followed by myalgia in Study V70P5, and headache followed by fatigue and myalgia in Study V87P6. Most systemic reactions across studies, vaccine groups and vaccinations were mild or moderate with only ≤3% of subjects per vaccine group reporting severe systemic reactions (Table 25). Across all studies, 5-17% of subjects reported fever (body temperature≥38°C for this document) after Fluad vaccination and 4-21% after vaccination with non adjuvanted influenza comparator. Body temperatures of ≥40°C were reported in Study V70P5 for <1% of subjects (range across vaccinations: Fluad 1-2 subjects, Flu comparator 1-1 subjects) in the Fluad and Flu comparator groups.

Table 25: Percentage of subjects with solicited systemic and other reactions by study, vaccination (15 µg) and vaccine group – 3 to <9 years.

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)							
Study	V70P2 [1] and V70P2E1 [1]		V70P6 [2]		V70P5		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [6]	Flu-vacc. Control [6]	Fluad	PanH5N1 [5]
1st vaccination	N=0	N=0	N=49	N=49	N=853	N=778	N=40	N=96
Chills, Shivering	–	–	8% (0)	8% (0)	10% (1%)	3% (<1%)	10% (3%)	6% (0)
Malaise	–	–	16% (2%)	16% (2%)	16% (2%)	11% (1%)	10% (3%)	6% (0)
Myalgia	–	–	8% (0)	6% (0)	15% (1%)	8% (<1%)	13% (3%)	6% (0)
Arthralgia	–	–	4% (0)	2% (0)	7% (1%)	3% (<1%)	5% (0)	2% (0)
Headache	–	–	12% (0)	18% (0)	17% (2%)	8% (1%)	23% (0)	17% (0)
Sweating	–	–	4% (0)	2% (0)	6% (<1%)	4% (1%)	8% (0)	5 %(0)
Nausea	–	–	NS	NS	NS	NS	5% (3%)	6% (0)
Vomiting	–	–	NS	NS	NS	NS	8% (3%)	2% (1%)
Diarrhea	–	–	NS	NS	NS	NS	5% (0)	10% (1%)
Fatigue	–	–	8% (0)	6% (0)	30% (3%)	20% (1%)	33% (3%)	15% (0)
Fever [7] (≥40°C)	–	–	6% (0)	4% (0)	17% (<1%))	7% (<1%)	5% (0)	4% (0)
Analgesics/Antipyretics	–	–	22%	12%	15%	7%	13%	6%
Stayed home due to reaction	–	–	6%	4%	NS	NS	5%	4%

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)							
Study	V70P2 [1] and V70P2E1 [1]		V70P6 [2, 3]		V70P5 [6]		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [6]	Flu-vacc. Control [6]	Fluad	PanH5N1 [5]
2nd vaccination	N=0	N=0	N=48	N=47	N=813	N=757	N=39	N=93
Chills	–	–	6% (0)	2% (0)	8% (1%)	4% (<1%)	15% (0)	5% (0)
Malaise	–	–	17% (0)	17% (0)	13% (2%)	8% (1%)	15% (0)	12% (1%)
Myalgia	–	–	13% (0)	6% (0)	14% (<1%)	8% (<1%)	21% (3%)	8% (0)
Arthralgia	–	–	4% (0)	0 (0)	4% (<1%)	2% (0)	0 (0)	1% (0)
Headache	–	–	13% (0)	9% (0)	12% (1%)	7% (<1%)	23% (0)	9% (1%)
Sweating	–	–	2% (0)	6% (0)	4% (<1%)	1% (0)	10% (0)	3% (1%)
Nausea	–	–	NS	NS	NS	NS	8% (5%)	10% (0)
Vomiting	–	–	NS	NS	NS	NS	3% (3%)	4% (0)
Diarrhea	–	–	NS	NS	NS	NS	5% (0)	9% (2%)
Fatigue	–	–	10% (0)	6% (0)	34% (2%)	17% (1%)	21% (0)	16% (0)
Fever [7] (≥40°C)	–	–	15% (0)	21% (0)	16% (<1%)	8% (<1%)	5% (0)	2% (0)
Analgesics/Antipyretics	–	–	17%	19%	14%	6%	8%	11%
Stayed home due to reaction	–	–	11%	9%	NS	NS	10%	4%

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)							
Study	V70P2 [1] and V70P2E1 [2]		V70P6 [3]		V70P5*		V87P6 [4]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [5]	Flu-vacc. Control [6]	Fluad	PanH5N1 [2]
3rd vaccination	N=18	N=23	*No 3rd vaccination as per protocol*					N=85
Chills	22% (0)	17% (0)						9% (0)
Malaise	11% (0)	17% (4%)						13% (0)
Myalgia	11% (0)	4% (0)						25% (2%)
Arthralgia	11% (0)	0 (0)						4%(0)
Headache	17% (0)	9% (0)						16% (2%)
Sweating	NS	NS						4% (0)
Nausea	NS	NS						4% (0)
Vomiting	NS	NS						1% (0)
Diarrhea	NS	NS						7% (0)
Fatigue	28% (0)	35% (0)						25% (2%)
Fever [7] (≥40°C)	11% (0)	9% (0)						6% (1%)
Analgesics/Antipyretics	22%	4%						12%
Stayed home due to reaction	NS	NS						6%

Source: ISS clinical safety reports from Studies V70P2E1 and V87P6 (. – = not applicable (no subjects in this age group), NS = not solicited, as per protocol *: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)". 1: Second vaccination given 4 weeks after the 1st vacc. 2: 3rd vacc. at 12 months post 2nd vacc. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age; "stayed home due to reaction" collected as solicited other reaction in all age groups. 4: Supportive study with PanH5N1: 2nd vacc. at 3 weeks post 1st vacc. 5: Randomisation ratio see. 6: Agrippal S1 for Part I, Influsplit SSW for Part II and Part III. 7: fever defined as body temperature≥38°C, and (% subjects with severe reaction/fever) = (body temperature≥40°C).

Children 9 to <18 years

In Study V7P29, the most frequently reported systemic reactions were headache (Fluad 27%, Flu-comparator 12%), followed by malaise (Fluad 24%, Flu comparator 6%). In this age group, only this study compared Fluad with a non adjuvanted influenza comparator. Frequency of all solicited systemic and other reactions was lower after vaccination with the non adjuvanted Flu comparator. Fever was reported by ≤9% of subjects in both vaccine groups and no subject had a body temperature of ≥40°C. Systemic reactions across vaccine groups were mild or moderate with the exception of severe headache (each 1% or 1 subject) in both vaccine groups of Study V7P29 (Table 26). In Study V87P6 the most frequently reported systemic reaction was headache (Fluad 25- 59%), followed by fatigue (Fluad 25-49%), and incidence rates for most systemic and other reactions were the same or slightly lower after the second vaccination than after the first vaccination (see percentage ranges below). Fever was reported by ≤2% of subjects in the Fluad group and no subject had a body temperature of ≥40°C. Systemic reactions across vaccine groups and vaccinations were mild or moderate with the exception of severe malaise, headache, nausea (2-3% or 1 subject) in the Fluad group of Study V87P6.

Table 26: Percentage of subjects with solicited systemic and other reactions by study, vaccination (15 µg) and vaccine Group – 9 to <18 years.

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)			
Study	**V87P6** [1]		**V7P29** [2]	
Vaccine group	**Fluad**	**PanH5N1** [3]	**Fluad**	**Flushield / Fluogen**
1st vaccination	**N=41**	**N=93**	**N=116**	**N=100**
Chills	34% (0)	11% (0)	11% (0)	1% (0)
Malaise	37% (2%)	22% (0)	24% (0)	6% (0)
Myalgia	37% (0)	37% (2%)	9% (0)	6% (0)
Arthralgia	10% (0)	4% (0)	2% (0)	0 (0)
Headache	59% (2%)	40% (1%)	27% (1%)	12% (1%)
Rash	NS	NS	0 (0)	1% (1%)
Sweating	15% (0)	13% (0)	NS	NS
Nausea	24% (2%)	14% (0)	10% (0)	4% (0)
Vomiting	5% (0)	1% (0)	NS	NS
Diarrhea	10% (0)	4% (0)	NS	NS
Fatigue	49% (0)	32% (0)	NS	NS
Fever [4] (≥40°C)	2% (0)	0 (0)	9% (0)	3% (0)
Analgesics/Antipyretics	22%	22%	37%	19%
Stayed home due to reaction	17%	5%	16%	8%
2nd vaccination	**N=40**	**N=91**	***No 2nd vaccination***	
Chills	5% (0)	3% (0)		
Malaise	13% (0)	14% (0)		
Myalgia	18% (0)	33% (1%)		
Arthralgia	5% (0)	2% (0)		
Headache	25% (3%)	22% (0)		
Sweating	5% (0)	4%(0)		
Nausea	15% (3%)	9% (1%)		
Vomiting	0 (0)	1% (0)		
Diarrhea	3% (0)	8% (1%)		
Fatigue	25% (0)	11% (1%)		
Fever [4] (≥40°C)	0 (0)	1% (0)		
Analgesics/Antipyretics	8%	13%		
Stayed home due to reaction	0	4%		

	% Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions)			
Study	**V87P6** [1]		**V7P29** [2]	
Vaccine group	**Fluad**	**PanH5N1** [3]	**Fluad**	**Flushield / Fluogen**
3rd vaccination	***No 3rd vacc.***	**N=83**	***No 3rd vacc.***	
Chills		14% (2%)		
Malaise		14% (2%)		
Myalgia		42% (2%)		
Arthralgia		4% (0)		
Headache		35% (6%)		
Sweating		5% (0)		
Nausea		8% (0)		
Vomiting		0 (0)		
Diarrhea		8% (0)		
Fatigue		20% (2%)		
Fever [4] (≥40°C)		2% (0)		
Analgesics/Antipyretics		16%		
Stayed home due to reaction		2%		

Source: ISS, CSRs V87P6, and V7P29. NS = not solicited, as per protocol 1: Supportive study with PanH5N1: Second vaccination given 3 weeks after the first vaccination. 2: Control vaccine was a non adjuvanted, trivalent split virus seasonal flu vaccine manufactured by Wyeth-Ayerst (Flushield) or by Parke-Davis (Fluogen). 3: Third vaccination of PanH5N1 given 12 months after 2nd vaccination. 4: fever defined as body temperature ≥38°C, and (% subjects with severe reaction/fever) = (body temperature ≥40°C). Subjects with Solicited Systemic and Other Reactions (% Subjects with Severe Reactions).

Severity and duration (all age groups)

In all studies, for all vaccinations most of the systemic reactions reported in any of the age groups were mild to moderate in severity and transient in duration

Systemic reactions - pooled analysis

Overall, pooled analyses for solicited systemic and other reactions were consistent with by study analyses. Within each age group, incidence rates of systemic and other reactions were higher for Fluad than for Flu comparators (excluding PanH5N1 in V87P6) and decreased slightly from first to second vaccination for most systemic and other reactions. Incidences of most systemic reactions were higher in the 9 to <18 years age group than in the 3 to < 9 years age group.

Children 6 to <36 months

The most frequently reported systemic reaction across vaccinations was irritability (range: Fluad 20-23%, Flu comparator 19-24%), followed by unusual crying (Fluad 20-21%, Flu comparator 18-20%). For this age group, systemic reactions were not classified as any, mild, moderate and severe, with the exception of V70P2. No severe systemic reactions were reported in Study V70P2. Across vaccinations, 20-22% of subjects reported fever (body temperature ≥38°C) after Fluad vaccination and 17-18% after vaccination with non- adjuvanted influenza comparator. Body temperatures of ≥40°C were reported for ≤1% of subjects (range across vaccinations: Fluad 1-6 subjects, Flu comparator 4-7 subjects) (Table 27).

Children 3 to <9 years

The most frequently reported systemic reaction across vaccinations was fatigue (range: Fluad 23-29%, Flu comparator 17-19%), followed by headache (Fluad 13-17%, Flu comparator 7- 8%) and malaise (Fluad 13-16%, Flu comparator 8-11%). Most systemic reactions across vaccine groups and vaccinations were mild or moderate, with only ≤5% of subjects reporting severe reactions. Across vaccinations, 16% of subjects reported fever after Fluad vaccination and 7-8% after vaccination with non adjuvanted influenza comparator. Body temperatures of ≥40°C were reported for <1% of subjects (range across vaccinations: Fluad 1-2 subjects, Flu comparator 1 subject) (Table 28).

Children 9 to <18 years

The most frequently reported systemic reaction across vaccinations was fatigue (range: Fluad 25-49%, Flu comparator 0%), followed by headache (Fluad 25-35%, Flu comparator 12%) and malaise (Fluad 13-27%, Flu comparator 6%). Most systemic reactions across vaccine groups and vaccinations were mild or moderate, with only 1-2 subjects (1-3% of subjects) per group reporting severe reactions for malaise, headache or nausea. After the first vaccination, 7% of subjects (11 subjects) reported fever after Fluad vaccination and 3% of subjects (3 subjects) after vaccination with non adjuvanted influenza comparator. Body temperatures of ≥40°C were not observed (Table 29).

Table 27: Subjects (%) with solicited systemic and other reactions in the pooled safety population by vaccination (7.5 µg) and vaccine group – 6 to <36 months.

V70P2, V70P6, V70P5, and V87P6	Number (%) of Subjects with Systemic and Other Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control [1]	Fluad	Flu-Control [1]
Pooled Safety Population	N=1494	N=1337	N=1408	N=1248
Sleepiness	304 (20%)	245 (18%)	256 (18%)	173/1247 (14%)
Diarrhea	195 (13%)	170 (13%)	159 (11%)	111/1247 (9%)
Vomiting	93 (6%)	84 (6%)	77 (5%)	63/1247 (5%)
Irritability	349 (23%)	317 (24%)	287 (20%)	241/1247 (19%)
Change in eating habits	262 (18%)	214 (16%)	206 (15%)	147/1247 (12%)
Shivering	57/1364 (4%)	47/1198 (4%)	38/1291 (3%)	30/1120 (3%)
Unusual Crying	314 (21%)	271 (20%)	277 (20%)	224/1247 (18%)
Fever (≥38°C)	292/1493 (20%)	240/1336 (18%)	305 (22%)	215 (17%)
severe (≥40°C)	6/1493 (<1%)	4/1336 (<1%)	1 (<1%)	7 (1%)
Stayed at home due to reaction	17/125 (14%)	10/122 (8%)	17/115 (15%)	17/114 (15%)
Analgesics/Antipyretics	284/1492 (19%)	238 (18%)	269 (19%)	207 (17%)

Source: ISS. 1: Flu-Control vaccines were: Vaxigrip for V70P2, Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6. V70P2, V70P6, V70P5, and V87P6

Table 28: Subjects (%) with solicited systemic and other reactions in the pooled safety population by vaccination (15 µg) and vaccine group – 3 to <9 years.

V70P6 [1], V70P5 [1], and V87P6	Number (%) of Subjects with Systemic and Other Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control [2]	Fluad	Flu-Control [2]
Pooled Safety Population	N=922	N=826	N=900	N=804
Chills	95/921 (10%)	31 (4%)	74 (8%)	29 (4%)
severe	7/921 (1%)	2 (<1%)	9 (1%)	1 (<1%)
Malaise	145/921 (16%)	90 (11%)	118 (13%)	66 (8%)
severe	21/921 (2%)	10 (1%)	13 (1%)	6 (1%)
Myalgia	132/921 (14%)	62 (8%)	128 (14%)	67 (8%)
severe	10/921 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Arthralgia	60/921 (7%)	25 (3%)	36 (4%)	17 (2%)
severe	9/921 (1%)	1 (<1%)	4 (<1%)	0
Headache	155/921 (17%)	69 (8%)	115 (13%)	54 (7%)
severe	17/921 (2%)	5 (1%)	11 (1%)	1 (<1%)
Sweating	52/921 (6%)	32 (4%)	36 (4%)	14 (2%)
severe	4/921 (<1%)	4 (<1%)	3 (<1%)	0
Nausea	2/40 (5%)	0	3/39 (8%)	0
severe	1/40 (3%)	0	2/39 (5%)	0
Fatigue	265/921 (29%)	156 (19%)	207 (23%)	134 (17%)
severe	23/921 (2%)	7 (1%)	14 (2%)	10 (1%)
Fever (≥38°C)	148 (16%)	54/825 (7%)	141 (16%)	68 (8%)
severe (>40°C)	2 (<1%)	1/825 (<1%)	1 (<1%)	1 (<1%)
Stayed home due to reaction	5/88 (6%)	2/47 (4%)	9/86 (10%)	4/46 (9%)
Analgesics/Antipyretics	145 (16%)	61/825 (7%)	128 (14%)	53 (7%)

Source: ISS. 1: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)". 2: Flu-Control vaccines were: Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6.

Table 29: Subjects (%) with solicited systemic and other reactions in the pooled safety population by vaccination (15 µg) and vaccine group – 9 to <18 years.

V87P6 and V7P29	Number (%) of Subjects with Systemic/Other Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control [1]	Fluad	Flu-Control [1]
Pooled Safety Population	N=157	N=100	N=40	N=0
Chills	27 (17%)	1 (1%)	2 (5%)	0
severe	0	0	0	0
Malaise	43 (27%)	6 (6%)	5 (13%)	0
severe	1 (1%)	0	0	0
Myalgia	26 (17%)	6 (6%)	7 (18%)	0
severe	0	0	0	0
Arthralgia	6 (4%)	0	2 (5%)	0
severe	0	0	0	0
Headache	55 (35%)	12 (12%)	10 (25%)	0
severe	2 (1%)	1 (1%)	1 (3%)	0
Sweating	6/41 (15%)	0	2 (5%)	0
severe	0	0	0	0
Nausea	22 (14%)	4 (4%)	6 (15%)	0
severe	1 (1%)	0	1 (3%)	0
Rash	0	1 (1%)	0	0
severe	0	1 (1%)	0	0
Fatigue	20/41 (49%)	0	10 (25%)	0
severe	0	0	0	0
Fever (≥38°C)	11/156 (7%)	3 (3%)	0	0
severe (≥40°C)	0	0	0	0
Stayed home due to reaction	25 (16%)	8 (8%)	0	0
Analgesics/Antipyretics	52 (33%)	19 (19%)	3 (8%)	0

Source: ISS.

Unsolicited adverse events

Information about unsolicited AEs (including solicited reactions persisting beyond the 7-day observation period) by age group and by vaccine group was collected in three ways:

1. An overview of unsolicited AEs is presented by study and by safety monitoring period.
2. An overview of unsolicited AEs by pooled safety population and by safety monitoring period is presented for all studies and vaccine groups.
3. An analysis of unsolicited AEs by preferred term.

Follow up consisted of a Primary Period (from day of first vaccination up to 21 days after last vaccination) and a Follow up Period (from >21 days after last vaccination until 6-month after last vaccination). For Study V70P5, the three seasons Part I, II and III were pooled within each of the three vaccine groups: Fluad (MF59-adjuvanted seasonal flu vaccine), (non adjuvanted seasonal) flu vaccine control, and (aluminum hydroxide adjuvanted Menjugate/Encepur Children) non flu vaccine control. This also included the Part III subjects (Study V70P5) voluntarily vaccinated with MF59 adjuvanted H1N1 swine flu vaccine (Fluad: 19 subjects, flu vaccine control: 11 subjects and non flu vaccine control: 9 subjects) more than 21 days after the last seasonal flu vaccine administration. The safety data from these few subjects with any H1N1 related data captured during the Follow up Period only) did not affect the results.

Overview of unsolicited AEs: By study analysis

Within each study and age group, no clinically meaningful differences between Fluad and Flu comparator vaccine groups for rates of unsolicited AEs or for incidence rates of related (judged possibly/probably related to study vaccine by investigator) unsolicited AEs were observed. Incidence rates of AEs were similar in the Primary and Follow-up Periods, with

the exception of Studies V70P2, V70P6 (3 to <9 years age group only) and V87P6 (Fluad group only; all three age groups), where incidence rates of unsolicited AEs were lower in the Follow up Period, and Study V7P29, where incidence rates were higher in the Follow up Period (Tables 30-32).

Related AEs with onset during the Primary Period (excluding vaccine groups with <100 subjects) were reported for approximately 10% of subjects across studies, age and vaccine groups (range: Fluad 4-16%, Flu-comparator 2-15%). Related AEs with onset during the Follow-up Period (excluding vaccine groups with <100 subjects) were reported only by 1 subject each in both vaccine groups of Study V70P5 and by one subject in the Flu comparator group of Study V7P29 (range: Fluad ≤1%, Flu comparator ≤1%). In Study V70P2E1 only few subjects were enrolled and results may be uninterpretable because of this (Tables 30-32).

Only few SAEs were reported throughout all studies (Tables 31-33). In the Phase 3 Study V70P5, an efficacy study that captured cases of any influenza like illness as SAEs, the incidence rates of SAEs, particularly in the Follow up Period, were higher than in the Phase 2 studies. Only few subjects withdrew due to an AE.

Table 30: Overview of unsolicited AEs by study and vaccine Group – 6 to <36 months.

	Number (%) Subjects with Unsolicited AEs									
Safety Monitoring Period	**Primary Period** [1]									
Study	**V70P2**		**V70P2E1** [2]		**V70P6** [3]		**V70P5**		**V87P6** [4]	
Vaccine group	**Fluad**	**Vaxigrip**	**Fluad**	**Vaxigrip**	**Fluad**	**Fluzone**	**Fluad**	**Control A** [6]	**Fluad**	**PanH5N1**
Safety Population	**N=130**	**N=139**	**N=25**	**N=23**	**N=136**	**N=132**	**N=1178**	**N=1068**	**N=56**	**N=145**
AEs: all	95 (73%)	97 (70%)	11 (44%)	9 (39%)	56 (41%)	45 (34%)	825 (70%)	745 (70%)	33 (59%)	81 (56%)
related (poss./prob.)	21 (16%)	21 (15%)	8 (32%)	1 (4%)	9 (6%)	3 (2%)	148 (13%)	123 (12%)	7 (13%)	24 (17%)
SAEs: all	0	1 (1%)	0	0	0	0	21 (2%)	20 (2%)	1 (2%)	0
related (poss./prob.)	0	0	0	0	0	0	1 (<1%)	1 (<1%)	0	0
AEs leading to premature withdrawal	1 (1%)	2 (1%)	0	0	0	0	5 (<1%)	8 (1%)	0	0
related (poss./prob.)	1 (1%)	0	0	0	0	0	2 (<1%)	2 (<1%)	0	0
Safety Monitoring Period	**Follow-up Period** [1]									
AEs: all	57 (44%)	66 (52%)	14 (56%)	11 (48%)	57 (42%)	49 (37%)	719 (68%)	651 (68%)	22 (39%)	55 (40%)
related (poss./prob.)	0	0	0	0	0	0	1 (<1%)	1 (<1%)	0	0
SAEs: all	2 (2%)	5 (4%)	0	0	1 (1%)	1 (1%)	52 (5%)	72 (8%)	1 (2%)	8 (6%)
related (poss./prob.)	0	0	0	0	0	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0	0	1 (1%)	1 (<1%)	1 (<1%)	0	1 (1%)
related (poss./prob.)	0	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	1 (1%)	0	0	0	0
related (poss./prob.)	0	0	0	0	0	0	0	0	0	0

Source: ISS. 1: Safety monitoring periods: Primary Period = Day 1 (1st vaccination) through 21 days post last vaccination, Follow-up Period = >21 days post last vaccination to 6 months after last vaccination. 2: About half of the subjects from V70P2 continuing in V70P2E1 were ≥36 months old. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1: 1st and 2nd vacc. given 3 weeks apart, and, only for PanH5N1: 3rd vacc. given at 12 months post 2nd vacc 6: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and III.

Table 31: Overview of unsolicited AEs by study and vaccine Group – 3 to <9 years.

	Number (%) Subjects with Unsolicited AEs							
Safety Monitoring Period	**Primary Period** [1]							
Study	**V70P2E1** [2]		**V70P6*** [3]		**V70P5***		**V87P6** [4]	
Vaccine group	**Fluad**	**Vaxigrip**	**Fluad**	**Fluzone**	**Fluad** [5]	**Control A** [6]	**Fluad**	**PanH5N1**
Safety Population	**N=18**	**N=23**	**N=44**	**N=48**	**N=834**	**N=778**	**N=40**	**N=96**
AEs: all	5 (28%)	11 (48%)	16 (36%)	17 (35%)	490 (59%)	461 (59%)	12 (30%)	37 (39%)
related (poss./prob.)	2 (13%)	1 (4%)	1 (2%)	1 (2%)	110 (13%)	78 (10%)	5 (13%)	14 (15%)
SAEs: all	0	0	0	0	9 (1%)	12 (2%)	0	1 (1%)
related (poss./prob.)	0	0	0	0	0	1 (<1%)	0	0
AEs leading to premature withdrawal	0	0	1 (2%)	1 (2%)	4 (<1%)	0	1 (3%)	0
related (poss./prob.)	0	0	0	0	1 (<1%)	0	1 (3%)	0
Safety Monitoring Period	**Follow-up Period** [1]							
AEs: all	8 (44%)	12 (52%)	8 (18%)	15 (31%)	402 (51%)	402 (54%)	8 (21%)	26 (28%)
related (poss./prob.)	0	0	0	0	1 (<1%)	1 (<1%)	0	0
SAEs: all	0	0	0	0	15 (2%)	39 (5%)	0	0
related (poss./prob.)	0	0	0	0	1 (<1%)	1 (<1%)	0	0
AEs leading to premature withdrawal	0	0	0	0	0	0	0	0
related (poss./prob.)	0	0	0	0	0	0	0	0

Source: ISS *: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)". 1: Safety monitoring periods: Primary Period = Day 1 (1st vaccination) through 21 days post last vaccination, Follow-up Period = >21 days post last vaccination to 6 months after last vaccination. 2: Of the subjects from V70P2 that continued in V70P2E1 about half were ≥36 months old. 3: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomised to age group 36 to <60 months, and are presented as treated (in the

3 to <9 years group) and not by actual age. 4: Supportive study with PanH5N1: 1st and 2nd vacc. given 3 weeks apart, and, only for PanH5N1: 3rd vacc. given at 12 months post 2nd vacc. 6: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II.

Table 32: Overview of unsolicited AEs by study and vaccine group – 9 to <18 years.

	Number (%) Subjects with Unsolicited AEs			
Safety Monitoring Period	**Primary Period [1]**			
Study	**V87P6 [3]**		**V7P29 [3]**	
Vaccine group	**Fluad**	**PanH5N1**	**Fluad**	**Flushield or Fluogen**
Safety Population	**N=41**	**N=93**	**N=116**	**N=100**
AEs: all	13 (32%)	31 (33%)	31 (27%)	38 (38%)
related (poss./prob.)	8 (20%)	8 (9%)	13 (11%)	11 (11%)
SAEs: all	0	0	0	0
related (poss./prob.)	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0
related (poss./prob.)	0	0	0	0
Safety Monitoring Period	**Follow-up Period [1]**			
AEs: all	3 (8%)	19 (21%)	90 (78%)	69 (69%)
related (poss./prob.)	0	0	0	1 (1%)
SAEs: all	0	2 (2%)	0	0
related (poss./prob.)	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0
related (poss./prob.)	0	0	0	0

Source: ISS. 1: Safety monitoring periods: Primary Period = Day 1 (1st vaccination) through 21 days post last vaccination, Follow up Period = >21 days post last vaccination to 6 months after last vaccination. 2: Supportive study with PanH5N1: 1st and 2nd vacc. given 3 weeks apart, and, only for PanH5N1: 3rd vacc. given at 12 months post 2nd vacc. Follow up Period = from >21 days post 2nd vaccination until 6 months post 2nd vaccination). 3: Supportive study with Fluad: only one vaccination.

Overview of unsolicited AEs: pooled analysis

Overall, the results from the pooled analyses were consistent with those from the by study analyses. In the 2 groups of children 6 months to <9 years, incidence rates of unsolicited AEs (any and related) were balanced between vaccination groups and similar for the Primary and the Follow up Periods. For children 9 to <18 years incidence rates in the Flu-comparator group were higher than in the Fluad group, and for both vaccination groups incidence rates were higher during the Follow up Period. In the Primary and Follow up Period, about 10-13% and ≤1% of subjects, respectively, experienced a probably/possibly related AE as judged by the investigator. Only few SAEs were reported and of these only <1% were judged by the investigator as probably/possibly related. Only in few subjects AEs led to premature withdrawal, and of these <1% were judged by the investigator as probably/possibly.

Children 6 to <36 months

Within this age group and across both safety monitoring periods, no clinically meaningful differences between the two vaccine groups were observed for incidence rates of unsolicited AEs and related unsolicited AEs. Most AEs (any or related) were transient and mild or moderate in severity. In the Primary Period, the 6 most frequently reported AEs (≥6% in the Fluad group) were upper respiratory tract infection (Fluad 17%, Flu comparator 16%), rhinitis (Fluad 16%, Flu comparator 14%), pyrexia (Fluad 13%, Flu comparator 12%), cough (Fluad 12%, Flu comparator 11%), otitis media (Fluad 7%, Flu comparator 7%), and nasopharyngitis (Fluad 6%, Flu comparator 7%), as summarised in Table 33. For all other preferred terms (PTs) in this table, incidence rates in the Fluad group range from 2-5%. For most of these PTs in Table 33 (except teething and diaper rash) a small number of events, ranging from <1% (1-6 subjects per group) up to 2% (25-37 subjects), were considered possibly/probably related to study vaccine by the investigator.

In the Follow up Period, the six most frequently reported PTs (≥6% in the Fluad group) were otitis media (Fluad 13%, Flu comparator 14%), upper respiratory tract infection (Fluad 11%, Flu comparator 11%), gastroenteritis (Fluad 9%, Flu comparator 8%), bronchitis (Fluad 8%, Flu comparator 8%), pyrexia (Fluad 7%, Flu comparator 7%), and

ear infection (Fluad 7%, Flu comparator 7%), as summarised in Table 33. For all other PTs in this table, incidence rates in the Fluad group range from 2-5%. For only three of these PTs in Table 33, one event (each) was considered possibly/probably related to study vaccine by the investigator.

Table 33: Subjects (%) with unsolicited AEs (all and possibly/probably related) in the pooled safety population: Preferred Terms (≥2% in Fluad Group) by safety monitoring period and vaccine group – 6 to <36 Months.

Preferred Term (Ordered by Decreasing Frequency in the Fluad Group)	Number (%) of Subjects with Unsolicited AEs			
	Primary Period			
	ALL		At Least Possibly Related	
	Fluad	Flu-Control[1]	Fluad	Flu-Control[1]
Pooled Safety Population	N=1500	N=1339	N=1500	N=1339
Upper Respiratory Tract Infection	260 (17%)	213 (16%)	26 (2%)	25 (2%)
Rhinitis	237 (16%)	186 (14%)	37 (2%)	18 (1%)
Pyrexia	196 (13%)	159 (12%)	18 (1%)	16 (1%)
Cough	183 (12%)	144 (11%)	23 (2%)	10 (1%)
Otitis Media	110 (7%)	96 (7%)	4 (<1%)	2 (<1%)
Nasopharyngitis	92 (6%)	93 (7%)	9 (1%)	8 (1%)
Conjunctivitis	72 (5%)	66 (5%)	4 (<1%)	1 (<1%)
Gastroenteritis	54 (4%)	63 (5%)	0	2 (<1%)
Diarrhoea	67 (4%)	49 (4%)	6 (<1%)	5 (<1%)
Bronchitis	63 (4%)	51 (4%)	3 (<1%)	1 (<1%)
Teething	47 (3%)	39 (3%)	0	0
Ear Infection	41 (3%)	52 (4%)	2 (<1%)	0
Crying	40 (3%)	32 (2%)	16 (1%)	12 (1%)
Irritability	40 (3%)	30 (2%)	16 (1%)	14 (1%)
Vomiting	40 (3%)	21 (2%)	2 (<1%)	3 (<1%)
Respiratory Tract Infection	32 (2%)	26 (2%)	1 (<1%)	1 (<1%)
Dermatitis Diaper	30 (2%)	16 (1%)	0	0
Rash	29 (2%)	22 (2%)	9 (1%)	7 (1%)

Source: ISS. 1: Flu control vaccines were: Vaxigrip for V70P2, Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6.

Children 3 to <9 years

Within this age group and across both safety monitoring periods, no clinically meaningful differences between the two vaccine groups were observed for incidence rates of unsolicited AEs and related unsolicited AEs. Most AEs (any or related) were transient and mild or moderate in severity.

In the Primary Period, the 6 most frequently reported PTs (≥40 subjects in the Fluad group) were cough (Fluad 13%, Flu comparator 14%), upper respiratory tract infection (Fluad 10%, Flu comparator 10%), rhinitis (Fluad 9%, Flu comparator 8%), pyrexia (Fluad 8%, Flu comparator 9%), vomiting (Fluad 4%, Flu comparator 5%), and nasopharyngitis (Fluad 4%, Flu comparator 5%), as summarised in Table 34. For all other PTs in this table, incidence rates in the Fluad group range from 1-4%. For most of these PTs in Table 34 (except bronchitis and varicella) a small number of events, ranging from <1% (1-4 subjects per group) up to 2% (15 subjects), were considered possibly/probably related to study vaccine by the investigator.

In the Follow up Period, the 6 most frequently reported PTs (≥37 subjects in the Fluad group) were otitis media (Fluad 8%, Flu comparator 9%), cough (Fluad 8%, Flu comparator 7%), upper respiratory tract infection (Fluad 7%, Flu comparator 8%), bronchitis and conjunctivitis (Fluad 5%, Flu comparator 4%), and rhinitis (Fluad 4%, Flu comparator 3%), as summarised in Table 34. For all other PTs in this table, incidence rates in the Fluad group range from 2-4%. For only one of these PTs in Table 34, one event was considered possibly/probably related to study vaccine by the investigator.

Table 34: Subjects (%) with unsolicited AEs (all and possibly/probably related) in the pooled safety population: Preferred Terms (≥2% in Fluad group) by safety monitoring period and vaccine group – 3 to <9 years.

Preferred Term (Ordered by Decreasing Frequency in the Fluad Group)	Number (%) of Subjects with Unsolicited AEs			
	Primary Period			
	ALL		At Least Possibly Related	
	Fluad	Flu-Control[1]	Fluad	Flu-Control[1]
Pooled Safety Population	N=918	N=826	N=918	N=826
Cough	117 (13%)	114 (14%)	15 (2%)	15 (2%)
Upper Respiratory Tract Infection	88 (10%)	80 (10%)	10 (1%)	9 (1%)
Rhinitis	82 (9%)	64 (8%)	15 (2%)	6 (1%)
Pyrexia	76 (8%)	71 (9%)	9 (1%)	6 (1%)
Vomiting	40 (4%)	42 (5%)	7 (1%)	4 (<1%)
Nasopharyngitis	40 (4%)	40 (5%)	7 (1%)	3 (<1%)
Gastroenteritis	35 (4%)	38 (5%)	1 (<1%)	0
Otitis Media	37 (4%)	34 (4%)	1 (<1%)	0
Diarrhoea	31 (3%)	33 (4%)	11 (1%)	6 (1%)
Oropharyngeal Pain	27 (3%)	20 (2%)	8 (1%)	3 (<1%)
Conjunctivitis	26 (3%)	22 (3%)	1 (<1%)	0
Headache	25 (3%)	14 (2%)	6 (1%)	6 (1%)
Bronchitis	23 (3%)	22 (3%)	0	0
Abdominal Pain	16 (2%)	13 (2%)	2 (<1%)	0
Ear Pain	14 (2%)	6 (1%)	0	1 (<1%)
Varicella	14 (2%)	6 (1%)	0	0
Abdominal Pain Upper	11 (1%)	14 (2%)	7 (1%)	4 (<1%)
Ear Infection	11 (1%)	13 (2%)	1 (<1%)	0

Preferred Term (Ordered by Decreasing Frequency in the Fluad Group)	Number (%) of Subjects with Unsolicited AEs			
	Follow-Up Period			
	ALL		At Least Possibly Related	
	Fluad	Flu-Control[1]	Fluad	Flu-Control[1]
Pooled Safety Population	N=1359	N=1213	N=1359	N=1213
Otitis Media	172 (13%)	175 (14%)	0	0
Upper Respiratory Tract Infection	146 (11%)	135 (11%)	0	0
Gastroenteritis	118 (9%)	91 (8%)	0	0
Bronchitis	111 (8%)	91 (8%)	0	1 (<1%)
Pyrexia	91 (7%)	89 (7%)	0	0
Ear Infection	90 (7%)	79 (7%)	0	0
Conjunctivitis	87 (6%)	94 (8%)	0	0
Cough	84 (6%)	85 (7%)	1 (<1%)	0
Nasopharyngitis	81 (6%)	70 (6%)	0	0
Rhinitis	68 (5%)	57 (5%)	1 (<1%)	0
Respiratory Tract Infection	48 (4%)	37 (3%)	0	0
Dermatitis Diaper	40 (3%)	33 (3%)	0	0
Tonsillitis	35 (3%)	23 (2%)	0	0
Pharyngitis	33 (2%)	26 (2%)	0	0
Enteritis	28 (2%)	29 (2%)	0	0
Eczema	28 (2%)	18 (1%)	0	0
Diarrhoea	27 (2%)	26 (2%)	0	0
Vomiting	26 (2%)	34 (3%)	0	0
Viral Infection	23 (2%)	27 (2%)	0	0
Laryngitis	23 (2%)	11 (1%)	0	0
Constipation	22 (2%)	18 (1%)	0	0
Varicella	21 (2%)	7 (1%)	0	0

Source: ISS. 1: Flu Control vaccines were: Vaxigrip for V70P2, Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6.

Children 9 to <18 Years

Within this age group and across both safety monitoring periods, no clinically meaningful differences between the two vaccine groups were observed for incidence rates of

unsolicited AEs and related unsolicited AEs. Most AEs (any or related) were transient and mild or moderate in severity.

In the Primary Period, the five most frequently reported PTs (≥2% in the Fluad group) were infection (Fluad 4%, Flu comparator 8%), nasopharyngitis (Fluad 4%, Flu comparator 3%), rhinorrhoea (Fluad 3%, Flu comparator 1%), cough (Fluad 2%, Flu comparator 2%), and abdominal pain upper (Fluad 2%, Flu comparator 1%), as summarised in Table 35. For all other PTs in Table 35, incidence rates in the Fluad group range were <2%. For most of these PTs in Table 35, a small number of events, ranging from 1% (1-2 subjects per group) up to 5% (five subjects in the Flu comparator group of Study V7P29), were considered possibly/probably related to study vaccine by the investigator (Table 35). In the Follow up Period, the six most frequently reported PTs (≥5 subjects in the Fluad group) were respiratory disorder (Fluad 13%, Flu comparator 16%), upper respiratory tract infection (Fluad 10%, Flu comparator 11%), oropharyngeal pain (Fluad 8%, Flu comparator 7%), pharyngitis streptococcal (Fluad 4%, Flu comparator 7%), vomiting (Fluad 4%, Flu comparator 1%), and injury (Fluad 3%, Flu comparator 4%), as summarised in Table 36. For all other PTs in this table, incidence rates in the Fluad group range from 2-3%. For none of these PTs in Table 35 was an event considered possibly/probably related to study vaccine by the investigator.

Table 35: Subjects (%) with unsolicited AEs (all and possibly/probably related) in the pooled safety population: Preferred Terms (≥2% in Fluad Group) by safety monitoring period and vaccine group – 9 to < 18 years.

Preferred Term (Ordered by Decreasing Frequency in the Fluad Group)	Number (%) of Subjects with Unsolicited AEs			
	Primary Period			
	ALL		At Least Possibly Related	
	Fluad	Flu-Control[1]	Fluad	Flu-Control[1]
Pooled Safety Population	N=157	N=100	N=157	N=100
Infection	7 (4%)	8 (8%)	2 (1%)	5 (5%)
Nasopharyngitis	7 (4%)	3 (3%)	3 (2%)	2 (2%)
Rhinorrhoea	4 (3%)	1 (1%)	2 (1%)	0
Cough	3 (2%)	2 (2%)	1 (1%)	0
Abdominal Pain Upper	3 (2%)	1 (1%)	1 (1%)	0

Source: ISS. 1: Flu-Control vaccines were: Fluzone for V70P6, Agrippal S1 for Part I of V70P5, Influsplit SSW for Part II and Part III of V70P5, and none for V87P6.

Serious adverse events (SAEs)

No death was reported in Studies V70P2, V70P2E1, V70P5, V87P6 and V7P29. One death occurred in the Flu comparator group of Study V70P6 (6 to <36 months) on Day 207 that was unrelated to the study vaccine.

No SAEs were observed in Phase 2 Studies V70P2E1 (both age groups) and V70P6 (3 to <9 years). Few SAEs were reported in the Phase 2 Studies V70P2, V70P6 age group 6 to <36 months, V7P29 and V87P6 (range across studies and age groups: Fluad 1-4% or 1-2 subjects, non adjuvanted Flu comparator 1-4% or 1-6 subjects), with none of them considered related to study vaccine. Study V70P5 captured cases of any influenza like illness as SAE. The incidence rates of SAEs were higher (range across age groups: Fluad 4-8% or 32-91 subjects, Flu comparator 8-10% or 64-104 subjects) than in the Phase 2 studies (Tables 36-38). In both age groups, subjects receiving Flu comparator had more SAEs than subjects receiving Fluad. Overall, very few of the SAEs in Study V70P5 were considered possibly/probably related to study vaccine by the investigator (one subject each in the Fluad and the Flu comparator group of both age groups).

Table 36: Subjects (%) with SAEs - 6 to <36 months.

	Number (%) of Subjects with SAEs									
Study	V70P2		V70P2E1 [1]		V70P6 [2]		V70P5		V87P6 [3]	
Vaccine group	Fluad	Vaxigrip	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [4]	Control A [5]	Fluad	PanH5N1
Safety Population	N=130	N=139	N=25	N=23	N=136	N=132	N=1178	N=1068	N=56	N=145
Any SAE	2 (2%)	6 (4%)	0	0	1 (1%)	1 (1%)	91 (8%)	104 (10%)	2 (4%)	16 (11%)
related (poss./prob.)	0	0	0	0	0	0	1 (<1%)	1 (<1%)	0	0

Source: ISS. 1: Of the subjects from V70P2 that continued in V70P2E1 about half were ≥36 months old,: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 3: Supportive study with PanH5N1: this table includes the entire follow-up for the PanH5N1 group (V87P6 CSR). 5: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 37: subjects (%) with SAEs - 3 to <9 years.

	Number (%) of Subjects with SAEs							
Study	V70P2E1 [1]		V70P6 [2,*]		V70P5*		V87P6 [3]	
Vaccine group	Fluad	Vaxigrip	Fluad	Fluzone	Fluad [4]	Control A [5]	Fluad	PanH5N1
Safety Population	N=18	N=23	N=44	N=48	N=834	N=778	N=40	N=96
Any SAE	0	0	0	0	32 (4%)	64 (8%)	0	3 (3%)
related (poss./prob.)	0	0	0	0	1 (<1%)	1 (<1%)	0	0

Source: ISS. *: Upper age limit lower than "<9 years": in V70P6 = "<5 years (60 months)" and in V70P5 = "<6 years (72 months)". 1: Of the subjects from V70P2 that continued in V70P2E1 about half were ≥36 months old 2: V70P6, for reactogenicity only: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as treated (in the 3 to <9 years group) and not by actual age. 3: Supportive study with PanH5N1: this table includes the entire follow up for the PanH5N1 group (V87P6 CSR). 5: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 38: Subjects (%) with SAEs - 9 to <18 years.

	Number (%) of Subjects with SAEs			
Study	V87P6 [1]		V7P29 [2]	
Vaccine group	Fluad	PanH5N1	Fluad	Flushield or Fluogen
Safety Population	N=41	N=93	N=116	N=100
Any SAE	0	3 (3%)	0 (0)	1 (1%)
related (poss./prob.)	0	0	0 (0)	0 (0)

Source: ISS. 1: Supportive study with PanH5N1: this table includes the entire follow-up for the PanH5N1 group (V87P6 CSR). 2: Supportive study with Fluad: only one vaccination.

The SAEs include the entire Study V87P6 (Table 38) with its 6 month follow up after the 3rd vaccination with PanH5N1 (overall duration approximately 18-19 months. A total of 22 subjects in the PanH5N1 group reported 29 SAEs and two subjects each in the Fluad group of both age groups reported one SAE. None of the SAEs reported were considered related.

Specific SAEs

Children 6 to <36 months

V70P2: There were 8 subjects who reported 9 SAEs (none related). Two subjects receiving Fluad reported pneumonia (Day 74 and Day 95, both considered unrelated). Six subjects receiving Vaxigrip reported the following SAEs: two with chronic bronchitis on Days 150 and 98, two had gastroenteritis (Days 58 and 93), one had otitis media on Day 136 and respiratory syncytial virus infection on Day 137, and one had asthma on Day 4.

V70P2E1: No SAEs.

V70P6: There were 2 subjects who reported 3 SAEs (none related; Fluad: 1 subject with 2 SAEs pneumonia and pleural effusion on Day 59); Fluzone: 1 subject with 1 SAE multiple trauma on day 202 with death on Day 207).

V70P5: There were 260 subjects with 313 SAEs. Five subjects reported the following related SAEs: Fluad – one subject had cyanosis, erythema and wheezing on Day 29; Flu comparator – one subject had gait disturbance on Day 4; one receiving Encepur Children had abnormal behaviour on Day 465; one receiving Encepur Children had influenza B on Day 79; and one receiving Encepur Children had asthma on Day 5.

V87P6: There were 18 subjects who reported 24 SAEs. Two subjects receiving Fluad reported the following 2 SAEs (none related) with onset given as Study Day: one subject had severe pyelonephritis acute on Day 12, and 1 subject had pneumonia on Day 62. In the PanH5N1 group, 16 subjects reported 22 SAEs: 17 SAEs with onset between >21 days after 2nd vaccination and the 3rd vaccination, and 5 SAEs with onset after 3rd vaccine.

Children 3 to <9 years

V70P2E1: No SAEs.

V70P6: No SAEs.

V70P5: There were 141 subjects with 161 SAEs. Two subjects reported the following related SAEs: one subject receiving Fluad had convulsions on Days 51, 118 and 219 and epilepsy on Day 121; and one subject receiving Flu comparator had autoimmune thyroiditis and diabetes mellitus on Day 33.

V87P6: No SAEs in the Fluad group. In the PanH5N1 group, three subjects reported the following three SAEs (none related): one subject had renal injury on Day 17, one subject had pyrexia on Day 350, and one subject had idiopathic thrombocytopenic purpura on Day 257. For all SAEs the seriousness criterion was hospitalisation.

Children 9 to <18 years

V87P6: No SAEs in the Fluad group. In the PanH5N1 group, three subjects reported the following four SAEs (none related) with onset given as Study Day: one subject had abdominal pain lower on Day 275, one subject had major depression on day 54 and depression on Day 284, and one subject had mental disorder on Day 109.

V7P29: There was one subject who reported one SAE. Subject received Fluogen had asthma with onset on Day 16, a duration of 156 days, an outcome of "alive with sequelae", no hospitalisation and remote relationship to study vaccine (that is, not related).

Laboratory findings

No analyses.

Safety in special populations

Safety analyses stratified by age (6 to <36 months, 3 to <9 years, and 9 to <18 years) are presented above. No other analysis of intrinsic factors was undertaken.

Immunological events

No analyses

Safety related to drug-drug interactions and other interactions

No analyses.

Discontinuation due to AEs

Across all vaccination groups, the frequency of AEs leading to withdrawal was less than or equal to 1.1%. None of the subjects in Study V70P2E1 and the 9 to <18 years age group studies V87P6 and V7P29 withdrew due to an AE. No more than 1% of subjects per vaccine group withdrew due to an AE in each study of age groups 6 to <36 months and 3 to <9 years, and no clinically meaningful differences between Fluad and Flu comparator were seen for incidence rates of AEs leading to premature withdrawal. The highest incidence of AEs leading to premature withdrawal, irrespective of vaccine group, were observed in

Study V70P5 age group 6 to <36 months (Fluad 1% or 6 subjects, Flu comparator 1% or 9 subjects).

With the exception of the 2009/10 season in Study V70P5, the majority of subjects completed the studies. Withdrawals were generally equally distributed among Fluad and control vaccine groups (Table 39). In Study V70P5, >95% of the subjects, by group, completed the study during seasons 2007/08 and 2008/09. In the 2007/08 season, a slightly higher percentage of premature withdrawals were observed in the Fluad and flu control (Agrippal) group with respect to the Menjugate/Encepur group. Most of the premature withdrawals were due to the subjects being lost to follow up. In the 2009/10 season, more than 50% of the subjects were withdrawn prematurely, mostly due to withdrawal of consent (33-37% across the vaccine groups) and protocol deviations (19-20% across vaccine groups). This was the direct result of the decision to favor vaccination against pandemic strains, rather than seasonal strains, during this season. In Phase 2 Studies V7P29 and V70P2, the most common reason for discontinuation was consent withdrawal, whereas in Study V70P6, it was lost to follow up (Table 39).

Table 39: Reasons for withdrawals by type of vaccination and study, all enrolled subjects.

		Total Subjects		N (%) Reasons for withdrawal			
Study	Vaccine	Enrolled	Completed (%)	AE/ Death	Withdrew Consent	Lost to Follow-Up	Other[a]
Pivotal Phase 3 study							
V70P5 (Season 2007/08)	Fluad	325	309 (95)	2 (<1)	1 (<1)	11 (3)	2 (<1)
	Agrippal	165	159 (96)	0	1 (<1)	5 (3)	0
	Menjugate/ Encepur	164	160 (98)	0	0	4 (2)	0
V70P5 (Season 2008/09)	Fluad	1616	1553 (96)	5 (<1)	25 (2)	24 (1)	9 (1)
	Influsplit	1608	1539 (96)	5 (<1)	31 (2)	26 (2)	7 (<1)
	Menjugate/ Encepur	829	793 (96)	1 (<1)	15 (2)	10 (1)	10 (1)
V70P5 (Season 2009/10)	Fluad	78	33 (42)	1 (1)	26 (33)	2 (3)	16 (21)
	Influsplit	76	28 (37)	0	28 (37)	3 (4)	17 (22)
	Menjugate/ Encepur	41	16 (39)	0	15 (37)	2 (5)	8 (20)
Phase 2 studies							
V70P2	Fluad	139	111 (80)	1 (<1)	14 (10)	2 (1)	11 (8)
	Vaxigrip	142	123 (87)	0	9 (6)	3 (2)	7 (5)
V70P2E1	Fluad	43	40 (93)	0	0	2 (5)	1 (2)
	Vaxigrip	46	44 (96)	0	1 (2)	0	1 (2)
V70P6	Fluad	180	165 (92)	1 (<1)	5 (3)	9 (5)	0
	Fluzone	180	162 (90)	2[b] (1)	7 (4)	9 (5)	0
V7P29	Fluad	117	114 (97)	0	3 (3)	0	0
	Fluvgen/ Flushield	100	99 (99)	0	0	1 (1)	0

a other = protocol deviations/violations, incorrect enrollment and reasons which the other categories b 1 subject died Sum of % completed and withdrawn may not be equal to 100% due to rounding. Source: V70P5 CSR; V70P2 CSR; V70P2E1 CSR; V70P6 CSR; V7P29 CSR A breakdown of withdrawals by number of doses actually received. Virtually all subjects enrolled into the studies received at least one dose of vaccine. In studies where two doses were administered, the majority of withdrawals occurred between the first and second dose in each treatment group.

Post marketing experience

There is no post marketing data for Fluad Paediatric.

Post marketing surveillance data from an estimate of 50 million doses of Fluad administered since its initial licensure in September 1997 to adults >65 years of age are available. The following AEs have been reported with Fluad in subjects older than 65 years:

- Blood and lymphatic system disorders

  - Rare (≥1/10,000, <1/1,000): Transient thrombocytopenia. Very rare (<1/10,000): Lymphadenopathy.
- Immune system disorders
  - Rare (≥1/10,000, <1/1,000): Allergic reactions, in rare cases leading to shock, have been reported.
- Nervous system disorders
  - Rare (≥1/10,000, <1/1,000): Neuralgia, paraesthesia, convulsions. Very rare (<1/10,000): Neurological disorders such as encephalomyelitis, neuritis and Guillain-Barrè syndrome.
- Vascular disorders
  - Very rare (<1/10,000): Vasculitis with transient renal involvement and exudative erythema multiforme.
- Skin and subcutaneous tissue disorders
  - Uncommon (≥1/1,000, <1/100) Generalised skin reactions including pruritus, urticaria or non specific rash.
- Musculoskeletal and connective tissue disorders
  - Very rare (<1/10,000): Pain in the extremity, muscular weakness.
- General disorders and administration site conditions
  - Very rare (<1/10,000): Asthenia, Influenza Like Illness (ILI).

A related vaccine containing H1N1v antigen and the same quantity of MF59C.1 (Focetria) was distributed widely in 2009 and 2010 and administered to both children and adults. Overall the safety profile of Fluad did not differ significantly from Focetria. The following additional AEs were reported via surveillance for Focetria:

- Cardiac disorders: Palpitation, tachycardia.
- Respiratory disorders: Cough.
- Gastrointestinal disorders: Gastrointestinal disorders such as nausea, vomiting, abdominal pain and diarrhoea.
- Nervous system disorders: Headache, dizziness, somnolence, syncope. neuritis.
- Immune system disorders: Allergic reactions, anaphylaxis including dyspnoea, bronchospasm, laryngeal oedema, in rare cases leading to shock.

Evaluator's overall conclusions on clinical safety

With respect to the safety data presented, there are a number of conclusions:

- The pooled data and the data from the individual studies at many different sites were very consistent.
- Local reactions are very common with Fluad (more common that with comparators) occurring in more than 50% of children overall (higher rate in the older children). In the younger children (babies), erythema and tenderness are most common. In the older children, pain at the injection site was more common (which may be a reflection of the ability of this group to articulate this).
- Despite this, local reactions were rarely cited as a reason for discontinuation, and the slightly higher incidence of local reactogenicity (about 10% compared to 'flu' vaccine

comparators), seemed to be acceptable (reactions usually mild moderate and short lasting).

- Systemic side effects, predominantly malaise and fever, were also more common with Fluad than with comparators. Once again, were common, usually mild moderate and were rarely a reason for study discontinuation.
- Unsolicited side effects that may have been related to study vaccine were reported with similar numbers between the two groups and generally related to upper respiratory tract infection symptoms (commonly reported in clinical practice post-influenza vaccine).
- There were few serious AEs and similarly, these were predominantly respiratory infections. These were more common with comparators, which is not surprising as influenza like illness was reported as a SAE.
- There were no febrile convulsions reported. This is important, given the suspension of influenza vaccination of children under 5 in Australia in 2010 following an excess in the number of reports of febrile convulsions after vaccination with Fluvax or Fluvax Junior. Although the same problem was not seen following vaccination with other licensed vaccines in children (Influvac and Vaxigrip), the concern was that the numbers vaccinated with these products may have been too low to detect the problem.[15]
- There were no reports of unusual neurological disorders or Guillain-Barre syndrome (also seen post influenza vaccine very rarely in adults).

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.

The sponsor responded to these questions posed by the clinical evaluator.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Question 1: efficacy

- "Are there any further studies currently underway or planned for the 6-18 year age group, as there is no efficacy data for these ages? Also, was there any particular reason that many of the studies only evaluated up to 72 months, rather than up to 9 years (the indication being sought) – for efficacy and safety?"

Sponsor's response

In the EU, Novartis has an approved Paediatric Investigational Plan for Fluad. As part of the PIP commitments, Novartis will conduct Study V7013 in the near future. This is a Phase 2, observer blind, randomised, multicentre study to evaluate the safety, tolerability and immunogenicity of a single dose of Fluad (rather than two doses) in healthy and at

[15] See: http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-110310.htm

risk children and adolescents aged 6 to <18 years versus a subunit vaccine to determine if a single dose is adequate in these populations and age group. While the study design may need revision based on data from subsequently completed studies (for example, dosing), the inclusion of children in the 6 to <9 year olds will not change. There are data currently available for the 6 to <18 year age group (and provided below), and more clinical data from Novartis' adjuvanted pandemic H1N1 formulations are in final stages of analysis for publication.

Our clinical development plan and clinical trials of Fluad in young children were motivated by observations that currently licensed influenza vaccines for children are suboptimal, and that a medical need exists for a more efficacious influenza vaccine for children under 6 years old and, in particular, for children under two years. Phase 2 and Phase 3 studies of safety, immunogenicity and efficacy were conducted in vaccine naive infants and children 6 months to 6 years of age, an age group still young enough to have escaped naturally acquired infections and priming. Fluad ultimately was shown to be substantially more efficacious than TIV in these unprimed children. The US ACIP (Advisory Committee on Immunization Practices), among other recommending bodies, stipulates that children under 9 years of age receiving influenza vaccine for the first time should receive two doses, as unprimed children do not mount a seroprotective antibody response after a single dose. Implicit in this recommendation is the presumption that children may remain naturally unprimed through the 9th birthday.

Data in support of this supposition are available from a recent seroprevalence study from the Netherlands that showed only ~30% of children were seropositive for the Victoria lineage of influenza B virus by their 7th birthday. Baseline seropositivity in our own V70P5 cohort show that 39-42%, 64% and 30% of children who were 5 years old at the time of study entry were seropositive for H1N1, H3N2, and B (Yamagata). Overall, a comparison of the Netherlands and V70P5 data suggest a lower age specific seroprevalence rates in the latter. This discrepancy illustrates the dependency on geography and birth year in the acquisition of influenza antibodies in growing children, and the role of serendipity for each birth cohort, whether influenza strains for each of the A subtypes and both B lineages circulated at sufficiently high attack rates to expose and infect (prime) them in the first decade of life. From the point seroprevalence rates measured in Study V70P5 cohort at the start of the autumn of 2008, and extrapolating from the immunogenicity subset day 180 titers in the non influenza vaccine recipients in the spring of 2009, it is clear that a substantial number of those children would not have been naturally primed and seropositive at age six years. The US ACIP recommendation, that requires two priming doses for children less than 9 years of age, recognizes this variability in natural exposure to influenza virus by birth year, and therefore specifies a ninth birthday cut off, based on conservative estimates that children up to that age may have escaped priming.

As evidence from the efficacy field trial showed, Fluad to be highly efficacious in preventing influenza in unprimed children, we believe that an age indication of 6 months to 9 years would serve a public health benefit and would avoid conflict with established recommendations.

While we acknowledge that a limited number of 6 to <9 year old children have been studied in Fluad clinical trials, we believe that an age indication for children up to the 9th birthday (6 to 8 years or 6 to <9 years) is justified for various reasons:

- Novartis recently completed Study V70P5E1, which provides additional data in children aged 6 to 9 years. Study V70P5E1 was a Phase 3B, observer blind, randomised, parallel groups, extension study to evaluate the immunogenicity and safety following a single intramuscular dose of Fluad or Agrippal influenza vaccines in healthy children previously vaccinated in Study V70P5. Approximately 95 subjects 6 to <9 years of age entered this study with 69 receiving Fluad. The available data show

that the safety results are comparable with those from the subsets of 6 to 36 months and 36 to 72 months old children vaccinated in V70P5. An additional 19 subjects from Study V87P6 were described as part of this submission and other data will be forthcoming from V7029 an ongoing Phase 3, observer blind, randomised, multicentre Study to Evaluate the Safety, Tolerability, and Immunogenicity of Fluad and Agriflu Compared to the Non Adjuvanted Trivalent Influenza Vaccine Fluzone in Children 6 to <72 Months of Age.

- In Novartis' Study V11103, a randomised, single blind, dose ranging study to evaluate immunogenicity, safety and tolerability of different formulations of adjuvanted and non adjuvanted egg derived, inactivated novel swine origin A/H1N1 monovalent subunit influenza virus vaccine in healthy subjects from 6 months to 17 years of age, up to 319 subjects that received MF59 (approximately 160 previously received two half doses of MF59 (3.75mg of HA H1N1), and 159 subjects previously received 2x full doses of MF59 (7.5mg of HA H1N1)), were revaccinated with Fluad, approximately one year later. A total of 361 subjects were revaccinated with Fluad for a second season (for example, third dose), of whom 176 subjects received Fluad at half dose (3.75 µg of HA + half MF59) and 185 subjects received Fluad at full dose (7.5 µg of HA + full MF59).
- In Novartis' Study V11004, a randomised, single blind, dose ranging study to evaluate immunogenicity, safety and tolerability of different formulations of adjuvanted and non adjuvanted cell derived, inactivated novel swine origin A/H1N1 monovalent subunit influenza virus vaccine in healthy subjects from 6 months to 17 years of age, up to 369 subjects that received an MF59 adjuvanted vaccine, were revaccinated with Fluad, approximately one year later. Analysis and report is available for 126 of them (approximately 53 previously received two half doses of MF59 (3.75mg of HA H1N1sw), and 59 subjects previously received 2x full doses of MF59 (7.5 mg of HA H1N1sw and 14 no prior MF59). A total of 48 subjects in the 3 to 17 years age cohort were revaccinated with Fluad for a second season (for example, third dose), of whom 22 subjects received Fluad at half dose (3.75 µg of HA + half MF59) and 26 subjects received Fluad at full dose (7.5 µg of HA + full MF59).
- Further supportive immunogenicity data come from head to head trials of unadjuvanted and adjuvanted pandemic H1N1 formulations in children 3-8 years old as well as in young adults (Figures 4-6). Adjuvanted formulations of Novartis' Fluvirin subunit TIV as well as Celtura, Novartis' cell culture derived H1N1 vaccine licensed in Germany and Switzerland, and Focetria, an egg derived MF59 adjuvanted H1N1 pandemic vaccine licensed under the Centralised Procedure, provided higher GMTs compared to those elicited by counterpart unadjuvanted vaccines in this age group, which includes children 6 to <9 years old. Children receiving adjuvanted vaccine reached the seroprotective threshold after one dose while two doses of the unadjuvanted vaccine were needed. Furthermore, even in young adults 18-60 years old, the adjuvanted formulation of Focetria provided higher GMTs compared to an otherwise identical unadjuvanted formulation (Figure 7). Of considerable interest, elevated seroprotective antibodies were maintained for one year after vaccination, a potential benefit for prevention of spring outbreaks now that vaccination campaigns begin as early as August while influenza outbreaks continue to occur through April and even later in the following calendar year.
- While the benefit of MF59 adjuvant in terms of clinical efficacy was described for children <6 years in Study V70P5, the elevated antibody titers seen in children <9 years and even in young adults receiving adjuvanted pandemic vaccine suggests that we can expect a similar incremental benefit in children aged 6 to <9 years old and, potentially, in yet older children.

Figure 4: Fluvirin A/2009 (H1N1) GMT HI titers: children 3 to 8 years of age (US).

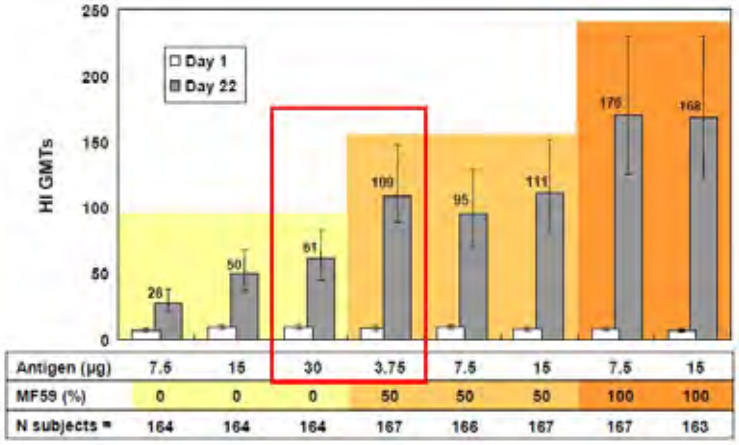


Figure 5: One dose of MF59 adjuvanted pandemic vaccine was immunogenic in children 6 months to <9 years.

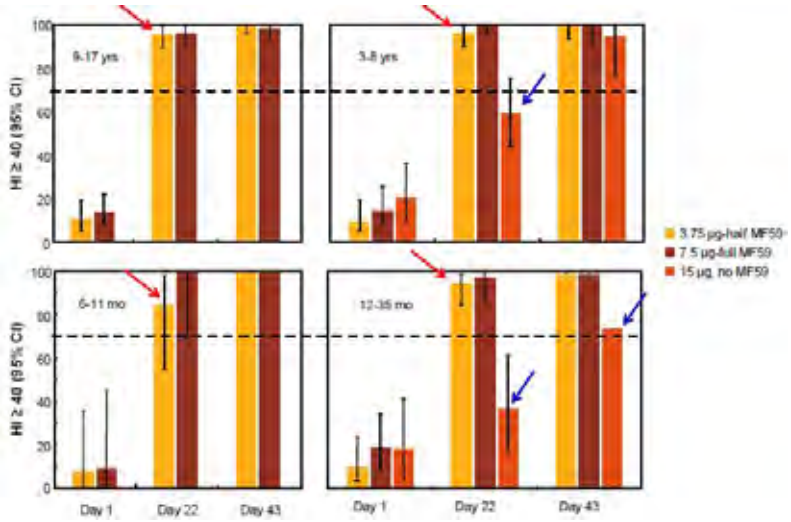


Figure 6: Antibody titers fell to below seroprotective levels in young adults primed with unadjuvanted vaccine.

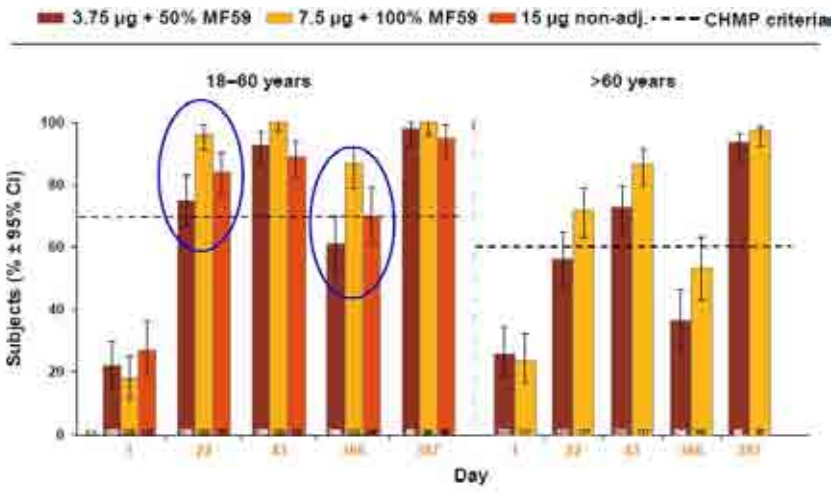
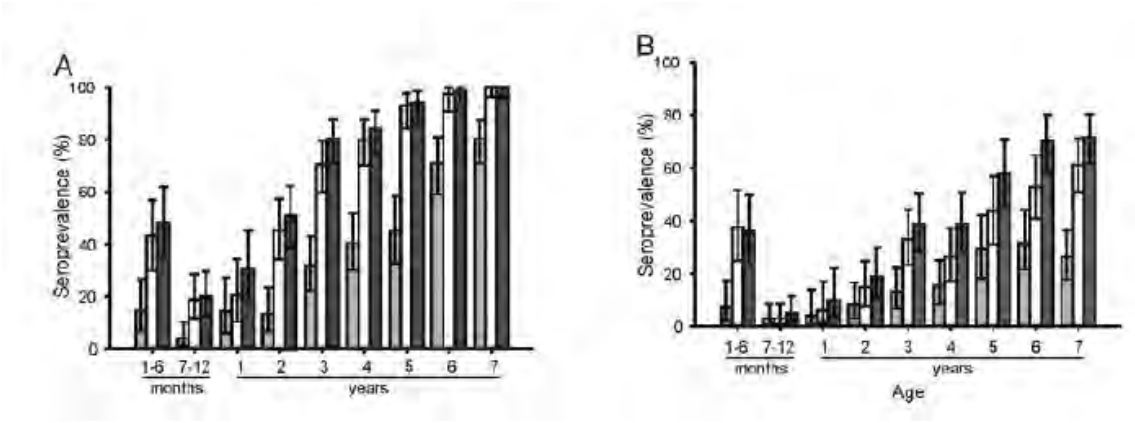


Figure 7: Seroprevalence to influenza A and B viruses by age (Netherlands).



(A) The percentages of serum samples from children in which antibodies against at least one of the representative influenza viruses were detected were calculated for influenza A/H1N1 viruses (light grey bars), influenza A/H3N2 viruses (white bars), and all influenza A viruses (dark grey bars). (B) The same procedures were used to calculate the seroprevalence of antibodies against at least one of the influenza B viruses from the Victoria lineage (light grey bars) and the Yamagata lineage (white bars) and all influenza B viruses (dark grey bars). Bars indicate the percentage of the serum samples in which antibodies were detected, and error bars indicate the 95% CIs.

In summary, available data and extrapolations indicate comparable safety and immunogenicity of Fluad for 6 to <9 years old children as in the 6 month to <6 year cohort, and that the slightly greater age range is more appropriate to avail immunologically naive children of a more efficacious priming vaccine while harmonising with public health recommendations.

Question 2: safety

- "What systems are in place for ongoing monitoring of low incidence but important adverse effects seen with other influenza vaccines (febrile convulsions) or in other age groups (for example, Guillain-Barre syndrome)?"

Sponsor's response

The sponsor has an established surveillance system in place for the detection and assessment of safety signals, also including those with of low incidence but medically relevant. Main activities are as follows:

- Real time notification of "key events": Based on internal procedures, a key event is defined as an important event, which has the potential to negatively affect the benefit-risk ratio of the vaccine; the list of key events is based on guidelines, published literature and medical experience with vaccines. Adverse events such as Guillain-Barre syndrome or febrile convulsion are also included in the list of key events. A key event is notified by the physician who performs the medical review of the case at the time of case data entry to the benefit risk physicians and pharmacovigilance managers, including the Qualified Person of Pharmacovigilance and the Global Head of Pharmacovigilance.
- Weekly medical review of key events. Key events are discussed on a weekly basis during a meeting involving benefits risk physicians, other members of pharmacovigilance and clinical cluster physicians.
- Automated signal detection using data mining. Novartis Vaccines is currently implementing Empirica Signal. This tool (already in use at Novartis Pharma) is a web based analysis environment for the detection and quantification of signals of disproportionate reporting through the use of advanced data mining techniques.
- Periodic Safety Update Reports (PSURs) and Development Safety Update Reports (DSURs).

Question 3: safety

- "Is there any further safety data in relation to the age group 6-18?"

Sponsor's response

Novartis recently completed Study V70P5E1, which provides additional data in children aged 6 to 9 years. Study V70P5E1 was a Phase 3B, observer blind, randomised, parallel groups, extension study to evaluate the immunogenicity and safety following a single intramuscular dose of Fluad or Agrippal influenza vaccines in healthy children previously vaccinated in Study V70P5. Approximately 95 subjects 6 to <9 years of age entered this study with 69 receiving Fluad.

Further data is constantly produced with Novartis' adjuvanted pandemic H1N1 formulations for the 6 to <18 year age group.

Clinical summary and conclusions

Clinical aspects

Clinical efficacy

The main clinical Study V70P5 was ambitious, well powered and well designed. It was unfortunately thwarted in its final year by a global recommendation for vaccination of children with a pandemic influenza vaccine. There is however very good clinical and immunological data from this study and good immunogenicity data to show that this vaccine is highly efficacious, in children 6-72 months. There is evidence of effective disease prevention and immunogenicity compliant with the CHMP recommendations, significantly higher than its active comparators. Disease prevention was significant both for homologous as well as heterogenous strains (except B strains) of influenza, as was immunogenicity. The data from the Phase 2 and supportive studies also showed good immunogenicity, higher than comparators and the pooled data reflects closely that of the individual studies. The efficacy of Fluad against vaccine matched strains was statistically significantly higher with respect to both non flu and flu control vaccines. There is not yet much data for Fluad in the 9-18 year age group, as this Study V7P29 was quite small. There may however be significant data from either licensed or 'off license' use in this age group in other countries.

Clinical safety

From the paediatric data, the side effect profile of Fluad paediatric seems very similar to that seen in adults. Of note, the higher reactogenicity of this vaccine in relation to its comparators, seems to result in a higher incidence of adverse events (as well as higher efficacy). There was a higher incidence of both local and systemic side effects than its comparators. It is important that health providers using this vaccine be aware of the high rate of both minor local and systemic side effects of this vaccine (and discuss this with parents and their children). The incidence of severe adverse events however, currently seems quite low and similar to the comparators. The rates of discontinuation due to adverse events were very low.

Given the issues with excess febrile convulsions in children vaccinated in Western Australia in 2010 and the changes in current TGA recommendations for paediatric influenza, there are now very strict regulations on sponsors for registration of paediatric influenza vaccines, relating mainly to ongoing vigilance in collecting data in relation to safety.

Benefit risk assessment

Benefits

- Fluad is a MF59 adjuvanted influenza subunit vaccine, registered since 1997 and currently licensed in 30 European and non European countries for use in elderly populations. To date more than 50 million doses of Fluad (and copy products) have been distributed worldwide.
- Conventional vaccines do not produce the same level of titers of protective antibodies (and are less likely to meet standards set by CHMP criteria for non elderly adults) in unprimed children, especially the very young ones.
- Given the high level data produced in these studies, the proposed posology is supported. Data from the V70P5 efficacy study suggest that HI titers much greater than 1:40 (that is, HI titers of 1:110) correlated with a 50% clinical protection rate against influenza illness. Further, higher titers correlated with higher levels of protection (HI titers of 1:215, 1:330, and 1:629 correlated with clinical protection rates of 70%, 80%, and 90%, respectively).
- In children 6 to <36 months and 36 to <72 months of age, two doses of Fluad (0.25mL and 0.5mL, respectively) were significantly more efficacious in preventing influenza infection (matched vaccine antigens), as measured by PCR than non adjuvanted split or subunit influenza vaccines. In both age groups Fluad was also found to be more efficacious than the flu control vaccines in providing protection against influenza regardless of the antigenic strain match. There were not enough cases to establish efficacy against the B strains; however, point estimates are favourable. After the first vaccination in unprimed children, higher GMT increases and higher seroprotection rates were already seen in the Fluad than non adjuvanted subunit or split influenza vaccine recipients. Nevertheless immunogenicity data (all three CHMP criteria were met) in unprimed children <72 months of age and the favourable safety data of a two dose schedule in children 6 months to <18 years (Study V87P6) showed that particularly for the B strain immune response a two dose schedule in children <9 years is recommended.
- Fluad consistently induced a higher immune response than conventional non-adjuvanted influenza vaccines after two doses in children <72 months in all studies, the difference was statistically significant with respect GMT and GMR vaccine ratios and vaccine group differences for seroconversion and seroprotection rates in the pivotal Phase 3 Study V70P5.
- Antibody persistence was shown in Studies V70P5 and V70P2. Approximately six months after vaccination HI antibody titers consistently remained significantly higher in the Fluad groups than in the non adjuvanted Flu comparator group. The persistence of antibodies was not as good for the B strains, although antibody levels remained above baseline.
- Unsolicited AE and AE leading to study discontinuation, medical consultation were similar to those reported to the conventional non adjuvanted influenza vaccines
- The demonstration of efficacy both against vaccine matched and also against other strains means this clinical benefit may continue when new or antigenically variant strains are circulating in the paediatric community.

Risks

- No immunogenicity data were obtained in clinical studies in children 6 to <9 years of age (only safety data from Study V87P6 are available), so immunogenicity in this age group has to be extrapolated.

- There was a higher incidence of solicited reactions (especially tenderness and erythema in children 6 to <36 months and injection site pain, erythema, fatigue and headache in children 3 to <18 years) following vaccination with Fluad compared to the other vaccines, although these were generally mild moderate.
- Most of the pooled safety data in children 3 to <9 years was from children 36 to <72 months (from Study V70P5). Data from 21 children 36 to <72 months and 19 children 6 years to <9 years is available from Study V87P6. Some increase in reactogenicity was observed relative to the overall reactogenicity in the 6 to <9 year old age group. Incidences of unsolicited AEs were comparable in the 2 subgroups and the pooled safety population.

Safety specification

Unexpected rare adverse events seen in children vaccinated with Fluad may still occur, as the numbers may yet not be sufficient to detect them (such as febrile convulsions).

Balance

Given the demonstrated benefits of Fluad, and the safety data available, the benefit-risk ratio of Fluad in children aged 6 months to 6 years is favourable. The evaluator would like to see efficacy data in the age group 7-9, but it is expected to be similar (or better) than in the younger groups.

Conclusions

Overall, the risk benefit balance favours registration of Fluad Paediatric, with a number of provisions.

V. Pharmacovigilance Findings

Risk management plan

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

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns, which are shown at Table 40.

Table 40: Ongoing Safety Concerns for Fluad.

Important identified risks:	**- Anaphylaxis**
Important potential risks:	- Neuritis - Convulsion - Encephalitis - Vasculitis - Guillain-Barré Syndrome - Demyelination - Bell's palsy - Immune thrombocytopenia - Vaccine failure (including pneumonia as a potential tracer

Important identified risks:	- Anaphylaxis
	of vaccination failure)
Important missing information:	CHILDREN - Safety in patients with underlying diseases - Safety in immunocompromised patients - Vaccination effectiveness - Potential interactions with other childhood vaccines
Other safety concerns:	- Potential for medication errors - Potential for off-label use

OPR reviewer's comment:

The sponsor has removed pregnant women from the important missing information. This would seem reasonable given the in the target population.

It is acknowledged that the sponsor has indicated that local and systemic events are expected from vaccines, however in light of the AEs reported in Australia during the 2010 seasonal influenza season, and because of the higher reactogenicity of Fluad than comparators in clinical trials, it is recommended that the sponsor be required to update the summary of ongoing safety concerns to include:

- Important identified risks
  - Febrile convulsions
  - Febrile reactions
  - Injection site reactions

Pharmacovigilance plan

In addition to routine pharmacovigilance, the sponsor has proposed to undertake additional pharmacovigilance activities.

In the RMP the sponsor identifies four key elements of the enhanced pharmacovigilance program:

1. Enhanced follow up of key events, including identified and potential risks
2. Automated signal detection using spontaneous reports. The analyses will be performed quarterly and will focus primarily on the following AEs of special interest:
   a. Neuritis
   b. Convulsion
   c. Anaphylaxis
   d. Vasculitis
   e. Encephalitis
   f. Guillain-Barré Syndrome
   g. Demyelination
   h. Bell's palsy
   i. Immune thrombocytopenia

In addition, the sponsor indicates via Section 31 questions that Novartis Vaccines is currently implementing Empirica Signal. The tool is described as a web based analysis environment for the detection and quantification of signals of disproportionate reporting through the use of advanced data mining techniques. The sponsor indicates this tool is to be fully implemented during Q1 2012 with a monthly frequency of signal runs.

3. Expected versus Observed sensitivity analysis for AESI (adverse events of special interest) performed quarterly.
4. Ongoing and planned clinical trials in paediatric patients (V7013, V7014, V7029)
5. Planned clinical trial in high risk children and adolescents 6 Years to <18 Years of Age (V7013, V7029)

In previous discussions between the sponsor and OPR, the sponsor has indicated they are preparing a proposal for active surveillance of their registered trivalent influenza vaccines. The sponsor has indicated via a response to a Section 31 request for additional information that it

a. Has provided safety data from Study V70P5
b. Has offered safety data from several large study of Focetria which indicated no increased risk for febrile seizures
c. It commits to making available to the TGA the Interim Report of V7029 (pending FDA approval), final Clinical Study Report V7029 and final Protocol for the extension Study V7029, to be provided to the TGA prior to the first supply of commercial Fluad Paediatric in Australia (not expected before the SH2013 season).

For these reasons the sponsor does *not* believe an active surveillance program for Fluad Paediatric is required.

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestone

There is no objection to the sponsor undertaking the above additional pharmacovigilance activities.

It is not acceptable for the sponsor to have no active surveillance program. The evaluator agrees with the rationale provided by the clinical evaluator for such a requirement.

The sponsor argues that data from trials with Focetria (a single valent adjuvant H1N1) is sufficiently similar to Fluad to be included for analysis is not agreed by the evaluator as this assumes the only reactogenic component of the vaccine is adjuvanted H1N1 which may not be the case.

The sponsor also argues that an extended protocol for Study V7029 will provide a better insight into the safety of Fluad than will an observational study however the study protocol has not been provided and will not be available until the end of 2011. The numbers of Australian children to be recruited and the general representation of that sample to the whole Australian paediatric population have not been established by the sponsor.

Therefore the evaluator supports the requirement of the clinical evaluator for active surveillance for this current strain and for future strains.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor has stated that labelling is considered sufficient at this point in time, based on the available safety information regarding Fluad use in clinical trials and post marketing surveillance.

OPR reviewer's comment:

This is considered acceptable.

Potential for medication errors

The sponsor acknowledges there is the potential for medication error leading to the use of Fluad 'elderly' in the paediatric population. To mitigate this risk the sponsor proposes to clearly mark the paediatric presentations with Fluad Paediatric on the labels, outer packages and in the package inserts, and to colour code (yellow for 0.25 mL dosage form and orange for 0.5 mL dosage form) the paediatric presentations (there will be no colour coding for the Fluad 'elderly' presentation).

OPR reviewer's comment:

This is considered acceptable.

Risk minimisation activities

Planned actions

As the sponsor has only proposed to undertake routine risk minimisation activities there is no risk minimisation plan.

OPR reviewer's comment:

The risk minimisation activities are acceptable.

Summary of recommendations

Safety specifications

In light of the AEs reported in Australia during the 2010 seasonal influenza season, and because of the higher reactogenicity of Fluad than comparators in clinical trials, it is recommended that the sponsor be required to update the summary of ongoing safety concerns to include:

- Important identified risks
  - Febrile convulsions
  - Febrile reactions
  - Injection site reactions

Pharmacovigilance plan

It is not acceptable for the sponsor to have no active surveillance program. The evaluator agrees with the rationale provided by the clinical evaluator for such a requirement.

The sponsor argues that data from trials with Focetria (a single valent adjuvant H1N1) is sufficiently similar to Fluad to be included for analysis is not agreed by the evaluator as this assumes the only reactogenic component of the vaccine is adjuvanted H1N1 which may not be the case.

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protocol has not been provided and will not be available until the end of 2011. The numbers of Australian children to be recruited and the general representation of that sample to the whole Australian paediatric population have not been established by the sponsor.

Therefore the evaluator supports the requirement of the clinical evaluator for active surveillance for this current strain and for future strains.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The vaccine virus is grown in fertilized chicken eggs and inactivated with formaldehyde. It is a surface antigen vaccine for intramuscular administration. It is not clear if this is a split virion or subunit vaccine. The sponsor is requested to comment in its pre Advisory Committee on Prescription Medicines (ACPM) response.

The currently registered product Fluad is reported (Australian Immunisation Handbook, 2008) to contain 0.05 mg thiomersal and traces of kanamycin and neomycin in addition to a number of excipients. No changes in manufacturing process or formulation are associated with the new paediatric presentations. The sponsor is requested to confirm whether thiomersal is present in Fluad Paediatric.

The summary of Quality and Biopharmaceutics by TGA evaluators indicates that the only changes associated with the product are the introduction of an alternative method to the EP method and the removal of abnormal toxicity test for lot release purposes as it is no longer an EP requirement. No outstanding Quality issues, including microbiology, have been identified. The product has not required referral to the Pharmaceutical Sub Committee (PSC).

Nonclinical

There are no outstanding objections from the Toxicology area. In part, the toxicology (vaccine & adjuvant) was supported by data previously evaluated for the registered products Fluad, Aflunov (pandemic influenza vaccine, MF59C adjuvanted) and Agrippal (unadjuvanted trivalent seasonal influenza vaccine from the same sponsor). Note this adjuvanted vaccine contains antigen in the same amount as the unadjuvanted vaccine.

Note toxicity studies have not been performed with Fluad in young animals. The current submission included three repeat dose studies in adult rabbits. The sponsor provided justification as follows:

> *'The safety of Fluad has been demonstrated clinically in children, and administration of vaccine results in the same pharmacological effect (elicitation of antibodies) in children and adults. Because the nonclinical and clinical programs have not identified any findings that require additional investigation, it was concluded that studies in juvenile animals are not justified. In Fluad toxicity studies the full human dose was administered to adult rabbits of ~3 kg body weight, and exposure multiples were adequate in terms of a conservative estimate of 5.7 kg body weight for a 6 month old human infant.'*

The toxicology area evaluators consider it acceptable. Overall, the dossier complies with the regulatory guidelines.

Clinical

The clinical evaluator recommends approval with implementation of active surveillance in the post approval phase.

The clinical dossier consisted of five controlled studies. These included 3 studies in children 6-72 months of age including one pivotal Phase 3 trial (V70P5), two Phase 2 trials (V70P2 and V70P6) and an extension study (V70P2E1).

Two supporting studies (V87P6 and V7P29) were included in the dossier. The Study V87P6 was conducted during development of H5N1 pandemic vaccine with Fluad comparator for assessment of safety in children 6 months to < 18 years of age. The Study V7P29 was designed to investigate immunogenicity of a single dose of Fluad in children 9 to < 18 years of age. Sponsor's response to the clinical evaluation report regarding lack of data in 6-18 years age group is included in the ACPM papers.

For further details, please refer to the clinical evaluation report, including extension Study V70P2E1 in which participants received another dose one year after completing vaccination in Study V70P2. The pivotal efficacy trial is discussed below in some detail:

The pivotal Study V70P5 was designed to assess efficacy, safety and immunogenicity (in a subset) of two doses of Fluad given 4 weeks apart in children 6 to < 72 months of age. This was a randomised, controlled, observer blind, multicentre study conducted over three consecutive seasons in Germany, Finland and Italy. Children with previous history of influenza vaccination were excluded. The children were stratified according to 6 to < 36 months and 36 months to < 72 months age groups.

Participants received Fluad or one of two vaccines as control - an influenza vaccine or a non influenza vaccine. A total of 4902 subjects were enrolled with 2019 in Fluad group, 1849 in flu control (Agrippal or Influsplit SSW) group and 1034 in non flu control (Menjugate/Encepur) group.

All subjects received two doses of vaccine at an interval of 4 weeks. In Fluad and flu control groups, children 6 to < 36 months of age received two 0.25 mL doses, children ≥ 36 months of age received two 0.5 mL doses. In accordance with the local usage guidelines, subjects who received two doses of Encepur, received a third dose after study unblinding.

Although the study aimed to evaluate vaccine efficacy over three seasons, the onset of H1N1 influenza pandemic during the 2009/10 season required administration of pandemic influenza vaccine to all participants according to national recommendations. The evaluation of efficacy of Fluad was therefore limited to 2007/08 and 2008/09 seasons.

Efficacy

The efficacy results, based on PCR confirmed cases of community acquired influenza, as shown in Table 41 (see also Tables 6-7).

Table 41: Summary of efficacy results.

Study V70P5	6 to <36 months			36 to <72 months			6 to <72 months		
	N	n (cases)	incidence	N	n (cases)	incidence	N	n (cases)	incidence
	Matched strains (seasons 2007/08 & 2008/09)								
Fluad	1103	7	0.63%	834	2	0.24%	1937	9	0.46%
Influenza control	995	22	2.21%	777	22	2.83%	1772	44	2.48%
non-influenza control	566	19	3.41%	427	22	5.15%	993	41	4.13%
	Any strain (seasons 2007/08 & 2008/09)								
Fluad	1103	9	0.82%	834	4	0.47%	1937	13	0.67%
Influenza control	995	25	2.51%	777	25	3.22%	1772	50	2.82%
non-influenza control	566	22	3.89%	427	25	5.85%	993	47	4.73%
Absolute (Fluad versus non-influenza control) Vaccine Efficacy (95% CI)									
Against matched strains	81.36% (49.24% to 93.16%)			95.5% (80.92% to 98.94%)			89.07% (77.55% to 94.68%)		
Against any strain	79.18% (54.78% to 90.42%)			92.1% (77.35% to 97.24%)			86.17% (74.48% to 92.51%)		
Relative (Fluad versus influenza control) Vaccine Efficacy (95% CI)									
Against matched strains	68.42% (26.59% to 86.41%)			91.36% (63.35% to 97.96%)			80.17% (59.44% to 90.31%)		
Against any strain	64.16% (23.21% to 83.28%)			85.66% (58.95% to 94.99%)			75.49% (54.97% to 86.66%)		

The two dose Fluad vaccination at 4 weeks interval in previously unprimed children aged 6 months to 72 months was thus found to be highly efficacious. Most cases were matched Type B strains.

The absolute vaccine efficacy (95% CI) for protection against matched strains (non flu control) was 81% (49% to 93%), 96% (81% to 99%) and 89% (78% to 95%) in the 6 to < 36 months age group, 36 to < 72 months age group and overall respectively.

The absolute vaccine efficacy (95% CI) for protection against any influenza strain (non flu control) was 79% (55% to 90%), 92% (77% to 97%) and 86% (74% to 92%) in the 6 to < 36 months age group, 36 to < 72 months age group and overall respectively.

Fluad vaccination was statistically superior to comparator trivalent flu vaccines as follows:

The relative vaccine efficacy (95% CI) for protection against matched strains (flu control) was 68% (27% to 86%), 91% (63% to 98%) and 80% (59% to 90%) in the 6 to < 36 months age group, 36 to < 72 months age group and overall, respectively.

The relative vaccine efficacy (95% CI) for protection against any influenza strain (flu control) was 64% (23% to 83%), 86% (59% to 95%) and 75% (55% to 87%) in the 6 to < 36 months age group, 36 to < 72 months age group and overall, respectively.

Immunogenicity

The clinical evaluation report includes discussion of immune correlates. Two doses were required to meet all three CHMP criteria by all strains. As also shown in Phase II studies, antibody titers elicited to B strain in younger age cohort were lower compared to immune response to A antigens.

Safety

Total Fluad exposure in this dataset consists of 1500 children in 6 to < 36 months age group, 918 in 3 to < 9 years age group and 157 in 9 to < 18 years age group.

The follow up of participants in the pivotal trial during 1st and 2nd seasons was for a period of 6 months. The solicited AEs were recorded up to 6 days after vaccination. Pooled results in the age group of most interest, that is, 6 months to < 36 months are in Tables 21 and 27.

Overall, AEs were reported with higher frequency in Fluad group compared to flu control in all age groups.

No instance of febrile convulsions or neurological disorders including Guillain-Barre syndrome were reported in this dataset. Post market surveillance data in children is not available.

Risk management plan

The RMP evaluation report is accompanying. In the main, the report recommends inclusion of active surveillance plan in the risk management plan.

Risk-benefit analysis

Delegate considerations

Administration of Fluad, an inactivated, seasonal TIV adjuvanted to MF59C, in 6-36 month old children was shown to be highly immunogenic but still required two doses at 4 weeks interval to meet all three CHMP criteria for immune correlates of influenza in adults (18-60 years) using HI or SRH assay. These correlates have not been validated for use in children. A recently published paper[16] discusses some regulatory issues and is included in the ACPM papers.

Although the availability of vaccine efficacy trial data in this submission overtakes any reliance on surrogate end points, the immunogenicity data in this trial may be very useful in validating these correlates and establishing protective thresholds in children. The results noted in the clinical evaluation report indicate that these thresholds be considerably higher in children than in adults.

The pivotal efficacy trial was well designed and met its objectives even though the data from the intended 3rd season could not be used. The vaccine is clearly highly effective. Estimates of vaccine efficacy of 89% and 86% were obtained against matched strains and all strains respectively in 6-72 months old children. As well, superior efficacy was shown against the comparator unadjuvanted trivalent seasonal vaccines of the order of 80% and 75% against matched strains and all strains respectively in the same age group. The limited efficacy of comparator trivalent inactivated influenza vaccines in this study is consistent with efficacy reported in other published reviews of these vaccines in young children.

In general, Fluad Paediatric was shown to be more reactogenic with respect to solicited local and systemic adverse effects relative to the comparator conventional unadjuvanted TIVs. In the 6-36 months age group, the reported rate of fever was 20% versus 18% after dose 1 and 22% versus 17% after dose 2 for Fluad and the flu control respectively. Elsewhere, 22.5% rates of fever have been reported in this age group with dose 1 and 2 with Fluvax and 39% following a booster.[17]

The use of influenza vaccines in the prevention of seasonal influenza implies repeated vaccination every year. This is of concern due to presence of the MF59C oil in water adjuvant.

[16] Granström M, Voordouw AC. Registration of influenza vaccines for children in Europe. *Vaccine* 29: 7572-7575 (2011).

[17] Nolan T, et al. Safety and immunogenicity of an inactivated thimerosal-free influenza vaccine in infants and children. *Influenza Other Respi. Viruses* 3:315-325 (2009).

Although extensive safety experience in the elderly and toxicological data are available for this adjuvant, these can only adequately define risk associated with one-off or a finite number of administrations of a vaccine - a situation which applies to almost all currently used vaccines with the exception of seasonal influenza.

In my opinion, risks associated with a potentially high number of repetitive injections of the MF59C adjuvanted vaccine Fluad Paediatric starting in infancy or early childhood and accumulating over life time are unknown and cannot be considered adequately qualified by the existing clinical and toxicological data. A surface antigen based vaccine for influenza even when adjuvanted is not expected to induce lasting immunity.

At present only unadjuvanted inactivated influenza vaccines are being used in comparable jurisdictions for prevention of seasonal influenza in children. A live intranasal influenza vaccine is also approved overseas.

Please note that thiomersal is currently not included in vaccines registered for use in children because of theoretical concerns raised in a US National Institutes of Health (NIH) Report. Thiomersal was removed or eliminated from many vaccines from 1999 as a precautionary measure to reduce exposure to mercury from all sources. The sponsor is being asked to confirm the presence or other wise of thiomersal in Fluad Paediatric.

At present, no specific guidance is available with respect to the use of adjuvanted influenza vaccines in children from the ACPM or the Australian Technical Advisory Group on Immunisation or from the overseas regulators.

The ACPM is therefore requested to provide advice about the suitability of use of adjuvanted vaccines for prevention of influenza in children with particular reference to Fluad which uses MF59C adjuvant.

Delegate's proposed action

Pending advice from ACPM, the Delegate is of the opinion that approval of MF59C adjuvanted trivalent influenza vaccine for seasonal prophylaxis of influenza in infants and children is not warranted due to unknown risks associated with multiple administrations and potential for cumulative toxicity.

The risk balance in elderly individuals over 65 years of age with identified high risks remains favourable.

Response from sponsor

Presented here is the Novartis pre ACPM Response to the TGA Delegate's overview and Request for ACPM Advice in relation to our Category 1 Application to vary the conditions of Registration (Extension of indication and new strength registration) of Fluad influenza vaccine subunit, prefilled syringe. Where appropriate, our comments have been cross referenced to the Delegate's overview (DO), the clinical evaluation report (CER), the nonclinical evaluation report (NER), the biochemistry evaluation report (BER) or to our submission for marketing authorisation (MA).

Introduction

The Delegate acknowledged that Novartis' Fluad Paediatric dossier provided in our MA is sufficient to meet regulatory requirements for registration and that evaluators of the individual sections recommend approval based on the data submitted.

Specifically, the Delegate confirmed all points mentioned in the evaluators reports, recognising that:

1. The biochemistry section of the dossier is acceptable since no outstanding Quality issues, including microbiology, have been identified (DO, page 1).

2. The toxicology section is considered adequate and in compliance with the regulatory guidelines (DO, page 8).
3. The pivotal trial [V70P5] was well designed and met the objectives including demonstrating a superior efficacy against the comparator. It is also stated that the vaccine is clearly highly effective. (DO, page 11) though it was also noted that Fluad is more reactogenic with respect to the comparator vaccines (DO, page 11);
4. Overall, current regulatory guidelines have been met for this type of therapeutic product (DO, page 2).

That said, contrary to the recommendations of the Biochemistry Evaluator (BER, page 10), the Nonclinical Evaluator (NER, page 4) and the Clinical Evaluator (CER, page 89-92), the TGA Delegate does not recommend approval of Fluad for the indication of active immunisation against influenza in infants and children (6 months to less than 9 years of age). Pending advice from the ACPM, the Delegate is of the opinion that approval of MF59C.1 adjuvanted trivalent influenza vaccine for seasonal prophylaxis of influenza in infants and children is not warranted due to unknown risks associated with multiple administrations and potential for cumulative toxicity (DO, page 6).

The sponsor welcomed the Evaluators' recommendations and address in our response below the specific concerns raised in the Delegate's overview. **It is Novartis' view that based on our below proposed concession to restrict the use of Fluad Paediatric to a maximum of two influenza seasons, approval of our MA is a viable outcome.** For the sake of clarity and convenience, the Delegate's comments are transcribed in *italics* throughout our response.

Responses to issues raised in the delegate's overview

> *"It is not clear if [Fluad Paediatric] is a split virion or subunit vaccine. The sponsor is requested to comment in its Pre ACPM response."* (DO, page 1)

Novartis also notes that on page 2 of the NER, the generic name of Fluad Paediatric is listed as "Seasonal trivalent influenza vaccine (split virion, inactivated, MF59C.1 adjuvanted)". However, Novartis confirms that Fluad Paediatric is a **subunit** vaccine.

> *"It is not clear whether immunogenicity data with the current strains [2012] have been provided. The sponsor is requested to confirm."* (DO, page 1)

As noted by the Delegate, the vaccine strains recommended by the WHO for the 2012 Southern Hemisphere seasonal influenza vaccines did not change from 2011. Novartis provided interim data on a subset of paediatric subjects with chronic diseases from Study V7029 to complement our response to Question 40 of the consolidated Section 31 Request for Information. This study used the recommended 2011 strains, and therefore includes immunogenicity data for 2012 strains as well.

> *"The sponsor is being asked to confirm the presence or otherwise [use] of thiomersal in Fluad Paediatric."* (DO, page 6)

Novartis understands that the 2008 version of the Australian Immunisation Handbook lists Fluad as a thiomersal containing vaccine; however, this information is not current. Novartis confirms that *no* thiomersal is present in Fluad Paediatric. Thiomersal was completely removed from all Fluad formulations in 2003. Corrective steps have been taken to update the Handbook accordingly.

> *"At present only unadjuvanted inactivated influenza vaccines are being used in comparable jurisdiction for prevention of seasonal influenza. A live intranasal influenza vaccine is also approved overseas."* (DO, page 6)

While conventional trivalent seasonal influenza vaccines are available for use in paediatric populations, they do not appear to be effective particularly in the

youngest age groups. In their Cochrane review, Jefferson et al. concluded from a metaanalysis of cohort studies (with 9213 observations), inactivated seasonal influenza vaccines are no more efficacious than placebo and there is no evidence of their effectiveness in children under the age of two years.[18]

While a live intranasal influenza vaccine is approved overseas, its indication is limited to children 2 years of age and older and is conditioned for children under the age of 5 years of age to the absence of a history of wheezing, which effectively leaves children with a great medical need without an effective vaccine.

While no adjuvanted vaccines are yet registered in comparable jurisdictions for the paediatric population, Novartis confirms that registration applications have been submitted for Fluad Paediatric in other jurisdictions. The efficacy data from Study V70P5 confirms the findings of Jefferson and colleagues.[18] **With regards to unadjuvanted TIV in children and documents a significant reduction in laboratory confirmed influenza in children that received the Fluad Paediatric:**

- Relative vaccine efficacy were 80% (95% confidence interval [CI], 59%-90% and 75%, 95% CI of 55%-87% for antigenically matched and any strain, respectively (CER, page 23-24).
- Study V70P5 also achieved its primary safety objective of non-inferiority of Fluad Paediatric compared with unadjuvanted TIV in children 6 to <36 months in terms of *combined* local and systemic reactogenicity with a relative risk of 1.03 and a non significant 97.66% CI of 0.98-1.09. Individually, there was a slightly higher, but not clinically significant, percentage of reported local reactions among subjects who received Fluad Paediatric compared with unadjuvanted TIV in both 6 to <36 month olds and 36 to <72 month olds, but, only a difference in reported systemic reactions among the 36 to <72 month olds. Most local and systemic reactions were mild or moderate; specifically pain at the injection site and low grade fever of 38.0°C-38.9°C were most common.

In summary, Study V70P5 demonstrates superior efficacy for Fluad Paediatric over conventional TIV in all age groups, supporting a favourable risk-benefit ratio across the age range of 6 months to <9 years of age. This is particularly the case when Fluad Paediatric is used for initial vaccination and then for only one subsequent revaccination year.

> *"Risks associated with the potentially high number of repetitive injections of MF59C.1 adjuvanted vaccine Fluad Paediatric starting in infancy or early childhood and accumulating over a life time are unknown and cannot be considered adequately qualified by the existing clinical and toxicological data."* (DO page 5)

M59C.1 is an oil and water emulsion, prepared with a low content of the biodegradable oil squalene, which is naturally occurring in plants and animals including humans. In humans, squalene is a direct precursor to cholesterol in the biosynthetic pathway of steroid hormones. Humans produce about 1 mg/day and ingest about 50 to 200 mg/day. In comparison Fluad contains 10 mg/dose. Moreover, preclinical experience with MF59C.1 is extensive.

Although extensive safety experience in the elderly (CER, page 86)[19] and toxicological data (NER, page 13-18) are available for this adjuvant, the Delegate is of the view that these

[18] Jefferson T, et al. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst. Rev.* Apr 16:CD004879 (2008).

[19] Pellegrini M, et al. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. *Vaccine* 27:6959-6965 (2009).

only adequately define risks associated with one off or a finite number of administrations of a vaccine. As noted in the DO, the use of influenza vaccines in the prevention of seasonal influenza implies repeated vaccination every year.

To further support changes in the dosage and administration information to initial vaccination and one revaccination year with Fluad Paediatric, Novartis refers to the results of three studies provided to the TGA in October 2011 in response to Question 32 of the consolidated Section 31 Request for Information:

- Study V70P5E1: 135 and 61 subjects aged 6 months to <96 months received Fluad Paediatric or Agrippal for a second season (third dose), respectively. The majority of subjects in the 6 to <36 months of age group (80%-100%) reported at least one reactogenicity event after booster vaccination. Local events were reported by 33% to 100% of subjects, and systemic events were reported by 33% to 71% of subjects. However, the small number of subjects in each group (total in this age group, n=17) makes it difficult to conclusively evaluate reactogenicity profiles across booster groups. For the 36 to <96 months of age group, the majority of subjects (82% to 96%) reported at least one reactogenicity event after vaccination. Local events were reported by 55% to 94% of subjects and systemic events were reported by 39% to 73% of subjects. There was a tendency for more subjects in the Fluad groups to report reactogenicity signs than subjects in the non adjuvanted group (Agrippal) but results were comparable.
- Study V11103: In the age range of 6 months to 17 years - up to 319 subjects that received MF59C.1 (approximately 160 previously received two half doses of MF59C.1 (3.75 µg H1N1), and 159 subjects previously received two full doses of MF59C.1 (7.5 µg H1N1) and were revaccinated with Fluad one year later. Although there appeared to be more subjects reporting local and systemic reactions after the booster vaccinations than after the primary doses of 7.5 µg H1N1 (with full strength MF59C.1) (local reactions: 46% in season 1 → 58% in season 2; systemic reactions: 48% in season 1 → 58% in season 2), this could possibly be a reflection of the 6 fold greater amounts of antigen in Fluad than in the priming vaccinations (45 µg versus 7.5 µg), while the amounts of adjuvant remain the same between the vaccines. Local and systemic reactions were typically mild or moderate in severity and were of short duration (generally resolving within the 7 day time window). Severe local and systemic reactions were infrequently reported, with the highest incidence being severe local tenderness.
- Study V11004: In the age range of 6 months to 17 years - up to 369 subjects that received MF59C.1 and were revaccinated with Fluad Paediatric, approximately one year later. Analysis and report is available for 126 subjects (approximately 53 previously received two half doses of MF59C.1 (3.75 µg H1N1sw), and 59 subjects previously received two full doses of MF59C.1 (7.5 µg H1N1sw and 14 no prior MF59C.1). A total of 48 subjects in the 3 to 17 years age cohort were revaccinated with Fluad Paediatric in a second season (for example, third dose), of whom, 22 subjects received Fluad Paediatric at half dose (3.75 µg) and 26 subjects received Fluad Paediatric at full dose (7.5 µg). Comparable to the V11103 there was an increase in local and systemic reactions in patients receiving the same dose of MF59C.1 in season 1 and season 2 but the increase was less marked: (local reactions: 38% in season 1 → 45% in season 2; systemic reactions: 45% in season 1 → 48% in season 2). AEs were reported rarely and few were considered related to vaccination.

None of the above studies raised safety concerns following revaccination with Fluad Paediatric. Additionally, the results of the V70P5 extension study (V70P5E1) provide evidence of a specific benefit of revaccinating with Fluad Paediatric after the two dose priming series (Table 42). This sequence provided higher titers to 2 of 3 homologous strains and heterologous strains. Higher titers were also seen in the original

Study V70P5 and therefore may correlate with improved efficacy and cross protection. For patients already primed with a seasonal influenza vaccine other than Fluad Paediatric, Study V70P5E1 demonstrated a similar but more modest improvement following a single vaccination with Fluad Paediatric in the post priming season with a comparable safety profile.

Table 42: HI GMT by priming and subsequent revaccination (Study V70P5E1).

		2010 vaccination					
		A/California/7/2009 (H1N1)		A/Perth/16/2009 (H3N2)		B/Brisbane/60/2008	
		ATIV	TIV	ATIV	TIV	ATIV	TIV
ATIV-Priming N=42,	GMT Day 1	57 (39-84)	55 (34-90)	123 (77-195)	109 (59-198)	7 (5-9)	11 (7-15)
	GMT Day 22	1228 (826-1825)	520 (311-869)	1871 (1481-2364)	735 (543-995)	127 (91-177)	115 (75-177)
TIV-Priming N=52,	GMT Day 1	56 (38-82)	48 (28-81)	55 (33-93)	29 (14-62)	6.89 (6-8)	5 (4-6)
	GMT Day 22	1396 (1051-1854)	666 (446-995)	830 (597-1155)	284 (178-453)	45 (31-64)	20 (12-33)
Non-influenza control-priming	GMT Day 1	63 (37-107)	-	130 (64-266)	-	5.9 (5-7)	-
	GMT Day 22	1810 (1229-2667)	-	1810 (1208-2713)	-	43 (22-85)	-

None of the subjects shown were vaccinated with pandemic or seasonal vaccine in 2009.

Nevertheless, Novartis recognises the clinical and public health importance to further demonstrate the safety of new adjuvanted vaccines in children. Controlled clinical trials are an optimal method for detecting potential safety signals. As part of the Fluad Paediatric development plan, Novartis will continue to collect safety data during clinical trials including the current year long pivotal trial under Study V7029 and its planned extension. Novartis will share any additional safety data with the TGA. Additionally, Novartis has no objection to a post approval commitment for a surveillance study.

Novartis understands the Delegate's concerns with regards to the presence of the MF59C.1 oil in water adjuvant and the limited availability of data from revaccinations across more than two seasons. Given the current lack of data for more than two years of exposure in the paediatric age group, Novartis would like the ACPM and the Delegate to consider, as a precautionary measure, to restrict Fluad dosing to only two seasons (initial vaccination and one revaccination) in this population until additional safety data is available.

Concluding remarks

Novartis thanked the Delegate and the ACPM for considering the sponsor's proposed dosing restriction in response to the Delegate's negative recommendation. The sponsor indicated that it considered that there is currently an important unmet medical need in the paediatric population for the effective prophylaxis of influenza and that the Delegate's safety concerns have been addressed by the limitation of the indication. Novartis also acknowledged the TGA's request for an active surveillance study to be conducted prior to launch in Australia. Details on how to best address this request, it was agreed, would be discussed with the TGA post approval. Novartis indicated that it considered the submitted dataset adequately supports the registration of Fluad Paediatric in Australia for the active immunisation against influenza in infants and children aged 6 months to less than 9 years with the proposed dosing restrictions.

Advisory committee considerations

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

The ACPM agreed with Delegate that the overall benefit-risk profile for this product for the proposed indication was negative.

The ACPM noted that, while efficacy was higher in Fluad Paediatric than the equivalent unadjuvanted vaccine; the safety risks as evidenced by the incidence of clinically significant solicited AEs were also higher, particularly in the 3-9 year age group.

The ACPM also noted the absence of data in high risk groups such as immune compromised children, and those with chronic comorbidities, in which the use of this vaccine might have been appropriate. The lack of inclusion of end points for prevention of severe cases of influenza in the clinical studies was also noted

While the ACPM did not express any concerns regarding repeat exposure to the squalene-based adjuvant, it did note that no repeat dose animal studies had been conducted. The ACPM advised that it was not practical to limit exposure to 2 seasons in children and therefore does not effectively balance of risk.

NOTE: The committee noted in ratification that nonclinical evaluation for Fluad contained several new repeat dose toxicity studies with Fluad adjuvanted with MF59, containing squalene the formulation. The appendix to the report also lists previously evaluation repeat dose, reproductive toxicity and genotoxicity studies with the squalene containing adjuvant alone.

Outcome

On 13 February 2012, Novartis Vaccines and Diagnostics Pty Ltd wrote to the TGA, asking for the application for Fluad Paediatric to be withdrawn before a decision was made.

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 #